

CLINICAL PRACTICE GUIDELINES FOR MENOPAUSE

2026

PART - 1

*"**Fit** @ Forty, **Strong** @ Sixty and **Independent** @ Eighty"*



Indian
Menopause Society

CLINICAL PRACTICE GUIDELINES FOR MENOPAUSE

Chair

Dr. Meeta

Co-Director and Senior Consultant Gynaecologist, Tanvir Hospital
Specialist: Menopause, Osteoporosis, Gyn Ultrasound
Hyderabad, Telangana, India

Co-chairs

Dr Anuradha M

Professor, HOD Obgyn, SRM Medical College
SRM Institute of Science and Technology, Kattankulathur,
Chengalpet district, Tamilnadu, India

Dr Asna Beg Ashraf

Consultant Obgyn and Director Ujala Medical Centre
Lucknow, India

Dr Kiran Aggarwal

Director Professor Obgyn, Lady Hardinge Medical College
New Delhi, India

Dr Leela Digumarti

Gynaecological Oncologist, St Theresa's Hospital and Asvins Hospital,
Hyderabad, Telangana, India

Dr Tanvir Singh

Minimally invasive gynaec surgeon, Urogynaecology
Tanvir Hospital Hyderabad, Telangana, India

Copyright and Disclaimer: © 2026 Indian Menopause Society. All rights reserved.

The copyright of these Clinical Practice Guidelines for Menopause rests with the Indian Menopause Society. No part of this publication may be reproduced, stored in a retrieval system, or transmitted in any form or by any means, electronic, mechanical, photocopying, recording, or otherwise, without prior written permission from the Indian Menopause Society. These Clinical Practice Guidelines are intended to support healthcare professionals in clinical decision-making by providing evidence-based recommendations relevant to local practice settings. They are advisory in nature and are not intended to substitute for the independent professional judgment of healthcare providers or to establish a standard of care applicable to all clinical situations. Individual patient circumstances, preferences, comorbidities, and available resources must be considered when applying these recommendations. While every effort has been made to ensure that the information contained herein is accurate, current, and based on the best available evidence at the time of publication, the Indian Menopause Society makes no representations or warranties regarding the completeness or accuracy of the content and does not guarantee that it is free from errors or omissions. To the fullest extent permitted by law, the Indian Menopause Society disclaims all liability for any direct, indirect, incidental, special, or consequential damages arising out of or in connection with the use, interpretation, or application of these guidelines.

Disclosure and Conflicts of Interest: In accordance with the International Committee of Medical Journal Editors' recommendations, all Resource Faculty involved in developing these guidelines have disclosed potential conflicts of interest. The Resource Faculty report no conflicts of interest relevant to the content of this publication.

Acknowledgment: *This project was completed under the aegis of the Indian Menopause Society.*

Funding Statement: The development of the Clinical Practice Guidelines for Menopause: 2026 was supported by the Indian Menopause Society, which provided organisational oversight and logistical support. No external entity had any role in the conception, methodology, content development, formulation of recommendations, review, or approval of these guidelines, and editorial independence was maintained.

Suggested Citation: *Meeta M, Anuradha M, Ashraf AB, Aggarwal K, Dugumarti L, Singh T. Clinical Practice Guidelines for Menopause. 3rd Edition. Mumbai. Indian Menopause Society. 2026*

Parts: This book is in two parts

Indian Menopause Society Website: www.indianmenopausesociety.org

Publisher: Indian Menopause Society, India

ISBN No: 978-93-342-5385-6

INDIAN MENOPAUSE SOCIETY EXECUTIVE COUNCIL MEMBERS 2025-26



Dr Anita Shah
President



Dr Arti Gupta
Vice President



Dr Ragini Agarwal
Secretary General



Dr Jyoti Jaiswal
Treasurer



Dr Hephzibah K
Joint Treasurer



Dr Binal Shah
Joint Secretary



Dr Sudhaa Sharma
President Elect



Dr Anju Soni
Immediate Past President



Dr Bipasa Sen
Ex-Officio Secretary General

INDIAN MENOPAUSE SOCIETY

PEER REVIEW TASK FORCE 2023-2026

Chair : Anita Shah, President, Indian Menopause Society | **Co Chair:** Ranu Patni | **Founder Chair:** Meeta

- | | | |
|---------------------|-------------------------|----------------------|
| • Rama A Vaidya | • Jaideep Malhotra | • Pushpa Sethi |
| • Sonia Malik | • Suvarna Khadilkar | • Rashmi Shah |
| • Duru Shah | • Ratnabali Chakravorty | • Sudhaa Sharma |
| • Sunila Khandelwal | • Neelam Aggarwal | • Yashodhara Pradeep |
| • Atul Munshi | • Jignesh Shah | • Annil Mahajan |
| • Jyothi Unni | • Ambuja C | • Vishal Tandon |
| • Maninder Ahuja | • Shobhana Mohandas | • Ruchika Garg |
| • H.P.Pattanaik | | |

EXTERNAL REVIEW BOARD

International-For the Executive Summary of the Clinical Practice Guidelines for Menopause

Ang Seng Bin

Senior Consultant at Family Medicine Service & Menopause Centre of KK Women's and Children's Hospital in Singapore. Director of innovations, SingHealth Duke-NUS FM ACP President-Elect, International Menopause Society

Martha Hickey

Professor of Obstetrics and Gynaecology, University of Melbourne, Head of Menopause Services and Co-Director of The Gynaecology Research Centre at The Royal Women's Hospital, Australia

National

Ajay Phatak

Professor of Bio-Statistics, Adjunct Professor of Public Health, Charutar Arogya Mandal, Karamsad

Balamba P

Senior consultant, OBGYN, Shalini hospital Hyderabad. Former Professor and HOD Osmania medical college Former Professor Emeritus NTR health university

Bhasker Pal

Senior Consultant, Apollo Multispecialty Hospital, Kolkotta, President FOGSI 2026

Dilip Banushali

Consultant Physician, Udai Omni Hospital, Hyderabad
National President, Indian Medical Association

Kaushik Pandit

Chief Consultant Endocrinologist, Belle Vue Clinic, Research Scientist, Dept. of IPGME&R, Kolkata.
National President, Endocrine Society of India

Krishna Reddy

Cardiac Care Center, Durgabai Deshmukh Hospital, Hyderabad. CEO, ACCESS Health International, Chairman & MD, Relisys Medical Devices Ltd, President, InOrder, the Health Systems Institute

Kripa A

Professor of Endocrinology, Christian Medical College, Vellore

Rakesh Sahay

Professor of Endocrinology, Osmania Medical College, Hyderabad. President South Asian Federation Of Endocrine Societies

Raman Marwah

Scientific Advisor and Senior consultant Endocrinology, International Life Sciences Institute (India) & Consultant to CCRH, Ministry of AYUSH. Former Additional Director, Institute of Nuclear Medicine & Allied Sciences, DRDO, Ministry of Defence

Reshma

Vice Chairperson, Guru Nanak Group of Institutions Bidar, Karnataka

Sesikaran

Nutrition and Food safety, Former Director ICMR NIN Hyderabad

Sushrut Babhulkar

Director, Sushrut Institute of Medical Sciences; Nagpur. President, Trauma Society of India; President, Osteoporosis Society of India

Thomas Paul

Professor of Endocrinology, Christian Medical College, Vellore

URK Rao

Senior Consultant, Sri Deepti Rheumatology Centre, Hyderabad

Vijay Anand Reddy

Professor, Head, Dept. of Oncology Apollo Cancer Centres, Hyderabad

V Mohan

Chairman, Madras Diabetes Research Foundation (ICMR- Collaborating Centre of Excellence) and Dr. Mohan's Diabetes Specialities Centre (IDF Centre of Excellence in Diabetes Care), Chennai

INDIAN MENOPAUSE SOCIETY CLINICAL PRACTICE GUIDELINES FOR MENOPAUSE EDITORIAL TEAM 2026

CHAIR



Dr Meeta

CO-CHAIRS



Dr Anuradha M



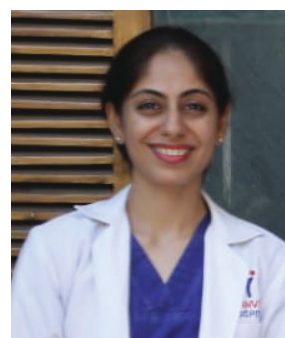
Dr Asna Beg Ashraf



Dr Kiran Aggarwal



Dr Leela Digumarti



Dr Tanvir Singh

RESOURCE FACULTY

Akrishti Gupta

Senior Resident Obgyn, SN Medical
College, Agra, Uttar Pradesh, India.

Anita Kant

Gynaecologist, Consultant, Asian Institute of
Medical Sciences, Faridabad, Haryana, India

Anjan Pyal

Consultant Neurophysician, CITI Neuro Centre,
Hyderabad, Telangana, India

Anuradha M

Professor and HOD of Obgyn, SRM Medical College,
SRM Institute of Science and Technology,
Kattankulathur, Chengalpattu district, Tamil Nadu, India

Asif Sultan

Consultant Nephrologist, University of Tennessee
Medical Ctr, Knoxville, TN. USA

Atul Munshi

Gynaecologist, Director, Munshi Group of Hospitals,
Ahmedabad, Gujarat, India

Bina Tandon

Director, Krishnalok Clinic,
Lucknow, India

Chandrashekar Reddy

Senior Consultant Neurophysician,
CITI Neuro Centre, Hyderabad, Telangana, India

Cherunur Ambuja

Gynecologist, Ret Prof & HOD
Osmania Medical college, Telangana, India

CH Trivedi

Gynaecologist, Consultant, Narayan
Clinic & Shivam hospital Udhna, Surat, Gujarat, India

Hara P Pattanaik

Gynaecologist, Joint Director
SCB Medical College, Cuttack, Odisha, India

Hepshiba Khurabani

Obstetrics & Gynaecology, Senior Consultant -
Multispecialty Hospital & Visiting Prof. Madha Medical
College, Chennai, Tamil Nadu, India

Alka Kumar

Gynaecologist, Wellness Consultant,
Nagpur, Maharashtra, India

Anita Shah

Gynaecologist, Consultant, Surat,
Gujarat, India

Annil Mahajan

Rheumatologist, Senior Consultant
Madaan Hospital and Research Centre,
Jammu- J&K Jammu and Kashmir, India

Asha Kapadia

Oncologist, Consultant Medical and Pediatric
Oncology, Head of Dept of Oncology and Medicine,
PD Hinduja National Hospital and Medical Research
Centre, Mumbai, Maharashtra, India

Asna Beg Ashraf

Consultant Obgyn and Director Ujala
Medical Centre Lucknow, India

Bhavana Sheth

Consultant Gynaecologist, Proprietor, CF Sheth
Memorial Hospital, Bharuch, Gujarat, India

Bipasa Sen

Gynaecologist, Consultant, Kolkata,
West Bengal, India

Chellamma VK

Gynaecologist Professor, Medical College,
Alappuzha, Calicut, Kerala, India

Ch Ratna Kishore

Senior Consultant Neurophysician,
CITI Neuro Centre, Hyderabad, Telangana, India

Duru Shah

Gynaecologist, Scientific Director, Gynecworld,
Mumbai, Maharashtra, India

Hema Karthik

Senior Consultant Ophthalmologist Royal Victorian
Eye and Ear Hospital, Melbourne, VIC, Australia

Jagmeet Madan

Director, Research Innovation Consultancy and
Collaboration Centre; Sir Vithaldas Thackersey
College of Home Science (Empowered Autonomous
Status), SNDTWU, Mumbai, India

Jaideep Malhotra

Gynaecology, Director, Rainbow
Hospital Agra, Uttar Pradesh, India

Jyothika A Desai

Gynaecologist Senior Consultant, Dr PR
Desai Hospital, Bangalore, India

Jyoti M Shah

Gynaecologist, Senior Consultant, Mamta Hospital,
Rajkot, Gujarat, India

Madhulika Agarwal

Gynaecologist, Senior Consultant Agarwal Hospital
& Maternity Centre Jaipur, Rajasthan, India

Lakshmi Ratna

Gynaecologist, Chief Consultant,
Ankura Hospital, Telangana, India

Madhukar Reddy K

Ophthalmologist, Director, Chief Consultant,
Drishti Hospital, Telangana, India

Mala Raj

Gynaecologist, Managing Director,
Firm Hospitals Chennai, Tamil Nadu, India

Meeta

Co Director, Senior Consultant Gynaecologist,
Tanvir Hospital, Hyderabad, Telangana, India

Monal Shah

Senior Resident, Department of Surgical
Gastroenterology, Indira Gandhi Institute of
Medical Sciences, Patna, Bihar, India

Nidhi Gupta

Gynaecologist, Professor,
SN Medical College, Agra, Uttar Pradesh, India.

Nikhileshwar Reddy C

Consultant Neurophysician, CITI Neuro Centre,
Hyderabad, Telangana, India

Jignesh Shah

Gynaecologist, Director, Dr Shah Institute for
Women's Health, Ahmedabad, Gujarat, India

Jyoti Hak

Gynaecologist, Former Professor and Head
Postgraduate Department of Obstetrics and Gynaecology
Government Medical College Jammu (J&K)

Jyothi Unni

Gynaecologist, Director Dept of Obs & Gyn
Jehangir Hospital, Pune, Maharashtra, India

K Thanigaimani

Professor and Unit Head Institute of Orthopaedics and
Trauma Madras Medical College, Chennai, India

Leela Digumarti

Gynaecological Oncologist, St Theresa's Hospital and
Asvins Hospital, Hyderabad, Telangana

Madhubabu Kothapalli

Physiotherapist, Sports Medicine,
PhD Student, University of Canterbury,
Christchurch, New Zealand

Maninder Ahuja

Gynaecologist, Director, Ahuja Hospital &
Infertility Centre, Faridabad, Haryana, India

Monal Garg

Mch Gynae Oncology Associate Consultant
Gynae Oncology Fortis Memorial Research
Institute, Gurugram Haryana, India

Navneet Takkar

Gynaecologist, Professor and Head of Department
Obgyn, Government Medical College & Hospital,
Chandigarh, Punjab, India

Nidhi Gupta

Assistant Professor, Department of Radiation
Oncology Government Medical College and Hospital,
Chandigarh, India

N. Vivek

Prof and Head. Department of Oral & Maxillofacial
Surgery, SRM Kattankulathur Dental College
Kattankulathur, Chengalpatt, Tamil Nadu, India

Padma Kurada

Consultant, Aarogyasri and EHS of Telangana
Consultant Ophthalmologist and Medical
Superintendent, Drishti Hospital, Telangana, India

Pooja Shah

Senior Consultant, Devpushp Maternity Hospital,
Vadodara, Gujarat, India

Prem Blaise Rejula

Associate Prof. Department of Periodontology.
Kattankulathur Dental College, Kattankulathur,
Chengalpet, Tamil Nadu, India

Rama Vaidya

Reproductive Endocrinologist, Director, Division
of Endocrine and Metabolic Disorders, Kasturba
Integrative Health Sciences- Medical Research
Foundation, Mumbai, Maharashtra, India

Reshmi Banerjee

Menopause consultant, CIMP
Senior consultant, Zydus Hospital
Vadodara, Gujarat, India

Rohit Raina

Obstetrics and Gynaecology, Associate Consultant,
Indraprastha Apollo Hospital, New Delhi, India

Sai Deepak Yaranagula

Consultant Neurophysician CITI Neuro Centre,
Hyderabad, Telangana, India

Saket Kumar

Additional Professor, Department of Surgical
Gastroenterology, Indira Gandhi Institute of Medical
Sciences, Patna, Bihar, India

Sharad Kumar

Medicine Professor, Eras Medical College,
Lucknow, Uttar Pradesh, India

Shobhana Mohandas

Gynaecologist, Consultant
Sun Medical Centre, Thrissur, Kerala, India

Smrity Shailly Bagde

Senior Resident, Department of Psychiatry, NKP
Salve Institute Of Medical Sciences Nagpur,
Maharashtra, India

Sudhaa Sharma

Gynaecologist, Madaan Hospital & Research Centre,
Jammu Tawi, Jammu and Kashmir, India

Padmanabhan Raghu

Senior consultant,
Apollo Main Hospitals,
Chennai, Tamilnadu

Preeti D Galvankar

Gynecologist, Dr Balabhai Nanavati
Hospital, Mumbai, Maharashtra, India

Pushpa Sethi

Gynaecologist, Menopause Consultant, Sethi
Hospital Pvt Ltd, Gurgaon, Haryana, India

Rashmi Shah

Gynaecologist, Ex Senior Deputy Director National
Institute for Research in Reproductive Health
(Indian Council Of Medical Research), Mumbai,
Maharashtra, India

Rathikha Kaartik

Physician Assistant Apollo
Main Hospitals, Chennai.

Sabahat Rasool

Associate Professor & Consultant Reproductive
Medicine, Govt. Medical College, Srinagar, India

Sai Praveen Haranath

Senior Consultant, Pulmonary and Critical Care Medicine
Apollo Hospitals Jubilee Hills Hyderabad, Telangana, India

Sardar Naunihal Singh

Director, Paediatrician, Adolescent Health
Tanvir Hospital, Hyderabad, Telangana, India

Sheela V Mane

Gynaecologist, Chief Consultant, Anugraha
Nursing Home, Consultant Bengaluru,
Karnataka, India

Shubhi Gupta

Assistant Professor, Obgyn, MMCMSR, Sadopur,
Ambala, Haryana, India

Sonia Malik

Gynaecologist, Chief Clinical Mentor Nova IVF and
Fertility, New Delhi, India

Sunila Khandelwal

Gynaecologist, Senior Consultant, Mid-life Women's
Health Care and Menopause Centre Fortis Escorts &
Apex Hospital, Jaipur, Rajasthan, India

Suvarna Khadilkar

Gynaecologist, Professor and Head of the Department
Obgyn, RSCM GMC, Mumbai, Maharashtra, India

Tanmaya Talukdar

Director, Professor, Department of Pulmonary
Medicine, Vardhaman Mahavir Medical College and
Safdarjung Hospital, New Delhi, India

Tanvir Singh

Minimally Invasive Surgeon, Urogynaecology,
Tanvir Hospital, Telangana, India

Thanuja Mannava

Founder ,Chief Plastic Surgeon, Youniq Center,
Hyderabad, Telangana, India

Tripti Nagaria,

Gynaecologist, Professor, Obgyn
Dean, Chandulal Chandrakar Memorial Govt. Medical
College, Durg Chhattisgarh, India

Tushar Patel

Senior Resident, Department of Surgical
Gastroenterology, Indira Gandhi Institute of Medical
Sciences, Patna , Bihar, India

Usha Rani Poli

Gynec Oncologist, Director of Oncology Research and
Education, Pragyaa Sustainable Health Outcomes
Foundation Hyderabad, Telangana, India

Urvashi Prasad Jha

Gynaecologist, Past Director & Head Department of
Minimal & Natural Access Gyne & Gyne Cancer, Fortis
Flt Lt Rajan Dhall Hospital & Fortis Memorial
Research Institute (FMRI), Gurgaon, India

Urvashi Yavalkar

Gynaecologist, Sr Consultant, Pratibha
Nursing Home, Pune, Maharashtra, India

Vishal Tandon

Professor, Postgraduate Department of Pharmacology
and Therapeutics Govt. Medical College,
Jammu-J&K, India

Yashodhara Pradeep

Professor Obgyn, Era Lucknow Medical college
Hospital, Lucknow, Uttar Pradesh, India

TABLE OF CONTENTS

PART-1

EDITORIAL

1

SECTION 1

MENOPAUSE TRANSITION

6

1. Basics of Menopause 7
Meeta, Rama Vaidya, Kiran Aggarwal*
2. Stages of Menopause 20
Asna Beg Ashraf, Meeta, Jignesh Shah*
3. Socioculture Dimension of Menopause 31
Meeta, Rashmi Shah, Anuradha M*
4. Clinical Evaluation at Menopause 44
Atul Munshil, Meeta, Anuradha M, Asna Beg Ashraf, Kiran Aggarwal, Leela Digumarti, Tanvir Singh*
5. Declining Fertility 55
Jaideep Malhotra, Nidhi Gupta, Akrishti Gupta*
6. Contraception at Perimenopause 68
Anita Shah, Kiran Aggarwal, CH Trivedi*
7. Abnormal Uterine Bleeding at Menopause Transition 80
Tanvir Singh, Meeta*
8. Postmenopause Bleeding 92
Tanvir Singh, Meeta*
9. Menopause Transition and Symptoms 102
Meeta, Asna Beg Ashraf, Mala Raj*
10. Genitourinary Syndrome of Menopause 129
Meeta, Tanvir Singh, Asna Beg Ashra*
11. Quality of Life 163
Jyothi Unni, Kiran Aggarwal, Meeta, Urvashi Yavalkar*

SECTION 2

CARDIOVASCULAR SYSTEM

173

12. Cardiovascular Disease 174
Kiran Aggarwal, Meeta*
13. Effects of Hormone Therapy on Cardiovascular Disease 202
Sudhaa Sharma, Annil Mahajan, Vishal R Tandon, Urvashi Prasad Jha*

SECTION 3

NERVOUS SYSTEM

212

14. Neurobiology and Neuropsychiatric Symptoms 213
Anjan Pyal, Ch Rathna Kishore, Chandrasekhar Reddy, Anuradha M, Pushpa Sethi*
15. Neurological Disorders 220
C Nikhileshwar Reddy, B Chandrasekhar Reddy, Ch Ratna Kishore, Anjan Pyal, Anuradha M*

- | | |
|---|-----|
| 16. Sleep Disorders | 230 |
| <i>Alka Kumar*, Sai Deepak Yaranagula, Chandra Sekhar Reddy, Smrity Shailly Bagde, Anuradha M</i> | |

SECTION 4

SKELETOMUSCULAR SYSTEM	243
-------------------------------	------------

- | | |
|--|-----|
| 17. Postmenopausal Osteoporosis | 244 |
| <i>Neelam Aggarwal*, Asna Beg Ashraf, Meeta, Shubhi Gupta</i> | |
| 18. Frailty and Sarcopenia | 281 |
| <i>Annil Mahajan*, Sudhaa Sharma, Vishal R Tandon, Jyoti Hak, Kiran Aggarwal</i> | |
| 19. Osteoarthritis | 298 |
| <i>Anuradha M*, Meeta, K Thanigaimani</i> | |

SECTION 5

MENOPAUSE AND OTHER SYSTEMS	304
------------------------------------	------------

- | | |
|---|-----|
| 20. Ocular Health | 305 |
| <i>Padma Kurada *, Madhukar Reddy K, Hema Karthik, Anuradha M</i> | |
| 21. Skin and Hair | 316 |
| <i>Anuradha M*, Thanuja Mannava</i> | |
| 22. Oral Health | 327 |
| <i>N. Vivek *, Anuradha M , Prem Blaise Rejula</i> | |
| 23. Respiratory System | 334 |
| <i>Tanmaya Talukdar*, Kiran Aggarwal</i> | |
| 24. Gastrointestinal System | 339 |
| <i>Saket Kumar K*, Monal Shah, Pooja Shah, Tushar Patel, Kiran Aggarwal</i> | |
| 25. Renal System | 355 |
| <i>Asna Beg Ashraf*, Asif Sultan</i> | |
| 26. Immune System | 363 |
| <i>Anuradha M*, Padmanabhan Raghu, Rathikha Kaartik</i> | |

SECTION 6

SEXUAL HEALTH	371
----------------------	------------

- | | |
|---|-----|
| 27. Sexual Health in Mid-life | 372 |
| <i>Bina Tandon*, Asna Beg Ashraf, Meeta</i> | |

SECTION 7

BREAST CANCER	385
----------------------	------------

- | | |
|--|-----|
| 28. Breast Cancer - Indian Context | 386 |
| <i>Navneet Takkar*, Meeta, Nidhi Gupta, Asha Kapadia</i> | |

29. Breast Cancer-Effects of Hormone Therapy 405
Meeta, Leela Digumarti

SECTION 8

GENITAL CANCERS 424

30. Cancer Cervix 425
Leela Digumarti, Meeta*
31. Cancer Endometrium 439
Usha Rani Poli, Leela Digumarti*
32. Cancer Ovary, Vulva and Vagina 447
Lakshmi Ratna, Leela Digumarti*

EDITORIAL

Keywords: Menopause diversity, FDA label revision, revision of clinical guidelines, appraisal

INTRODUCTION

As medical professionals, we work with “what is available, where we are, rather than what we wish for, to deliver the best possible care within existing constraints”.

As early as 1959, Simpson described menopause as a physiological state that requires intervention only when symptoms interfere with daily life.¹ Progressive for its time, this view nonetheless describes menopause as an endpoint rather than a transition, and as a symptom complex rather than a biological window of opportunity. Today, it is recognised as an important transition affecting various aspects of health, including heart health, bones, mental well-being, and overall ageing. Instead of being merely an endpoint, menopause now presents a vital opportunity to prevent future health issues and enhance quality of life.

For the busy obstetrician and gynaecologist, shifting from a procedure-driven, high-intensity speciality to the broader responsibilities of midlife and ageing medicine presents a challenge. Clinical guidelines are essential for guiding doctors in making well-informed decisions. The real question, therefore, is not whether guidelines are needed, but whether they can be applied universally across different countries. The answer is clearly no. Guidelines must be tailored to the population they serve, as health systems, cultures, and patient needs differ across countries.

The Indian Menopause Society (IMS) has prepared Clinical Practice Guidelines for Menopause (CPGM) tailored specifically for Indian women. These guidelines integrate global research with Indian data and expert opinion, making them both scientifically valid and practically applicable. They are intended not only for doctors but also for women, healthcare workers, and policymakers.

Recent global changes, such as the U.S. Food and Drug Administration’s removal of the black box warning on menopause hormone therapy in November 2025, signal a move away from fear towards evidence-based, individualised care.² This shift reinforces the responsibility and need for careful, selective prescribing, clear counselling, and ongoing review, principles central to these guidelines.

Menopause, however, is not a disease. It is a natural life event, no less universal than childbirth. The creation of antenatal clinics demanded vision, advocacy, and ongoing effort, yet the results, measurably healthier mothers and infants, are now universally accepted. Similarly, the systematic development of dedicated menopause clinics has the potential to transform not only individual health outcomes but also the course of population ageing, creating a society that is healthier, more active, and resourceful well into later life.

A JOURNEY OF LEARNING WITH THE INDIAN MENOPAUSE SOCIETY

On a personal note, my professional journey has unfolded alongside the growth of the Indian Menopause Society. I have evolved with it, through phases of learning and reaffirming, gathering strength, facing uncertainty in the post-WHI era, and ultimately emerging with greater clarity and conviction, both as a clinician and as an individual.

The IMS family, as we fondly call it, is distinctive in its holistic approach. It addresses not only the physical manifestations of ageing, but also the psychological, emotional, and social dimensions of a woman’s life. What binds the IMS together is not merely an academic interest, but a shared ethos of sensitivity, patience, and unwavering dedication to the well-being of the adult woman. Beyond scientific engagement, the society takes pride in actively encouraging and nurturing the diverse talents of its members. Cultural expression, culinary creativity, fitness, self-care, and emotional well-being are embraced as integral to personal and professional growth, reflecting the IMS’s truly holistic and humane vision of healthy ageing.

The theme for my presidential year 2012, “**Fit @ Forty, Strong @ Sixty, Independent @ Eighty**”, captures this philosophy succinctly. It reflects a life-course approach to health, resilience, and autonomy. The colours chosen to represent this vision are intentional: red for dynamism and vitality, blue for stability and confidence, and green for renewal, healing, and freedom. Together, they mirror the evolving physical and emotional landscape of a woman’s life.

The artwork chosen for the 2026 edition reflects this spirit and has emerged from an unexpected place, a photograph taken from an aircraft. Amid routine and predictable options, it was the image of a tranquil blue sky with sun-kissed clouds that resonated most deeply, a quiet reminder that even in transition and uncertainty, there is always a bright silver lining. That image now frames this book, much as the vision of comprehensive menopause care frames our collective work. This volume is not merely an academic update; it reflects the evolution of evidence, practice, and perspective. Above all, it is an invitation to reimagine menopause not as an endpoint, but as an opportunity to shape healthier ageing for generations of women to come. We hope it will be read with interest, implemented with confidence, and translate into better care for women.

Meeta

GUIDELINES: QUALITY AND IMPLEMENTATION

Before the formal era of guideline appraisal, the Indian Menopause Society benefited from the guidance of internationally respected experts, including Dr Wulf H. Utian, Professor John A. Kanis, Dr Anna Fenton, and Dr Pem Gooneratne, whose commentaries strengthened the quality of guideline published in 2012 and 2015.³ In an era of evidence-based practice and rapidly evolving data, the credibility of menopause guidelines is particularly important. Independent appraisal studies have highlighted both strengths and limitations in existing global guidance, emphasising the need for greater rigour and consistency. Notably, the Executive Summary on Postmenopausal Osteoporosis developed in 2018 by IMS was among a small group of guidelines selected for rigorous quality assessment using internationally accepted instruments.⁴

In the critical domain of rigour of development, it achieved a score substantially higher than the global mean, underscoring the value of transparent methodology, systematic evidence synthesis, and explicit recommendation formulation.⁵

Independent systematic reviews have consistently shown that only a small proportion of menopause guidelines worldwide achieve high methodological quality.⁶ Guidelines developed by recognised professional organisations, including the Indian Menopause Society, have demonstrated moderate to good quality, indicating sound development processes while highlighting opportunities for improvement.^{6,7}

They highlight that the true strength of a guideline lies not only in its recommendations but in its transparency, adaptability, and usability in daily practice. For a country as diverse as India, acknowledging these realities is essential and lends greater credibility to guidelines designed with context in mind.

OBJECTIVES OF THE CPGM 2026

- This monograph serves as the core reference text for the Credentialed IMS Menopause Practitioner (CIMP) examination conducted annually by the Indian Menopause Society.
- To guide health-care practitioners in the systematic clinical assessment, diagnosis, risk stratification, and individualised management of women during the menopausal transition and postmenopausal period.
- To support primary care physicians in understanding the fundamentals of menopausal health and to facilitate appropriate and timely referral to specialists when required.
- To inform and support health policy formulation by providing an evidence-based framework for integrating menopausal health into national noncommunicable disease (NCD) strategies, primary health-care services, and women's health programs.
- To raise awareness among health professionals and policymakers regarding the health priorities of the ageing woman and to promote the establishment of structured menopause clinics across all levels of care.
- To stimulate research interest and academic engagement across all aspects of menopausal medicine, with particular relevance to the Indian context.

METHODS

The 2026 CPGM builds on earlier IMS guideline documents released in 1998, 2002, 2008, 2010, 2012, and 2020. The methodology underpinning guideline development was detailed in the 2012 /2020 editorial and has been updated and expanded for the current edition.

Planning and execution of the 2026 guidelines spanned over 3 year. Key clinical questions were structured using the PICOTS framework, specifying the population, intervention, comparator, outcomes, timing, and setting, to inform systematic evidence identification and review.³

Evidence was sourced through systematic searches of electronic databases, including PubMed, MEDLINE, and the Cochrane Database of Systematic Reviews, as well as from published international and national guidelines, consensus statements, and standard reference textbooks on menopause management. The document also incorporates relevant abstracts from oral and poster presentations at national IMS scientific meetings, along with structured expert opinion where high-quality evidence was limited.

The Core Guideline Committee (Chair and Co-Chairs) conducted multiple online meetings to critically appraise evidence and review, refine, and finalise each recommendation. The draft guidelines underwent internal review by the IMS Peer Review Task Force, followed by an external review by National and International Review Boards comprising multidisciplinary medical experts, patient advocates, and ethicists.

GRADING OF EVIDENCE AND STRENGTH OF RECOMMENDATIONS

The following grading system was used in developing the Executive Summary of the CPGM 2026, published in the Journal of Mid-life Health (<https://journals.lww.com/jomh/pages/default.aspx>).

The quality of evidence and strength of recommendations were determined using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) framework.^{8,9} Recommendations are based on high-quality evidence and suggestions from expert consensus.⁹

Genetic Factors

- Grade A (High quality): Further research is unlikely to change confidence in the estimate of effect
- Grade B (Moderate quality): Further research may influence confidence and alter the estimate
- Grade C (Low quality): Further research is likely to substantially impact confidence and estimates
- Grade D (Very low quality): The estimate of effect remains highly uncertain

Strength of Recommendations

- Strong recommendations use the term “recommend”
- Conditional recommendations use the term “suggest”

To encourage ongoing interest, research questions are suggested at the end of each chapter.

BENEFITS OF USING THE GUIDELINES

Implementation of these guidelines is expected to improve the quality and consistency of menopause care, facilitate early detection and management of non-communicable diseases, and strengthen the emphasis on preventive health strategies for midlife and ageing women. By identifying gaps in existing Indian data, the guidelines also aim to stimulate locally relevant research and evidence generation to inform future practice.

LIMITATIONS AND FUTURE RESEARCH PRIORITIES

The guideline is limited by the paucity of robust pharmacological data from Indian populations. Future research priorities include longitudinal studies across the menopausal transition, qualitative research exploring women’s experiences and preferences, and interventional studies evaluating the effectiveness and safety of therapeutic strategies in Indian settings.

DISSEMINATION OF THE GUIDELINE

To ensure wide accessibility and effective implementation, the Executive Summary and Recommendations are available on the IMS website and published in the Journal of Mid-Life Health.¹⁰ Dissemination will be supported through IMS-accredited CME programs, national and regional conferences, webinars, and structured training initiatives, including the CIMP examination; open-access, mobile-friendly digital resources; engagement with academic institutions, professional bodies, and policymakers; and patient-facing educational materials in regional languages through the IMS 35-Plus Committee.

BARRIERS AND FACILITATORS TO IMPLEMENTATION

Implementation of the guidelines may be constrained by limited recognition of menopause as a preventive health opportunity, time pressures within busy clinical practices, unequal access to diagnostic and specialist services, sociocultural stigma with low health-seeking behaviour, and the paucity of India-specific longitudinal and interventional data. Facilitators include integration of menopause care into primary health services, establishment of dedicated menopause clinics analogous to antenatal clinics, structured training initiatives such as the CIMP certification, use of simplified clinical algorithms and digital decision-support tools, multidisciplinary collaboration with patient-centred counselling, and sustained advocacy and policy engagement through professional bodies such as the Indian Menopause Society. Addressing these factors is critical to translating guideline recommendations into effective clinical practice.

REVISION OF THE GUIDELINE

The guideline was revised in 2026, and the updated Executive Summary was published in the Journal of Midlife Health.¹⁰ Planned updates every five years are recommended to ensure alignment with emerging evidence and evolving clinical practice.¹⁰

EDITORIAL INDEPENDENCE

The development of this guideline was conducted independently. All recommendations are based on systematic evidence review, expert consensus, and clinical judgment. No external organisation or commercial entity influenced the content, interpretation, or final recommendations of the guideline.

ACKNOWLEDGEMENTS

I have been privileged to learn from the personal journeys of pioneers of the menopause movement, including Dr Rama Vaidya, founder of the Indian Menopause Society, and Dr Wulf H. Utian, founder of the International Menopause Society and The Menopause Society. This shared commitment was reinforced by pioneers and key national and international stakeholders alike, highlighting collective responsibility for robust, credible, and implementable menopause guidelines.

I extend my sincere thanks to all experts who generously contributed their time and expertise to the development of this guideline on menopause management in India. I also acknowledge technical and editorial assistance received during guideline preparation, including exceptional facilitation of access to selected full-text scientific literature and professional copy-editing support. These contributions were limited to logistical and editorial assistance and had no role in the conception, analysis, interpretation, or formulation of recommendations contained in this guideline.

I am deeply grateful to my co-authors, Anuradha M, Asna A B, Leela D, Kiran A, and Tanvir S, for their sustained commitment, scholarly rigour, and collaborative spirit throughout the guideline development process.

Meeta

REFERENCES

1. Simpson SL. Major Endocrine Disorders. 3 rd ed. Oxford: Oxford University Press; 1959. p. 459.
2. FACT SHEET: FDA Initiates Removal of “Black Box” Warnings from Menopausal Hormone Replacement Therapy Products <https://www.hhs.gov/press-room/fact-sheet-fda-initiatesremoval-of-black-box-warnings-from-menopausal-hormone-replacement-therapy-products.html>, Accessed on 19/02/2026
3. Meeta M, Digumarti L, Agarwal N, Vaze N, Shah R, Malik S. Clinical Practice Guidelines on Menopause. Indian Menopause Society; 2020:487–489. Available at: www.indianmenopausesociety.org.
4. Meeta, Harinarayan C V, Marwah R, Sahay R, Kalra S, Babhulkar S. Clinical practice guidelines on postmenopausal osteoporosis: An executive summary and recommendations. J Midlife Health [Internet]. travanj 2013. [citirano 13. siječanj 2017.]; 4(2):107–26. Dostupno na: <http://www.jmidlifehealth.org/text.asp?2013/4/2/107/115293>
<https://doi.org/10.4103/0976-7800.115293> PMID: 24082708
5. Hayawi LM, Graham ID, Tugwell P, Yousef Abdelrazeq S (2018) Screening for Osteoporosis: A systematic assessment of the quality and content of clinical practice guidelines, using the AGREE II instrument and the IOM Standards for Trustworthy Guidelines. PLoS ONE 13(12): e0208251. <https://doi.org/10.1371/journal.pone.0208251>
6. Hemachandra C, Taylor S, Islam RM, Fooladi E, Davis SR. A systematic review and critical appraisal of menopause guidelines. BMJ Sex Reprod Health. 2024 Apr 11;50(2):122-138. doi: 10.1136/bmjsexrh-2023-202099. PMID: 38336466.

7. Meeta M, Digumarti L, Agarwal N, Vaze N, Shah R, Malik S. Clinical practice guidelines on menopause: *An executive summary and recommendations: Indian Menopause Society 2019–2020. J Mid-life Health 2020;11:55-95 Meeta M. Introduction to the guidelines on menopause and postmenopausal osteoporosis. J Midlife Health 2020;11:534..
8. Whitlock EP, Lopez SA, Chang S, Helfand M, Eder M, Floyd N. AHRQ series paper 3: Identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the effective healthcare program. J Clin Epidemiol 2010;63:491501.
9. Atkins D, Best D, Briss PA, Eccles M, FalckYtter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
10. Meeta, M, Anuradha, M, Ashraf AB, Aggarwal, K. Dugmarti L, Singh T. Clinical Practice Guidelines for Menopause: *An Executive Summary and Recommendations: Indian Menopause Society 2026. Journal of Mid-life Health 17(Suppl 1):p S12-S116, February 2026. | DOI: 10.4103/jmh.jmh_302_25

Section 1

MENOPAUSE TRANSITION

1. Basics of Menopause
2. Stages of Menopause
3. Socioculture Dimension of Menopause
4. Clinical Evaluation at Menopause
5. Declining Fertility
6. Contraception at Perimenopause
7. Abnormal Uterine Bleeding at Menopause Transition
8. Postmenopause Bleeding
9. Menopause Transition and Symptoms
10. Genitourinary Syndrome of Menopause
11. Quality of Life

BASICS OF MENOPAUSE

Keywords: Terminology, age and determinants of menopause, medical challenges

01

INTRODUCTION

Menopause represents a physiological transition from the reproductive to the non-reproductive stage of a woman's life.¹ It is considered a natural adaptive process that may serve as a protective mechanism against reproductive morbidity and mortality in the ageing population. The menopausal experience, however, is highly individualised, with variability as distinctive as a personal fingerprint.²

Evidence indicates that menopause has much broader implications than simply the loss of fertility.³ Menopause is a significant physiological milestone in a woman's life and sets the stage for ageing, accelerating the process of noncommunicable disorders (NCDs).² The biology and symptomatology of menopause are blurred due to its relationship to the underlying ageing process. Research consistently demonstrates that Indian women experience menopause at a younger age than their Western counterparts, with significant regional and socioeconomic variation.²

The menopausal transition (MT) is influenced by a range of factors, including genetics, socioeconomic status, education, nutrition, and lifestyle. Premature ovarian insufficiency (POI) before age 40 and early menopause (EM) between ages 40–44 are increasingly recognised in India, with prevalence rates of 2–7% and 13–17%, respectively, and are more common among women with lower education, rural residence, and those undergoing surgical interventions such as hysterectomy.⁴ This earlier onset has important implications for fertility, long-term health, and preventive care, as Indian women may spend more than thirty years of their lives in the postmenopausal stage. Menopausal symptoms such as vasomotor disturbances, psychological changes, and physical complaints are widespread, yet often underreported due to sociocultural factors and limited awareness. Despite the significant impact of menopause on quality of life (QOL) and the risk of chronic diseases like cardiovascular disease (CVD) and osteoporosis, menopause-specific health education and services remain limited in India.⁵

TERMINOLOGY

There is a need for universally accepted terminology in menopause medicine.⁶ The history of the evolution of the terminology related to menopause is interesting. The initial attempt to define different aspects of menopause was at the first International Menopause Congress in France in 1976.⁷ Later, the World Health Organisation (WHO) Scientific Group on Research in the Menopause met in 1980, and published the recommendations in 1981. These definitions were revisited in 1994 and published in 1996.⁸ Korpilampi, in 1986, suggested a time-related definition, and later Utian proposed an ovarian function therapy-oriented definition.⁹ The Board of the International Menopause Society in 1999 approved a list of menopause-related definitions, which are universally applicable.¹⁰

- **Natural or spontaneous menopause:** It is recognised to have occurred after 12 consecutive months of amenorrhea, for which there are no obvious pathological causes; it is a retrospective diagnosis. It results from the depletion of ovarian follicles, leading to a near-complete, natural reduction in ovarian hormone secretion. There are no independent biological markers for menopause.^{9,11}
- **Premenopause:** This term is often used ambiguously to encompass the entire reproductive period up to the final menstrual period.⁹
- **Perimenopause:** It is a broader clinical term covering the menopause transition and the first 12 months after the final menstrual period (FMP). The perimenopause represents a critical period in women's reproductive aging, characterized by hormonal fluctuations and various physical and psychological symptoms.^{12–14} This term is used interchangeably with menopause transition.
- **Menopause transition:** A term used by the Staging of Reproductive Ageing Workshop (STRAW+10).^{15,16} The progression from the onset of variable cycle length ≥ 7 days difference from normal to the FMP. The transition phase is divided into early transition, with persistent cycle variability (≥ 7 days) and late transition, with skipped cycles (≥ 60 days of amenorrhea) and increased vasomotor symptoms.^{15,16} Similar to the landmark study by Treloar, shorter ovulatory cycles were observed in early MT and may persist alongside longer cycles during late MT, alternating with longer cycles. The most substantial increase in mean cycle length did not occur until the year

before menopause.¹⁷ Understanding the duration and stages of this transition is essential for healthcare providers and women navigating this life phase. It is characterized by irregular menstrual cycles, endocrine changes, and symptoms such as hot flushes that may affect QOL. The characteristics include erratic menstrual periods, anovulatory cycles, significantly reduced fertility, increased risk of foetal genetic abnormalities, early onset of menstrual symptoms, and increased FSH levels.¹⁸ It may last for a median of 4 years or longer, up to 8-10 years. It may be considered a biological marker for chronic disease. Long-term effects on bone and heart have been related to estrogen deficiency.

- *Climacteric*: Literally means the rungs of a ladder. It is a broader, age-related term that indicates the transition in women from the reproductive to the non-reproductive stage. It describes a longer variable period before and after the perimenopause, as in MT. The term climacteric "should preferably not be used in scientific papers. When associated with symptoms, it is termed climacteric syndrome.
- *Postmenopause*: This is the period from the final menstrual period, regardless of whether menopause was spontaneous or induced.¹¹ The postmenopausal stage is further divided into early (within 5-8 years) and late (8 or more years) after the final period.¹¹
- *Premature ovarian insufficiency (POI)*: The term POI is used to replace premature menopause.¹⁹ POI is defined as spontaneous menopause occurring below two standard deviations (SDs) below the mean estimated age for the reference population.⁹ The estimated average age of menopause in India is 46.6 years; hence, we may consider POI to occur before age 36.6 years.³ However, population-based studies are needed to determine the cut-off values. This is a state of female hypergonadotropic hypogonadism.²⁰ It can manifest as primary amenorrhea with onset before menarche or as secondary amenorrhea due to the loss of ovarian function before the age of 40, a universally accepted cut-off value. POI is a pathological condition that should not be considered a hastening of natural menopause. POI is a spectrum of disorders and is a continuum of impaired ovarian function and reduced fecundity. The term "insufficiency" is the modern, accurate term that reflects the variable and sometimes reversible nature of ovarian dysfunction. The term POI is considered more sensitive and empowering for patients, helping to reduce the emotional impact of the diagnosis. It better reflects the potential for natural pregnancy, reported in 5-10% of women after diagnosis. The terminology evolved from "premature ovarian failure" (POF) to "primary ovarian insufficiency" by Fuller Albright in 1942, and then to "premature ovarian insufficiency". The International Menopause Society (IMS) and the partnership that developed the European Society of Human Reproduction and Embryology (ESHRE) POI guidelines adopted and promoted the use of "premature ovarian insufficiency" as the standard terminology in 2015.²¹
- *Induced menopause*: Cessation of menstruation following bilateral oophorectomy or iatrogenic ablation of ovarian function by chemotherapy or irradiation.¹¹
- *Temporary menopause*: It is preferable not to use this term, since the definition of menopause is the complete cessation of menstruation.¹¹ Rarely, ovarian function is interrupted for a period of time and then resumes.²²
- *Early menopause (EM)*: The time span between spontaneous or induced menopause and the accepted typical age of menopause for a given population.²³
- *Late-onset menopause/delayed menopause*: There is a lack of standardised definitions, limiting comparability of research on health outcomes and providing unclear guidelines for clinicians. This is important given the increased problems associated with hyperestrogenism.² It is two standard deviations above the population mean age at menopause at the 5% significance level. The estimated average age of menopause in India is 46.6 years; by statistical definition, we may consider delayed menopause as occurring above the age of 52 years.⁹ Population-based studies are needed to determine the cut-off values. Most studies on delayed menopause use a cutoff of 55 years.²⁴
- *Postmenopausal bleeding (PMB)*: Is clinically defined as any vaginal bleeding occurring 12 months or more after the final menstrual period in women not taking hormone replacement therapy.⁴ However, any vaginal bleeding that occurs 6 months after the last period, presumed menopause, should be investigated.²⁴
- *Genitourinary Syndrome of Menopause (GSM)*: Was introduced in 2014 and encompasses symptoms such as vaginal dryness, burning, irritation, sexual discomfort, and urinary issues, replacing the older term "vulvovaginal atrophy."²⁵
- *Musculoskeletal Syndrome of Menopause*: Coined in 2024 to describe the collective musculoskeletal symptoms associated with estrogen loss, such as joint pain, cartilage damage, sarcopenia, and loss of bone density, in a paper

by Wright.²⁶ The pathophysiological foundation of this syndrome centres on estrogen's multifaceted role in musculoskeletal homeostasis.²⁷ Estrogen deficiency during menopause precipitates increased inflammatory responses, compromised muscle protein synthesis, accelerated bone resorption, and cartilaginous structure degradation. These hormonal changes result in clinical manifestations that affect up to 80% of menopausal women, with approximately 25% experiencing severe, debilitating symptoms.²⁸ The proposed syndrome requires extensive validation through rigorous clinical research, including prospective cohort studies, randomised controlled trials (RCTs) examining therapeutic interventions, and cross-sectional studies establishing prevalence and risk factors across diverse populations. They should lead to standardised diagnostic criteria, validated assessment tools, and evidence-based treatment protocols. Until such validation occurs, the terminology should be employed with appropriate caveats acknowledging its provisional status within the evolving understanding of menopause-related musculoskeletal health.

- *Mid-Life*: Mid-life, or middle adulthood, is generally defined as the period between ages 40 and 64, but this definition is not used in academic papers. It marks a transitional phase between young adulthood and old age, characterised by significant biological (onset of menopause and andropause, increased risk of chronic conditions) and psychosocial (caregiving for ageing parents, launching children, career reassessment).²⁸ Mid-life is divided into early and late phases, with early mid-life before age 50 and late mid-life after 50 years. It is relevant to note that early midlife spans the MT, and some studies show a U-shaped pattern in well-being, with midlife often a time of lower happiness than younger or older adulthood.^{29, 30}

TERMINOLOGY RELATED TO AGEING

While formal classification varies, most gerontological and public health literature supports the following terminology. Ageing is characterised by a gradual functional decline across multiple organ systems, leading to progressive deterioration in organ function. Consequently, age is a risk factor for many diseases.

- *Senescence*: It is the cellular ageing process in which cells irreversibly stop dividing but remain metabolically stable. It is a response that limits the proliferation of aged or damaged cells.³¹ Age-based classifications vary slightly across organisations and cultures, but here's a general framework. Chronological age doesn't always reflect biological or functional age.
- The World Health Organisation (WHO) uses age-based cut-off points to classify older adults. It considers 60-plus years as older or elderly, 80-plus years as the oldest old, 100-plus years as centenarians, and 110-plus years as super-centenarians.³² Medical professionals commonly use a three-tier system that divides elderly patients into more specific age groups: the middle-aged are 45–64 years old, the youngest-old are 65–74 years old, the middle-old are 75–84 years old, and the oldest-old are 85 years old and older.³³
- *Super Agers*: There is no uniform definition of super-ageing or cognitive super-ageing. Most studies define cognitive super-ageing based on verbal memory. Superagers are individuals aged 80 or older whose memory and mental performance match or exceed that of people 30 years younger, typically those in their 50s or early 60s.^{34, 35} The key characteristics of superagers are exceptional episodic memory (recalling past events and experiences), brain structures that resist age-related shrinkage, higher densities of Von Economo neurons, linked to social intelligence and decision-making, a thicker cingulate cortex, associated with attention and motivation, and lower levels of Alzheimer's pathology and inflammation.³⁶
- The lifestyle traits often found in superagers include strong social connections, mental challenges such as learning and enjoyment of life.³⁷ Interestingly, lifestyle alone doesn't predict super-ageing; some superagers had unhealthy habits yet still maintained cognitive resilience. However, social engagement appears to be a consistent trait.³⁷

AGE AT NATURAL MENOPAUSE

A systematic review and meta-analysis found that the mean age at natural menopause among Indian women is 46.6 years (95% confidence interval: 44.83–48.44 years).^{38–40} This finding indicates an earlier onset than in developed Western nations, where the median age at natural menopause typically ranges from 50.0 to 52.7 years, resulting in a disparity of approximately 4–5 years.^{41, 42} The global mean age at menopause is 48.8 years.^{41, 42} Kerala has the highest average at 47.6 years, while Bihar has the lowest at 44 years.^{43, 44}

These figures are primarily derived from hospital-based studies, and obtaining data from the National Family Health Survey (NFHS) and the Longitudinal Ageing Study in India (LASI) is challenging due to methodological and data-related limitations. The NFHS surveys include only women aged 15 to 49, while

Table 1: Indian Studies on Age at Natural Menopause

Study/Population & Location	Study Design All Cross-sectional	No. of Participants	Urban/Rural	Mean/Median Age at Natural Menopause (years)	Citations
Systematic Review (10 studies, India)	2021	Not specified	Urban/Rural	46.6 (mean, range: 44.7–48.9)	Prasad et al. ³⁸ (2021)
IMS (10 cities, clinics)	Hospital-based	1,765	Urban	46 (mean)	Singh et al, ³⁹ (2012)
PAN India (IMS Survey)	2021	1707	Urban/Rural	46.2 (mean); regional: East 47.3, North 45.5, Kerala 47.8	Ahuja et al. ⁴⁰ (2016)
Punjab	Community-based cross-sectional	1,856	Urban/Rural	46.8 ± 4.1	Ahuja et al. ⁴⁰ 2016
Anjarakandy, Kerala	Community-based	106	Rural	48.44 ± 0.10 (mean)	Sharma et al. ⁴⁸ (2025)
National (DLHS, 15–49 yrs)	Population-based	6,43,944	Urban/Rural	Not directly stated; early menopause <40: 1.5%	Pallikadavath et al. ⁴⁵ (2016)
Mishing Tribal Women, Assam	Community- based cross- sectional	331	Rural	48.44 ± 0.10 (mean)	Sharma et al. ⁴⁸ (2025)
Northern India (AIIMS, Delhi)	Community- based cross- sectional	201	Urban/Rural	48 (median), 46.7 (mean)	Kriplani et al. ⁴⁹ (2005)
National (NFHS-5, LASI)	Population-based	Large-scale survey	Urban/Rural	46 (mean); Bihar: 44, Kerala: 47.6	Ghosh et al. ⁵⁰ (2024)
Rajbanshi, North Bengal, West Bengal	Community- based cross- sectional	510	Rural	50 (median)	Sinha et al. ⁵¹ (2020)
Rural/Urban Punjabi Brahmin, Punjab	Community- based cross- sectional	870	Urban/Rural	Rural: 48.2 (mean), Urban: 49.3 (mean)	Kaur et al. ⁵² (2009)
Himachal Pradesh	Community- based cross- sectional	500	Urban/Rural	43.55 (mean)	Randhawa et al. ⁵³ (1987)
Dehradun, Uttarakhand	Community- based cross- sectional	211	Urban/Rural	46 (mean)	Singh et al. ⁵⁴ (2022)
Bhopal, Madhya Pradesh	Hospital-based	232	Urban	46.77 ± 3.52 (mean)	Singh et al. ⁵⁵ (2018)

Table 1: Indian Studies on Age at Natural Menopause

Kerala	Community-based cross-sectional	120	Urban/Rural	48.3 ± 4.15 (mean), 50 (median)	Sarika et al. ⁵⁶ (2013)
Lobanas, North West India	1996	Not specified	Not stated	47.68 (mean)	Mastana ⁵⁷ (1996)
West Bengal	Community-based cross-sectiona	1,200	Urban/Rural	46.2 ± 4.5	Dasgupta et al. ⁵⁸ (2009)
West Bengal	Community-based cross-sectional	620	Urban/Rural	46.2 ± 4.0	Dasgupta et al. ⁵⁸ (2009)
Bangalore	Hospital-based	680	Urban	47.3 ± 3.9	Rajaram et al. ⁵⁹ 2013
Punjab	Community-based cross-sectional	564	Semi-urban	47.91 ± 3.16	Pathak et al. ⁶⁰ (2010)
Odisha (Ganjam district)	Community-based cross-sectional	650	Rural	46.98 ± 4.08	Satpathy et al. ⁶¹ (2022)
Assam (Dhemaji district)	Community-based cross-sectional	516	Rural tribal	45.2 ± 4.5	Sharma ⁶² (2022)
Gujarat (Vadodara)	Community-based cross-sectional	750	Urban/Rural	46.8 ± 4.2	Shringarpur et al. ⁶³ (2022)
Australia (Indian immigrants)	Community-based	203	Urban	48.2 ± 4.6	Hafiz et al. ⁶⁴ (2007)
Mumbai	Community-based	300	Urban	46.3 ± 3.9	Jadhav et al. ⁶⁵ (2017)
New Delhi	Community-based	252	Rural	46.2	Singh et al. ⁶⁶ (2014)
South Canara District	Hospital-based	110	Urban/Rural	48.4 ± 4.5	Joseph et al. ⁶⁷ (2014)
Bathinda, Punjab, India	Community-based	425	Rural	47.97 ± 3.4	Samtani et al. ⁶⁸ (2020)
Etawah, Uttar Pradesh,	Community-based	199	Rural	45.38 ± 3.58	Mathew et al. ⁶⁹ (2020)
Haridwar district, Uttarakhand	Community-based	129	Urban/Rural	45.02 ± 4.35	Kapur et al. ⁷⁰ (2009)

the LASI targets adults aged 45 and above; neither distinguishes between natural and surgical menopause.⁴⁵⁻⁴⁷ There is a pressing need for longitudinal, population-based studies with validated measures of menopause status, as well as a clear distinction between natural and surgical menopause, to accurately determine the average age at menopause.

Indian Studies on age at natural menopause are tabulated in Table 1, according to the cited references.^{36-38,40,41,43,46-68}

According to a survey across 24 countries and six continents, the overall mean age at menopause was 48.8 years.⁴²

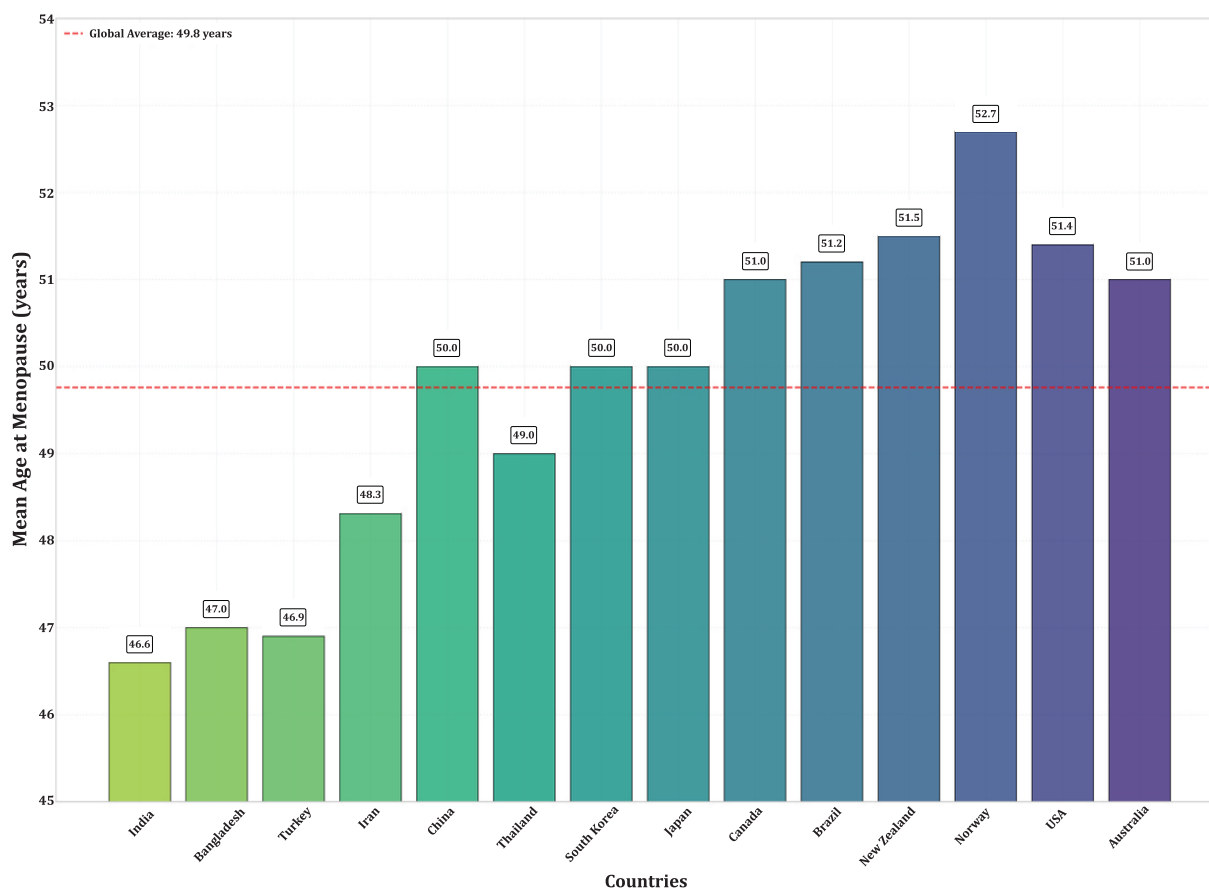


Figure 1: Global Average of Age at Natural Menopause

Figure 1 compares the global average age at menopause. India is below the global average of 51 years and well below the highest age at menopause seen in Norway.⁷¹⁻⁷⁷

Prevalence Of Premature Ovarian Insufficiency And Early Menopause

Indian studies report a POI prevalence of 1.5–5%, with considerably higher rates in some states, over 8% in Telangana and Andhra Pradesh, and EM affects 16.2%.^{45,78-80} A 2019 meta-analysis calculated the pooled prevalence of POI and EM as 3.7% (95% confidence interval: 3.1, 4.3) and 12.2% (95% confidence interval: 10.5, 14), respectively. The prevalence of POI was higher in countries with a medium or low Human Development Index. The prevalence trend did not change over time.⁸¹ A 2023 systematic review and meta-analysis reported a global overall prevalence of POI among women of 3.5%. The highest prevalence of POI was 11.3% in North America, followed by South America (5.4%). In a developing country, the prevalence was 5.3%, higher than 3.1% in a developed country. The trend in POI prevalence over the past 20 years was upward (although $p > 0.05$).⁸²

MEDICAL CHALLENGES

Understanding the timing of menopause is crucial as it has far-reaching implications for women's health, including cardiovascular disease risk, bone health, and overall quality of life.^{83,84} It is well established that an earlier age at menopause increases the risk of CVD, osteoporosis, all-cause mortality, and decreases life expectancy.^{85,86}

The available Indian data from 2012 indicated that an early age of menopause predisposes a woman to chronic health disorders a decade earlier than a Caucasian woman.⁸⁷⁻⁸⁹ In India, type 2 diabetes mellitus (T2DM) occurs a decade earlier than in Caucasians.⁹⁰ It was reported that osteoporotic fractures occur 10–20 years earlier in Indians compared to Caucasians.⁹¹⁻⁹⁴ Earlier, the incidence of breast cancer peaked in the forties.⁹⁵

The evidence is building up. Between 2004 and 2018, the median age at onset for NCDs overall dropped from 57 to 53 years, with diabetes, hypertension, heart disease, asthma, mental diseases, eye disease, and osteoporosis all showing earlier onset by 2–7 years.⁹⁶ This trend is particularly pronounced in peri- and postmenopausal women, with evidence indicating that several NCDs such as diabetes, hypertension, osteoporosis, and CVD are manifesting at younger ages compared to previous decades and to women in other populations.^{2,83,97,98} Notably, osteoporosis tends to present about a decade earlier in Indian women than in Caucasian populations, often coinciding with early menopause. Unlike other NCDs, the median age at onset for cancer in Indian women has increased by 2–14 years over recent decades.⁹⁹ For example, the peak age of incidence for cervical cancer is 55–59 years, and for breast and ovarian cancer, the peak is a decade earlier than in high-income countries, but is not decreasing further.^{99,100}

In 2025, recent studies from India showed that breast cancer incidence peaked after the age of 50, suggesting that the age of onset in India has changed since the previous decade, moving from the forties to the fifties, unlike the steady peak in the sixties in developed countries.^{101,102} This suggests that cancer does not follow the same early onset trend as osteoporosis or metabolic disease, possibly reflecting improved detection, changing risk profiles, or demographic shift.⁹⁹ Multi-morbidity, having multiple chronic conditions, also emerges earlier, with many women developing two or more chronic diseases by their mid-30s to mid-40s.^{103,104} Several comparative studies and reviews have documented that South Asians, including Indian women, develop type 2 diabetes and metabolic syndrome at younger ages and lower body mass indices and waist circumference thresholds than their Caucasian counterparts, with some reporting onset differences of up to 10 years.¹⁰⁵⁻¹⁰⁷ Similarly, studies show that cardiovascular risk factors and disease manifest earlier in Indian women. Note that clustering of cardiovascular risk factors and related chronic diseases is generally high and increases further in postmenopausal Indian women, and presents almost a decade earlier than in Western women.¹⁰⁸⁻¹¹⁰

EM and POI are associated with reduced muscle mass, strength, and performance compared with women who reach menopause at the usual age.¹¹¹ While extensive prospective data from India are lacking, small cross-sectional studies suggest a similar pattern.¹¹² In a Central India cohort, earlier perimenopause was negatively correlated with skeletal muscle mass.¹¹³ This earlier onset is attributed to a combination of genetic predisposition, higher central adiposity at lower BMI, lifestyle factors, and possibly lower disease awareness, delayed diagnosis and early age of menopause in women. The clinical and public health implications are profound, as this early onset leads to a longer disease duration, increased risk of complications, and higher lifetime healthcare costs. Early screening, prevention, and tailored interventions are needed, especially for skeletal and metabolic diseases in Indian women. The other medical issues are the complex burden of malnutrition (obesity and underweight) with micronutrient deficiency, poor acknowledgement of menopausal symptoms, widespread use of complementary and alternative medicine, which may not be standardized.^{114,115} Presently, the compounded hormones companies have not invaded India's pharmaceutical industry.

DETERMINANTS OF MENOPAUSE

The age at which women experience menopause varies considerably across populations and is influenced by multiple factors, including genetics, lifestyle, socioeconomic status, and environmental conditions.^{116,117} Various factors influence the timing and experience of menopause. Regional variations exist: Kerala has the highest average (47.6 years), while Bihar has the lowest (44 years).^{82,95} The prevalence of surgical menopause (primarily due to hysterectomy) is also notable, especially among women with lower educational attainment.¹¹⁸

Genetic Factors

Genetics plays a significant role, with family history influencing the age at menopause.¹¹⁹ Specific genetic variants

(single-nucleotide polymorphisms in estrogen receptor and hormone-metabolism genes) influence menopausal age.¹²⁰

Ethnicity and Industrialisation

According to a survey across 24 countries and six continents, the overall mean age at menopause was 48.8 years.¹²¹ According to previous literature, the age of natural menopause is slightly higher in Western than in Eastern countries. The average age of natural menopause (ANM) in women is 46.2–50 in the eastern countries, versus 50 and more than 50 in the western countries.^{117–119}

Higher socioeconomic status is associated with slightly later menopause, with no significant changes in the reporting of age at menopause over the periods from 1992–93 to 2005–06 among Indian women.⁴⁴ A population-based study of 312,656 women in Norway from 1936–1964 found that age at menarche did not change substantially across birth cohorts, but age at natural menopause advanced by 3 years.⁷⁶ The average age at menopause in industrialised countries is 4–6 years higher than in underdeveloped countries. Poor socioeconomic status during childhood or adulthood is associated with earlier menopause.⁴⁴

Lifestyle and Environmental Factors

- **Tobacco:** Smoking is a significant independent factor for early age at natural menopause.¹²² Tobacco consumption has been identified as a cause of early menopause by approximately 1.5–2 years. However, there was no clear evidence that the duration of smoking and quantity of cigarettes smoked had any association with age at natural menopause.¹²³ Compared to current smokers, the risk of early menopause was significantly lower in women who had quit smoking.¹²⁴ Indoor air pollution from sources such as smoke and pollutants significantly increased the risk of early menopause in Indian women. Urban women are more affected by pollution, whereas indoor smoking affects both urban and rural women.¹²⁵
- **Endocrine-disrupting chemicals:** Exposure to environmental toxins, especially endocrine-disrupting chemicals (EDCs) such as phthalates, bisphenols (BPA), polychlorinated biphenyls (PCBs), dioxins, certain pesticides, and persistent pollutants such as per- and polyfluoroalkyl substances (PFAS), is consistently associated with an earlier onset of menopause in women. Multiple extensive studies have demonstrated that higher blood or urinary levels of EDCs (notably phthalates and PCBs) are correlated with menopause occurring on average 1.8–2.5 years earlier than in women with lower exposure.^{42,126}
- **Other lifestyle factors:** A healthy diet, especially high intake of oily fish, legumes, vitamin B6, and zinc, is linked with later menopause, while refined carbs and vegetarianism are associated with earlier menopause. Factors such as birth weight, obesity, physical activity, and alcohol use may also affect the timing of menopause, although the evidence is mixed.¹²⁷
- **Social Determinants:** Socioeconomic factors, education, cultural factors, and rural-urban residence significantly influence the age at menopause and its prevalence, with lower education and rural residence associated with earlier onset.^{42,47,48} Urban women experience menopause slightly later than their rural counterparts (urban mean: roughly 48 years, rural and tribal: 44.8–45.5 years).^{43,46}
- **Reproductive History:** Age at menarche is associated with menopausal timing, with early menarche linked to early menopause. Later age at menarche, longer menstrual cycles, and longer breastfeeding duration have been linked to delayed menopause. Nulliparity and having no partner are linked to earlier menopause, whereas higher parity (number of childbirths) and being currently married are consistently linked to delayed menopause. Oral contraceptive use has been associated with later menopause onset.⁴²
- **Medical and Surgical Factors:** Surgical removal of ovaries, chemotherapy, or radiation can induce premature menopause. Data from longitudinal and review studies indicate that hysterectomy with ovarian preservation may lead to menopause up to four years earlier than the typical age.¹²⁸ Premenopausal unilateral oophorectomy (UO) significantly reduces the age of menopause by 8 years, and a younger age at UO leads to a significantly younger age at menopause.¹²⁹ While childhood cancer treatment with pelvic radiation and alkylating agents is a well-established cause of earlier menopause, evidence for the impact of medically treated depression and epilepsy is limited or inconsistent.

In conclusion, genetics plays a role in the age at the onset of menopause, smoking, and a low socioeconomic status are strongly associated with early menopause. In contrast, higher education and increasing parity are associated with later menopause.

DIAGNOSIS OF MENOPAUSE

From a clinical perspective, the likely age at menopause is used to guide decision-making regarding contraception, assisted reproduction, management of menorrhagia, and conditions that may fluctuate with menstrual cycle hormonal variations, including migraine and premenstrual dysphoric disorder. Thus, markers that help predict menopause are of interest to women and their providers. There are no potent markers for predicting menopause. Clinically, the most reliable objective sign of menopausal transition is menstrual irregularity, and shorter cycle length is believed to be one of the most sensitive and earliest signs of climacteric syndrome.^{130,131}

SYNOPSIS

- Menopause is a transition phase from the reproductive to the non-reproductive phases in a woman's life.
- Menopause is diagnosed retrospectively by history, and blood markers should be reserved for specific situations and fertility issues.
- FSH levels > 10 IU/L indicate declining ovarian function, and FSH levels > 20 IU/L are diagnostic of ovarian insufficiency in the perimenopausal age group.

RESEARCH AGENDA

Population-based study to derive the age at natural menopause and premature ovarian insufficiency.

REFERENCES

1. Hill K. The demography of menopause. *Maturitas*. 1996 Mar;23(2):113-27. doi: 10.1016/0378-5122(95)00968-x
2. Meeta M, Digumarti L, Agarwal N, Vaze N, Shah R, Malik S. Clinical Practice Guidelines on Menopause: *An Executive Summary and Recommendations: Indian Menopause Society 2019-2020. *J Midlife Health*. 2020 Apr-Jun;11(2):55-95. doi: 10.4103/jmh.JMH_137_20
3. Birkhauser M, Rees M, Barlow D. Management Handbook Health Plan for the Adult Woman. Taylor and Francis; 2005. doi:https://doi.org/10.3109/9780203490099
4. Halder P, Kansal S, Mamgai A, Rathor S, Das A, Garg G. Untimely Menopause, State Wise Longitudinal Aging Study in India (LASI-1). *J Obstet Gynaecol India*. 2025 Apr;75(2):106-114. doi: 10.1007/s13224-024-02094-1
5. Meeta M, Guduru S, Tanvir T, Madan A. Awareness of menopause and menopause hormone therapy in India: perspectives of healthcare providers and consumers. *Climacteric*. 2025 Jun;28(3):286-295. doi: 10.1080/13697137.2025.2503876
6. Ambikairajah A, Walsh E, Cherbuin N. A review of menopause nomenclature. *Reprod Health*. 2022 Jan 31;19(1):29. doi: 10.1186/s12978-022-01336-7
7. Utian WH, Serr D. The climacteric syndrome. In: *Consensus on Menopause Research: A Summary of International Opinion The Proceedings of the First International Congress on the Menopause held at La Grande Motte, France, in June, 1976, under the auspices of The American Geriatric Society and The Medical Faculty of The University of Montpellier 1976* (pp. 1-4). doi: 10.1007/978-94-011-7179-3_1
8. Research on the menopause in the 1990s. Report of a WHO Scientific Group. *World Health Organ Tech Rep Ser*. 1996;866:1-107. URL: <https://pubmed.ncbi.nlm.nih.gov/8942292/>
9. Kaufert P, Lock M, McKinlay S, Beyenne Y, Coope J, Davis D, Eliasson M, Gagnalons-Nicolet M, Goodman M, Holte A. Menopause research: the Korpilampi workshop. *Soc Sci Med*. 1986;22(11):1285-9. doi: 10.1016/0277-9536(86)90196-6
10. Utian WH. The International Menopause Society menopause-related terminology definitions. *Climacteric*. 1999 Dec;2(4):284-6. doi: 10.3109/13697139909038088
11. Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. *Int J Fertil*. 1967 Jan-Mar;12(1Pt2):77-126. URL: <https://pubmed.ncbi.nlm.nih.gov/5419031/>
12. Treloar AE. Menstrual cyclicity and the pre-menopause. *Maturitas*. 1981 Dec;3(3-4):249-64. doi: 10.1016/0378-5122(81)90032-3
13. McKinlay SM, Brambilla DJ, Posner JG. The normal menopause transition. *Maturitas*. 1992 Jan;14(2):103-15. doi: 10.1016/0378-5122(92)90003-m
14. Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, Woods N. Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Fertil Steril*. 2001 Nov;76(5):874-8. doi: 10.1016/s0015-0282(01)02909-0
15. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab*. 2012 Apr;97(4):1159-68. doi: 10.1210/jc.2011-3362
16. Ferrell RJ, Simon JA, Pincus SM, Rodríguez G, O'Connor KA, Holman DJ, et al. The length of perimenopausal menstrual cycles increases later and to a greater degree than previously reported. *Fertil Steril*. 2006 Sep;86(3):619-24. doi: 10.1016/j.fertnstert.2006.01.045
17. Milsom I. Menopause-related symptoms and their treatment. *The menopause*. 2006;12(46):9-16.
18. Welt CK. Primary ovarian insufficiency: a more accurate term for premature ovarian failure. *Clin Endocrinol (Oxf)*. 2008 Apr;68(4):499-509. doi: 10.1111/j.1365-2265.2007.03073.x
19. Bruni V, Bucciattini S, Ambroggio S. From Primary Hypergonadotropic Amenorrhea to "POI": Aetiology and Therapy. In: *Frontiers in Gynecological Endocrinology: Volume 4: Pediatric and Adolescent Gynecological Endocrinology 2017 Feb 17* (pp. 67-109). doi:10.1007/978-3-319-41433-1_7
20. Dunselman GA, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, et al. ESHRE guideline: management of women with endometriosis. *Hum Reprod*. 2014 Mar;29(3):400-12. doi: 10.1093/humrep/det457
21. Ali M, Raslan M, Ciebiera M, Zaręba K, Al-Hendy A. Current approaches to overcome the side effects of GnRH analogs in the treatment of patients with uterine fibroid

22. Shifren JL, Gass ML; NAMS Recommendations for Clinical Care of Midlife Women Working Group. The North American Menopause Society recommendations for clinical care of midlife women. *Menopause*. 2014 Oct;21(10):1038-62. doi: 10.1097/GME.0000000000000319
23. Abulajiang Y, Liu T, Wang M, Abulai A, Wu Y. The influence of menopause age on gynecologic cancer risk: a comprehensive analysis using NHANES data. *Front Oncol*. 2025 Feb 11;15:1541585. doi: 10.3389/fonc.2025.1541585
24. Munro MG, Critchley HO, Fraser IS; FIGO Menstrual Disorders Working Group. The FIGO classification of causes of abnormal uterine bleeding in the reproductive years. *Fertil Steril*. 2011 Jun;95(7):2204-8, 2208.e1-3. doi: 10.1016/j.fertnstert.2011.03.079
25. Portman DJ, Gass ML; Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Menopause*. 2014 Oct;21(10):1063-8. doi: 10.1097/GME.0000000000000329
26. Wright VJ, Schwartzman JD, Itiniche R, Wittstein J. The musculoskeletal syndrome of menopause. *Climacteric*. 2024 Oct;27(5):466-472. doi:10.1080/13697137.2024.2380363
27. El Khoudary SR, Greendale G, Crawford SL, Avis NE, Brooks MM, Thurston RC, Karvonen-Gutierrez C, Matthews K. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). *Menopause*. 2019 Oct;26(10):1213-1227. doi: 10.1097/GME.0000000000001424
28. Lu CB, Liu PF, Zhou YS, Meng FC, Qiao TY, Yang XJ, Li XY, Xue Q, Xu H, Liu Y, Han Y, Zhang Y. Musculoskeletal Pain during the Menopausal Transition: A Systematic Review and Meta-Analysis. *Neural Plast*. 2020 Nov 25;2020:8842110. doi: 10.1155/2020/8842110
29. Carr D, Pudrovskaya T. Midlife and mental health. Howard S. Friedman, Encyclopedia of Mental Health Second Edition. 2022. Elsevier. doi:10.1016/B978-0-12-397045-9.00109-9
30. Lulle A. Midlife Geographies: Changing Lifecourses Across Generations, Spaces and Time. Policy Press; 2024 Sep 23.
31. Dodig S, Čepelak I, Pavić I. Hallmarks of senescence and aging. *Biochem Med (Zagreb)*. 2019 Oct 15;29(3):030501. doi: 10.11613/BM.2019.030501
32. Ageing. World Health Organization; Available from: https://www.who.int/health-topics/ageing#tab=tab_1
33. Steinmo S, Wright JD. International Encyclopedia of the Social and Behavioral Sciences. Sciences (Second Edition), Elsevier, 2015, Pages 857-860, ISBN 9780080970875, <https://doi.org/10.1016/B978-0-08-097086-8.62016-0>.
34. Borelli WV, Carmona KC, Studart-Neto A, Nitrini R, Caramelli P, da Costa JC. Operationalized definition of older adults with high cognitive performance. *Dement Neuropsychol*. 2018 Jul-Sep;12(3):221-227. doi: 10.1590/1980-57642018dn12-030001
35. Powell A, Page ZA, Close JCT, Sachdev PS, Brodaty H. Defining exceptional cognition in older adults: A systematic review of cognitive super-ageing. *Int J Geriatr Psychiatry*. 2023 Dec;38(12):e6034. doi: 10.1002/gps.6034
36. Garo-Pascual M, Gaser C, Zhang L, Tohka J, Medina M, Strange BA. Brain structure and phenotypic profile of superagers compared with age-matched older adults: a longitudinal analysis from the Vallecas Project. *Lancet Healthy Longev*. 2023 Aug;4(8):e374-e385. doi: 10.1016/S2666-7568(23)00079-X
37. Kristin Samuelson. What Makes a SuperAger? News Center. 2025. Available from: <https://news.feinberg.northwestern.edu/2025/08/12/what-makes-a-superager/>
38. Prasad JB, Tyagi NK, Verma P. Age at menopause in India: A systematic review. *Diabetes Metab Syndr*. 2021 Jan-Feb;15(1):373-377. doi: 10.1016/j.dsx.2021.01.013
39. Singh M. Early age of natural menopause in India, a biological marker for early preventive health programs. *Climacteric*. 2012 Dec;15(6):581-6. doi: 10.3109/13697137.2011.643514
40. Ahuja M. Age of menopause and determinants of menopause age: A PAN India survey by IMS. *J Midlife Health*. 2016 Jul-Sep;7(3):126-131. doi: 10.4103/0976-7800.191012
41. InterLACE Study Team. Variations in reproductive events across life: a pooled analysis of data from 505 147 women across 10 countries. *Hum Reprod*. 2019 May 1;34(5):881-893. doi: 10.1093/humrep/dez015
42. Schoenaker DA, Jackson CA, Rowlands JV, Mishra GD. Socioeconomic position, lifestyle factors and age at natural menopause: a systematic review and meta-analyses of studies across six continents. *Int J Epidemiol*. 2014 Oct;43(5):1542-62. doi: 10.1093/ije/dyu094
43. Borker SA, Venugopalan PP, Bhat SN. Study of menopausal symptoms, and perceptions about menopause among women at a rural community in Kerala. *Journal of mid-life health*. 2013 Jul 1;4(3):182-7. doi:10.4103/0976-7800.118997
44. Mozumdar A, Agrawal PK. Prevalence, trends, and determinants of menopause in India: NFHS 1992-93 to NFHS 2005-06. *Am J Hum Biol*. 2015 May-Jun;27(3):421-5. doi: 10.1002/ajhb.22648
45. Pallikadavath S, Ogollah R, Singh A, Dean T, Dewey A, Stones W. Natural menopause among women below 50 years in India: A population-based study. *Indian J Med Res*. 2016 Sep;144(3):366-377. doi: 10.4103/0971-5916.198676
46. Dewangan KK, Pattanaik S, Patnaik L, Sahu T. Prevalence of morbidities among peri-menopausal and postmenopausal women in selected urban slums of Eastern India. *Int J Curr Res Rev*. 2020 Sep;12(18):55-60. doi:http://dx.doi.org/10.31782/IJCRR.2020.12188
47. Kumari M, Mohanty SK. Caste, religion and regional differentials in life expectancy at birth in India: cross-sectional estimates from recent National Family Health Survey. *BMJ Open*. 2020 Aug 20;10(8):e035392. doi: 10.1136/bmjopen-2019-035392
48. Sharma M. Risk Factors Associated with Early and Late Age at Natural Menopause: Evidence from Mishing Tribal Women of Assam in Northeast India. *Journal of the Anthropological Survey of India*. 2025 Dec;74(2):189-204. doi: 10.1177/2277436X251335522
49. Kriplani A, Banerjee K. An overview of age of onset of menopause in northern India. *Maturitas*. 2005 Nov-Dec;52(3-4):199-204. doi: 10.1016/j.maturitas.2005.02.001. PMID: 16257611.
50. Ghosh R, Syamala TS. Estimation of mean menopausal age and spatial variations of menopause in India: evidence from large scale surveys. *GeoJournal*. 2024 Nov 22;89(6):244. doi: 10.1007/s10708-024-11245-w
51. Sinha I, Tigga P, Mondal N, Sen J. Association between age at menarche and age at menopause among women of an indigenous population of North Bengal, India. *J Biosoc Sci*. 2021 May;53(3):319-335. doi: 10.1017/S002193202000019X
52. Kaur M, Talwar I. Age at natural menopause among rural and urban Punjabi Brahmin females. *The Anthropologist*. 2009 Oct 1;11(4):255-8.
53. Randhawa I, Premi HK, Gupta T. The age at menopause in the women of Himachal Pradesh, and the factors affecting the menopause. *Indian J Public Health*. 1987 Jan-Mar;31(1):40-4

54. Singh P, Vyas S, Vallabh V, Nautiyal R, Srivastava A. Age at natural menopause and factors affecting its onset: A cross-sectional study among postmenopausal females in District Dehradun. *Indian Journal of Community Health*. 2022 Jun 30;34(2):241-7. doi: <https://doi.org/10.47203/IJCH.2022.v34i02.018>
55. Singh N, Shinde M, Dafal H, Trivedi A, Chouhan Y. Age at natural menopause and factors affecting menopausal age: A cross-sectional study among postmenopausal female attendees of obstetrics and gynecology outpatient department. *Int J Med Sci Public Health*. 2018 Dec 1;7(11):1. doi:10.5455/ijmsph.2018.0926316092018
56. Sarika KS, Bhavani N, Saraswathy L. Average age of Menopause in Kerala Women & Factors Influencing age of Menopause. *Kerala Medical Journal*. 2013 Dec 30;6(4):93-6.
57. Mastana SS. Age at menopause among the Lobanas of North West India. *J Hum Ecol*. 1996 May 1;7(2):151-3.
58. Dasgupta D, Ray S. Menopausal problems among rural and urban women from eastern India. *Journal of social, behavioral, and health sciences*. 2009;3(1):2.
59. Kaulagekar A. Age of menopause and menopausal symptoms among urban women in Pune, Maharashtra. *J Obstet Gynaecol India*. 2011 Jun;61(3):323-6. doi: 10.1007/s13224-011-0036-5
60. Pathak RK, Parashar P. Age at menopause and associated bio-social factors of health in Punjabi women. *Open Anthropol J*. 2010 Jan;3(2):172-80. doi: 10.2174/1874912701003010172
61. Satapathy SP, Dash R. Socio-health seeking profile of women in Post Menopausal Age group: A study in a Rural block of Ganjam district, South Odisha. 2022;14(2)
62. Sharma M. Epidemiologic Risk Factors for Variation in Age at Natural Menopause: Shreds of Evidence from a Tribal Community in North-East India. *The Oriental Anthropologist*. 2022 Dec;22(2):293-312. doi: <https://doi.org/10.1177/0972558X221122833>
63. Shringarpure KS, Kharawala A, Panchal PP, Brahme KM, Baxi SR, Baxi RK. Prevalence of menopausal symptoms among women in Vadodara, Central Gujarat: The urban-rural divide. *J Family Med Prim Care*. 2022 Oct;11(10):6049-6055. doi: 10.4103/jfmpc.jfmpc_115_22
64. Hafiz I, Liu J, Eden J. A quantitative analysis of the menopause experience of Indian women living in Sydney. *Aust N Z J Obstet Gynaecol*. 2007 Aug;47(4):329-34. doi: 10.1111/j.1479-828X.2007.00746.x
65. Jadhav A, Bavaskar Y. An epidemiological study of the perimenopausal and menopausal health problems in women living in an urban area of Mumbai, Maharashtra. *Int J Community Med Public Health*. 2017 Aug 23;4(9):3088-93. doi: <https://doi.org/10.18203/2394-6040.ijcmph20173700>
66. Singh A, Pradhan SK. Menopausal symptoms of postmenopausal women in a rural community of Delhi, India: A cross-sectional study. *Journal of mid-life health*. 2014 Apr 1;5(2):62-7. doi:10.4103/0976-7800.133989
67. Joseph N, Nagaraj K, Saralaya V, Nelliyanil M, Rao PJ. Assessment of menopausal symptoms among women attending various outreach clinics in South Canara District of India. *J Midlife Health*. 2014 Apr;5(2):84-90. doi: 10.4103/0976-7800.133996
68. Samtani R, Garg D, Sharma N, Deb R. Sociodemographic Pattern of Postmenopausal Women and Health Issues: A Study in Rural Bathinda, Punjab. *J Midlife Health*. 2020 Jul-Sep;11(3):168-170. doi: 10.4103/jmh.JMH_139_19
69. Mathew DJ, Kumar S, Jain PK, Shukla SK, Ali N, Singh DR. A Cross-Sectional Study to Assess the Quality of Life of Perimenopausal and Post menopausal Women in Rural Etawah, Uttar Pradesh, India. *J Midlife Health*. 2020 Jul-Sep;11(3):161-167. doi: 10.4103/jmh.JMH_88_19
70. Kapur P, Sinha B, Pereira BM. Measuring climacteric symptoms and age at natural menopause in an Indian population using the Greene Climacteric Scale. *Menopause*. 2009 Mar-Apr;16(2):378-84. doi: 10.1097/gme.0b013e31818a2be9
71. Kutenae MA, Dashti S, Rafati S, Moannaei M, Masoudi M, Nejatizadeh A, Shahmoradi M, Roozbeh N. Factors predicting age at menopause among Iranian women in the Bandare-Kong cohort study (a cross-sectional survey of PERSIAN cohort study). *Womens Midlife Health*. 2023 Nov 20;9(1):8. doi: 10.1186/s40695-023-00091-4
72. Pirincci E, Oguzoncul AF, Tasdemir R. Age at the onset of menopause and its influencing factors in Turkish women in a rural area. *J Women Aging*. 2016 May-Jun;28(3):238-46. doi: 10.1080/08952841.2014.951231Z
73. Gold EB, Bromberger J, Crawford S, Samuels S, Greendale GA, Harlow SD, et al. Factors associated with age at natural menopause in a multiethnic sample of midlife women. *Am J Epidemiol*. 2001 May 1;153(9):865-74. doi: 10.1093/aje/153.9.865
74. Fang Y, Liu F, Zhang X, Chen L, Liu Y, Yang L, et al. Mapping global prevalence of menopausal symptoms among middle-aged women: a systematic review and meta-analysis. *BMC Public Health*. 2024 Jul 2;24(1):1767. doi: 10.1186/s12889-024-19280-5
75. Palacios S, Henderson VW, Siseles N, Tan D, Villaseca P. Age of menopause and impact of climacteric symptoms by geographical region. *Climacteric*. 2010 Oct;13(5):419-28. doi: 10.3109/13697137.2010.507886
76. Gottschalk MS, Eskild A, Hofvind S, Gran JM, Bjelland EK. Temporal trends in age at menarche and age at menopause: a population study of 312 656 women in Norway. *Hum Reprod*. 2020 Feb 29;35(2):464-471. doi: 10.1093/humrep/dez288
77. World Population Review (2026). Age of Menopause by Country 2026. Available from: <https://worldpopulationreview.com/country-rankings/age-of-menopause-by-country>
78. Kundu S, Acharya SS. Exploring the triggers of premature and early menopause in India: A comprehensive analysis based on National Family Health Survey, 2019–2021. *Scientific Reports*. 2024 Feb 6;14(1):3040. doi: <https://doi.org/10.1038/s41598-024-53536-9>
79. Singh A, Govil D, Ladusingh L. Premature menopause among women in India: Evidence from NFHS-4. In: *Proceedings of the International Population Conference 2021; Hyderabad, India. IUSSP; 2021*. Available from: <https://ipc2021.popconf.org/uploads/210152>
80. Meher T, Sahoo H. Premature menopause among women in India: Evidence from National Family Health Survey-IV. *J Obstet Gynaecol Res*. 2021 Dec;47(12):4426-4439. doi: 10.1111/jog.15041. Epub 2021 Sep 27. PMID: 34580955.
81. Golezar S, Ramezani Tehrani F, Khazaei S, Ebadi A, Keshavarz Z. The global prevalence of primary ovarian insufficiency and early menopause: a meta-analysis. *Climacteric*. 2019 Aug;22(4):403-411. doi: 10.1080/13697137.2019.1574738
82. Li M, Zhu Y, Wei J, Chen L, Chen S, Lai D. The global prevalence of premature ovarian insufficiency: a systematic review and meta-analysis. *Climacteric*. 2023 Apr;26(2):95-102. doi: 10.1080/13697137.2022.2153033
83. Mohanty SK, Rodgers J, Singh RR, Mishra RS, Kim R, Khan J, Behera P, Subramanian SV. Morbidity compression or expansion? A temporal analysis of the age at onset of non-communicable diseases in India. *Geroscience*. 2021 Feb;43(1):409-422. doi: 10.1007/s11357-020-00296-9
84. Mishra GD, Anderson D, Schoenaker DA, Adami HO, Avis NE, Brown D, et al. InterLACE: A New International Collaboration for a Life Course Approach to Women's Reproductive Health and Chronic Disease Events. *Maturitas*. 2013 Mar;74(3):235-40. doi: 10.1016/j.maturitas.2012.12.011

85. Peycheva D, Sullivan A, Hardy R, Bryson A, Conti G, Ploubidis G. Risk factors for natural menopause before the age of 45: evidence from two British population-based birth cohort studies. *BMC Womens Health*. 2022 Nov 8;22(1):438. doi: 10.1186/s12905-022-02021-4
86. Huang S, Gongye R, Zou S, Hee JY, Tang K. Menopausal status, age at menopause and risk of all-cause mortality among Chinese women: findings from a 10-year prospective study. *BMJ Public Health*. 2023 Dec 22;1(1):e000332. doi: 10.1136/bmjph-2023-000332
87. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004 Sep 11-17;364(9438):937-52. doi: 10.1016/S0140-6736(04)17018-9
88. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation*. 2001 Nov 27;104(22):2746-53. doi: 10.1161/hc4601.099487
89. Das SK, Banerjee TK, Biswas A, Roy T, Raut DK, Mukherjee CS, et al. A prospective community-based study of stroke in Kolkata, India. *Stroke*. 2007 Mar;38(3):906-10. doi: 10.1161/01.STR.0000258111.00319.58
90. Ramachandran A, Ma RC, Snehalatha C. Diabetes in Asia. *Lancet*. 2010 Jan 30;375(9712):408-18. doi: 10.1016/S0140-6736(09)60937-5
91. Gupta A. Osteoporosis in India--the nutritional hypothesis. *Natl Med J India*. 1996 Nov-Dec;9(6):268-74
92. Singh M, Magon N, Singh T. Major and minor discordance in the diagnosis of postmenopausal osteoporosis among Indian women using hip and spine dual-energy X-ray absorptiometry. *J Midlife Health*. 2012 Jul;3(2):76-80. doi: 10.4103/0976-7800.104457
93. Unni J, Garg R, Pawar R. Bone mineral density in women above 40 years. *Journal of mid-life health*. 2010 Jan 1;1(1):19-22. doi: 10.4103/0976-7800.66989
94. Shatrugna V, Kulkarni B, Kumar PA, Rani KU, Balakrishna N. Bone status of Indian women from a low-income group and its relationship to the nutritional status. *Osteoporos Int*. 2005 Dec;16(12):1827-35. doi: 10.1007/s00198-005-1933-1
95. Agarwal G, Pradeep PV, Aggarwal V, Yip CH, Cheung PS. Spectrum of breast cancer in Asian women. *World J Surg*. 2007 May;31(5):1031-40. doi: 10.1007/s00268-005-0585-9
96. Ahmed W, Muhammad T, Akhtar SN, Ali WK. Association of early and late onset of chronic diseases with physical frailty among older Indian adults: study based on a population survey. *BMC Public Health*. 2025 Feb 19;25(1):688. doi: 10.1186/s12889-025-21706-7
97. Rashmi R, Mohanty SK. Examining chronic disease onset across varying age groups of Indian adults using competing risk analysis. *Sci Rep*. 2023 Apr 10;13(1):5848. doi: 10.1038/s41598-023-32861-5
98. Shah D, Yadav V, Singh UP, Sinha A, Dumka N, Banerjee R, et al. Prevalence of non-communicable chronic diseases in rural India amongst peri- and post-menopausal women: Can artificial intelligence help in early identification? *Maturitas*. 2024 Aug;186:108029. doi: 10.1016/j.maturitas.2024.108029
99. Sundar S, Khetrpal-Singh P, Frampton J, Trimble E, Rajaraman P, Mehrotra R, Hariprasad R, Maitra A, Gill P, Suri V, Srinivasan R, Singh G, Thakur JS, Dhillon P, Cazier JB. Harnessing genomics to improve outcomes for women with cancer in India: key priorities for research. *Lancet Oncol*. 2018 Jun;19(6):e283. doi: 10.1016/S1470-2045(18)30330-9. PMID: 29413464.
100. Sreedevi A, Javed R, Dinesh A. Epidemiology of cervical cancer with special focus on India. *Int J Womens Health*. 2015 Apr 16;7:405-14. doi: 10.2147/IJWH.S50001
101. Kulothungan V, Ramamoorthy T, Sathishkumar K, Mohan R, Tomy N, Miller GJ, Mathur P. Burden of female breast cancer in India: estimates of YLDs, YLLs, and DALYs at national and subnational levels based on the national cancer registry programme. *Breast Cancer Res Treat*. 2024 Jun;205(2):323-332. doi: 10.1007/s10549-024-07264-3
102. Ugai T, Sasamoto N, Lee HY, Ando M, Song M, Tamimi RM, Kawachi I, Campbell PT, Giovannucci EL, Weiderpass E, Rebbeck TR, Ogino S. Is early-onset cancer an emerging global epidemic? Current evidence and future implications. *Nat Rev Clin Oncol*. 2022 Oct;19(10):656-673. doi: 10.1038/s41571-022-00672-8
103. Puri P, Sinha A, Mahapatra P, Pati S. Multimorbidity among midlife women in India: well-being beyond reproductive age. *BMC Womens Health*. 2022 Apr 12;22(1):117. doi: 10.1186/s12905-022-01693-2
104. Puri P, Kothavale A, Singh SK, Pati S. Burden and determinants of multimorbidity among women in reproductive age group: a cross-sectional study based in India. *Wellcome Open Res*. 2021 Feb 18;5:275. doi: 10.12688/wellcomeopenres.16398.2
105. Misra A, Khurana L. Obesity-related non-communicable diseases: South Asians vs White Caucasians. *Int J Obes (Lond)*. 2011 Feb;35(2):167-87. doi: 10.1038/ijo.2010.135
106. Ramachandran A, Snehalatha C, Vijay V. Low risk threshold for acquired diabetogenic factors in Asian Indians. *Diabetes Res Clin Pract*. 2004 Sep;65(3):189-95. doi: 10.1016/j.diabres.2004.03.012
107. Misra A, Tandon N, Ebrahim S, Sattar N, Alam D, Shrivastava U, Narayan KM, Jafar TH. Diabetes, cardiovascular disease, and chronic kidney disease in South Asia: current status and future directions. *BMJ*. 2017 Apr 11;357:j1420. doi: 10.1136/bmj.j1420
108. Kamath SK, Hussain EA, Amin D, Mortillaro E, West B, Peterson CT, Aryee F, Murillo G, Alekel DL. Cardiovascular disease risk factors in 2 distinct ethnic groups: Indian and Pakistani compared with American premenopausal women. *Am J Clin Nutr*. 1999 Apr;69(4):621-31. doi: 10.1093/ajcn/69.4.621
109. Chopra SM, Misra A, Gulati S, Gupta R. Overweight, obesity and related non-communicable diseases in Asian Indian girls and women. *Eur J Clin Nutr*. 2013 Jul;67(7):688-96. doi: 10.1038/ejcn.2013.70
110. Pandey RM, Gupta R, Misra A, Misra P, Singh V, Agrawal A, Dey S, Rao S, Menon VU, Kamalamma N, Devi KP, Revathi K, Sharma V. Determinants of urban-rural differences in cardiovascular risk factors in middle-aged women in India: a cross-sectional study. *Int J Cardiol*. 2013 Feb 20;163(2):157-62. doi: 10.1016/j.ijcard.2011.06.008
111. Divaris E, Anagnostis P, Gkekakos NK, Kouidi E, Goulis DG. Early menopause and premature ovarian insufficiency may increase the risk of sarcopenia: A systematic review and meta-analysis. *Maturitas*. 2023 Sep;175:107782. doi: 10.1016/j.maturitas.2023.05.006
112. Bhat G, Ireland A, Shah N, Gondhalekar K, Mandlik R, Kajale N, Katapally T, Bhawra J, Damle R, Khadilkar A. Prevalence and factors associated with sarcopenia among urban and rural Indian adults in middle age: A cross-sectional study from Western India. *PLOS Glob Public Health*. 2024 Oct 1;4(10):e0003553. doi: 10.1371/journal.pgph.0003553
113. Panhale V, Mayuri K, Anulucia A, Sakina K. Risk of sarcopenia with physical activity and performance, menopausal symptoms, and QOL in postmenopause. *Bulletin of Faculty of Physical Therapy*. 2025 Jul 23;30(1):47. doi:https://doi.org/10.1186/s43161-025-00306-x
114. Venkatesh U, Sharma A, Ananthan VA, Subbiah P, Durga R; CSIR Summer Research training team. Micronutrient's deficiency in India: a systematic review and meta-analysis. *J Nutr Sci*. 2021 Dec 21;10:e110. doi: 10.1017/jns.2021.102

115. Jindal H, Suresh V, Agarwal S, Vyas P, Bari N. Understanding the dynamics of malnutrition dichotomy in India: Trends and insights from the National Family Health Surveys. *Dialogues Health*. 2025 Feb 23;6:100209. doi: 10.1016/j.dialog.2025.100209
116. United Nation Department of Economic and Social Affairs-Population Division. World Population Prospects 2024. Available from: <https://population.un.org/wpp/>
117. Namazi M, Sadeghi R, Behboodi Moghadam Z. Social Determinants of Health in Menopause: An Integrative Review. *Int J Womens Health*. 2019 Dec 9;11:637-647. doi: 10.2147/IJWH.S228594
118. Biradar RA, Prasad JB, Asagi RE. Factors of induced and noninduced menopause in India. *BLDE University Journal of Health Sciences*. 2021 Jul 1;6(2):156-63. doi: 10.4103/bjhs.bjhs_108_20
119. Murabito JM, Yang Q, Fox C, Wilson PW, Cupples LA. Heritability of age at natural menopause in the Framingham Heart Study. *J Clin Endocrinol Metab*. 2005 Jun;90(6):3427-30. doi: 10.1210/jc.2005-0181
120. Stolk L, Perry JR, Chasman DI, He C, Mangino M, Sulem P, et al. Meta-analyses identify 13 loci associated with age at menopause and highlight DNA repair and immune pathways. *Nat Genet*. 2012 Jan 22;44(3):260-8. doi: 10.1038/ng.1051
121. Loh FH, Khin LW, Saw SM, Lee JJ, Gu K. The age of menopause and the menopause transition in a multiracial population: a nation-wide Singapore study. *Maturitas*. 2005 Nov-Dec;52(3-4):169-80. doi: 10.1016/j.maturitas.2004.11.004
122. Sun L, Tan L, Yang F, Luo Y, Li X, Deng HW, Dvornyk V. Meta-analysis suggests that smoking is associated with an increased risk of early natural menopause. *Menopause*. 2012 Feb;19(2):126-32. doi: 10.1097/gme.0b013e318224f9ac
123. Mckinlay SM, Brambilla DJ, Posner JG. "Reprint of" the normal menopause transition. *Maturitas*. 2008 Sep 1;61(1-2):4-16. doi: <https://doi.org/10.1016/j.maturitas.2008.09.005>
124. Hayatbakhsh MR, Clavarino A, Williams GM, Sina M, Najman JM. Cigarette smoking and age of menopause: a large prospective study. *Maturitas*. 2012 Aug;72(4):346-52. doi: 10.1016/j.maturitas.2012.05.004
125. Halder P, Soni A, Seth A, Vijayakumar D, Das A, Sankhyan S, et al. Association of early menopause with indoor air pollution: A multilevel modelling analysis of the nationally representative cross-sectional study in India. *J Family Med Prim Care*. 2025 Jan;14(1):173-183. doi: 10.4103/jfmpc.jfmpc_1046_24
126. Levine L, Hall JE. Does the environment affect menopause? A review of the effects of endocrine disrupting chemicals on menopause. *Climacteric*. 2023 Jun;26(3):206-215. doi: 10.1080/13697137.2023.2173570
127. Babbar K, Singh V, Sivakami M. Rising premature menopause and variations by education level in India. *Scientific Reports*. 2024 Aug 6;14(1):18238. doi: <https://doi.org/10.1038/s41598-024-67730-2>
128. Huang Y, Wu M, Wu C, Zhu Q, Wu T, Zhu X, et al. Effect of hysterectomy on ovarian function: a systematic review and meta-analysis. *J Ovarian Res*. 2023 Feb 9;16(1):35. doi: 10.1186/s13048-023-01117-1
129. Rosendahl M, Simonsen MK, Kjer JJ. The influence of unilateral oophorectomy on the age of menopause. *Climacteric*. 2017 Dec;20(6):540-544. doi: 10.1080/13697137.2017.1369512
130. Parry JP, Koch CA. Ovarian Reserve Testing. In: Feingold KR, Adler RA, Ahmed SF, Anawalt B, Blackman MR, Chrousos G, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2026 Jan 21]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK279058/>
131. Fritz MA. Female infertility. In: Speroff L, Fritz MA, editors. *Clinical Gynecological Endocrinology and Infertility*. 8th ed. Philadelphia, PA: Lippincott Williams & Wolters Kluwer; 2011. p. 681.

STAGES OF MENOPAUSE

02

Keywords: Staging, WHO, Modified Anklesaria's IMS Consensus Group, STRAW, STRAW 10+

INTRODUCTION

The menopausal transition (MT) typically begins several years before the final menstrual period (FMP) and continues into the postmenopausal years, with symptoms and health implications varying across different stages.^{1,2} The early symptoms and subsequent complications of menopause follow a sequential pattern due to gradual, progressive estrogen deprivation. The staging system is crucial for understanding the physiological, hormonal, and symptomatic changes women experience and for guiding research, clinical care, and public health strategies.³ Recent advances in reproductive endocrinology and population health research have refined our understanding of menopausal staging systems and their clinical applications.⁴

MENOPAUSE AS A POTENTIAL ENDOCRINOPATHY

At each stage of a woman's life, changes in the hormonal milieu bring varied challenges to her physical and emotional well-being. Despite being a natural biological process, menopause has been classified as a disease in the International Classification of Diseases (ICD) because of its associated health implications and symptom burden.⁵ This classification underscores the importance of viewing menopause as a natural and healthy transition requiring medical attention and management.⁶ A well-managed MT sets the stage for active and healthy ageing. A healthy woman can cope with the challenges, as nature brings about physiological changes to compensate for the physical and emotional demands of each life event.

Each woman is as unique as her fingerprint, and her response to various life events would depend on her sociodemographic profile, educational status, baseline physical and mental health, genetics, comorbidities, awareness, empowerment, and support system. Well-constructed antenatal programmes have dramatically reduced the incidence of maternal and fetal morbidity and mortality over the years. A similar model needs to be applied to adolescent and menopausal health.

Natural biomarkers indicate the need for additional care during vulnerable phases of a woman's life to maintain health, prevent complications, and improve quality of life (QoL). However, overt medicalisation or the pathologisation of the physiological life stages, may create unintended harm. The ideal approach is a thoughtful, balanced perspective that acknowledges the potential benefits of medical advances while recognising the importance of embracing natural life processes and, when appropriate, promoting holistic well-being through social and lifestyle interventions.

IS STAGING OF MENOPAUSE NECESSARY?

Menopause is a physiological event comparable to menarche, pregnancy, and the postpartum period, each characterised by distinct hormonal changes that affect women's physical and emotional health. Staging systems exist for puberty, pregnancy, labour, and the postpartum period, and have helped achieve meaningful clinical outcomes.

There is a gap in the uptake of staging systems for menopause. Staging systems are primarily used as research and clinical tools to predict outcomes. They support communication, maintain a common language, help understand the progress of the disease or physiological process, and aid clinical management decisions.⁴

Staging of menopause is needed, similar to Marshall Tanner's stages for puberty. Pregnancy is divided into trimesters for antenatal care, stages of labour for labour progression, and also for the postpartum period. Staging is essential in research on midlife women, particularly in studies of menopausal symptoms, ageing, and the role of reproductive hormones in various diseases.^{7,8}

Menopausal status classification is also important for clinicians treating midlife women, enabling identification of perimenopausal women so they can be counselled on fertility needs, contraception, the management of abnormal uterine bleeding, risk assessment and the prevention of chronic diseases, immunisation, and the provision of treatment options for menopausal symptoms, such as hot flushes and night sweats. The timing of interventions in menopausal management has become increasingly important, with concepts such as the "window of opportunity" for hormone replacement therapy being critically time-bound.⁹ Such precise timing requirements necessitate accurate

staging systems that can guide clinical decision-making and optimise treatment outcomes. Moreover, an individual woman's needs change at different stages of menopause. Therefore, a competent physician will adjust management to each patient's needs, which is easily achieved with a simple, user-friendly staging system.

EVOLUTION OF MENOPAUSE STAGING SYSTEMS

Historical Background

The concept of menopause staging has evolved from early clinical observations to sophisticated frameworks incorporating menstrual patterns, hormonal changes, and symptom profiles. The World Health Organisation (WHO) first recognised the need for standardised menopause terminology in the 1980s, establishing foundational definitions that guided subsequent developments. Dr P.K. Devi of India was a member of this expert body, serving on the WHO Scientific Group on Research on the Menopause in 1980.¹⁰

In 1997, Anklesaria published a simple three-stage staging system for the MT to help manage perimenopausal symptoms and expected postmenopausal complications in a Gujarat journal.³ In 2008, the Indian Menopause Society (IMS) adapted and modified it at the third consensus meeting.¹¹ This staging system was incorporated into undergraduate teaching in the IMS teaching module for undergraduates and into postgraduate teaching in the textbook Jeffcoate's Principles of Gynaecology.¹² The staging system was presented at the International Menopause Society Conference in Madrid.¹²

The Stages of Reproductive Ageing Workshop (STRAW) convened in 2001 to develop a comprehensive staging system for reproductive ageing. The original STRAW criteria established a framework dividing reproductive life into seven stages, from early reproductive years to late post menopause.⁷ The STRAW+10 workshop, held in 2011, refined the original criteria based on accumulated evidence and clinical experience and developed STRAW+10, the current gold standard for staging menopause.⁸

STAGING SYSTEMS

WHO Classification System.^{10,11} Refer to Figure 1

The WHO describes menopause as "the permanent cessation of menstruation resulting from the loss of ovarian follicular activity."

- Menopause: It occurs with the FMP, which is known with certainty only in retrospect, a year or more after the event.
- Perimenopause: Perimenopause includes the period immediately before menopause and the first 12 months post-menopause.
- Postmenopause: This refers to the time period dating from the FMP, regardless of whether menopause was natural or induced.
- Climacteric: A traditionally used term describing the transitional period around menopause marked by declining ovarian function; it is now largely obsolete in modern research, having been replaced by standardised menopause staging systems.
- Strengths and Limitations: The WHO classification provides fundamental terminology and broad categories that facilitate international communication and basic research design; however, its broad scope limits its utility in clinical settings, where more precise categorisation is required for treatment decisions.

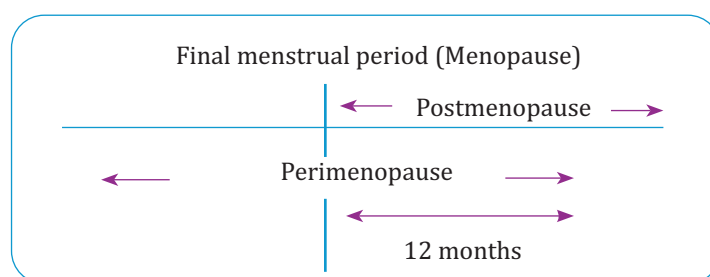


Figure 1 : Time Period surrounding menopause

ANKLESARIA STAGING SYSTEM¹²

This staging was based on the premise that menopausal symptomatology occurs in a chronological order. Refer to Table 1. Menstrual bleeding is most variable during the MT, when both anovulatory and ovulatory cycles are experienced, and when ovulatory cycles exhibit elevated estradiol (E2) levels, leading to luteal out-of-phase events.¹³ The stages may overlap owing to individual variations.

Table 1 : Anklesaria's stages of menopause

Stage	Time	Events	Action
I	3–5 years before menopause	IA: Menstrual irregularity IB: Vasomotor instability IC: Early psychosomatic	Establish communication
II	IIA: Up to 1 year post menopause IIB: Up to 5 years post menopause	Confirmation Local atrophic changes Late psychosomatic symptoms	Treat
III	Beyond 5 years post menopause	IIIA: Late atrophic changes IIIB: Ischemic heart disease IIIC: Osteoporosis IIID: Very late complication (Cerebrovascular accidents, Alzheimer's disease)	Prevent

MODIFIED ANKLESARIA'S IMS CONSENSUS GROUP STAGING SYSTEM.¹¹

The IMS consensus group recommends that a modified classification, based on Anklesaria's staging and the STRAW classifications, be used for clinical purposes and in the treatment of menopause, and that it be named Modified Anklesaria's IMS consensus group staging. Refer to Table 2. The staging begins with the MT in the STRAW classification. This staging system considers multiple factors, including:

- Menstrual pattern changes¹³
- Clinical symptoms^{14,15}
- Long-term health implications

Table 2: Modified Anklesaria's Indian Menopause Society (IMS) consensus group staging

Menopause			
Stage I	Stage IIA	Stage IIB	Stage III
Roughly 2 years before menopause Early (premenopausal symptoms): IA Vasomotor instability IB Early psychosomatic symptoms Menstrual problems	1 year after last period Atrophic changes Genitourinary Vasomotor Weight gain Osteopenia	Up to 5 years after menopause intermediate (postmenopausal symptoms): Late psychosomatic and genital symptoms Sexual disorders Residual changes from stage IIA Osteopenia or osteoporosis	From 5 years post menopause till late (postmenopausal) complications: Residual changes from stage II Ischemic heart changes Other late complications, Alzheimer's disease, Osteoporosis
Prevent and treat	Treat	Treat	Treat and palliate

Source: Indian Menopause Society consensus statement 2008.

Clinical Application -A hypothesis (Not evidence-based)

The duration of each stage is highly variable, but a rough 5-year-per-stage estimate is clinically useful. Consider a woman who reaches menopause at age 50. This can lead to the following approximations:

40–45 years: She is at stage I and needs initial counselling.

45–55 years: She will be in stages II A and II B, the window of opportunity for treatment.

55 years or older: She will experience earlier Stage III complications, which can be prevented.

Strengths: This staging system offers several strengths, including its basis on clinical parameters, the FMP, and symptoms, making it clinically relevant and practical for healthcare providers. It is particularly well-suited to the Indian context, where staging without extensive investigations may be more cost-effective for diagnosing menopause. Additionally, there is considerable variability in the biomarkers used for menopause diagnosis, and none has been validated exclusively for determining menopausal status. An individual woman may vary widely in the time leading up to the FMP, and biochemical markers are variable at this stage. Therefore, we cannot use them in isolation to determine menopausal status.¹⁵ Estrogen levels have also been shown to be highly variable during the MT.¹⁶ A single follicle-stimulating hormone (FSH) measurement is an independent marker of the late MT, but FSH concentrations are less predictive in the early transition stage. The criterion FSH values for the late transition were similar across studies by Burger and Randolph.¹⁷

The findings from the Women's Ischemia Syndrome Evaluation (WISE) study suggest that a menstrual status classification algorithm that relies solely on bleeding data can effectively distinguish between premenopausal, perimenopausal, and postmenopausal women. This strengthens the menstrual bleeding-based staging for clinical use. Hormone levels alone should not be used to determine menopausal status. The WISE algorithm, which combines hormone measurements with age and bleeding history, may be well-suited to study populations and clinical samples in epidemiological studies.¹⁸

The WISE 's limitations include its retrospective design and the potential for recall bias. It cannot be used for premature ovarian insufficiency (POI), infertility, or hormone-based research studies.

STRAW 2001 MENOPAUSE STAGING⁷

The STRAW members considered several potential components of a staging system: menstrual cycles, hormonal factors, fertility, signs and symptoms in other organ systems, and uterine and ovarian anatomy.⁷ STRAW recommends that menstrual bleeding should be the primary criterion for defining the stages of the transition. The key point in the staging system is the FMP, with five stages preceding and two stages following this pivotal event.⁷

Criteria for STRAW Staging System

The STRAW criteria establish specific requirements for an ideal staging system. These criteria mandate the use of objective data rather than subjective symptoms, employ reliable, inexpensive, and readily available tests, and allow prospective classification of women. A woman cannot be placed in more than one stage at a given point in time. This staging system is not applicable to women who use tobacco, are underweight or obese, engage in heavy exercise (>10 hours/week of aerobic exercise), have chronic menstrual cycle irregularity, have had a prior hysterectomy, have abnormal uterine anatomy like fibroids, or have abnormal ovarian anatomy like an endometrioma.

The STRAW system divides adult female reproductive life into three main phases: reproductive, MT, and post menopause, and seven sub-stages. The reproductive phase includes stages -5, -4, and -3 (early, peak, and late reproductive stages); the MT comprises stages -2 and -1 (early and late transition); and postmenopause encompasses stages 1+ and +2 (early and late postmenopause). Specific menstrual cycle patterns and associated hormonal changes characterise each stage.

THE STAGES OF REPRODUCTIVE AGEING WORKSHOP+10 (STRAW+10, 2011)⁸

Need For Re-Staging

A workshop, STRAW+10, 2011, was held in Washington to address gaps in the menopausal staging of STRAW 2001, supported by results from population-based studies. The main limitations of the 2001 STRAW recommendations were that they were not database-driven, empirically evaluated, or established specific cut-off points for FSH.

ReSTAGE used data from prospective menstrual calendars collected in four extensive longitudinal cohort studies of the MT: TREMIN,¹⁹ the Melbourne Women's Midlife Health Project (MWMHP)²⁰ the Seattle Midlife Women's Health Study (SMWHS)²¹, and the multi-site, multi-ethnic Study of Women's Health Across the Nation (SWAN)²². The significant advantage of these four studies was their inclusion of menstrual calendars to record menstrual bleeding prospectively. Prospective recording of menstrual bleeding is widely regarded as the optimal approach to obtaining data on menstrual cycle characteristics.^{23,24}

Objectives

To re-evaluate the criteria for staging the onset of late reproductive life and the early MT, based on population data from prospective menstrual calendars and from FSH, antral follicle count (AFC), anti-Müllerian hormone (AMH), and inhibin-B. Given new population-based data since 2001 on changes in FSH and E2 concentrations after FMP, the criteria for staging postmenopause need to be re-evaluated.¹⁹⁻²⁵ To reevaluate the applicability to women based on variations in body size, lifestyle characteristics, and health status. To identify the remaining gaps in scientific knowledge and research priorities.

Evidence-Based Recommendations

The same widely accepted nomenclature was retained. Menstrual pattern changes were used as the primary staging criterion, in accordance with the STRAW 2001.⁷ The changes in STRAW+10 are in the early transition; staging is defined by increased cycle-length variability, specifically a persistent difference of ≥ 7 days between consecutive cycles (persistence defined as recurrence within 10 cycles). In the late menopausal transition, staging is defined by the occurrence of amenorrhea lasting ≥ 60 days.

Consider the biomarker criteria as supportive criteria. Supportive criteria are to be used only as necessary and should not be interpreted as required for diagnosis. The inclusion of the FSH criterion of a serum FSH value of 40 IU/l is intended to facilitate the prediction of proximity to the FMP. Serum E2, AMH measurements and antral follicular counts are not used as diagnostic markers for confirmation of the natural age at menopause.¹⁹⁻²⁷

Additional supportive criteria for staging include age, symptoms, and individual risk factors.¹⁹⁻²⁴ Use criteria that are independent of age, symptoms, and pathology, as no universal menopausal syndrome has been established across ethnic groups. Two key symptoms are incorporated only as descriptive additional information that may support other criteria in assessing the stage. Multiple factors are considered together to achieve accurate staging.

Menstrual Cycle Patterns

The cycles may be ovulatory, anovulatory, or present as luteal out-of-phase (LOOP) events.²⁸ The LOOP cycle is defined by a second, out-of-phase rise in E2 during the luteal phase, mimicking a new follicular phase superimposed on an ongoing ovulatory cycle, and is associated with lower luteal-phase progesterone, higher early-cycle FSH, and lower early-cycle inhibin B, often resulting in abnormally short or long cycles. These hormonal patterns are thought to be triggered by prolonged high FSH levels due to declining inhibin B production, leading to the end of reproductive life. This pattern is observed in approximately 37% of ovulatory cycles during the early and late MT. In contrast, anovulatory cycles are marked by persistently high FSH, low E2, and low inhibin B, without the distinctive second E2 rise seen in LOOP cycles. Ovulatory cycles have a single, well-defined E2 peak and normal luteal-phase progesterone.

Menstrual cycle length begins to increase about 7.5 years before the FMP, with the steepest increase occurring 4 years before the FMP. There is a marked increase in cycle length variability about 2 years before the FMP. There may be prolonged and heavy bleeding.

Early transition: The first clinical sign of declining ovarian reserve is a shortening of the menstrual cycle, due to shorter follicular phases (11 ± 2 days vs. 14 ± 1 days in younger women), resulting in shorter overall menstrual cycles.²⁹

Late transition: There may be episodes of 60 or more days of amenorrhoea, beginning on average two may still be ovulatory. The day of ovulation shifts later, with the mean cycle day increasing to 27 (± 25) compared with earlier stages.

Biochemical Biomarkers

Biochemical biomarkers are used as supporting evidence. Supportive criteria are to be used only as necessary (for infertility, secondary amenorrhoea and other conditions necessitating a diagnosis of menopause), and should not be interpreted as required for the diagnosis of natural age-appropriate menopause.

Follicle Stimulating Hormone

FSH is the most commonly used test for evaluating perimenopausal status, hypergonadotropic and hypogonadotropic hypogonadism, and central precocious puberty. It is less important in assessing ovarian reserve for fertility. A decrease in the number of follicles reduces inhibin and lowers E2 levels, causing FSH to rise. With ageing, aromatase expression increases in women who regularly cycle. This compensates for the known age-related decrease in granulosa cell numbers in the dominant follicle, leading to increased E2 levels. Elevated E2 can suppress FSH, giving “falsely” normal

FSH levels. Therefore, FSH levels should be interpreted in conjunction with E2 levels for the diagnosis of menopause in the early transition. Elevated FSH levels can be found in normal ovarian reserve if measured at the time of the LH surge.²⁹ Low FSH levels are seen before puberty or with hypogonadotropic hypogonadism.³⁰⁻³⁴

- **Variability:** Individual variation is considerable, single hormone measurements may be misleading during the transition. During the MT, FSH shows significant associations with metabolic changes, including alterations in fat and lean mass distribution.³⁰⁻³⁴
- **Medications:** Exogenous hormones and selective estrogen receptor modulators such as clomiphene and letrozole, cimetidine, phenothiazines, and other medications can affect FSH levels.
- **Timing:** FSH is optimally measured during the early follicular phase (cycle days 2–5), with day 1 defined as the first full day of menstrual bleeding. In women with amenorrhoea, a random FSH measurement is preferred to testing following hormonally induced withdrawal bleeding, as exogenous hormones may confound results. In such cases, a concurrent serum progesterone level <2 ng/mL may be used to support a follicular-phase state. Given biological and assay variability, repeat measurements may be required for accurate assessment.
- **Clinical Correlation:** Interpretation of FSH levels must be undertaken in conjunction with clinical symptoms, menstrual pattern, age, and reproductive stage, rather than in isolation.

Evidence-Based Interpretation (WHO Second International Standard, IRP 78/549)^{34, 35}

Based on calibration to the World Health Organisation Second International Standard 1978, for human pituitary FSH (IRP 78/549), the following reference ranges are commonly used:

>16.7 mIU/mL - high: >11.4 mIU/mL - moderately high: <10 mIU/mL normal

Clinical Interpretation by Reproductive Stage

- FSH >10 IU/L: Suggestive of declining ovarian reserve or early ovarian aging, particularly when accompanied by menstrual irregularity.
- FSH >25 IU/L: Consistent with ovarian insufficiency, especially when associated with vasomotor symptoms and cycle disturbance.
- FSH ≥40 IU/L: confirmed on two measurements at least six weeks apart. Considered a reliable biochemical marker of menopause in the appropriate clinical context.

Estradiol

For assessing decreasing ovarian reserve, the sensitivity and specificity of E2 is low. E2 levels help to understand the stage and pattern of the menstrual cycle in conjunction with FSH levels. Elevated E2 (>60-80 pg/mL) may also lead to an artificially normal FSH, as higher E2 levels suppress FSH secretion. Conversely, E2 levels <20 pg/mL on day three, depending on the circumstances, can be consistent with normal ovarian function, hypogonadotropic hypogonadism, or ovarian failure.

From the SWAN study, four distinct trajectories of E2 changes with different menstrual cycle patterns emerged.

- **Rise/Steep Decline:** In 32% women, E2 levels rise about 5.5 years before the FMP, followed by a steep decline almost one year before the FMP.
- **Rise/Slow Decline:** In 13% of women, E2 levels rise before the FMP, but the decline is gradual and extends over two years after the FMP.
- **Slow Decline:** In 30% of women, there is no significant rise in E2 before the FMP; instead, there is a slow, steady decline across the transition.
- **Flat:** In 29% of women, E2 levels remain relatively flat, with only a limited decline across the FMP.
- Irrespective of race or ethnicity, a midlife rise in E2 before the FMP is most common in non-obese women, whereas obese midlife women are more likely to experience a non-rise in E2 (a flat trajectory) and a low-rise in FSH over the MT.³⁶

In Conclusion

- E2 levels <30 pg/mL, in conjunction with elevated FSH levels, support a diagnosis of late menopausal transition and postmenopause.
- In the late reproductive stage, the E2 level in the early follicular phase is either normal or elevated (>80 pg/ml).

Higher E2 levels predict entry into the earliest transition stage but not into subsequent stages.

- The variability of E2 levels during the MT is influenced by ethnic group, body mass index (BMI) and the assay. This limits its utility as a stand-alone diagnostic marker; however, it remains valuable when interpreted within the clinical context and in relation to FSH.
- Oral estrogens, are metabolised into many by-products and cannot be monitored by serum E2 levels, unlike transdermal estrogen. Medical conditions, glucocorticoids, sex steroids, clomiphene, letrozole, Gonadotropin-releasing hormone (GnRH) agonists and antagonists, and other medications can alter E2 levels, as can FSH levels. Mass spectrometry is the best method for measuring E2 levels, but it may not always be available.

Anti Mullerian Hormone

AMH in reproductive-aged women is produced by the granulosa cells of small preantral and antral follicles up to approximately 7 mm in size, and expression ceases as the follicle size increases. AMH decline precedes FSH elevation by several years, providing an early indication of ovarian reserve depletion. In a study, AMH levels of < 0.2 ng/ml were observed, on average, 6 years prior to menopause in women aged 45-48 years and 10 years prior in women aged 35-40.³⁷ The threshold for menopause is typically lower than the lower detectable limit for many assays, being slightly below 0.1 ng/ml. AMH <0.5 ng/mL seems associated with fewer than three follicles available at retrieval. Normal AMH values often exceed 2 ng/mL at age 30, 1.5 ng/mL at age 35, and 1 ng/mL at age 40, providing a quick reference for expected reserve at a given age.

AMH has substantial predictive value for the time to menopause, improving accuracy when combined with age and other clinical factors.⁴⁰ Population-specific AMH reference ranges vary significantly, with higher age-specific concentrations observed in Caucasian women than in African-American, Hispanic, and Chinese women.³⁸ A study comparing AMH levels between healthy European and Indian women concluded that AMH is substantially lower in healthy Indian women at all ages, consistent with a study in 2014.^{39,40} The results indicate a smaller primordial follicle pool size and an earlier age at natural menopause.⁴¹

The advantages are that AMH is a stable and reliable marker of ovarian reserve, can be measured on any day of the cycle, and is not significantly influenced by hormonal contraceptives or menopausal hormone therapy (MHT). AMH remains a valid assay even when ovarian suppression occurs through smoking, oral contraceptives, GnRH agonists, and pregnancy.⁴²

Inhibin B

Inhibin B is a glycoprotein secreted by preantral follicles, and levels decline with age. For assessing ovarian reserve, Inhibin B is typically measured on the third day of the menstrual cycle in ovulatory women. Inhibin B levels should be consistently low in postmenopausal women. Inhibin B is measured randomly to monitor and follow up on granulosa cell tumours (>89% have elevated inhibin B) and some epithelial cell ovarian tumours.²⁹

Vaginal pH

Increased vaginal pH (>5) can support a diagnosis of menopause.

Ultrasound

AFC is the total number of ovarian follicles measuring between two and nine millimetres. AFC can be measured at any time during the menstrual cycle, as well as when a woman is on hormonal contraceptives or is pregnant. AFC as a continuum, with four total antral follicles reflecting limited reserve, but five antral follicles not being entirely reassuring. No detectable antral follicles in a patient without ovarian suppression is consistent with a perimenopausal state, and fewer than two antral follicles have been deemed a more sensitive cutoff.⁴³

Caution In The Use Of Tests To Stage Menopause

A three-month washout period after stopping combined hormonal contraceptives or MHT before assessing natural FSH, Luteinizing hormone (LH), and androgen levels is ideal. For AMH and AFC, a two-month washout period is acceptable.⁴⁴ American Society for Reproductive Medicine says that “combined ovarian reserve tests models do not consistently improve predictive ability over that of single ovarian reserve tests.”⁴³

RECOMMENDATIONS FOR DOCUMENTATION

Clinical Records

- *Stage Assignment:* Document the current STRAW stage
- *Criteria Used:* Note the specific criteria for staging
- *Date of Assessment:* Important for tracking progression

CLINICAL APPLICATION OF STAGING

Refer to Table 3. For details on diagnostic criteria, age ranges, and clinical characteristics for the three main stages of the life span (reproductive phase, early and late MT, and post-menopause period) and the seven substages of STRAW+10, it serves as a quick reference for clinical staging and patient assessment.

STAGING CHALLENGES AND CONSIDERATIONS

Individual Variation

- *Menstrual Pattern Variation:* The SWAN study defines four distinct trajectories of menstrual cycle patterns, associated with changes in E2 levels. Not all women follow these exact patterns, and some may have different transition patterns. These patterns are influenced by ethnicity, genetics, medical and surgical conditions, and the use of exogenous hormones. Some populations may exhibit different patterns, such as the consistently earlier age of menopause in Indian women compared with Western populations, suggesting the need for population-specific staging criteria that account for these differences.
- *Age Ranges:* Considerable variation between individuals.
- *Symptom Patterns:* Not all women follow typical symptom progression.
- *Duration:* Stage duration varies significantly.
- *Clinical applicability:* In a review of 128 studies on menopause nomenclature, it was found that there is significant heterogeneity in the definition of premenopause compared with postmenopause. Major inconsistencies in the premenopause definition were due to a total lack of reporting of any definitions or criteria for premenopause in 40% of studies. In contrast, 80% reported definitions or criteria for postmenopause.⁴⁵
- The STRAW staging system does not apply to women with underlying menstrual disorders, such as polycystic ovary syndrome (PCOS) or hypothalamic amenorrhoea.

Strengths

Evidence now supports the applicability of the STRAW+10 recommendations for most women, and the system's prospective design and objective criteria enhance reliability and reproducibility across populations, as shown by longitudinal cohort studies.⁴⁶ Epidemiological and clinical studies have documented that the reproductive ageing process, although influenced by demographic factors, lifestyle, and BMI, follows a robust and predictable pattern. Although smoking and BMI influence hormonal levels and the timing of transition, they do not alter the trajectory of change in bleeding patterns or hormonal levels during reproductive ageing. Therefore, the STRAW+10 staging system applies to women regardless of age, demographic factors, BMI, or lifestyle characteristics.

FUTURE DIRECTIONS

Future research priorities include empirical analysis across multiple cohorts to define precise menstrual cycle criteria for specific stages, characterisation of hormonal changes across postmenopausal stages, development of highly sensitive and reliable biomarker assays, and improved understanding of reproductive ageing in women with various conditions, including PCOS, POI, single ovary removal, hysterectomy, chronic illness, and cancer treatment.

Integrating multiple biomarkers into composite staging algorithms may provide more accurate and reliable staging than single-parameter approaches. Machine learning and artificial intelligence techniques can potentially identify optimal biomarker combinations and develop predictive models for reproductive ageing trajectories, enabling more personalised approaches to menopausal management.

Table 3: Reproductive Stages

Parameter	Stage -5 Early Reproductive	Stage -4 Peak Reproductive	Stage -3 Late Reproductive	Stage -2 Early Menopausal Transition	Stage -1 Late Menopausal Transition	Stage +1a early postmen- opause	Stage +1b Early Postmeno- pause	Stage +2 Late Postme- nopause
Menstrual cycles	Regular cycles 21–35 days	Regular cycles 21–35 days	Regular, minimal change	Cycle variabilit y ≥7 days	Amenorrhea ≥60 days	12 months amenorrhea	Continued amenorrhea	Long- term amenor- rhea
Hormone Levels	FSH 3–10 E2 50–400 AMH >2	FSH 3–10 E2 50–400 AMH >2	FSH 10–15 E2 50–400 AMH <1.5	FSH 15–30 E2 N/>80 AMH <1.0	FSH >25 E2 N/ >80 AMH <0.5	FSH >40 E2 <30 AMH <0.1	FSH >40 E2 <30 AMH undetectable	FSH >40 E2 <30 AMH unde- tectable
Typical Age Range	18–25 yrs	25–35 yrs	35–45 yrs	40–50 yrs	45–55 yrs	48–55 yrs	52–60 yrs	beyond 55–60yr
Duration	variable	variable	variable	variable	1–3 yrs	≈2 yrs	3–6 yrs	Remain- der of life
Clinical Features	Optimal fertility	Peak fertility	Fertility decline, subtle changes	Irregular cycles, early VMS	Peak VMS, Sleep and mood changes	Peak VMS, Sleep and mood issues Early GSM	Declining VMS, GSM/bone changes	GSM/ Osteopo- rosis /Chronic disease
Management Focus	Contracep- tion, health maintenance	Family planning, preconce ption health	Fertility counseling, health baseline	Symptom management, screening	Comprehe- nsive care, bone/ heart /mental health	HT, bone density, CV screening	Ongoing manageme- nt, bone monitoring	Chronic disease preven- tion, Qol

Day 2-5 of menstrual cycle --FSH -IU/ml ; E2 - pg/ml ; AMH- ng/ml ; N -normal ; GSM-Genitourinary syndrome;

SYNOPSIS

- Menopause staging systems are designed to standardise a physiological life event, improving comparability across studies and facilitating evidence-based clinical decision-making.
- Staging functions both as a clinical tool to guide counselling, screening, and treatment and as a research framework to predict health outcomes across the reproductive ageing continuum.
- Women experience distinct needs at different stages of menopause; therefore, optimal care requires stage-specific management rather than a uniform approach.
- Recognition of the “window of opportunity,” particularly in the early menopausal transition, is critical for timely interventions that optimise long-term outcomes related to cardiovascular health, bone density, cognition, and quality of life.
- In 1997, Behram Anklesaria (India) proposed a simple, clinically oriented menopause staging system, which was subsequently adopted and modified by the Indian Menopause Society (IMS) as the Modified Anklesaria’s IMS Consensus Group menopause staging.
- The IMS Consensus Group recommends:
 - Modified Anklesaria’s staging for routine clinical practice, especially in low- and middle-resource settings.
 - STRAW+10 criteria for research and specialised clinical contexts, such as fertility, where comprehensive evaluation, including biomarkers, is feasible.
- In the Indian context, economic constraints and variable healthcare infrastructure favour simpler, symptom- and cycle-based staging systems that minimise reliance on laboratory testing while retaining clinical relevance.
- The Modified Anklesaria’s IMS staging is particularly well-suited to these settings, offering a practical, cost-effective, and clinically intuitive framework.
- Conversely, STRAW+10 provides a more rigorous and standardised approach for research, enabling precise phenotyping when resources permit.

RESEARCH AGENDA

Does adapting the modified Anklesaria’s IMS consensus group staging help clinicians plan management?

EDITOR’S COMMENT

This chapter is dedicated to Late Behram Anklesaria, the original author.

REFERENCES

1. Freeman EW, Sammel MD, Lin H, Gracia CR, Pien GW, Nelson DB, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. *Obstet Gynecol*. 2007 Aug;110 (2 Pt 1):230–40. doi: 10.1097/01.AOG.0000270153.59102.40.
2. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med*. 2015 Apr;175(4):531–9. doi: 10.1001/jamainternmed.2014.8063.
3. Anklesaria BS, HRT for Mature women using a clinical staging system, *Gujrat Medical Journal*, Volume 54, Dec 1997
4. Burger HG, Hale GE, Robertson DM, Dennerstein L. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women’s Midlife Health Project. *Hum Reprod Update*. 2007;13(6):559–65. doi: 10.1093/humupd/dmm020.
5. 2026 ICD-10-CM Diagnosis Code N95.1: Menopausal and female climacteric states [Internet]. [cited 2026 Jan 27]. Available from: <https://www.icd10data.com/ICD10CM/Codes/N00-N99/N80-N98/N95-/N95.1>
6. Assaf AR, Bushmakin AG, Joyce N, Louie MJ, Flores M, Moffatt M. The Relative Burden of Menopausal and Postmenopausal Symptoms versus Other Major Conditions: A Retrospective Analysis of the Medical Expenditure Panel Survey Data. *Am Health Drug Benefits*. 2017 Sept;10(6):311–21.
7. Soules MR, Sherman S, Parrott E, Rebar R, Santoro N, Utian W, et al. Executive summary: Stages of Reproductive Aging Workshop (STRAW). *Fertil Steril*. 2001 Nov;76(5):874–8. doi: 10.1016/s0015-0282(01)02909-0.
8. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *J Clin Endocrinol Metab*. 2012 Apr;97(4):1159–68. doi: 10.1210/jc.2011-3362.
9. Santoro N, Sutton-Tyrrell K. The SWAN song: Study of Women’s Health Across the Nation’s recurring themes. *Obstet Gynecol Clin North Am*. 2011 Sept;38(3):417–23. doi: 10.1016/j.ogc.2011.05.001.
- Research on the menopause. *World Health Organ Tech Rep Ser*. 1981;670:1–120.
10. Unni J. Third consensus meeting of Indian Menopause Society (2008): A summary. *J -Life Health*. 2010;1(1):43–7. doi: 10.4103/0976-7800.66987.
11. Anklesaria BS. The Staging of Menopause. *J SAFOMS*. 2013 June;1(1):1–3. doi: 10.5005/jp-journals-10032-1001.
12. Bell RJ, Lijovic M, Fradkin P, Davis SR. A pragmatic approach to the classification of menopausal status for community-based research. *Menopause*. 2008;15(5):978–83. doi: 10.1097/gme.0b013e318162c487.
13. Ashraf AB, Meeta M, Chitra AB, Pahwa S, Shah J, Mohi M, et al. Genitourinary syndrome of menopause: a multicenter study from the Indian Midlife Registry. *Climacteric J Int Menopause Soc*. 2025 June;28(3):329–36. doi: 10.1080/13697137.2025.2496681.

14. Dasgupta, Doyel & Roy, Subho & Pal, Baidyanath. (2022). How Menopausal Symptoms are Related to Different Stages of Postmenopausal Years: A Study from Eastern India. *Journal of the Anthropological Survey of India*. 71. 2277436X2210745. 10.1177/2277436X221074502.
16. Burger HG. Diagnostic role of follicle-stimulating hormone (FSH) measurements during the menopausal transition—an analysis of FSH, oestradiol and inhibin. *Eur J Endocrinol*. 1994 Jan;130(1):38–42. doi: 10.1530/eje.0.1300038.
17. Randolph JF, Crawford S, Dennerstein L, Cain K, Harlow SD, Little R, et al. The value of follicle-stimulating hormone concentration and clinical findings as markers of the late menopausal transition. *J Clin Endocrinol Metab*. 2006 Aug;91(8):3034–40. doi:10.1210/jc.2006-0243.
18. Johnston JM, Colvin A, Johnson BD, Santoro N, Harlow SD, Bairey Merz CN, et al. Comparison of SWAN and WISE menopausal status classification algorithms. *J Womens Health*. 2006 Dec;15(10):1184–94. doi: 10.1089/jwh.2006.15.1184.
19. Treloar AE, Boynton RE, Behn BG, Brown BW. Variation of the human menstrual cycle through reproductive life. *Int J Fertil*. 1967;12(1 Pt 2):77–126.
20. Dennerstein L, Dudley EC, Hopper JL, Guthrie JR, Burger HG. A prospective population- based study of menopausal symptoms. *Obstet Gynecol*. 2000 Sept;96(3):351–8. doi: 10.1016/s0029-7844(00)00930-3.
21. Mitchell ES, Woods NF, Mariella A. Three stages of the menopausal transition from the Seattle Midlife Women's Health Study: toward a more precise definition. *Menopause*. 2000;7(5):334–49. doi: 10.1097/00042192-200007050-00008.
22. SWAN: A multicenter, multiethnic, community-based cohort study of women and the menopausal transition – Kaiser Permanente Division of Research [Internet]. [cited 2026 Jan 27]. Available from: <https://divisionofresearch.kaiserpermanente.org/publications/swan-a-multicenter-multiethnic-community-based-cohort-study-of-women-and-the-menopausal-transition/> Accessed on 01/12/2025
23. Bean JA, Leeper JD, Wallace RB, Sherman BM, Jagger H. Variations in the reporting of menstrual histories. *Am J Epidemiol*. 1979 Feb;109(2):181–5. doi: 10.1093/oxfordjournals.aje.a112673.
24. Women's bleeding patterns: ability to recall and predict menstrual events. World Health Organization Task Force on Psychosocial Research in Family, Planning, Special Programme of Research, Development and Research Training in Human Reproduction. *Stud Fam Plann*. 1981 Jan;12(1):17-27. PMID: 7466887.
25. Tepper PG, Randolph JF, McConnell DS, Crawford SL, El Khoudary SR, Joffe H, et al. Trajectory clustering of estradiol and follicle-stimulating hormone during the menopausal transition among women in the Study of Women's Health across the Nation (SWAN). *J Clin Endocrinol Metab*. 2012 Aug;97(8):2872–80. doi: 10.1210/jc.2012-1422.
26. Li HWR, Nelson SM, Ledger WL. Editorial: Clinical Applications of Anti-Müllerian Hormone and Its Measurement in Reproductive Medicine and Women's Health. *Front Endocrinol*. 2022 Mar 14;13:879053. doi: 10.3389/fendo.2022.879053.
27. Nelson SM, Davis SR, Kalantaridou S, Lumsden MA, Panay N, Anderson RA. Anti- Müllerian hormone for the diagnosis and prediction of menopause: a systematic review. *Hum Reprod Update*. 2023 May 2;29(3):327–46. doi: 10.1093/humupd/dmac045.
28. Hale GE, Hughes CL, Burger HG, Robertson DM, Fraser IS. Atypical estradiol secretion and ovulation patterns caused by luteal out-of-phase (LOOP) events underlying irregular ovulatory menstrual cycles in the menopausal transition. *Menopause*. 2009;16(1):50–9. doi: 10.1097/GME.0b013e31817ee0c2.
29. Parry JP, Koch CA. Ovarian Reserve Testing. In: Feingold KR, Adler RA, Ahmed SF, Anawalt B, Blackman MR, Chrousos G, et al., editors. *Endotext* [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000 [cited 2026 Jan 27]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK279058/> Accessed on 10/12/2025
30. Spicer J, Malaspina D, Blank SV, Goosens KA. Follicle-stimulating hormone: More than a marker for menopause: FSH as a frontier for women's mental health. *Psychiatry Res*. 2025 Mar;345:116239. doi: 10.1016/j.psychres.2024.116239.
31. Wang Y, Tang R, Luo M, Sun X, Li J, Yue Y, et al. Follicle stimulating hormone and estradiol trajectories from menopausal transition to late postmenopause in indigenous Chinese women. *Climacteric J Int Menopause Soc*. 2021 Feb;24(1):80–8. doi: 10.1080/13697137.2020.1775807.
32. Ausmanas MK, Tan DA, Jaisamrarn U, Tian XW, Holinka CF. Estradiol, FSH and LH profiles in nine ethnic groups of postmenopausal Asian women: the Pan-Asia Menopause (PAM) study. *Climacteric J Int Menopause Soc*. 2007 Oct;10(5):427–37. doi: 10.1080/13697130701610780.
33. Chen Y, Wang C, Sun B, Wang B, Lu X, Gao B, et al. Associations of follicle-stimulating hormone and luteinizing hormone with metabolic syndrome during the menopausal transition from the National Health and Nutrition Examination Survey. *Front Endocrinol*. 2023;14:1034934. doi: 10.3389/fendo.2023.1034934.
34. Liu X, Xu J, Wei D, Chen Y. Associations of Serum Follicle-Stimulating Hormone and Luteinizing Hormone Levels with Fat and Lean Mass during Menopausal Transition. *Obes Facts*. 2022 Dec 2;16(2):184–93. doi: 10.1159/000528317.
35. Esposito MA, Coutifaris C, Barnhart KT. A moderately elevated day 3 FSH concentration has limited predictive value, especially in younger women. *Hum Reprod*. 2002 Jan;17(1):118–23. doi: 10.1093/humrep/17.1.118.
36. Randolph JF, Sowers M, Gold EB, Mohr BA, Luborsky J, Santoro N, et al. Reproductive hormones in the early menopausal transition: relationship to ethnicity, body size, and menopausal status. *J Clin Endocrinol Metab*. 2003 Apr;88(4):1516–22. doi: 10.1210/jc.2002-020777.
37. Freeman EW, Sammel MD, Lin H, Gracia CR. Anti-müllerian hormone as a predictor of time to menopause in late reproductive age women. *J Clin Endocrinol Metab*. 2012 May;97(5):1673–80. doi: 10.1210/jc.2011-3032.
38. Bleil ME, Gregorich SE, Adler NE, Sternfeld B, Rosen MP, Cedars MI. Race/ethnic disparities in reproductive age: an examination of ovarian reserve estimates across four race/ethnic groups of healthy, regularly cycling women. *Fertil Steril*. 2014 Jan;101(1):199–207. doi: 10.1016/j.fertnstert.2013.09.015.
39. Gromski PS, Patil RS, Chougule SM, Bhomkar DA, Jirge PR, Nelson SM. Ethnic discordance in serum anti-Müllerian hormone in European and Indian healthy women and Indian infertile women. *Reprod Biomed Online*. 2022 Nov;45(5):979–86. doi: 10.1016/j.rbmo.2022.06.023.
40. Iglesias C, Banker M, Mahajan N, Herrero L, Meseguer M, Garcia-Velasco JA. Ethnicity as a determinant of ovarian reserve: differences in ovarian aging between Spanish and Indian women. *Fertil Steril*. 2014 July;102(1):244–9. doi: 10.1016/j.fertnstert.2014.03.050.
41. Depmann M, Broer SL, van der Schouw YT, Tehrani FR, Eijkemans MJ, Mol BW, et al. Can we predict age at natural menopause using ovarian reserve tests or mother's age at menopause? A systematic literature review. *Menopause*. 2016 Feb;23(2):224–32. doi: 10.1097/GME.0000000000000509.
42. Ledger WL. Clinical utility of measurement of anti-müllerian hormone in reproductive endocrinology. *J Clin Endocrinol Metab*. 2010 Dec;95(12):5144–54. doi: 10.1210/jc.2010-0701.
43. Practice Committee of the American Society for Reproductive Medicine. Electronic address: asrm@asrm.org, Practice Committee of the American Society for Reproductive Medicine. Testing and interpreting measures of ovarian reserve: a committee opinion. *Fertil Steril*. 2020 Dec;114(6):1151–7. doi: 10.1016/j.fertnstert.2020.09.134.
44. Goldzieher JW, Kleber JW, Moses LE, Rathmacher RP. A cross-sectional study of plasma FSH and LH levels in women using sequential, combination or injectable steroid contraceptives over long periods of time. *Contraception*. 1970 Oct 1;2(4):225–48. doi: 10.1016/0010-7824(70)90035-1.
45. Ambikairajah A, Walsh E, Cherbuin N. A review of menopause nomenclature. *Reprod Health*. 2022 Jan 31;19(1):29. doi: 10.1186/s12978-022-01336-7.
46. El Khoudary SR, Greendale G, Crawford SL, Avis NE, Brooks MM, Thurston RC, et al. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). *Menopause*. 2019 Oct;26(10):1213–27. doi: 10.1097/GME.0000000000001424.

SOCIOCULTURAL DIMENSION OF MENOPAUSE

03

Keywords: Evolution, history, medicalisation, demography, sociocultural, living will, attitude, workplace, transgender

INTRODUCTION

Humans are inherently social beings; environmental interactions influence cognitive function and behaviour, collectively termed sociocultural factors.¹ Menopause is a universal biological transition, and the individual perspective on the change shapes health outcomes by acknowledging, accepting, and seeking help from family, peers, and healthcare professionals. This perspective affects the experience of menopause and is profoundly influenced by biological, cultural, psychological, income, job security, social support, social media, and workplace variables.^{2,3} Factors such as strong family support, higher education and higher economic status have a positive impact. Employment situations and cultural attitudes influence the experience and reporting of symptoms.^{4,5}

This chapter examines the multifaceted nature of menopause, with a particular focus on the Indian context. It covers evolution and history, menopausal age, knowledge-attitude-practice patterns, educational initiatives, policy frameworks, workplace implications, and transgender individuals. The analysis reveals significant knowledge gaps, policy deficits, and the urgent need for comprehensive interventions to support women during this critical transition.

EVOLUTION AND HISTORY OF MENOPAUSE

Evolutionary Theories of Menopause

All mammals undergo reproductive senescence and oopause, the irreversible depletion of ovarian follicles, and typically progress until the end of life, but only humans and a few cetaceans experience true menopause, the loss of fertility decades before death (<0.1% of mammals). Menopause continues to raise important evolutionary and biological questions.

Multiple theories have been proposed to explain why natural selection would favour reproductive cessation in humans. No evolutionary theory fully explains menopause; current evidence suggests it likely arose from a combination of adaptive and non-adaptive processes.

Adaptive Hypothesis

- *Mother Hypothesis*: Suggests that menopause evolved to protect mothers from the rising risks of childbirth at older ages, thereby increasing the survival chances of existing dependent children.⁶
- *Grandmother Hypothesis*: This hypothesis proposes that post-reproductive women increase their inclusive fitness by helping care for grandchildren, thereby enhancing the survival and reproductive success of their descendants. Comparative studies of orcas and pilot whales, which exhibit post-reproductive lifespans, further support this evolutionary perspective.⁶
- *Reproductive Conflict Hypothesis*: Argues that menopause reduces reproductive competition between generations of females, minimising conflict and increasing group fitness.⁷
- *Life History and Environmental Factors*: Genetic, ecological, and life-history factors (nutrition, disease, reproductive patterns) influence somatic ageing and the timing of menopause, explaining observed diversity across populations.⁸ Moreover, modern lifestyles such as fewer pregnancies, longer lifespans and different diets mismatch our evolved physiology, potentially increasing the risk of postmenopausal disease in industrialised societies.⁹

Non-adaptive Hypothesis

- *Lifespan Artefact Hypothesis*: Menopause is primarily a by-product of overall somatic ageing, particularly of ovarian follicles, and a consequence of the decoupling of reproductive and somatic lifespan in humans. In ancestral populations, few women lived long enough to experience it.⁸
- *Mutation Accumulation/Mate Choice Hypothesis*: It suggests that male preference for younger mates relaxed selection on fertility in older women, allowing infertility mutations to accumulate and leading to menopause. Experimental work in model organisms like *Drosophila* supports the mate choice hypothesis, showing that age-restricted mating can lead to reproductive senescence in the sex excluded from late-life reproduction.¹⁰

History of Menopause

Historically, the phenomenon lacked a unified medical label until Gardanne's 1821 treatise "ménopause," which reframed the broader idea of a woman's critical age¹¹ Aristotle noted the cessation of menses between ages 40 and 50, but detailed symptomatology was rare.¹² India's classical Ayurvedic tradition conceptualised menopause as 'Rajonivṛtti,' a normal physiological transition described in canonical texts, with some passages interpreted as placing the typical cessation around age fifty.^{13,14} In the 19th century, menopause became increasingly medicalised, with physicians attributing a wide range of physical and mental symptoms to the cessation of menstruation. Treatments ranged from leeching and sedatives to ovarian extracts, reflecting limited scientific understanding and prevailing gender biases.¹⁵

The History of Critique of the Medicalisation of Menopause

The naturalist critique of the medicalisation of menopause began in the mid-20th century. The debate over the medicalisation of menopause gained significance in the 1930s and 40s, in response to the popularisation of menopause as a hormone-deficiency state, with the isolation of estrogen and the rise of hormone replacement therapy (HRT) as an "elixir of youth".¹⁵ The Women's Health Movement, which included critiques of the medicalisation of women's bodies, including menopause, began in the 1960s and took root in the 1970s as social studies and observations showed that in some non-Westernised countries, menopause is not as readily medicalised and is often viewed as a natural ageing process. These women managed symptoms primarily through self-care practices, cultural remedies, and religious activities, often avoiding medical intervention. Cross-cultural comparisons fuelled the debate by showing that the relationship between hormones and symptoms is complex.¹⁶ There are significant differences in the patterns and prevalence of symptoms between countries, and, interestingly, in the types of symptoms reported by different ethnic groups within countries.^{17,18} Because all symptoms are individual and modulated by cognitive processes to a certain extent, they can be influenced by cultural factors. A clear, perhaps related, example of such influences is the cultural variation in pain perception.¹⁹ Meyer's 2001 analysis documented how "menopause is in the process of becoming medicalised" with midlife women being told that "natural menopause is a deficiency condition requiring replacement hormones".²⁰

Evidence Contradicting the Pure Naturalist Approach

However, substantial scientific evidence supports viewing menopause as a biological change with significant pathological potential, paralleling other life transitions such as puberty and pregnancy. Large-scale studies, such as the Study of Women Across the Nation (SWAN), have expanded understanding of the diverse experiences and health outcomes associated with menopause, highlighting the influence of ethnicity, lifestyle, and genetics.²¹ Research shows that these transitions share common ground as periods of dramatic hormonal fluctuation that can trigger short-term development of depression and anxiety, and long-term cardiovascular risks, genitourinary syndrome, skeletal-muscular problems, neurological and autoimmune conditions.²²⁻²⁴ Multiple therapeutic approaches, including menopausal hormone therapy, lifestyle modifications, and complementary approaches, demonstrate efficacy for menopausal symptoms and long-term health outcomes.²⁵⁻²⁹

Contemporary Thought on Medicalisation of Menopause

There is growing concern that social media platforms are promoting unproven or poorly evidenced treatments and products related to menopause, often with a focus on commercialisation and glamour around the topic.³⁰ A group of naturalists remains in the denial phase of accepting that menopause is similar to puberty and pregnancy as biological changes with potential for pathology, and that they are treatable by therapeutic lifestyle modifications and medications. Protagonists of menopause hormone therapy (physicians and industry) are blamed for the medicalisation of menopause. The physiological aspects have been the domain of gynaecologists, with deliverable results. However, research in the social sciences indicates the need to integrate the medical and sociocultural aspects of menopause to best serve women at midlife, as Flint suggests.³¹⁻³³

Bell's three models of menopause care, biological (physiological changes helped by hormone therapy), psychological (women's inherent personalities relieved by cognitive behavioural therapy), and environmental (self-help), form the basis for guiding medical practice.³⁴ Hickey and group provide the final word on this debate in the Lancet 2024, stating that for most women, menopause should be viewed as part of healthy ageing rather than "framing this natural period of transition as a disease of estrogen deficiency" and preventing "over-medicalisation" by promoting hormone therapy as empowerment.³⁵

Rama Vaidya, founder president of the Indian Menopause Society (IMS), envisaged that the society should adopt a holistic approach to menopausal health and not restrict research and implementation to medication. In line with this,

the IMS is open to membership for non-clinical professionals (paramedical, social scientists, anthropologists, and anyone interested in the welfare of women at midlife). The IMS website emphasises the importance of emotional well-being, lifestyle management, and life-skills enhancement techniques.³⁶ The branch of menopause medicine needs to be part of the undergraduate and postgraduate curricula to enhance healthcare professionals' skills in managing midlife.

DEMOGRAPHY

India's population is 1,465,465,981 as of Sunday, 17 August 2025, based on Worldometer's analysis of the latest United Nations (UN) data. It is expected to reach 1,679,589,259 by 2050. India's population is equivalent to 17.78% of the world's population, and 37.08% of its population lives in urban areas. The median age in India is 28.8 years.³⁷ The total fertility rate (TFR) is the number of live births per woman. A TFR of 2.1 represents Replacement-Level Fertility: the average number of children per woman needed for each generation to replace itself exactly without international immigration. A value below 2.1 will cause the native population to decline. India's fertility rate has dropped from 2 in 2020 to 1.9 in 2025.³⁷

India is witnessing a demographic shift, with a rapidly growing population of menopausal women, a trend with significant public health implications. According to the UN World Population Prospects 2024 Revision (medium variant), India had approximately 46 million women aged 45–49 years in 2024 and is projected to have approximately 57 million in 2050, compared with 30 million in 2011.^{38,39} Rising trends between 2005 and 2021 suggest an increasing burden of early ovarian ageing in Indian women. The life expectancy of Indian women has increased from 40.4 years in 1950 to approximately 73.6 years in 2023. In 2025, India's female life expectancy is around 74.1 years, slightly above the projected global average of 73.4 years.^{40–42} According to the latest state-level data, regional disparities and socioeconomic inequalities within India also mean that the national average may mask significant variation,⁴² with Kerala, where female life expectancy is already nearing 77.8 years. As India's population grows, its expanding share of older adults is particularly notable. In India, the population share of adults 60 and up grew from 5.4% in 1950 to 9% today, representing an almost sixfold increase.^{43,44} The COVID-19 pandemic caused a temporary decline in life expectancy, with a larger impact on females in India than on males.⁴⁵

The potential benefit is that older populations contribute valuable knowledge, experience, and social stability. When managed well, ageing populations can provide significant benefits. Research shows that improved labour market outcomes for people aged 50 and older, thanks to better health, could contribute about 0.4 percentage points to global Gross Domestic Product (GDP) growth annually.⁴⁶ The most critical issue is that healthspan (years lived in good health) has not kept pace with lifespan (total years lived). Recent research shows the gap between healthspan and lifespan was 9.6 years globally in 2019, climbing from 8.5 years in 2000 a 13% increase over two decades.⁴⁷ These statistics underscore the need for targeted health policies and support systems for menopausal women in India.⁴⁷

MENOPAUSE AND SOCIOCULTURAL FACTORS

Culture is inherited as a member of a particular society. It guides how to view the world, experience it emotionally, behave towards other people, supernatural forces or God, and the natural environment. The culture of any group of people at any particular point in time is always influenced by many other factors, such as historical, economic, social, political and geographical elements. Sociocultural attitudes influence how menopause is perceived, discussed, and managed, either considered as a negative attitude of decay and loss versus a positive sign of freedom and liberation.^{48–51} The commonality in both situations globally is the lack of awareness and correct information, often leading to silence and inadequate support at home, healthcare and employment settings.^{16,35,52,53}

Self: Midlife for women is often marked by restlessness, reorientation, giving up unattainable dreams, and making new plan, all with heightened awareness of time and how much one is left with. A fear of time running out, of ageing, death and dying, may intensify as peers and parents begin to die. At midlife, "body monitoring" becomes more dominant, as the growing attention to one's health and physical status intensifies in the attempt to slow or ward off physical changes and decline. Earlier, most women did not involve their physicians and managed their care through self-care.

Family: Children grow up and leave home, causing the well-known "empty nest syndrome". Women with children may fear losing their identity, as it is tied to day-to-day mothering. Many will be making decisions about entering the paid workforce for the first time, or re-entering under new circumstances. Others outside the workforce may consider new directions, career shifts, or partial or complete retirement. Fears connected with ageing include anxieties about training and retraining, and financial and social planning.

One of the most under-recognised anxieties about ageing for women stems from their growing involvement, often

beginning in midlife, in caring for older parents or in-laws. Their direct experience of the realities of life for the very old may have a double impact. As they learn to handle the often challenging responsibilities of elder care, and because women generally outlive men, they observe firsthand the financial and social perils of being an older woman in Indian society. As a result, many fear for their future.

Social dynamics have changed with the nuclear family structure in urban and rural areas, which has reduced traditional support systems, creating new challenges for menopausal women who previously relied on extended family networks for guidance and support. Urbanisation, education, and changing family structures are altering how Indian women experience and perceive menopause. Younger generations of women have different expectations and seek more active management of menopausal symptoms compared to their mothers and grandmothers.

Social Challenges: Table 2 provides a global overview of the cultural behaviours that affect ageing and elder care approaches.

Table 2. Cultural Approaches to Ageing and Elder Care.			
Area	Living Arrangement	Cultural Values	Elder Care System
Western Culture	Independent living, retirement communities	Youth-centric, independence	Government/private services, risk of isolation
Eastern Culture	Multigenerational households	Filial piety, respect for elders	Family-based care, elders help raise children
Middle Eastern & Hispanic Culture	Family-centered care at home	Honor and family duty	Stigma around nursing homes
Scandinavian Culture	Aging in place with state support	Social equality, dignity in aging	High-quality public elder care

In India, social challenges include an ageing population, eroding family traditions and ties, small nuclear families, a significant exodus of urban and international populations, an increasing burden of non-communicable diseases (NCDs) and degenerative diseases, limited government policies for midlife health, problems with implementing the national health programme for the elderly, and a shortage of trained personnel in menopausal/geriatric medicine. The need is to retain and revive Eastern culture and to adopt and integrate the Scandinavian model.

DEATH-LIVING WILL CLINIC

At the individual level, the concept of a "good death" underscores the potential for personal growth and heightened awareness, even as it acknowledges the inevitability of death. Historically, both birth and death have been medicalised, contributing to reduced maternal and neonatal mortality and longer healthspans. However, research suggests that excessive medical intervention, particularly in low-risk pregnancies and end-of-life care, can compromise patient autonomy, escalate healthcare costs, and inflict avoidable psychological distress.^{54,55}

Medical professionals must distinguish between failures in medical systems and the acceptance of natural physiological processes. The optimal approach involves evidence-based, risk-stratified care, in which intensive medical management is reserved for clinically indicated cases and natural processes are supported when appropriate.⁵⁶ Psychiatrist Elisabeth Kübler-Ross (1969) famously proposed five stages of dying: denial, anger, bargaining, depression, and acceptance (DABDA).⁵⁷ Embracing the final stage, acceptance, as an intentional and proactive phase, much like preparing for a birth, is a step towards respectful dying, akin to respectful birthing. Such preparation necessitates collaborative, patient-centred care planning that honours an individual's definition of dignity and quality of life, moving beyond outdated models in favour of individualised, evidence-based practices. These approaches aim to integrate the benefits of modern medicine while respecting the integrity of natural life processes.

True demedicalisation requires enhanced training of healthcare providers in medical decision-making that emphasises preventive, non-pharmacological interventions while adhering to rigorous safety standards.⁵⁸ This judicious balance should not be misconstrued as clinical failure but recognised as clinical wisdom in action.

In India, the concept of the "right to die with dignity" has gained legal and ethical recognition. In a landmark 2023 ruling, the Supreme Court of India revised the 2018 guidelines on end-of-life care and legalised the use of "living wills"

or advance medical directives. These instruments enable individuals of sound mind to specify their preferences for life-sustaining treatments in advance, allowing refusal of such interventions under clearly defined conditions. The implementation of passive euthanasia is tightly regulated, requiring adherence to strict protocols. These include approval by medical boards, family consent (when applicable), and, in some cases, formal clearance from a Judicial Magistrate First Class (JMFC).⁵⁹ A significant milestone in this area is the establishment of India's first "living will clinic" at P.D. Hinduja Hospital in Mumbai, pioneering institutional support for dignified, autonomous end-of-life care.

ATTITUDE OF WOMEN

The beliefs, expectations, and attitudes of women towards menopause determine whether an individual woman will experience menopause as a negative and troublesome phase in her life or as a positive and liberating one. Though most women report a positive or neutral feeling towards menopause, many also have a negative attitude. Early studies suggest that menopause is viewed positively in some cultures, including freedom from social taboos and restrictions associated with menstruation, as well as from the burdens of repeated pregnancies.^{19,60} In many developing countries, menopause is not considered a medical problem and is thus accepted with less focus on symptoms and more as a natural part of life or "God's will".⁶¹ Mayan women do not report menopausal symptoms, and rural Greek women have been found to report them as not very troublesome and tend not to seek medical help. Mayan and rural Greek women view menopause as a life-stage free from taboos and restrictions.^{19,62} Non-European and non-American women tend to have more favourable attitudes and expectations of menopause, and they report fewer hot flushes unlike the westerners.^{63, 64}

In Western nations, where ageing is sometimes linked to declining attractiveness and career relevance, men may enter menopause with more negative expectations and thus report more symptoms, mood disturbances, or even career impacts. Prospective studies have shown that negative attitudes before menopause predict depressed mood and hot flushes during menopause, suggesting that negative attitudes towards menopause can affect symptom experience.⁶⁵

Postmenopausal women in India are believed to enjoy a higher social status, and ageing is regarded with respect. Women can enter Hindu temples freely without restrictions and participate in rituals, making it a celebration of reaching an age of wisdom and experience.⁶⁶ A study conducted by Meeta et al. for the IMS in 2012 reported that 1,007 (85.19%) of 1,182 respondents had a positive attitude towards menopause. Of 1,650 respondents, 1,054 (63.88%) were unaware of hormone therapy (HT); for those who were aware of HT, the primary sources of knowledge were the media (39.50%) and family (21.22%).⁶⁷ A recent population-based study surveyed 32,518 women in underserved communities and found that 50% were unaware of menopause effects; 62% were unaware of available treatment; and 48% would accept treatment if offered.⁵²

A study of Indian women living in the United Kingdom found that most regarded menopause as a natural event (69%).⁶⁸ Similarly, a study from Australia found that lower scores for menopausal symptoms indicate that Indian women have fewer complaints and a positive attitude towards menopause.⁶⁹

Indian studies have shown that most women (57–95%) considered menopause convenient and socially suitable, and welcomed it. However, an Indian study found that approximately 69–85% of women felt that menopause adversely affected women's physical health.⁷⁰ Rural studies found that 58.41% of women held positive attitudes towards menopause, while 41.62% maintained negative views.⁷¹⁻⁷⁴ A study undertaken in Chandigarh among 528 women, both urban and rural, showed a lack of awareness regarding menopause and related aspects, and 65.6% of urban and 21.2% of slum dwellers considered menopause to be harmful.⁷⁵ Collectivist cultures such as Indian, Asian and African tend to frame menopause positively and rely more on extended family and traditional medicine. In contrast, individualistic Western cultures tend to have more biomedically oriented, negative perceptions.⁵⁰

In India, coping mechanisms reported include yoga, exercise, and social support, and there is a growing trend towards herbal and alternative remedies over HRT due to cost, access issues, and concerns about side effects. Awareness of menopause is predominantly from family and friends; knowledge of HT is limited and needs to be addressed. Educational interventions have had a significant impact on attitudes.⁵² Knowledge can bring about changes in attitudes and lifestyle behaviours. Women in India have a positive attitude towards life, menopause, and ageing. Taking advantage of this attitude, healthcare professionals must be proactive in implementing health programmes.

Health-Seeking Behavior

Few Indian studies of health-seeking behaviour have limitations, including geographical bias, small sample sizes, and a lack of cost analysis, yet the influence of sociocultural factors is well demonstrated. Rural women have substantially lower healthcare utilisation rates (25-30%) than urban women (42-48%).⁷⁶ This disparity is attributed to multiple

factors, including distance to healthcare facilities, financial constraints, and cultural barriers. Women with higher education show 3-4 times higher consultation rates than illiterate women.⁷⁷ Employment status also significantly influences healthcare utilisation, with employed women showing 90% utilisation rates, compared with much lower rates among unemployed women.⁷⁸ The socioeconomic gradient is particularly pronounced, with women from Class II socioeconomic status showing 97% healthcare facility utilisation, indicating the strong influence of economic capacity on healthcare access. Financial constraints are the most significant barrier, cited by 54% of women who do not seek healthcare for menopausal symptoms.⁷⁹ This is followed by a lack of awareness (43%) and distance to healthcare facilities (38%). The barrier profile differs significantly between rural and urban areas, with rural women facing greater challenges related to distance and cultural stigma.⁸⁰ Care-seeking patterns show concerning delays, particularly in rural areas, where 68% of women seek care more than 18 months after symptom onset, compared with 35% in urban areas. The primary reason for delayed care is the belief that "symptoms will resolve naturally" (43% of women), indicating significant knowledge gaps about menopause and available treatments.⁸¹

Menopause Health Promotion For Consumers

There is a policy gap in managing midlife health. At the international level, the World Health Organisation (WHO) published a comprehensive fact sheet on menopause in October 2024, establishing menopause as "one point in a continuum of life stages for women" that marks the end of the reproductive years. Beyond this, there is limited specific guidance on menopause. International societies on menopause have been actively promoting the concept of active ageing.

India lacks a dedicated national policy on menopause, unlike countries such as the United Kingdom (UK) and Australia. Government funding for menopause-related research and programme evaluation is limited. There are no specific policies addressing menopause in workplace settings. There is no formal education on menopause in schools, colleges, or workplaces. Menopause is indirectly covered under the broad umbrella of the National Health Mission (NHM), which focuses on universal, equitable healthcare and includes NCDs, women's health screening, and wellness clinics. In 2025, NHM for Women launched the programme "MENO-MIND: Menopause Matters, So Does Mind" to raise awareness of the mental and physical problems women face after menopause.

Non-governmental organisations like the IMS are leading the charge in championing midlife health. IMS publishes and conducts regular Community workshops, wellness camps, and public awareness programs for consumers under the banner of "Club 35 Plus." Federation of Obstetric and Gynaecological Societies of India (FOGSI) is addressing the issue by having a focus group Midlife committee.

Barriers to Implementation

Women with lower education, limited resources, and weak social support face greater barriers to accessing and benefiting from these programs. The barriers to implementation of these programs are women are more likely to have unhealthy baseline behaviors such as poor diet, less physical activity, low literacy, women's inability to prioritise their health, lack of family support (especially working women), women's heavy workload and time constraints make it challenging to attend health programs or seek care, especially when combined with migratory lifestyles or unstable housing.^{78,82-84} The program design should address individual and environmental barriers to reduce health disparities.⁸⁵

WORKPLACE AND MENOPAUSE

Global Workplace Menopause Challenges

A significant and growing proportion of the midlife female workforce is experiencing menopause at work, with global estimates showing that up to 47% of women now work throughout their menopausal years. Research from Ireland, the UK, and the United States (US) reveals that most women experience considerable occupational impact, with about 65% reporting reduced work performance, 18% taking sick leave, 84% wanting more workplace support, and over 70% hiding symptoms due to stigma or lack of accommodations. Commonly cited disruptive symptoms include fatigue, poor concentration, mood swings, anxiety, insomnia, and joint pain, as well as adverse effects on confidence and ambition, discouraging career advancement, or even leading to premature workforce exit. The "menopause penalty" has been quantified in economic terms, with research suggesting significant lifetime earnings losses for women experiencing severe symptoms.⁸⁶⁻⁹¹

Guidance from leading organisations (Menopause Society, European menopause and andropause society (EMAS), Catalyst) and consensus statements recommend employer-driven educational efforts, flexible schedules, work-

environment modifications (ventilation, temperature control, relaxed dress codes), peer support, and healthcare access for symptomatic women. Forward-thinking companies in the UK, US, Australia, Canada and some European countries are developing menopause leave options, awareness campaigns, and employee resource groups. However, implemented policies remain uncommon globally.^{35,92-94}

Indian Workplace Trends

The Indian workplace landscape regarding menopause remains largely unaddressed.

The key challenges include limited awareness, cultural barriers, lack of policies and healthcare access. Survey data show that nearly 82% of Indian women believe menopause impacts workplace wellbeing and career, while 18–26% work through symptoms or take time off without disclosure. Many still fear stigma or fear undermining their leadership prospects.

India is witnessing a slow but positive shift towards supporting women through menopause at work, though most organisations remain behind their global counterparts. Nationally, few companies have implemented formal menopause leave (most focus on "wellbeing" or sick leave). Companies such as Tata Consultancy Services (TCS), Infosys and the Godrej Group, leading banks, and global multi-national company (MNC)s such as The Hongkong and Shanghai Banking Corporation Limited (HSBC), International Business Machines (IBM), Standard Chartered Bank, NatWest, and Hindustan Univer Limited (HUL) recognise menopause as a key gender equity and talent retention issue. They have developed and implemented women's health programmes, including menopause awareness, and introduced flexible working arrangements and health support for menopausal employees.⁹⁵ Women receiving appropriate support showed a 23% improvement in work productivity, a 31% reduction in sick leave usage, and an 18% increase in job satisfaction scores.⁹⁴ A recent systematic review found that cognitive behavioural therapy, Raja yoga, support to adopt healthy lifestyles, and menopause awareness interventions improved various aspects of wellbeing among menopausal women and could be combined in future and customised to individual women's or organisations' needs as appropriate.⁹⁶

Future policy development should prioritise the establishment of a comprehensive national menopause strategy, integration of menopause care into existing health systems, development of supportive workplace legislation, increased research funding, strengthened international collaboration, and the use of technology and innovation, including mobile health applications, telemedicine, artificial intelligence, and digital therapeutics, to enhance symptom management and care delivery.

TRANSGENDER INDIVIDUALS AND MENOPAUSE

As the first generation of transgender women who initiated gender-affirming hormone therapy (GAHT) in adulthood reaches midlife and beyond, unique clinical considerations arise, particularly regarding menopause and optimal hormone management strategies for ageing transgender individuals. Unlike cisgender women, who experience natural menopause with declining estrogen levels, transgender women on GAHT maintain exogenous hormone supplementation, creating distinct clinical scenarios that require specialised medical guidance.^{97,98}

While most transgender healthcare research originates from Western countries, emerging evidence from Indian and South Asian contexts offers valuable insights into population-specific considerations. India's recognition of transgender rights and the traditional hijra community offer unique perspectives on long-term transgender healthcare needs. The Indian Endocrine Society has developed consensus statements for gender-affirming care.⁹⁹

The traditional definition of menopause inadequately captures the experiences of transgender and non-binary individuals, whose hormonal and physiological transitions may not align with normative menopausal trajectories. Menopause in gender-diverse (TGD) individuals is deeply intertwined with identity, embodiment, and societal norms. Many report distress when menopausal symptoms are framed through cisnormative lenses, which can exacerbate gender dysphoria. Non-binary individuals, in particular, may reject binary categorisations of hormonal change altogether.¹⁰⁰

Moreover, the use of GAHT, which can mimic or mask menopausal symptoms, coupled with the complex biopsychosocial aspects of menopause, requires dedicated research and guidelines to manage transgender individuals.¹⁰¹

TERMINOLOGY

- Cisgender people have a gender identity that matches the sex assigned at birth.

- TGD individuals are an umbrella term for gender identities that express beyond the binary framework of cisgender male and cisgender female.
- Transgender individuals - whose gender identity differs from the sex assigned at birth.
- Transgender women or male-to-female, individuals assigned male at birth (AMAB or MTF) who identify as female, represent a growing population seeking gender-affirming healthcare services.
- Trans men or female-to-male (assigned female at birth, AFAB or FTM) on long-term testosterone or after oophorectomy can experience hypoestrogenic symptoms (vasomotor symptoms [VMS], genitourinary syndrome of menopause [GSM]) and bone loss. Hijra is the terminology for transgender population in India.
- LGBTQIA acronym for lesbian, gay, bisexual, transgender, queer, intersex, asexual, plus the many other identities encompassing gender and sexuality.
- GAHT aims to maintain sex steroid levels within physiologically appropriate ranges for the affirmed gender and to alleviate gender dysphoria within a multidisciplinary model.
- "Transgender menopause" is a practical clinical term yet to be defined. Trans men may be hypoestrogenic due to testosterone-induced amenorrhoea, surgical oophorectomy, or ageing; GSM and VMS can occur despite therapeutic testosterone.^{102,103} Trans women have no ovarian cycle; however, dose reduction, perioperative interruption, or discontinuation of estradiol can provoke VMS and sleep/mood disruption analogous to menopausal symptoms.¹⁰⁴ Care is individualised and organ-based, screen for what an organ needs, independent of gender identity.¹⁰⁵ Healthcare providers must balance the benefits of continued feminising hormone therapy for gender affirmation and quality of life against potential age-related health risks, including cardiovascular disease, thromboembolism, osteoporosis and cancer.¹⁰²

Hormonal Transitions and Menopause Symptoms at Midlife

Trans men (AFAB or FTM): Testosterone suppresses the endometrium and lowers vaginal estrogen; epithelial atrophy, dryness and dyspareunia, pelvic examination discomfort, and a BV-prone microbiome are reported.^{106,107} Severe VMS may follow bilateral oophorectomy, even on stable testosterone. Trans women (AMAB or MTF): With estradiol maintained, there is no physiologic menopause; abrupt or planned reductions can trigger hot flashes, night sweats, insomnia, and mood symptoms.¹⁰⁵ In a survey (n=15 TGD respondents), hot flashes occurred in 74%, memory and concentration issues in 87%, and sleep disturbances in 67%.¹⁰¹

Management

The evidence shows that current guidelines for transgender women's hormone therapy are primarily derived from expert consensus, clinical experience, and treatments used for postmenopausal cisgender women.^{101,108,109} There are no dedicated guidelines for managing midlife. Hence, current clinical practice shows significant variation in approaches to managing ageing transgender women and a lack of standardised treatment algorithms.

General Principles

- *Individualised Care Approach:* Adopt an individualised, patient-centred approach to general and hormone therapy management in ageing transgender women. Establish multidisciplinary care teams comprising primary care providers, endocrinologists, mental health professionals, and other specialists as needed. Review surgeries, GAHT history, comorbidities, medication history, and risk factors. Identify treatment goals and quality-of-life priorities. Document the rationale for decisions in medical records. Regularly reassess treatment goals and patient preferences.
- *Advice on lifestyle management:* Non-hormonal therapy for VMS (all genders): When estrogen is contraindicated or undesired, guideline-supported options include Selective Serotonin Reuptake Inhibitors (SSRI)s/Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)s like paroxetine, venlafaxine, gabapentin, oxybutynin, and the neurokinin-3 receptor antagonist fezolinetant. Cognitive-behavioural therapy and clinical hypnosis have evidence; clonidine and many supplements are not recommended.⁹⁴ Continue GAHT in ageing transgender women unless contraindicated by significant health risks, with consideration of dose adjustment or route modification. Estradiol within normal female range, testosterone suppression to 50 ng/dL.
- *Estradiol administration:* Consider dose reduction if clinically appropriate while maintaining therapeutic benefit; prefer transdermal estradiol to oral formulations in women with increased thrombotic risk. Local vaginal estrogen at a low dose is effective for genitourinary syndrome.

- *Antiandrogen therapy:* Spironolactone (100-300 mg daily) or cyproterone acetate (25-50 mg daily, not available in India).
- *Monitoring Requirements:* Evidence supports regular clinical and laboratory monitoring. Every 3 months during the first year, hormone levels (estradiol, testosterone) are monitored, along with a basic metabolic panel, liver function tests, and assessments of treatment satisfaction and quality of life. Annual assessments include hormone levels, cardiovascular risk factors, bone density when indicated, metabolic and mental health evaluations, and cancer screening of the organs (breast, cervix, prostate) based on age.¹¹⁰⁻¹¹²

Risks of Therapy

- *Cardiovascular Risks:* Multiple studies have identified increased cardiovascular risk in transgender women on GAHT, with elevated risks of venous thromboembolism (VTE), stroke, and myocardial infarction compared with cisgender men.^{113,114} Risk levels are similar to or slightly higher than those in cisgender women.
- *Metabolic Effects:* Hormonal therapy's effects on the components of the metabolic syndrome are sex-specific and involve a complex interplay of direct hormonal effects, changes in body composition, and cytokine-mediated metabolism.¹¹⁵
- *Bone Health:* There is a risk of osteoporosis, particularly if hormone therapy is discontinued after gonadectomy. Bone density monitoring is recommended for those with additional risk factors, and there is insufficient evidence for optimal bone health management protocols.^{116,117}
- *Barriers to healthcare:* Healthcare interactions often reflect systemic cisnormativity, with providers lacking training in TGD-specific menopausal care. This can lead to misdiagnosis, inappropriate treatment, or neglect of symptoms.¹¹⁸ Additionally, TGD individuals face barriers to accessing hormone therapy, which may be disrupted by ageing, comorbidities, or systemic discrimination.¹¹⁹

Menopause research requires a multidisciplinary approach, drawing on the expertise of gynaecologists, endocrinologists, psychiatrists, psychologists, and anthropologists to address its biological, psychological, social, and cultural dimensions. There is a relationship between religious affiliation and the menopausal experience. A spiritual mindset and mindfulness strategies may, therefore, be very helpful in managing menopausal symptoms, as shown in several other studies.¹²⁰

SYNOPSIS

- Menopause is a rare evolutionary event in mammals, explained by theories such as the mother, grandmother, and reproductive conflict hypotheses.
- India's Ayurveda conceptualised menopause as Rajonivṛtti, a normal phase of life. Menopause has been increasingly medicalised since the 19th century. Modern research such as SWAN confirms menopause has biological and pathological implications for example CVD, osteoporosis. Bell's three models: biological (HRT), psychological (CBT), and environmental (self-help).
- Female life expectancy has increased to 74.1 years. Mean age at menopause in India: 46.6 years, earlier than the global average (51 years). Early menopause is associated with higher risks of chronic diseases, including CVD, diabetes, osteoporosis, and cancers.
- Cultural perceptions vary: some view menopause as liberating, while others see it as a decline.
- Midlife is often marked by an "empty nest," eldercare duties, and identity shifts. Indian women generally have positive or neutral attitudes towards menopause. Urbanisation and nuclear families reduce support systems. Fear of ageing, illness, and loss of social identity are common.
- Education programmes significantly improve knowledge and attitudes. Urban women (42–48%) use healthcare services more than rural women (25–30%). Major barriers: cost, distance, lack of awareness, and beliefs that symptoms will resolve naturally.
- 47% of women work through menopause; 65% report reduced performance. In India, 82% believe menopause affects work, and 70% fear stigma or a career impact. Few Indian companies have formal menopause policies.
- India's hijra community adds cultural context to transgender care. Trans women on GAHT don't experience natural menopause but may experience symptoms due to changes in hormone dosing. Trans men can develop hypo-estrogenic symptoms due to testosterone or oophorectomy. Clinical management requires individualised, multidisciplinary, and organ-based approaches.

RESEARCH AGENDA

Intervention effectiveness: Rigorous evaluation of educational and policy interventions.

REFERENCES

- Sanderson C. Social psychology. Hoboken (NJ): John Wiley & Sons Inc.; 2010. p. 19–22. ISBN 978-0470-55646-7.
- Cortés Y. Diverse experiences of menopause. *Menopause*. 2025;32(3):278-280. <https://doi.org/10.1097/GME.0000000000002510>
- Ayers BN, Forshaw MJ, Hunter MS. The menopause. *Psychologist*. 2011;24(5):348-53.
- Dhanaraj S, Mahambare V. Family structure, education and women's employment in rural India. *World Dev*. 2019;115:17–29. doi:10.1016/j.worlddev.2018.11.004.
- Pandya N, Bhangaokar R. Equal but different: views on gender roles and responsibilities among upper-class Hindu Indians in established adulthood. *J Adult Dev*. 2022;30:1–11. doi:10.1007/s10804-022-09417-4.
- Rashidi A, Shanley D. Evolution of the menopause: life histories and mechanisms. *Menopause Int*. 2009;15:26–30. doi:10.1258/mi.2009.009005.
- Skjærvø GR, Røskoft E. Menopause: no support for an evolutionary explanation among historical Norwegians. *Exp Gerontol*. 2013;48:408–413. doi:10.1016/j.exger.2013.02.001.
- Fraser A, Whitley E, Johnman C, Alvergne A. The evolutionary ecology of age at natural menopause: implications for public health. *OSF Preprints*. 2020. doi:10.32942/osf.io/s59rh.
- Froehle A. Postmenopausal health and disease from the perspective of evolutionary medicine. *Anthropol Aging*. 2013;34:61–86. doi:10.5195/AA.2013.8
- Purohith D, Chaudhary M, Gomes A, Rajapakse N, Das A, Dhanvanthry N et al. Men in menopause? Experimental verification of the mate choice theory with *Drosophila melanogaster* shows that both sexes can undergo menopause. *bioRxiv*. 2024. doi:10.1101/2022.04.18.488714.
- Moore ADM. The french invention of menopause and the medicalisation of women's ageing. Oxford University Press; 2022.
- Geraghty P. History and Overview of the Menopause Experience. In: *Each Woman's Menopause: An Evidence Based Resource*. Springer; 2021. https://link.springer.com/chapter/10.1007/978-3-030-85484-3_
- Bhardwaj A. Rajonivritti: A physiological study. *J Ayurveda Integr Med Sci*. 2022;7(5).
- Review of Rajonivritti Lakṣaṇas in menopausal women. *WJPMR*. 2018; <http://www.wjpmr.com> Accessed on 10/02/2025
- Moscucci, O. (1999). *Medicine, Age and Gender: The Menopause in History*. Menopause International, 5, 149 - 153. <https://doi.org/10.1177/136218079900500408>
- Collins A. Sociocultural issues in menopause. In: *National Institutes of Health. Women's health and menopause: a comprehensive approach*. Washington DC: National Institute of Health; 2002. pp. 65-75. 28. <https://doi.org/10.1111/hex.70163>
- Avis NE, Kaufert PA, Lock M, McKinlay SM, Vass K. The evolution of menopausal symptoms. *Baillieres Clin Endocrinol Metab* 1993;7(1):17–32
- Lock M. Ambiguities of aging: Japanese experience and perceptions of menopause. *Cult Med Psychiatry* 1986;10(1):23–46.
- Bates MS, Edwards WT, Anderson KO. Ethnocultural influences on variation in chronic pain perception. *Pain* 1993;52(1):101–12.
- Meyer VF. The medicalization of menopause: critique and consequences. *Int J Health Serv*. 2001;31(4):769-92. doi: 10.2190/M77D-YV2Y-D5NU-FXNW. PMID: 11809008.
- Santoro N, Sutton-Tyrrell K. The SWAN song: Study of Women's Health Across the Nation's recurring themes. *Obstet Gynecol Clin North Am*. 2011 Sep;38(3):417-23. doi: 10.1016/j.ogc.2011.05.001. PMID: 21961710; PMCID: PMC3185240.
- El Khoudary SR, Greendale GA, Santoro N, Avis NE, Brooks MM, Thurston R et al. The menopause transition and women's health at midlife. *Menopause*. 2019;26(10):1071–1089.
- Meeta M, Anuradha M, Ashraf AB, Aggarwal K, Digumarti L, Singh T. Clinical Practice Guidelines for Menopause: An Executive Summary and Recommendations: Indian Menopause Society 2026. *J MidlifeHealth*. 2026 Feb;17(Suppl 1):S12-S116. doi: 10.4103/jmh.jmh_302_25. Epub 2026 Feb 1. PMID: 41767293; PMCID: PMC12948155.
- North American Menopause Society. Practitioner's Toolkit for Managing Menopause. 2023. Available from: on 14/12.2025 <https://www.menopause.org/>. Accessed on 14/12/2025
- Kim JE, Chang JH, Jeong MJ, Choi J, Park J, Baek C, et al. A systematic review and meta-analysis of effects of menopausal hormone therapy on cardiovascular diseases. *Sci Rep*. 2020 Nov 26;10(1):20631. doi: 10.1038/s41598-020-77534-9. PMID: 33244065; PMCID: PMC7691511.
- Andy C, Nerattini M, Jett S, Carlton C. Systematic review and meta-analysis of the effects of menopause hormone therapy on cognition. *Front Endocrinol (Lausanne)*. 2024 Mar 4;15:1350318. doi: 10.3389/fendo.2024.1350318. PMID: 38501109; PMCID: PMC10944893.
- Benkhadra K, Mohammed K, Al Nofal A, Carranza Leon BG, Alahdab F, et al. Menopausal Hormone Therapy and Mortality: A Systematic Review and Meta-Analysis. *J Clin Endocrinol Metab*. 2015 Nov;100(11):4021-8. doi: 10.1210/jc.2015-2238. PMID: 26544652.
- Wang Y, Miao X, Viwattanakulvanid P. Effects of a therapeutic lifestyle modification intervention on cardiometabolic health, sexual functioning and health-related quality of life in perimenopausal Chinese women: protocol for a randomised controlled trial. *BMJ Open*. 2024 Apr 15;14(4):e082944
- Johnson A, Roberts L, Elkins G. Complementary and Alternative Medicine for Menopause. *J Evid Based Integr Med*. 2019 Jan-Dec;24:2515690X19829380. doi: 10.1177/2515690X19829380. PMID: 30868921; PMCID: PMC6419242.
- Combating Menopause Myths: Clinicians' Guide to Navigating Online Health Hype - Medscape - May 01, 2024. Accessed on 14/10/2025
- Avis NE, Stellato R, Crawford S, et al. Is there amenopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Soc Sci Med*. 2001;52(3):345-56.
- Flint M. Menopause: the global aspect. In: Hammar M, Berg G, editors. *The modern management of the menopause: A perspective for the 21st century*. The International Congress, Symposium, and Seminar Series, vol. 8. Proceedings of the Seventh International Congress on the Menopause, Stockholm, Sweden, June 1993. New York: Parthenon, 1994;17–22.
- Cronin C, Donevant S, Hughes KA, Kaunonen M, Marcussen J, Wilson R. Amplifying Women's Voices in Menopause Research: The Importance of Inclusive Perspectives. *Health Expect*. 2025 Feb;28(1):e70163. doi: 10.1111/hex.70163. PMID: 39840667; PMCID: PMC11751719.
- Bell SE. Changing ideas: the medicalization of menopause. *Soc Sci Med*. 1987;24(6):535-42. doi: 10.1016/0277-9536(87)90343-1. PMID: 3296222

35. Hickey M, LaCroix A, Doust J, Mishra G, Sivakami M, Garlick D, Hunter M. An empowerment model for managing menopause. *Lancet*. 2024;403:947–957. doi:10.1016/S0140-6736(23)02799-X.
36. Munshi A, Garg R. The Medicalization of Menopause: Understanding the Evolution of Treatment Approaches. *J Midlife Health*. 2024 Jul-Sep;15(3):133-134. doi: 10.4103/jmh.jmh_153_24. Epub 2024 Oct 17. PMID: 39610969; PMCID: PMC11601936.
37. United Nations, Department of Economic and Social Affairs, Population Division. *World Population Prospects 2024: Summary of Results (Medium-fertility variant)* New York: United Nations; 2024. Available from: <https://population.un.org/wpp/>. Accessed on 2025 Oct 18.
38. Pallikadavath S, Ogollah R, Singh A, Dean T, Dewey A, Stones W. Natural menopause among women below 50 years in India: a population-based study. *Indian J Med Res*. 2016;144:366–377. doi:10.4103/0971-5916.198676.
39. Dewangan K, Pattanaik S, Patnaik L, Sahu T. Prevalence of morbidities among peri-menopausal and postmenopausal women in selected urban slums of eastern India. *Int J Curr Res Rev*. 2020;12:55–60. doi:10.31782/ijcrr:2020.12188.
40. Kumari M, Mohanty SK. Caste, religion and regional differentials in life expectancy at birth in India: cross-sectional estimates from recent National Family Health Survey. *BMJ Open*. 2020 Aug 20;10(8):e035392. doi: 10.1136/bmjopen-2019-035392. PMID: 32819936; PMCID: PMC7440832.
41. Mishra V. India's Projected Aged Population (65+), Projected Life Expectancy at Birth and Insecurities Faced by Aged Population. *Ageing Int* 45, 72–84 (2020). <https://doi.org/10.1007/s12126-019-09350-0>
42. Cao X, Hou Y, Zhang X, Xu C, Jia P, Sun X et al. A comparative, correlate analysis and projection of global and regional life expectancy, healthy life expectancy, and their GAP: 1995–2025. *J Glob Health*. 2020 Dec;10(2):020407. doi: 10.7189/jogh.10.020407. PMID: 33110572; PMCID: PMC7568920.
43. Asaria M, Mazumdar S, Chowdhury S, Mazumdar P, Mukhopadhyay A, Gupta I. Socioeconomic inequality in life expectancy in India. *BMJ Glob Health*. 2019 May 9;4(3):e001445. doi: 10.1136/bmjgh-2019-001445. PMID: 31179039; PMCID: PMC6528758.
44. Giridhar G, Sathyanarayana KM, Kumar S, James KS, Alam M, editors. *Population ageing in India*. Cambridge University Press; 2014 Jul 14. https://books.google.com/books/about/Population_Ageing_in_India.html?hl=fr&id=24LRaWAAQBAJ. Accessed on 12/12/2025
45. Gupta A, Hathi P, Banaji M, Gupta P, Kashyap R, Paikra V et al Large and unequal life expectancy declines during the COVID-19 pandemic in India in 2020. *Sci Adv*. 2024 Jul 19;10(29):eadk2070. doi: 10.1126/sciadv.adk2070. Epub 2024 Jul 19. PMID: 39028821; PMCID: PMC11259167.
46. International Monetary Fund |,the Rise of the Silver Economy: Global Implications of Population Aging,Chapter 2, April 2025;<http://www.imf.org>. Accessed on 14/10/2025
47. Garmany A, Terzic A. Global Healthspan-Lifespan Gaps Among 183 World Health Organization Member States. *JAMA Netw Open*. 2024 Dec 2;7(12):e2450241. doi: 10.1001/jamanetworkopen.2024.50241. PMID: 39661386; PMCID: PMC11635540
48. Namazi M, Sadeghi R, Behboodi Moghadam Z. Social Determinants of Health in Menopause: An Integrative Review. *Int J Womens Health*. 2019 Dec 9;11:637-647. doi: 10.2147/IJWH.S228594. PMID: 31849539; PMCID: PMC6910086.
49. Aaron R, Mulivet J, Abrehan S. Medicosocial dimension of menopause: a cross national study from rural south India. *Natl Med J India*. 2002;15:14.
50. Avis NE, Crawford S. Cultural differences in symptoms and attitudes towards menopause. *Menopause management: NAMS*. 2008;(17)3:8-13.
51. Ayers B, Forshaw M, Hunter MS. The impact of attitudes towards the menopause on women's symptom experience: a systematic review. *Maturitas*. 2010 Jan;65(1):28-36. doi: 10.1016/j.maturitas.2009.10.016. Epub 2009 Dec 1. PMID: 19954900.
52. Meeta M, Guduru S, Tanvir T, Madan A. Awareness of menopause and menopause hormone therapy in India: perspectives of healthcare providers and consumers. *Climacteric*. 2025 Jun;28(3):286-295. doi: 10.1080/13697137.2025.2503876. Epub 2025 Jun 2. PMID: 40455559.
53. Richard-Davis G, Singer A, King DD, Mattle L. Understanding Attitudes, Beliefs, and Behaviors Surrounding Menopause Transition: Results from Three Surveys. *Patient Related Outcome Measures*;2022 Dec 14;13, 273–286. <https://doi.org/10.2147/PROM.S375144>
54. Maaløe N, Kujabi ML, Nathan NO, Skovdal M, Dmello BS, Wray S et al. Inconsistent definitions of labour progress and over-medicalisation cause unnecessary harm during birth. *BMJ*. 2023 Dec 6;383:e076515. doi: 10.1136/bmj-2023-076515. PMID: 38084433; PMCID: PMC10726361.
55. Hetzler PT, Dugdale LS. How do medicalization and rescue fantasy prevent healthy dying? *AMA J Ethics*. 2018;20(8):766–773.
56. Hall L. *Rehumanizing birth and death in America*. Society;2017; 54(3), 285-292.
57. Tyrrell P, Harberger S, Siddiqui W. *Kubler-Ross Stages of Dying and Subsequent Models of Grief(Archived)* [Updated 2023 Feb 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: on 12/12/2025<https://www.ncbi.nlm.nih.gov/books/NBK507885/>. Accessed on 12/12/2025
58. Wasserman LS. Respectful death: a model for end-of-life care. *Clin J Oncol Nurs*. 2008 Aug;12(4):621-6. doi: 10.1188/08.CJON.621-626. PMID: 18676328.
59. Varunsriram S, Sasirekha K. An analytical study on euthanasia in India and its constitutional validity *Indian Journal of Integrated Research in Law* Volume IV Issue V | ISSN: 2583-0538
60. Melby MK, Lock M, Kaufert P. Culture and symptom reporting at menopause. *Hum Reprod Update*. 2005;11(5):495-512
61. Hunter MS, Gupta P, Papitsch-Clarkema, Sturdee D. (2009). Mid-aged health in women from the Indian subcontinent (MAHWIS): A quantitative and qualitative study of experience of menopause in UK Asian women, compared to UK Caucasian and women living in Delhi. *Climacteric*, 12, 26–37. 10.1080/13697130802556304 [DOI] [PubMed] [Google Scholar]
62. Martin MC, Block JE, Sanchez SD, Arnaud CD. Menopause without symptoms: the endocrinology of menopause among rural Mayan Indians. *Am J Obstet Gynecol*, 1993;168(6 Pt1):1839–45.
63. Beyene Y. Cultural significance and physiological manifestations of menopause: a biocultural analysis. *Cult Med Psychiatry*. 1986;10(1):47-71.
64. Freeman EW, Sherif K. Prevalence of hot flushes and night sweats around the world: a systematic review. *Climacteric*. 2007;10(3):197-214.
65. Avis NE, Brambilla DJ, McKinlay SM, Vass K. A longitudinal analysis of the association between menopause and depression: results from the Massachusetts Women's Health Study. *Ann Epidemiol*. 1994;4(3):214-20.
66. Singh A, Arora AK. Profile of menopausal women in rural north India. *Climacteric*. 2005;8(2):177-84
67. Singh M. Early age of natural menopause in India, a biological marker for early preventive health programs. *Climacteric*. 2012 Dec;15(6):581-6. doi: 10.3109/13697137.2011.643514. Epub 2012 Feb 18. PMID: 22339416.
68. Sethi K, Pitkin J. British-Asian women's view on and attitudes towards menopause and hormone therapy. *Climacteric*. 2000;3(4):248-53
69. Hafiz I, Liu J, Eden J. A quantitative analysis of the menopause experience of Indian women living in Sydney. *Aust N Z J Obstet Gynaecol*. 2007 Aug;47(4):329-34. doi: 10.1111/j.1479-828X.2007.00746.x. PMID: 17627691.
70. Akbar S. Study to assess knowledge, attitude and practice regarding menopause among menopausal women attending outdoor in tertiary care hospital. *Int J Sci Res*. 2023;5(6):11367.

71. Devi R, Singh P, Kaur J. Knowledge, attitude and practices regarding menopause among rural women. *Indian J Community Health*. 2022;34(2):234-9.
72. Nagaraj D, Ramesh N, Devraj D, Umman M, John AK, Johnson AR. Experience and Perceptions Regarding Menopause among Rural Women: A Cross-Sectional Hospital-Based Study in South Karnataka. *J Midlife Health*. 2021 Jul-Sep;12(3):199-205. doi: 10.4103/jmh.JMH_196_20. Epub 2021 Oct 16. PMID: 34759701; PMCID: PMC8569466.
73. Sivasubramanian N, Saravanan N, Seshadri A. Knowledge, attitudes and demographic effect on menopausal experiences among Indian rural women. *J Family Med Prim Care*. 2024;13: ePub.
74. Bala K, Gupta R, Gupta RK, Akhtar N. Knowledge and Perceptions Regarding Climacteric Among Rural Women in Jammu District of UT of J and K, India: A Cross-Sectional Study. *Journal of Mid-life Health*. 2022 Apr 1;13(2):163-8..
75. Puri S, Bhatia V, Mangat C. Perceptions of menopause and postmenopausal bleeding in women of Chandigarh, India. *Internet J Fam Pract*. 2008;6(2).
76. Madhukumar S, Gaikwad V, Sudeepa D. A Community Based Study on Perceptions about Menopausal Symptoms and Quality of Life of Post Menopausal Women in Bangalore Rural. *Indian J Community Med*. 2012;37(3):167-172.
77. Gupta G, Kumari R, Mishra P, Gupta B. Factors Associated with Quality of Life among Menopausal Women in Lucknow – A Cross- Sectional Study. *J Mid-life Health*. 2024;14:257-264.
78. Roy P, Bose S, Suvvari T, Sivaraj N. Health-care-seeking Behavior of Postmenopausal Women in an Urban Slum of Srikakulam Town. *Apollo Medicine*. 2023;20(4):245-250.
79. Sarkar A, Thakur RP, Taraphdar P. Postmenopausal Experiences and Constraints in Seeking Health Care in A Rural Area of West Bengal, India. *Natl J Community Med*. 2023;14(4):288-294.
80. Shilpa K, Ugargol AR. A comparative study on postmenopausal symptoms in rural and urban women. *Int J Community Med Public Health*. 2015;2(4):604-609.
81. Singh, N, Chouhan Y, Patel S. Treatment seeking behavior among post-menopausal females attending out-patient clinic of Obstetrics and Gynecology at a tertiary care centre, Bhopal, Madhya Pradesh. *International Journal Of Community Medicine And Public Health*, (2018). 5(12), 5365–5370. <https://doi.org/10.18203/2394-6040.ijcmph20184818>
82. Arun A, Prabhu MP. Social determinants of health in rural Indian women & effects on intervention participation. *BMC Public Health*, 2023 May 19;23(1):921. <https://doi.org/10.1186/s12889-023-15743-3>.
83. Nissy V, Bhaskaran G, Lal S, Mini G. Menopause-Specific Quality of Life among Rural Women: A Community-based Cross-sectional Study in Kerala, India. *Journal of Mid-Life Health*, (2025). 16, 67 - 75. https://doi.org/10.4103/jmh.jmh_171_24
84. Divya K, Nimithamohan K, Bilimale A, Muralidhar K, Krupp K, & Madhivanan P. Role of Social Support in Reducing the Severity of Menopausal Symptoms among Women Living in Rural Mysuru, Karnataka: An Analytical Cross-sectional Study. *Journal of Mid-Life Health*, 15, 12 – 18, Jan–Mar 2024.. https://doi.org/10.4103/jmh.jmh_180_23
85. Van De Ven D, Robroek S, Burdorf A. Are workplace health promotion programmes effective for all socioeconomic groups? A systematic review. *Occupational and Environmental Medicine*. 2020 Sep 1; 77, 589 - 596. <https://doi.org/10.1136/oemed-2019-106311>
86. Faubion SS, Enders F, Hedges M, Chaudhry R, Kling J, Shufelt C, et al Impact of Menopause Symptoms on Women in the Workplace. *Mayo Clinic Proceedings*. 2023 Jun;98(6):833-845. <https://doi.org/10.1016/j.mayocp.2023.02.025>.
87. Atkinson C, Carmichael F, Duberley J. A bio-psycho-social investigation of menopause transition and job satisfaction.. *Maturitas*, 2025 Feb 193, 108187. <https://doi.org/10.1016/j.maturitas.2024.108187>
88. Walker-Bone K, and Davis S. Menopause, women and the workplace. *Climacteric* 2025 July 4; 28(4): 423-30. <https://doi.org/10.1080/13697137.2025.2480591>
89. Rottenberg C, and Gilchrist K. The menopausal subject at work: gendered embodiment and neoliberal management in the UK. *Journal of Gender Studies*. 2026, 35(1).92-107 <https://doi.org/10.1080/09589236.2025.2451202>
90. Coenen P, Robroek SJ, Van Der Beek AJ, Boot CR, Van Lenthe FJ, Burdorf A, Socioeconomic inequalities in effectiveness of and compliance to workplace health promotion programs: an individual participant data (IPD) meta-analysis. *The International Journal of Behavioral Nutrition and Physical Activity*, 2020 Sept 4; 17(1):112. <https://doi.org/10.1186/s12966-020-01002-w>
91. DePree B, Lohrberg, B. Effect of Menopause in the Workplace– Socioeconomic Differences. *Current Obstetrics and Gynecology Reports*. 2024 Dec 5; 14(1):4. <https://doi.org/10.1007/s13669-024-00410-0>.
92. Jack G, Riach K, Bariola E, Pitts M, Schapper J, Sarrel P. Menopause in the workplace: What employers should be doing. *Maturitas*. 2016 Mar 1;85: 88-95. <https://doi.org/10.1016/j.maturitas.2015.12.006>
93. Rees M, Bitzer J, Cano A, Ceausu I, Chedraui P, Durmusoglu F, Erkkola R, Geukes M, Godfrey A, Goulis DG, Griffiths A. Global consensus recommendations on menopause in the workplace: a European Menopause and Andropause Society (EMAS) position statement. *Maturitas*. 2021 Sep 1;151:55-62.
94. Faubion SS, Bigler JK, Christmas MM, Cortes YI, Green-Smith P, Kapoor E et al .Menopause and the workplace: consensus recommendations from The Menopause Society. *Menopause*. 2024 Sep 1;31(9):741-9.
95. Sreeradha Basu, Brinda Sarkar, ET Bureau, Breaking the menopause taboo: How a bunch of companies in India are raising awareness and providing support, *Careers on 10/10/2025* https://economictimes.indiatimes.com/jobs/hr-policies-trends/breaking-menopause-taboo-how-many-companies-in-india-are-raising-awareness-and-providing-support/articleshow/109093585.cms?utm_source=contentofinterest&utm_medium=text&utm_campaign=cpst. Accessed on 10/12/2025
96. Ndindeng A. The Impact of Effective Menopausal Symptom Management on Workplace Performance and Well-being: A Comprehensive Analysis. *Res Sq*. 2024. [researchsquare.com](https://www.researchsquare.com). Accessed on 10/10/2025
97. Mehta J, Kanell S, Borowicz C, Fisher M. Transgender patients and gender-affirming hormone therapy through midlife. *Maturitas*. 2024, Nov 1;189:108093.
98. Unger CA. Hormone therapy for transgender patients. *Transl Androl Urol*. 2016 Dec;5(6):877-884. doi: 10.21037/tau.2016.09.04. PMID: 28078219; PMCID: PMC5182227.
99. Majumder A, Chatterjee S, Maji D, Roychaudhuri S, Ghosh S, Selvan C, et al. IDEA Group Consensus Statement on Medical Management of Adult Gender Incongruent Individuals Seeking Gender Reaffirmation as Female. *Indian J Endocrinol Metab*. 2020;24(2):128-135.
100. Toze M, Westwood S. Experiences of menopause among non-binary and trans people. *Int J Transgend Health*. 2025;26(2):447–58. <https://doi.org/10.1080/26895269.2024.2389924>
101. Vaupel-Klein AM, Walsh RJ. Considerations in genetic counselling of transgender patients: cultural competencies and altered disease risk profiles. *J Genet Couns*. 2021;30(1):98–109. doi: 10.1002/jgc4.1372. [DOI] [PMC free article] [PubMed] [Google Scholar]

102. Defreyne J, Vander Stichele C, Iwamoto SJ, T'Sjoen G. Gender-affirming hormonal therapy for transgender and gender-diverse people-A narrative review. *Best Pract Res Clin Obstet Gynaecol*. 2023 Feb;86:102296. doi: 10.1016/j.bpobgyn.2022.102296. Epub 2022 Dec 16. PMID: 36596713; PMCID: PMC11197232.
103. Casimiro I, Cohen R. Severe vasomotor symptoms post-oophorectomy despite testosterone therapy in a transgender man: case study. *AACE Clin Case Rep*. 2019;5(3):e199-e202
104. Lee AH, Spiegel JH. Should Exogenous Estrogens Be Stopped for Surgery in Transgender Women? *Laryngoscope*. 2022 May;132(5):918-919. doi: 10.1002/lary.29786. Epub 2021 Jul 29. PMID: 34324205.
105. UCSF Transgender Care. General approach to cancer screening in transgender people. 17 June, 2016. <https://transcare.ucsf.edu>. Accessed on 12/10/2025
106. Tordoff DM, Lunn MR, Chen B, Flentje A, Dastur Z, Lubensky ME, Testosterone use and sexual function among transgender men and gender diverse people assigned female at birth. *Am J Obstet Gynecol*. 2023 Dec;229(6):669.e1-669.e17. doi: 10.1016/j.ajog.2023.08.035. Epub 2023 Sep 9. PMID: 37678647; PMCID: PMC11182338.
107. Krakowsky Y, Potter E, Hallarn J, Monari B, Wilcox H, Bauer G et al. The Effect of Gender-Affirming Medical Care on the Vaginal and Neovaginal Microbiomes of Transgender and Gender-Diverse People. *Front Cell Infect Microbiol*. 2022 Jan 21;11:769950. doi: 10.3389/fcimb.2021.769950. PMID: 35127550; PMCID: PMC8814107.
108. Cortez S, Moog D, Lewis C, Williams K, Herrick C, Fields ME, et al. Effectiveness and Safety of Different Estradiol Regimens in Transgender Women (TREAT Study): Protocol for a Randomized Controlled Trial. *JMIR Res Protoc*. 2023;12(1):e53092.
109. Hembree WC, Cohen-Kettenis PT, Gooren LJ, Hannema SE, Meyer WJ, Murad MH, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903
110. Expert Panel on Breast Imaging; Brown A, Lourenco AP, Niell BL, Cronin B, Dibble EH, DiNome ML, et al. ACR Appropriateness Criteria® Transgender Breast Cancer Screening. *J Am Coll Radiol*. 2021 Nov;18(11S):S502-S515. doi: 10.1016/j.jacr.2021.09.005. PMID: 34794604.
111. Hsiao KT. Screening for cervical cancer in transgender men. UCSF transgender care June 17, 2016. <https://transcare.ucsf.edu>. Accessed on 12/12/2025
112. Nguyen DD, Ahmad I, Al-Daqqaq Z, Rosella LC, Hird A, Wallis CJD et al. Prostate cancer screening in transgender patients Why current Canadian screening policies need to be better tailored to our patients. *Can Urol Assoc J*. 2025 Jun;19(6):202-204. doi: 10.5489/cuaj.9005. PMID: 40031946; PMCID: PMC12158456.
113. Cheung AS, Nolan BJ, Zwickl S. Transgender health and the impact of aging and menopause. *Climacteric*. 2023;26(3):258-265.
114. Ott J, Kaufmann U, Bentz EK, Huber JC, Tempfer CB. Incidence of thrombophilia and venous thrombosis in transsexuals under cross-sex hormone therapy. *Fertil Steril*. 2010;93(4):1267-1272
115. Auer MK, Ebert T, Pietzner M, Defreyne J, Fuss J, Stalla GK et al. Effects of sex hormone treatment on the metabolic syndrome in transgender individuals: focus on metabolic cytokines. *The Journal of Clinical Endocrinology & Metabolism*. 2018 Feb;103(2):790-802.
116. Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, et al. Preservation of volumetric bone density and geometry in trans women during cross-sex hormonal therapy: a prospective observational study. *Osteoporos Int*. 2015;26(1):35-47.
117. Giacomelli G, Meriggiola MC. Bone health in transgender people: a narrative review. *Ther Adv Endocrinol Metab*. 2022 May 27;13:20420188221099346. doi: 10.1177/20420188221099346. PMID: 35651988; PMCID: PMC9150228.
118. Westwood S. Lesbian, gay, bisexual, transgender and queer (LGBTQ+) menopause: Literature review, knowledge gaps and research agenda. *Health*. 2024. <https://doi.org/10.1177/13634593241270923>.
119. Safer JD, Coleman E, Feldman J, Garofalo R, Hembree W, Radix A, et al. Barrier to healthcare for transgender individuals. *Curr Opin Endocrinol Diabetes Obes*. 2016;23(2):168-171.
120. Agarwal A, Thomas HN. The relationship between religious affiliation and menopause symptoms and attitudes in United States women. *Maturitas*. 2024 Jul 1;185.

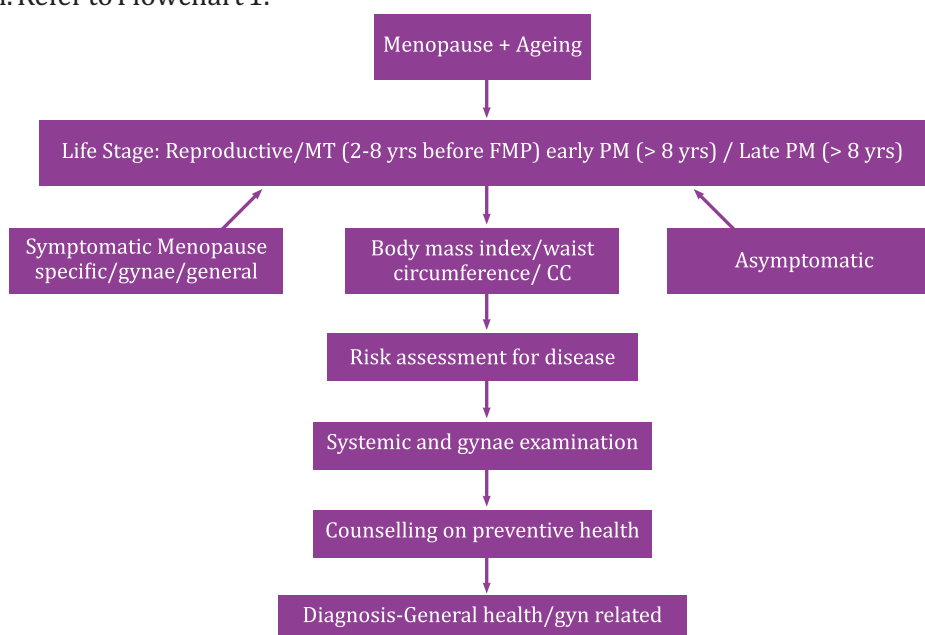
CLINICAL EVALUATION AT MENOPAUSE

04

Key words: History, clinical examination, risk categorisation, personalised management plan

INTRODUCTION

Menopausal health is an important issue globally. Women do not raise their menopause related concerns unless prompted. The World Health Organisation (WHO), along with multiple national menopause societies, advocates integrating menopause care into routine health services.¹⁻⁵ Preventive and health care needs of women vary across the different phases of a woman's life. Regular periodic health examinations are the standard of care. Clinical evaluation at menopause aims to identify individual woman's risk factors for various age-related diseases, identify specific menopause-related issues, evaluate a woman's needs, assess her general condition, and then plan management strategies. This comprehensive approach aims to promote optimal health and functional independence throughout ageing, encapsulated in the goal of ensuring women are "Fit @ Forty, Strong @ Sixty and Independent @ Eighty".⁵ Women may present at the menopause clinic with menstrual problems, menopausal symptoms, or a request for a general health check-up.⁶⁻⁹ It is most important to distinguish between symptomatic and asymptomatic menopausal women. Refer to Flowchart 1.



Flowchart 1: Physician's approach to evaluate a women at 35 years or older

MT: Menopause transition, FMP: Final menstrual period, PM : Post menopause, CC:Calf circumference The approach to clinical examination should focus on a comprehensive health evaluation rather than on menopausal issues alone. A thorough assessment of health-related problems helps formulate a treatment plan. A comprehensive history is the foundation for evaluating perimenopausal or menopausal women, followed by clinical examination and laboratory investigations. It is important to document this systematically to plan management and follow-up. Refer to the Menopause Proforma in Chapter 51.

MENOPAUSAL TRANSITION SYMPTOMS

Women may experience symptoms during the premenopausal phase of their lives. The symptom complex of the menopausal transition (MT) varies across social, cultural, and ethnic groups. Perimenopause, or the MT, is a period of declining ovarian function that precedes the final menstrual period by 2–8 years.

The clinical manifestations of this transition to menopause are not well understood; however, some symptoms, such as hot flushes, begin during the perimenopausal period and increase as women progress through menopause. The diagnosis of MT /menopause in females over 45 years of age is clinical and based on the presence of irregular menses

and/or menopausal symptoms. Laboratory evaluation is not necessary or recommended unless indicated to rule out secondary causes. In women aged 40 to 45, the presence of irregular periods and hot flushes strongly suggests MT. However, laboratory evaluation should be performed first to rule out other endocrine disorders. Women under 40 years presenting with new-onset irregular cycles or amenorrhoea, with or without menopausal symptoms, need laboratory evaluation.

COMPONENTS OF CLINICAL EVALUATION

Clinical evaluation should adopt a holistic, preventative, and diagnostic approach, extending beyond isolated menopausal symptoms to identify both hidden and overt noncommunicable diseases (NCDs).⁶⁻⁹ Age-related biological changes, along with lifestyle and socioeconomic factors, require tailored risk assessment and long-term management strategies.

- *History and physical examination:* Take a thorough history, including menstrual, reproductive, sexual, psychosocial, and family histories. Perform general and systemic physical examinations, as well as breast and pelvic examinations. Measure Body Mass Index (BMI), waist circumference, and calf circumference.
- *History:* The information gathered should be under the following headings.
- *Menopause-specific:* A detailed history of menopausal symptoms, with grading of these symptoms by frequency, severity, duration, and the extent to which they affect quality of life (QoL).
- *Symptom assessment tools:* Record menopausal symptoms using a validated scale. Menopause-related symptoms may be documented using the Menopause Rating Scale (MRS).¹⁰⁻¹² Refer to Table 1. The MRS demonstrates excellent reliability, with Cronbach's alpha values of 0.84-0.87 across international validations.¹²

Symptom severity is documented using the individual item boxes to assess baseline severity and monitor treatment response. The Total MRS Score is calculated from the scale, and menopausal symptoms are classified as None: 0-4; Mild: 5-8; Moderate: 9-16; Severe: 17 or more. The total score reflects global symptom burden, whereas domain and individual item scores guide targeted management. Treat any symptom scoring ≥ 2 if it is bothersome or affects quality of life; treat actively when any item scores 3-4, any domain is moderate/severe, or total MRS is $\geq 14-16$.

Based on the MRS outcome, the Female Sexual Function Index (FSFI-6, refer to Table 2) for sexual health assessment,¹³ the Insomnia Severity Index (ISI, refer to Table 3) for sleep disturbances,¹⁴ and the Patient Health Questionnaire (PHQ-4, refer to Table 4) for psychological health are documented as needed.¹⁵ The short-form Montreal Cognitive Assessment (s-MoCA) is a short tool for dementia (<https://mocacognition.com/>).¹⁶

- *Sexual history:* This focuses on the conditions or circumstances that affect sexual function. Sexual history should be confidential, non-judgmental, and sensitive to the woman's specific conditions. The FSFI is a brief self-report measure. The FSFI comprises six domains: desire, subjective arousal, lubrication, orgasm, satisfaction, and pain associated with intercourse. Several other instruments for measuring sexual function, interest, or desire are available, but their reliability and validity vary.

Table 1: Menopause Rating Scale (MRS)

Which of the following symptoms apply to you at this time?
(X ONE Box For EACH Symptom) For symptoms that do not apply, please mark 'none'

Symptoms	Score	none 0	mild 1	moderate 2	severe 3	very severe 4
1. Hot Flashes, Sweating (episodes of sweating)		☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)		☐	☐	☐	☐	☐
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through, waking up early)		☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)		☐	☐	☐	☐	☐
5. Irritability (feeling nervous, inner tension, feeling aggressive)		☐	☐	☐	☐	☐
6. Anxirty (inner restlessness, feeling panicky)		☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)		☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, sexual satisfaction)		☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)		☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)		☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)		☐	☐	☐	☐	☐

Table 2: Sexual Health -FSFI-6 Form

Description (Range)	1	2	3	4	5
1. Desire Very low → Very high	☐	☐	☐	☐	☐
2. Arousal No arousal → Very high arousal	☐	☐	☐	☐	☐
3. Lubrication None → Adequate	☐	☐	☐	☐	☐
4. Orgasm Never → Almost always	☐	☐	☐	☐	☐
5. Satisfaction Very dissatisfied → Very satisfied	☐	☐	☐	☐	☐
6. Pain Always pain → No pain	☐	☐	☐	☐	☐

Total score = 30. A score of ≤ 19 suggests dysfunction

- Sleep History: sleep difficulties (insomnia, night awakenings) are common.

Table 3: Sleep: Insomnia Severity Index (ISI), 7-item questionnaire

Score	0	1	2	3	4
1. Difficulty falling asleep	☐	☐	☐	☐	☐
2. Difficulty staying asleep	☐	☐	☐	☐	☐
3. Problems waking up too early	☐	☐	☐	☐	☐
4. Satisfaction with current sleep	☐	☐	☐	☐	☐
5. Interference with daily functioning	☐	☐	☐	☐	☐
6. Noticeability of sleep problems by others	☐	☐	☐	☐	☐
7. Worry/distress about sleep problem	☐	☐	☐	☐	☐

Total Score: 28 Cut-offs: 0–7: No clinically significant insomnia, 8–14: Sub-threshold insomnia, 15–21: Moderate insomnia, ≥22: Severe insomnia

Neuropsychological and sleep symptoms: mood swings, irritability, and depressed mood; short-term cognitive complaints (“brain fog”) are frequent.

Table 4: Psychological Health, Patient Health Questionnaire PHQ-4, past 2 wk

S. No	Description	0	1	2	3
1.	Little interest or pleasure in doing things	☐	☐	☐	☐
2.	Feeling down, depressed, or hopeless	☐	☐	☐	☐
3.	Feeling nervous, anxious, or on edge	☐	☐	☐	☐
4.	Not being able to stop or control worrying	☐	☐	☐	☐

Each item scored 0–3; Total Score: 0–12

≥6 suggests clinically relevant psychological distress

- *Genitourinary Syndrome of Menopause (GSM):* includes vaginal dryness, dyspareunia, vulval itching/burning, urinary urgency, and recurrent urinary tract infection (UTI)s.¹⁷
- *Gynaecological history:* Current menstrual status, age at menarche/menopause, last menstrual period, flow pattern before age 35, and any change in pattern in a woman with regular cycles. Check for early cycles, variable cycle length > 7 days, or two consecutive missed cycles lasting more than 60 days—document abnormal bleeding according to the PALM–COIEN classification.¹⁸ History of polycystic ovarian disease. Encourage the maintenance of a menstrual diary, which would be most useful for tracking the transition phase.¹⁸
- *Obstetric history:* Number of pregnancies, abortions, living children, lactation, and postpartum depression. History of gestational diabetes and gestational hypertension.
- *Contraception history:*
- *Surgical history:* History of surgery.
- *Family history:* Of chronic disorders such as diabetes mellitus, hypertension, cardiovascular disease, stroke, history of endometrial /ovarian/breast and other cancers, early menopause, osteoporosis, Alzheimer's disease, and rheumatoid arthritis.

- *Medical history:* Same as above.
- *Personal history:* Diet, calcium intake, level of physical activity, exercise, mental attitude, social relationships, habits, stress, mood changes, memory and concentration, and use of caffeine, tobacco, and alcohol. Details of bowel and urinary dysfunction. Exposure to sunlight.
- *Weight history:* Changes in weight over the stages of reproductive aging according to STRAW 10.¹⁹
- *Medication history:* Current medication, use of prescription and non-prescription drugs, complementary and alternative therapies, allergies to any medication, and use of therapy for the treatment of menopause symptoms.
- *Immunisation history:* History of immunisation against common infections is recorded.
- *Quality of life:* Maintaining an optimal QoL is a priority for women during the perimenopause and beyond. A woman's perception of her QoL is not limited to menopausal symptoms. It encompasses a broader sense of well-being across the physical, behavioural, cognitive, and emotional functioning domains. QoL is a state of mind that extends beyond the presence or absence of disease symptoms. Comprehensive clinical evaluation should ideally incorporate validated questionnaires (instruments) that measure both symptom profiles and well-being. These scales can be used in women with various diseases, especially those related to or affecting menopause. The Menopause-Specific QoL (MENQOL)²⁰ Questionnaire, Utian QoL Scale (UQOL)²¹, and Cervantes Short-Form Scale 13 are commonly used. The UQOL was developed for research and clinical applications. This 23-item questionnaire is validated, reliable, and easily administered and scored in an office setting. (See www.menopause.org/qol.htm to download the questionnaire and scoring instructions.) The Cervantes Short-Form Scale maintains the original dimensional structure and psychometric properties. This version can be administered in 51% of the original length, making it especially suitable for routine clinical practice.²²

ASSESSMENT FOR DISEASE

Risk factors for NCDs and screening methods are given in Table 5.

The risk score guide categorises women as low, moderate, or high risk for NCDs.

- *Breast:* A woman may be categorised as low, moderate or high risk for developing invasive breast cancer using the Gail Model, although it has not been validated in India (<https://www.cancer.gov/bcrisktool>).
- *CVD:* 10-year risk of myocardial infarction or stroke, based on the Globorisk India tool (use the web calculator at www.globorisk.org or the validated desk/pocket chart) and/or the Reynolds Risk Score (www.mdcalc.com/calc/3932/reynolds-risk-score-cardiovascular-risk-women?utm). Refer to Chapter CVD.

Table 5: Risk factors and methods of screening of diseases

Diseases	Risk factors		Method/Tool
	Modifiable	Non-modifiable	
Osteoporosis	Low BMI (≥ 20) Nutritional deficiency Physical inactivity Prolonged immobilization Calcium and Vitamin D deficiency Estrogen deficiency Smoking Excessive alcohol intake	Female sex Advanced age Family history of osteoporosis H/o osteoporotic fracture Disease and Disorders Hypogonadal status, Endocrine disorders - Crushing's insufficiency, Malabsorption syndrome, Renal Insufficiency Hematological disorders Medications, Steroids & anticonvulsants	Refer chapter 16 OSTA SCORE FRAX
Coronary heart disease	Gestational Diabetes Pregnancy Induced Hypertension Polycystic Ovarian Disease Obesity Smoking Dyslipidemia (High LDL, low HDL, elevated TG) Anemia	Age >55 yrs. Premature ovarian insufficiency Family history of CHD	Refer chapter 12 WHO/ISH Risk prediction charts
Stroke	All the CVD risk factors and Atrial Fibrillation Asymptomatic carotid stenosis		WHO/ISH Risk prediction charts
Diabetes mellitus	Physical inactivity Obesity Polycystic ovary syndrome Dyslipidemia	Family history, Advancing age, Personal history of gestational diabetes mellitus or impaired glucose tolerance	FBS/HbA1C/ 2hrs 75 gms. oral Glucose tolerance testing (GTT)
Thyroid dysfunction	Dyslipidemia Anemia	Family history of thyroid disease Prior thyroid dysfunction Autoimmune disorder. High dose neck radiation	S.TSH
Alzheimer's Disease	Physical inactivity Obesity Polycystic ovary syndrome Dyslipidemia	Age >65 Female Family history: First degree Genetic factor: Apolipoprotein E-4 (APOE-4) Minimal cognitive impairment (MCI) Auto-immune diseases Head trauma Traumatic brain injury	Criteria for probable AD Dementia of indolent onset Progression of symptoms No disturbance of consciousness Absence of other systemic or brain disease that produce cognitive & behavioral change
Deep vein thrombosis	Prolonged immobilization Oral contraceptive pills Norethisterone and norethisterone derivatives, MHT	Personal or family history History of treatment with anticoagulants	Activated partial thromboplastin time and prothrombin time, antithrombin, protein C and S, factor V Leiden, lupus anticoagulant and anticardiolipin antibodies (immunoglobulins G and M)

- *Skeletal health:* Risk assessment for osteoporosis may be performed using Osteoporosis self-Assessment tool for Asians (OSTA)/Fracture Risk Assessment tool (FRAX) (<http://www.shef.ac.uk/FRAX>). Refer to Chapter on osteoporosis.
- *Muscle health:* Evaluated using the SARC-calf, a 6-item questionnaire. Refer to Chapter, sarcopenia.

The results for risk assessment for diseases are documented in Table 6. The risk status is categorised as low, moderate, or high risk for disease.

Table 6: Comprehensive chart for documenting the risk score for NCDs over 5/10 years and lifetime results by noting the most bothersome symptoms and the vaginal pH using a narrow-range litmus paper and the signs noted on examination.

Tool	5/10 Yr risk Score	Lifetime risk Score	Risk Status
Invasive Breast cancer Gail			
WHO/ISH;Globorisk- India			
OSTA/SCORE/ FRAX			
SARC - F			
WHO: World Health Organization, FRAX: Fracture Risk Assessment Tool			

- *Assess Risk Factors for Cancers in General:* increasing age, parity, obesity, physical inactivity, genetic factors, viral infections (human papillomavirus (HPV), surface antigen of the hepatitis B virus (HBsAg)), a diet high in saturated fats and low in fibre, fruits, and vegetables, and sun sensitivity.
- *Risk Factors for Endometrial Cancer:* Refer to Chapter 26
- *Risk Factors for Cervical Cancer:* Refer to Chapter 25
- *Risk Factors for Ovarian Cancer:* Refer to Chapter 27

Clinical Examination

Examinations can be broadly divided into three main categories:

General Physical Examination

- *General:* Pulse, Blood pressure (BP)
- Optimal BP (<130/85 mm Hg) to be rechecked every 1year
- Normal BP level (<140/90 mm Hg) should be checked more often
- BP above 140/90 mm Hg requires a second measurement to confirm a diagnosis of hypertension.
- *To test for postural hypotension, BP is measured in the supine and standing positions, and the difference between them is calculated. A difference of 20 mmHg is considered significant.*
- *Cardiorespiratory:* heart and lung auscultation
- *Breast:* clinical breast exam; include inspection and palpation; encourage “breast self- awareness”
- *Abdominal:* palpation for organomegaly and masses; Musculoskeletal/neurological: Assessment of the spine, posture, gait, balance, muscle strength, joint status, and SARC-F for sarcopenia risk.
- *Eyes and dental:* recommend referral for eye and dental examinations; both are part of healthy ageing.
- *Pallor, pedal oedema, spine and varicose veins are checked, and physical fitness is assessed.* Refer to chapter 51
- *Pelvic examination:* Visual inspection of the external genitalia for atrophic changes; speculum examination for urinary and rectal problems, vaginal pH, and Pap smear; bimanual examination of the uterus, adnexa, and pelvic floor, prolapse palpable ovary at postmenopause is abnormal

Investigation

These are necessary to establish the diagnosis, determine the aetiology, and screen for complications. Some investigations may be necessary to reach a diagnosis or to help formulate a management plan.

- **Baseline tests:** Complete blood count, urine routine, fasting glucose and glycaemic haemoglobin, lipid profile, and thyroid-stimulating hormone.²³
- **Additional tests as needed:** 25-hydroxyvitamin D levels, micronutrient levels, C-reactive protein, creatinine kinase.²⁴
- **Interpreting hormonal tests supporting evidence to diagnose menopause transition and menopause:** Refer to Chapter 2
- **For Reproductive Health:** Vaginal pH, and transvaginal ultrasound.
- **Cancer screening:** Pap smear, stool for occult blood, and mammography/ultrasound of the breast. Evidence supports annual screening mammography for women aged 40-49. Models consistently show the greatest mortality reduction with annual screening starting at age 40.²³
- **Bone Density Assessment:** DXA scanning based on risk stratification 2; Monitor therapy intervals: 1-5 years, depending on individual risk.²⁵
- Investigations should be individualised based on clinical findings. The investigations listed in Table 7, should be chosen judiciously, depending on the woman's history and examination.

Table 7: Tests performed solely on indication

Test	Indication
FSH	Premature ovarian insufficiency, women on contraceptive pills, women who had hysterectomy, doubt as to the cause of secondary amenorrhoea or hot flushes, fertility
Estradiol	Premature ovarian insufficiency, women on contraceptive pills, women who had hysterectomy, doubt as to the cause of secondary amenorrhoea or hot flushes
Tests to assess increased risk of thrombosis	Where there is relevant past or family history, previous history of unexplained thromboembolic episodes -antithrombin III, protein C and protein S are to be estimated. Lupus anticoagulant, anticardiolipin antibodies Factor V Leiden assay as needed
Endometrial biopsy	Postmenopausal bleeding, recent irregular bleeding, previous use of unopposed estrogen in the presence of uterus, Endometrial thickness >11mm; 4-11mm with risk factors
Bone mass measurement	For specific indication. Refer to Chapter
LFT/RFT	When relevant as with suspected liver disease or recent history of liver disease, fatty liver on USG/ Known diabetes / hypertension/ CKD risk/ kidney disease
Urodynamic study	To diagnose and differentiate on the severity and type of Incontinence before planning surgery
ECG, 2D Echo, CT/USG CAC	CVD assessment

FSH: Follicle-stimulating hormone; OCPs: Oral contraceptive pills; LFT: Liver function tests; ECG: Electrocardiogram; 2D Echo: Two-dimensional echocardiography; CVD: Cardiovascular disease, 25, OH vitamin D: 25-hydroxy vitamin D, VMI: Vaginal Maturation index; CT/USG based CAC -Computerised tomography/Ultrasound coronary artery calcium score; CKD: Chronic kidney disease

- **Monitoring and Surveillance:** Annual comprehensive evaluation, risk reassessment using validated tools, screening programme adherence, and hormone therapy monitoring, if applicable.

Documentation

Systematic documentation using standardised forms and validated assessment scales ensures continuity of care and enables monitoring of treatment outcomes.

Diagnosis

The woman's general and menopause-related problems are documented, and disease screening is performed. The health status of an individual, based on the results of tools for invasive breast cancer, CVD, and musculoskeletal health, can be documented in a comprehensive chart for quick reference. Refer to Table 4. The information obtained from the MRS scale and the risk screening results defines the stage of lifespan and health status.

Document under the following headings

- The life stage: Reproductive / Early MT; Late MT / Menopause: Early postmenopause < 8yrs / Late postmenopause >8yrs
- Type of menopause: Natural / POI / Early menopause / Surgical menopause
- Asymptomatic women: with no menopausal symptoms /healthy/ healthy with risk factors for disease/ women with latent disease/ women with comorbidities.
- Symptomatic women: with menopausal symptoms /healthy/ healthy with risk factors for disease/ women with latent disease/ women with comorbidities
- Weight status: underweight/normal weight/overweight/obese

The diagnosis will state all five parameters. For example, Early MT, natural, asymptomatic, overweight, healthy

MANAGEMENT

In practice, the first consultation, as in antenatal care, requires detailed contact to capture all aspects of a woman's health. Planning individualised long-term management becomes straightforward.¹⁹ Management would depend on symptoms, co-morbidities, lifestyle, socio-economic status and acceptance. In an asymptomatic woman, disease prevention is emphasised.²⁶

The woman's general and menopause-related problems are documented, and screening for diseases is performed. The health status of an individual, based on the results of the tools used for invasive breast cancer, CVD, and skeletal-muscular health, may be documented in a comprehensive chart for quick reference. Refer to Table 4. The information obtained from the MRS scale and the risk screening results defines the woman's health status, which forms the basis for classifying her into one of the two major groups. Refer to Tables 5 and 6.

Individualised Health Plan

Each woman needs a personalised health management plan for menopause. Planning is based on information from the history, clinical examination, risk assessment tools, and investigation results.²⁷ Refer to Tables 8 and 9.

Based on the symptom profile, women can generally be categorised as either symptomatic or asymptomatic.²⁸

Based on the health profile, they are further classified as low, moderate, or high risk to personalise care and treatment decisions.

The individualised management has to lay a heavy focus on presentation of symptoms -single or cluster of symptoms, co-morbidities and target interventions more effectively. The most effective strategies include hormonal, nonhormonal pharmacological, lifestyle, and dietary approaches. For management of GSM refer to chapter 10

Table 8: Management plan for women without menopausal symptoms

Woman's Profile	Category Risk for Disease	Management plan
< 10 yrs postmenopause, normal and overweight low risk for NCD/ breast cancer No co morbidities	Healthy - Low risk	Counsel on preventive health care Oral MHT for bone health

>10 yrs postmenopause, obese Women at moderate risk for NCD Well controlled co morbidities Moderate risk for breast cancer	Moderate risk	Counsel on preventive health care Treat the disease individualise Avoid oral MHT
>20 yrs postmenopause Congenital heart disease/Established CVD/VTE/Stroke/ Transient ischaemic attack/ myocardial infarction/High risk for breast cancer/breast ca survivor uncontrolled co-morbidities	High risk	Counsel on preventive health care/ Treat the disease Avoid oral MHT

Table 9: Management plan for women with menopausal symptoms (VMS/ Bone health)

Woman's Profile	Category Risk for Disease	Management plan
< 10 yrs postmenopause, normal and overweight low risk for NCD/breast cancer No co morbidities	Healthy - Low risk	Counsel on preventive health care MHT
>10 yrs postmenopause, obese Women at moderate risk for NCD Well controlled co morbidities Moderate risk for breast cancer	Moderate risk	Counsel on preventive health care Treat the disease individualise MHT
>20 yrs postmenopause Congenital heart disease/Established CVD/VTE/Stroke/ Transient ischaemic attack/ myocardial infarction/High risk for breast cancer/breast ca survivor uncontrolled co-morbidities	High risk	Counsel on preventive health care/ Treat the disease Avoid oral MHT

CONCLUSION

In all aspects, menopause offers healthcare providers an important opportunity to assess each woman's health, concerns, and need for further preventive measures. Clinical evaluation should address symptom burden, risk stratification for diseases, and preventive care opportunities to optimise long-term health outcomes.

RESEARCH AGENDA

Development of a risk assessment model for breast cancer in Indian women.

REFERENCES

- Menopause [Internet]. WHO; 2024 [cited 2026 Feb 2]. Available from: <https://www.who.int/news-room/fact-sheets/detail/menopause>
- Lee WK, Ooi NZM, Goh SL. Clinical Practice Guidelines on the Management of Menopause in Malaysia 2022: A review from a primary care perspective. Malays Fam Physician Off J Acad Fam Physicians Malays. 2025 July 22;20:50. doi: 10.51866/cpg.910.
- Lumsden MA, Davies M, Sarri G, for the Guideline Development Group for Menopause: Diagnosis and Management (NICE Clinical Guideline No. 23). Diagnosis and Management of Menopause: The National Institute of Health and Care Excellence (NICE) Guideline. JAMA Intern Med. 2016 Aug 1;176(8):1205–6. doi: 10.1001/jamainternmed.2016.2761.
- Faubion SS, Enders F, Hedges MS, Chaudhry R, Kling JM, Shufelt CL, et al. Impact of Menopause Symptoms on Women in the Workplace. Mayo Clin Proc. 2023 June;98(6):833–45. doi: 10.1016/j.mayocp.2023.02.025.
- Meeta M, Digumarti L, Agarwal N, Vaze N, Shah R, Malik S. Clinical Practice Guidelines on Menopause: *An Executive Summary and Recommendations: Indian Menopause Society 2019–2020. J -Life Health. 2020;11(2):55–95. doi: 10.4103/jmh.JMH_137_20.
- Lakshmi RM, Kusumalatha K, Shraddha S. Analysis of 200 perimenopausal women: A Prospective Study. In: 12th National Indian Menopause Society Meeting, Rajkot. 2007.
- Bipasa S. First Time Detection of Medical Disorders in Forty-Plus Women in Health Camps. In: 15th National Indian Menopause Society Meeting, Chennai. 2010.

8. Santhakumar K, Nivedita Bharati K, Jaishree Gajraj A, Samundeswari V. Routine Investigations in Women 40 Years and Above. In: 15th National Indian Menopause Society Meeting, Chennai, Souvenir. 2010.
9. Hina K, Manju T, Mehendale SS, Wagh GN. Midlife management clinic for screening of metabolic disorders and osteoporosis in women aged above 35 yrs. 17th National Indian Menopause Society. Faridabad Souvenir. 2012;45.
10. Heinemann K, Ruebig A, Potthoff P, Schneider HPG, Strelow F, Heinemann LAJ, et al. The Menopause Rating Scale (MRS) scale: a methodological review. *Health Qual Life Outcomes*. 2004 Sept 2;2:45. doi: 10.1186/1477-7525-2-45.
11. Hauser GA, Huber IC, Keller PJ, Lauritzen C, Schneider HP. [Evaluation of climacteric symptoms (Menopause Rating Scale)]. *Zentralbl Gynakol*. 1994;116(1):16–23.
12. Schneider HP, Heinemann LA, Rosemeier HP, Potthoff P, Behre HM. The Menopause Rating Scale (MRS): reliability of scores of menopausal complaints. *Climacteric J Int Menopause Soc*. 2000 Mar;3(1):59–64. doi: 10.3109/13697130009167600.
13. Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, et al. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000;26(2):191–208. doi: 10.1080/009262300278597.
14. Bastien CH, Vallières A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med*. 2001 July;2(4):297–307. doi: 10.1016/s1389-9457(00)00065-4.
15. Kroenke K, Spitzer RL, Williams JBW, Löwe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics*. 2009;50(6):613–21. doi: 10.1176/appi.psy.50.6.613.
16. Roalf DR, Moore TM, Wolk DA, Arnold SE, Mechanic-Hamilton D, Rick J, et al. Defining and validating a short form Montreal Cognitive Assessment (s-MoCA) for use in neurodegenerative disease. *J Neurol Neurosurg Psychiatry*. 2016;87(12):1303–10.
17. Portman DJ, Gass MLS, Vulvovaginal Atrophy Terminology Consensus Conference Panel. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Menopause*. 2014 Oct;21(10):1063–8. doi: 10.1097/GME.0000000000000329.
18. Munro MG, Critchley HOD, Broder MS, Fraser IS, FIGO Working Group on Menstrual Disorders. FIGO classification system (PALM-COEIN) for causes of abnormal uterine bleeding in nonpregnant women of reproductive age. *Int J Gynaecol Obstet Off Organ Int Fed Gynaecol Obstet*. 2011 Apr;113(1):3–13. doi: 10.1016/j.ijgo.2010.11.011.
19. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the Stages of Reproductive Aging Workshop + 10: addressing the unfinished agenda of staging reproductive aging. *Menopause N Y N*. 2012 Apr;19(4):387–95. doi: 10.1097/gme.0b013e31824d8f40.
20. Hilditch JR, Lewis J, Peter A, van Maris B, Ross A, Franssen E, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas*. 1996 July;24(3):161–75. doi: 10.1016/s0378-5122(96)82006-8.
21. Utian WH, Janata JW, Kingsberg SA, Schluchter M, Hamilton JC. The Utian Quality of Life (UQOL) Scale: development and validation of an instrument to quantify quality of life through and beyond menopause. *Menopause*. 2002;9(6):402–10. doi: 10.1097/00042192-200211000-00005.
22. Coronado PJ, Borrego RS, Palacios S, Ruiz MA, Rejas J. Structural validity of a 16-item abridged version of the Cervantes Health-Related Quality of Life scale for menopause: the Cervantes Short-Form Scale. *Menopause*. 2015 Mar;22(3):325–36. doi: 10.1097/GME.0000000000000321.
23. Unni J. Third consensus meeting of Indian Menopause Society (2008): A summary. *J -Life Health*. 2010;1(1):43–7. doi: 10.4103/0976-7800.66987.
24. Kim HJ, Sohn IS. Early Menopause and Heart Disease: A Crosstalk With Cardiometabolic Syndrome. *CardioMetabolic Syndr J*. 2024 Sept;4(2):49–56. doi: 10.51789/cmsj.2024.4.e8.
25. Ray KM, Joe BN, Freimanis RI, Sickles EA, Hendrick RE. Screening Mammography in Women 40-49 Years Old: Current Evidence. *AJR Am J Roentgenol*. 2018 Feb;210(2):264–70. doi: 10.2214/AJR.17.18707.
26. Meeta M, Harinarayan CV, Marwah R, Sahay R, Kalra S, Babhulkar S. Clinical Practice Guidelines on Postmenopausal Osteoporosis: *An Executive Summary and Recommendations – Update 2019–2020. *J -Life Health*. 2020;11(2):96–112. doi: 10.4103/jmh.JMH_143_20.
27. Birkhauser M, Barlow D, Notalovitz M, Rees M, editors. *Health Plan for the Adult Woman: Management Handbook*. First. London: CRC Press; 2005. 280 p. doi: 10.3109/9780203490099.
28. Notalovitz M. Individualizing Hormone Therapy: Principles and Practice [Internet]. Medscape. [cited 2026 Feb 2]. Available from: <https://www.medscape.org/viewarticle/412853>

DECLINING FERTILITY

Keywords: Causes, management options, ethics

05

INTRODUCTION

Infertility is a social issue, and the consequences may be devastating to the couple. The World Health Organisation (WHO) defines infertility as a disease of the male or female reproductive system characterised by the failure to achieve a pregnancy after 12 months or more of regular unprotected sexual intercourse.¹ In 2023, the American Society for Reproductive Medicine (ASRM) expanded its definition of infertility to encompass a broader range of individuals.² Infertility is now recognised as a disease, condition, or status characterised by one or more of the following:

- *The inability to achieve a successful pregnancy based on a patient's medical, sexual, and reproductive history, age, physical findings, diagnostic testing, or other relevant clinical factors.*
- *The need for medical intervention, such as the use of donor gametes or embryos, to achieve a successful pregnancy.*
- *The inability to achieve a successful pregnancy due to the lack of appropriate gametes, reproductive anatomy, or exposure to sperm.*

This inclusive definition acknowledges that individuals, regardless of relationship status, sexual orientation, or gender identity, may face challenges in achieving pregnancy and may require medical assistance. Primary infertility is when a couple has never had a child. Secondary infertility is the failure to conceive following a previous pregnancy.

GENERAL PROTOCOLS FOR INVESTIGATIONS

The timing for offering investigations in an infertile couple is based on the duration of unsuccessful attempts to conceive, the age of the female partner, and known or suspected risk factors.³ Refer to Table 1 for general protocols to initiate investigations for infertility.

DEMOGRAPHIC TRANSITIONS

Almost all developed countries are currently experiencing a demographic transition, albeit at varying paces and stages, and the past two decades have witnessed a substantial global decline in fertility rates.⁴ India is similarly undergoing a demographic transition characterised by declining fertility and mortality, reflecting ongoing social and economic development. The country is presently in late Stage 3 and transitioning into Stage 4 of the demographic transition model, a phase marked by rapid fertility decline, the gradual emergence of an ageing population, and pronounced regional heterogeneity in the pace of transition. India's total fertility rate has declined from approximately 6.0 in the 1950s to a projected 1.29 by 2050, indicating a shift from high fertility to sub-replacement fertility and an emerging phase of population stabilisation.⁴

CAUSES OF DECLINING FERTILITY

The causes of primary and secondary infertility affect both males and females and vary widely by socioeconomic status and region. Refer to Table 2. According to the WHO multicentric studies of infertility in India, 40% of women and 73% of men had no demonstrable cause of infertility. Tubal factor was the most common cause of infertility among women (nearly 30%), followed by anovulation (22%). In India, approximately 15–20% of married couples in their fertile age group suffer from infertility, and it is on the increase because of a changing lifestyle. A decline in fertility is quite apparent today.

Table 1 General Protocols to Initiate Investigations

CRITERIA	TIMING FOR INVESTIGATIONS
Couples < 35 years old	After 12 months of regular, unprotected intercourse without conception ³
Women ≥35 years old	After 6 months of trying ³
Women ≥40 years old	Consider immediate evaluation and referral ³
Start earlier if risk factors present	
FEMALE RISK FACTORS 3	
- Irregular or absent menstrual cycles	Suggests ovulatory dysfunction
- Known or suspected uterine/tubal pelvic disease	Includes conditions like endometriosis, pelvic inflammatory disease
- History of recurrent miscarriage	
- Previous abdominal or pelvic surgery	
- Endocrine issues	Thyroid dysfunction, hyperprolactinemia
MALE RISK FACTORS 3	
- Testicular trauma, varicocele, mumps orchitis, chemotherapy/radiation	
- Previous genital surgery	
- Known or suspected sexual dysfunction	
- Prior paternity issues or abnormal semen parameters	

Table 2: Major causes of decreasing fertility

Urbanization, Pollution Chemical exposure, Stress, Competitive work environment, Fast-paced lifestyles ⁵
Late settlement in life, More women opting to work Increased incidence of diabetes and pelvic inflammatory diseases, etc. Social changes and demographic transitions ⁶
Late marriage, increasing divorce rates and favorable labor force conditions, Knowledge of contraception and dominance of sterilization, Obesity epidemic ⁷
Increased abortion rates for male child, Role of religion, Environment Female education and empowerment, Increasing female age

Table 3: Causes for declining fertility in men

Smoking and tobacco chewing ⁸ , Reproductive tract infections, Exposure to xenoestrogens, Varicoceles, Heat exposure to scrotum, Tight underwear
Moderate use of social drugs Stress Obesity ⁹ , Endocrine disruptors

In infertility treatment and results, the age of the female partner remains the single most determining factor. Refer to Table 4. Refer to Table 5 for causes of infertility

Table 4: Impact of age on fertility

Age Group	Female Fertility	Male Fertility	Notes / Risks
<30	Peak fertility	Normal sperm quality	Highest natural conception rates
30–34	Mild decline begins	Slight decline	Still good outcomes with natural or assisted conception
35–37	Noticeable decline in egg quality and quantity	Slight drop in motility	Fertility evaluation recommended after 6 months
38–40	Marked fertility drop	Increased sperm DNA fragmentation	Higher miscarriage & chromosomal risks
41–45	Very low natural fertility	Declining testosterone, reduced sperm count	In Vitro Fertilisation (IVF) success rates <15%; increased congenital risk
>45 (Women)	Natural conception rare	Further sperm quality decline	Assisted Reproductive Technology (ART) often required; low success
>50 (Men)	-	Higher risk of autism, schizophrenia in offspring	Advanced paternal age risk considerations

Table 5: Causes Of Primary and Secondary Infertility and its Impact on Fertility

Cause / Factor	Prevalenc (India & World)	Impact on fertility	Mechanism / notes
Age (maternal & paternal)^{2,10,11}	India: substantial proportion of delayed parenthood; female fertility decline after ~35; paternal age effects also reported	Lower egg/sperm quality, ↑ miscarriage, aneuploidy	Maternal meiotic failure → aneuploid embryos; paternal age → sperm DNA fragmentation
Female literacy / education¹²	India: literacy associated with lower completed fertility (NFHS data)	Lower total fertility (social/economic drivers)	Education → delayed childbearing, career choices, contraceptive access
Sex ratio at birth (proxy for gender bias)	NFHS-5 SRB ≈ 929/1000 (improvement from NFHS-4)	Not a direct infertility cause but indicates sex-selection pressures & gender bias	Social drivers (son preference) — policy relevance
Smoking (incl. vaping)⁸	India males: ~10–20%; global variable	↓ sperm count/motility, ↑ miscarriage risk, ↓ AR success	Nicotine/toxicants → oxidative stress, sperm DNA damage; some effects reversible after cessation
Smokeless tobacco (chewing)^{6,1}	India: common (varies by region)	↓ sperm motility/count; linked with male subfertility	Local toxic exposures, oxidative stress; documented in Indian cohorts
Obesity⁷	India: rising (15–25% males); global higher	↓ conception rates; poor ART outcomes; PCOS association in women	Hormonal dysregulation (insulin, androgens), anovulation, impaired sperm parameters

PCOS⁵	India: pooled prevalence estimates vary (≈8–20% by criteria)	Leading cause of anovulatory infertility	Hyperandrogenism, insulin resistance → anovulation
Endocrine disruptors / xenoestrogens	Environmental exposure significant; prevalence hard to quantify	Hormonal disruption → ovarian/sperm function, ↑ PCOS/endometriosis associations	Endocrine-Disrupting Chemicals (EDCs) mimic/block hormones; epigenetic effects reported
Alcohol¹⁴	India moderate rates; global variable	Heavy use → impaired sperm, possible ↑ time to conception and miscarriage risk	Dose-dependent; oxidative stress and hormonal disruption
Rising temperature / heat & radiation^{15,16}	Environmental occupational heat exposures increasing	↓ sperm count, motility; possible oocyte effects	Elevated scrotal/ovarian temperature; oxidative stress; climate change relevance
Stress / mental health¹⁷	High prevalence (India & world)	Hormonal disturbances, menstrual irregularities, variable sperm effects	Cortisol/ Hypothalamic-Pituitary-Gonadal (HPG) axis effects; stress increases oxidative stress
Oxidative stress¹⁶	Common (varied %) in infertile cohorts	Sperm/Oocyte DNA damage → lower fertilization, ↑ miscarriage	Reactive oxygen species (ROS) → DNA fragmentation; antioxidant deficit implicated
STIs (Chlamydia, Gonorrhoea etc.)¹⁸	High, variable; major in LMICs	Tubal factor infertility (women), epididymal damage (men)	Ascending infection → (Pelvic Inflammatory Disease) PID → tubal scarring/occlusion
Genital tuberculosis (FGTB) — India¹⁹	In infertility clinics in India: variable, sometimes high (reports up to 3–26% depending on setting)	Tubal blockage, endometrial damage → high infertility rates	Often subclinical; diagnostic challenge; major LMIC contributor
Endometriosis	Global: common (est. ~5–15% of women of reproductive age); high among infertile women	Anatomical distortion, inflammation → reduced fertility	Adhesions, poor oocyte quality, implantation impairment
Varicocele²⁰	Reported in 5–10% of infertile men	↓ sperm production/motility	Venous reflux → ↑ scrotal temperature → oxidative stress

MANAGEMENT

Preventive Measures

- Lifestyle modification²¹ such as exercise, diet, healthy Body mass index (BMI), avoiding smoking, alcohol, caffeine, and recreational drugs
- Early treatment of diabetes, thyroid disease, safe sex and prompt Sexually Transmitted Infection (STI) care
- Avoid delaying parenthood; earlier planning with a family history of premature menopause suitable for routine clinical practice.²²

Couple-Centred Care

- Individualised, problem-based management with shared decision-making
- Continuous psychological support and counselling
- Couple counselling is preferred over individual counselling
- Support groups for coping and motivation

Male Factor – Semen Analysis

- Repeat test after ~3 months if abnormal (full spermatogenesis cycle)
- Repeat sooner in azoospermia/severe oligozoospermia

Sexual Intercourse Guidance

- Regular intercourse every 2–3 days
- Avoid strict ovulation-timed intercourse (adds stress, limited benefit)

INVESTIGATION Refer to Table 6

Table 6: Investigations and indications^{22,23}

Category	Investigation	Purpose	Indication / Notes	Grade
Female – Clinical	Menstrual, sexual, medical/surgical history	Assess ovulation, intercourse, prior conditions	All patients	A
Female – Clinical	BMI & physical exam	Detect PCOS, thyroid disease, galactorrhea	All patients	A
Female – Basic Labs	Day 2–3 Follicle stimulating hormone (FSH) Leutinizing hormone (LH), E2	Ovarian reserve/function	All patients	A
	Thyroid stimulating hormone (TSH)	Thyroid dysfunction	All patients	A
	Prolactin	Hyperprolactinemia	Oligo/amenorrhea, galactorrhea	A
	Mid-luteal progesterone	Confirm ovulation	Regular cycles	B
	CBC, glucose, insulin, lipids	PCOS/metabolic screen	Overweight/PCOS	B
	Vit D, B12, Ferritin	General optimization	Optional	C
Female – Imaging/ Procedures	Transvaginal USG	Uterus, follicles, AFC, fibroids, PCOS	First-line	A

	Hysterosalpingogram (HSG) Sonohystero-graphy	Tubal patency, uterine shape Endometrial cavity	After 12 months infertility Abnormal HSG/suspected pathology	A
Female – Advanced	AMH, AFC	Ovarian reserve	>35 yrs, IVF candidates	A
	Hysteroscopy	Uterine cavity (polyps, adhesions)	Suspected lesions	B
	Laparoscopy + chromopertubationhormone	Endometriosis, adhesions, tubal disease	Unexplained infertility/pelvic pain	B
	Endometrial biopsy	Endometritis, luteal defect	Recurrent failure/ miscarriage	B
	Karyotype	Chromosomal abnormalities	Recurrent miscarriage, IVF failure	B
	Thrombophilia screen	Clotting disorders	Recurrent miscarriage	C
	TORCH screen	Infections	Selective	C
	Vaginal/cervical swabs	STIs	PID, abnormal discharge	B
	Pap smear/human papillomavirus (HPV)	Cervical pathology	Routine preventive	C
Male – Clinical	History, physical exam	Detect varicocele, infection, anomalies	All patients	A
	Sexual function assessment	Erectile/ejaculatory disorders	All patients	A
Male – Basic Labs	Semen analysis	Primary fertility test	Repeat ≥2 time	A
	Urinalysis	Infection	Abnormal semen	B
	Scrotal ultrasound	Varicocele, testicular lesions	Abnormal exam	B
	Scrotal ultrasound	Varicocele, testicular lesions	Abnormal exam	B
Male – Advanced	Hormonal profile (FSH, LH, T, E2, Prolactin)	Endocrine causes	Abnormal semen/ sexual dysfunction	B
	Karyotype	Chromosomal issues (e.g., Klinefelter)	Azoospermia, severe oligospermia	B
	Y-chromosome microdeletion	Spermatogenesis defects	Non-obstructive azoospermia	B
	CFTR mutation	Congenital absence of vas deferens	Obstructive azoospermia	B
	Sperm DNA fragmentation	Assess sperm integrity	IVF failure, miscarriage	C

	Anti-sperm antibody tests (MAR/IBT)	Immunologic infertility	Suspected immune cause	C
	Testicular biopsy	Differentiate obstructive vs. non-obstructive azoospermia	Sperm retrieval consideration	B
	Post-ejaculatory urine	Retrograde ejaculation	Low semen volume/ no sperm	C

INFERTILITY MANAGEMENT

Weight & Lifestyle

- Normal BMI restoration:
 - Lean women → weight gain may restore ovulation.
 - Obese women → obesity linked with ↓ Anti-Müllerian Hormone (AMH), ↓ implantation, ↓ pregnancy, ↓ live births.
 - *Lifestyle modifications*: regular exercise, balanced diet, avoiding caffeine, alcohol, smoking, and recreational drugs.

Infectious & Male Factor Management

- *STDs (especially chlamydia)* → cause epididymitis, obstruction; treat both partners simultaneously.
- *Male infertility options*:
 - Lifestyle and medical therapy → marginal improvement in semen quality.
 - Endocrine therapy → for hypothalamic-pituitary failure.
 - Surgery → for obstructive azoospermia, varicocele repair.
 - Antibiotics → for leukocytospermia.
 - ART pathways:
 - Intrauterine Insemination (IUI)/IVF for mild-moderate oligozoospermia.
 - ICSI for severe oligo/astheno/teratozoospermia, azoospermia (retrieved sperm).
 - Donor insemination for azoospermia, HIV, and genetic risk.

Female Factor Management

- *Ovulatory dysfunction*
 - Weight restoration → spontaneous ovulation return.
 - Pulsatile Gonadotropin-releasing hormone (GnRH) → stimulates FSH/LH release.
- *Tubal factor*:
 - Proximal block → selective salpingography, tubal catheterisation, or hysteroscopic cannulation.
- *Ovarian failure (post-chemo/radiotherapy)*:
 - Oocyte cryopreservation (limited success).
 - Embryo cryopreservation (more reliable).
 - Oocyte donation + IVF.

Repeated IVF failures: consider oocyte donation.

Donor Gametes & ART

- Oocyte donation indicated in:
 - Premature ovarian failure, gonadal dysgenesis, bilateral oophorectomy, ovarian failure post-therapy, repeated IVF failures.

- Donor insemination indicated in:
 - Obstructive/non-obstructive azoospermia.
 - Severe male factor infertility where ICSI not desired.
 - Infectious disease risk (HIV).
 - Severe rhesus isoimmunization.
 - Prevention of genetic disease transmission.

Complications of ART

- Risks:
 - Ovarian hyperstimulation syndrome (rare but potentially fatal).
 - Trauma, infection, ectopic pregnancy.
 - Multiple pregnancy risk.
 - Possible ovarian cancer association (under study).
- ICSI-specific: ↑ risk of nonlethal sex chromosome abnormalities.

Ethics, Religion & Legal Concerns

- Ethics:
 - Informed consent, donor anonymity, and legal rights of donors.
 - Debates: commercialisation of gametes, late-age parenthood, embryo freezing.
- Religion:
 - Objections to embryo freezing, surrogacy, destruction of embryos.
- Cryopreservation: sperm & embryos permitted (up to 10 years).

Surrogacy

- Partial surrogacy: insemination of the surrogate with partner/donor sperm.
- Full surrogacy: IVF embryo transfer to a surrogate.
- Issues: must consider the rights of the child, the surrogate, and the couple.
- Counseling: essential for all parties.

Preimplantation Genetic Diagnosis (PGD)

- Use: screen embryos for genetic disorders or sex before transfer.
- Ethical issues:
 - Discarding embryos.
 - Use for non-medical traits (e.g., sex selection).
 - Only affected embryos available → patient requests transfer → ethical dilemma.

RECOMMENDATIONS

Infertility is a growing public health issue, affecting nearly 1 in 6 adults globally. Beyond the clinical dimension, it carries profound psychological, social, and economic impacts, often compounded by stigma and gendered blame. In India, the Assisted Reproductive Technology (Regulation) Act, 2021²⁴ and the Surrogacy (Regulation) Act, 2021²⁵ provide an important legal framework for ART services and surrogacy practices. However, gaps remain in terms of equitable access, financial support, inclusivity (LGBTQ+, single parents), and comprehensive psychosocial support.

International guidance from WHO²², ASRM²⁶, National Institute for Health and Care Excellence (NICE)²⁷, and European Society of Human Reproduction and Embryology (ESHRE)²³ underscores that infertility must be treated as a medical condition, with services integrated into universal health coverage, supported by registries, transparent regulation, ethical oversight, and mental health support. To ensure humane, patient-centred, and evidence-based care, India needs to align its regulatory framework with global best practices while strengthening implementation, affordability, and inclusivity.

KEY GOVERNMENT POLICIES AND REGULATIONS (INDIA)

Assisted Reproductive Technology (Regulation) Act, 2021²⁴

- Establishes National and State ART Boards for oversight.
- Mandates a National ART Registry of clinics and banks.
- Requires written informed consent from all parties.
- It imposes a strict prohibition on sex selection.
- Introduces pre-implantation genetic testing (PGT) to detect abnormalities.
- Sets severe penalties for violations, including gamete trafficking and embryo sale.

Surrogacy (Regulation) Act, 2021²⁵

- Allows only altruistic surrogacy; bans commercial surrogacy.
- Eligibility: Surrogate must be a close relative with at least one biological child.
- Requires mandatory insurance coverage for surrogates.
- Penalties: imprisonment up to 10 years for violations like exploitation or embryo sale.

Programme Best Practices under Acts

- Mandatory counselling services in ART clinics.²⁶
- Insurance coverage for oocyte donors and surrogate mothers.
- Enforcement of ethical practices: ban on sex selection, no gamete/embryo sale. Regular audits and inspections of ART clinics and banks.

INTEGRATED POLICY & PROGRAM RECOMMENDATIONS

Awareness, Prevention, and Stigma Reduction

- Nationwide campaigns to normalise infertility as a medical issue, reduce stigma, and encourage early diagnosis.
- Youth fertility awareness programs in schools and colleges focus on healthy lifestyles, STIs, and reproductive health.²⁷
- Male infertility education campaigns to counter gendered blame

Equitable Access to Fertility Treatments

- Ensure universal healthcare coverage²⁸ includes ART (IVF, IUI, donation, surrogacy)
- Define the minimum number of funded ART cycles to prevent inequities (postcode lottery).
- Use telemedicine and mobile clinics to expand access in rural/remote areas

Financial Support and Subsidies

- Mandate insurance coverage for infertility treatments.
- Provide tax benefits, grants, or subsidies to lower-income families.
- Introduce targeted funding programs for onco-fertility and fertility preservation.

Regulation, Ethical Oversight, and Transparency

- Strengthen implementation of the ART & Surrogacy Acts with strict audits and enforcement.
- Establish a comprehensive ART Registry²⁹ with annual public reporting on outcomes, safety, and equity.
- Develop patient decision aids: clear, lay-friendly data on success rates, risks, and costs.
- Reassess restrictive surrogacy eligibility criteria to balance protection with access

Research and Development

- Fund national research into male infertility, environmental exposures, unexplained infertility, and long-term ART outcomes.³⁰
- Incentivize public-private innovation partnerships for ART technology.
- Align national research priorities with the WHO and ESHRE research agendas

Mental Health and Psychosocial Support

- Make counselling and psychological services mandatory and funded at all fertility clinics.
- Establish peer support groups and online communities to reduce isolation.

Protection for Donors and Surrogates

- Mandate comprehensive insurance and independent counselling for donors and surrogates.
- Maintain a protected registry of donors to balance safety, privacy, and the rights of future children.

International Collaboration

- Engage in global infertility conferences and knowledge-sharing initiatives.
- Adopt WHO/ESHRE standards for clinical practice, ethics, and safety.
- 89 Develop cross-border reproductive care regulations to prevent exploitation.

RECOMMENDATIONS FOR COUPLES FACING INFERTILITY

Seek Early Diagnosis and Professional Help

- If pregnancy has not occurred after 12 months of regular unprotected intercourse (or 6 months if the woman is ≥ 35 years), seek specialist care.
- Both partners should be evaluated to identify potential male and female factors.
- Steps:
 - Consult a reproductive endocrinologist/fertility specialist.
 - Comprehensive testing: semen analysis (men), ovulation tracking, ovarian reserve testing, ultrasound, and screening for conditions like PCOS, endometriosis, or tubal blockages.
- Why: Early intervention improves treatment outcomes and prevents delayed care.

Maintain a Healthy Lifestyle

- Fertility is closely linked to overall health for both men and women.
- Steps:
 - Diet & Nutrition: Eat a balanced diet rich in fruits, vegetables, lean proteins, and whole grains; women should take folic acid supplements.
 - Exercise: Engage in moderate exercise; avoid over-exertion (especially women) and extreme heat (especially for men).
 - Avoid Toxins: Stop smoking, reduce alcohol, avoid recreational drugs, and limit exposure to pesticides or environmental pollutants.
 - Stress Management: Use yoga, meditation, or counselling to reduce stress, which can impact hormonal balance.
- Why: Strong evidence supports lifestyle changes as low-cost, high-impact interventions that improve natural fertility and ART outcomes.

Understand and Track the Fertility Window

- Learning about menstrual cycles helps maximise chances of conception.
- Steps:
 - Track ovulation using ovulation predictor kits (OPKs), basal body temperature (BBT), or fertility apps.
 - Aim for intercourse every 2–3 days during the fertile window (5 days before and 1 day after ovulation).
- Why: Strong evidence shows that timing intercourse with ovulation significantly increases conception chances.

Explore Fertility Treatments When Needed

- If natural conception doesn't occur, consider medical treatment options.
- Steps:
 - Medications: Ovulation induction drugs (e.g., clomiphene, letrozole).

- Intrauterine Insemination (IUI): Sperm are placed directly in the uterus during ovulation.
- In Vitro Fertilisation (IVF): Eggs are fertilised outside the body, and the embryo is transferred to the uterus.
- Donor Gametes or Surrogacy: If the function of eggs, sperm, or the uterus is impaired.
- *Why:* Treatments like IVF are well established with clear evidence of benefit, though costs and access vary.

Consider Fertility Preservation

- Fertility may decline with age or medical treatments.
- Steps:
 - Egg or sperm freezing for individuals delaying parenthood.
 - Embryo freezing during IVF for later use.
 - Onco-fertility: Preserve gametes before chemotherapy/radiation.
- *Why:* Evidence supports fertility preservation for medical indications; elective use is increasingly common, but cost and availability are limiting factors.³¹

Consider Complementary/Alternative Therapies (with caution)

Some couples explore non-traditional therapies for added support.

- Options:
 - Acupuncture: May improve blood flow and help relaxation, though evidence is mixed.
 - Herbal supplements can affect hormones and should only be taken under medical supervision.
- *Why:* Evidence is inconsistent; use only as supportive measures, not replacements for evidence-based medicine.

Seek Psychological and Emotional Support

- Infertility can cause stress, depression, anxiety, grief, and relationship strain.
- Steps:
 - Couples counselling for relationship support.
 - Individual therapy with mental health professionals trained in infertility.
 - Support groups (online or in-person) for peer connections.
- *Why:* Strong evidence and guideline consensus show that mental health support improves coping and quality of life.

Communicate Openly and Support Each Other

- Infertility challenges can strain relationships.
- Steps:
 - Practice open, non-blaming communication.
 - Celebrate small milestones (e.g., successful ovulation tracking).
 - Develop coping strategies together.
- *Why:* Emotional resilience improves adherence to treatment and reduces relationship breakdown.

Know When to Consider Adoption or Other Family-Building Options

- If medical treatments are unsuccessful or unsuitable, alternatives exist.
- Steps:
 - Research adoption and fostering pathways early.
 - Consider surrogacy where legal and ethically permitted.
- *Why:* Adoption and fostering offer fulfilling paths to parenthood; evidence supports their role in improving family outcomes when ART fails.

Stay Informed and Take Control of the Journey

- Empowerment helps couples make better decisions.

- Steps:
 - Learn about available treatments, risks, costs, and success rates.
 - Participate actively in medical consultations and decision-making. 92
 - Keep track of your records, tests, and treatment progress.

Why: Strong evidence that patient education improves adherence, satisfaction, and outcomes.

SYNOPSIS

- Early diagnosis and timely testing (Grade A): Improves reproductive outcomes and prevents unnecessary delays in care.
- Healthy lifestyle optimisation (Grade A): Strong evidence supports improved natural fertility and assisted reproductive technology (ART) outcomes.
- Tracking the fertile window (Grade A): Maximises the likelihood of natural conception.
- Stepwise fertility treatments (Grade A): Based on well-established, evidence-based clinical interventions.
- Fertility preservation (Grade B): Strongly supported for medical indications; elective use is context and resource-dependent.
- Alternative and complementary therapies (Grade C): Limited evidence; should be used only as adjuncts to standard care.
- Psychological and emotional support (Grade A): Enhances coping, reduces emotional distress, and improves overall well-being.
- Open communication between partners (Grade B): Reduces relational strain and improves treatment adherence.
- Adoption and surrogacy (Grade B): Important family-building options when ART is unsuccessful or not feasible.
- Staying informed and actively engaged in care (Grade A): Patient empowerment improves decision-making and satisfaction.

RESEARCH AGENDA

Effectiveness of preconceptional counselling in maternal and fetal outcomes in infertile women

REFERENCES

1. Infertility. World Health Organization. 2026. <https://www.who.int/news-room/fact-sheets/detail/infertility>. Accessed on 12/11/2025
2. The ASRM's New Infertility Definition and Its Impact on Care - Medical Electronic Systems. 2023. <https://mes-global.com/blog/the-asrms-new-infertility-definition-and-its-impact-on-care/> Accessed on 12/11/2025
3. CDC. Infertility: Frequently Asked Questions. Reproductive Health. 2025. <https://www.cdc.gov/reproductive-health/infertility-faq/index.html> Accessed on 12/11/2025
4. UNdata | record view | Total fertility rate (live births per woman) [Internet]. 2026. Available from: <https://data.un.org/Data.aspx?q=india&d=PopDiv&f=variableID%3A54%3BcrID%3A356> Accessed on 12/11/2025
5. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod. 1992 Nov;7(10):1342–6. doi: 10.1093/oxfordjournals.humrep.a137570. Accessed on 12/11/2025
6. Gaur DS, Talekar MS, Pathak VP. Alcohol intake and cigarette smoking: impact of two major lifestyle factors on male fertility. Indian J Pathol Microbiol. 2010;53(1):35–40. doi: 10.4103/0377-4929.59180. Accessed on 12/11/2025
7. Hammoud AO, Wilde N, Gibson M, Parks A, Carrell DT, Meikle AW. Male obesity and alteration in sperm parameters. Fertil Steril. 2008 Dec;90(6):2222–5. doi: 10.1016/j.fertnstert.2007.10.011. Accessed on 12/11/2025
8. James KS, Subhramaniam SV. [] Decline in Fertility in Andhra Pradesh: A Re-examination of Conflicting Arguments [Internet]. 2026 [cited 2026 Feb 2]. Available from: <https://scienceon.kisti.re.kr/srch/selectPORSrchArticle.do?cn=NPAP05539083> Accessed on 12/11/2025
9. James KS. Fertility decline in Andhra Pradesh: a search for alternative hypotheses. Econ Polit Wkly [Internet]. 1999 [cited 2026 Feb 2]; Available from: <https://www.semanticscholar.org/paper/Fertility-decline-in-Andhra-Pradesh%3A-a-search-for-James/749da01bae98c7718ed5a13d45aeb7ecc4638fd7> Accessed on 12/11/2025
10. Menken J, Trussell J, Larsen U. Age and Infertility. Science. 1986 Sept 26;233(4771):1389–94. doi: 10.1126/science.3755843.

11. de La Rochebrochard E, Thonneau P. Paternal age and maternal age are risk factors for miscarriage; results of a multicentre European study. *Hum Reprod.* 2002;17(6):1649–56. doi: 10.1093/humrep/17.6.1649.
12. Robey B. How female literacy affects fertility: The case of India. *Asia-Pac Popul Policy.* 1990;(15):1–3. PMID: 12283968.
13. Said TM, Ranga G, Agarwal A. Relationship between semen quality and tobacco chewing in men undergoing infertility evaluation. *Fertil Steril.* 2005 Sep;84(3):649–53. doi: 10.1016/j.fertnstert.2005.03.052
14. Muthusami KR, Chinnaswamy P. Effect of chronic alcoholism on male fertility hormones and semen quality. *Fertil Steril.* 2005 Oct;84(4):919–24. doi: 10.1016/j.fertnstert.2005.04.025
15. Sheynkin Y, Jung M, Yoo P, Schulsinger D, Komaroff E. Increase in scrotal temperature in laptop computer users. *Hum Reprod.* 2005 Feb 1;20(2):452–5. doi: 10.1093/humrep/deh616.
16. Sinawat S. The environmental impact on male fertility. *J Med Assoc Thai Chotmaihet Thangphaet.* 2000;83(8):880–5.
17. Pellestor F, Andréo B, Arnal F, Humeau C, Demaille J. Maternal aging and chromosomal abnormalities: new data drawn from in vitro unfertilized human oocytes. *Hum Genet.* 2003 Feb;112(2):195–203. doi: 10.1007/s00439-002-0852-x.
18. Scholes D, Stergachis A, Heidrich FE, Andrilla H, Holmes KK, Stamm WE. Prevention of Pelvic Inflammatory Disease by Screening for Cervical Chlamydial Infection. *N Engl J Med.* 1996 May 23;334(21):1362–6. doi: 10.1056/NEJM199605233342103.
19. Tripathy SN, Tripathy SN. Infertility and pregnancy outcome in female genital tuberculosis. *Int J Gynecol Obstet.* 2002;76(2):159–63. doi: 10.1016/S0020-7292(01)00525-2.
20. Pook M, Tuschen-Caier B, Krause W. Is infertility a risk factor for impaired male fertility? *Hum Reprod.* 2004 Apr 1;19(4):954–9. doi: 10.1093/humrep/deh167.
21. Khanna J, van Look PF, Gri in PD, Activities UNF for P. Challenges in reproductive health research: biennial report: 1992–1993. In: *Challenges in reproductive health research: biennial report: 1992–1993* [Internet]. 1994 [cited 2026 Feb 4]. Available from: <https://pesquisa.bvsalud.org/portal/resource/pt/who-39653> Accessed on 12/11/2025
22. Infertility [Internet]. [cited 2026 Feb 4]. Available from: <https://www.who.int/news-room/fact-sheets/detail/infertility> Accessed on 12/11/2025
23. Romualdi D, Ata B, Bhattacharya S, Bosch E, Costello M, Gersak K, et al. Evidence-based guideline: unexplained infertility†. *Hum Reprod Oxf Engl.* 2023 Aug 21;38(10):1881–90. doi: 10.1093/humrep/dead150.
24. Ministry of Law and Justice, Government of India. The Assisted Reproductive Technology (Regulation) Act, 2021. No. 42 of 2021. 2021. <https://www.indiacode.nic.in/bitstream/123456789/17031/1/aA2021-42.pdf> Accessed on 12/11/2025
25. Ministry of Law and Justice, Government of India. The Surrogacy (Regulation) Act, 2021. No. 47 of 2021. 2021. <https://www.icmr.gov.in/the-assisted-reproductive-technology-regulation-act-2021-and-the-surrogacy-regulation-act-2021> Accessed on 12/11/2025
26. Definition of infertility: a committee opinion (2023) [Internet]. [cited 2026 Feb 4]. Available from: <https://www.asrm.org/practice-guidance/practice-committee-documents/definition-of-infertility/> Accessed on 12/11/2025
27. Overview | Fertility problems: assessment and treatment | Guidance | NICE [Internet]. NICE; 2013 [cited 2026 Feb 4]. Available from: <https://www.nice.org.uk/guidance/cg156> Accessed on 12/11/2025
28. United Nations Population Fund (UNFPA). State of World Population Report 2025 – Insights on infertility and reproductive choice. New York; UNFPA; 2025.; 2025.
29. Indian Council of Medical Research (ICMR). Guidelines for ART clinics in India. https://www.isarindia.net/ile/prilim_pages.pdf Accessed on 12/11/2025
30. Kaur G, Chawla R. Surrogacy in India: ethics versus incentive. *Int J Community Med Public Health* [Internet]. 2021 Jun. 25 [cited 2026 Feb. 17];8(7):3713–8. doi: 10.18203/2394-6040.ijcmph20212633. Accessed on 12/11/2025
31. HFEA: UK fertility regulator: Human Fertilisation & Embryology Authority (HFEA). Available from: <https://www.hfea.gov.uk/> Accessed on 12/11/2025

CONTRACEPTION AT PERIMENOPAUSE

Keywords: Contraception, perimenopause, progesterone-only pill (POP), obesity, venous thromboembolism.

06

INTRODUCTION

Perimenopause is a period which is a bridge in a woman's life from the reproductive to the postmenopause phase. It lasts 2-8 years prior to the final menstrual period and usually begins after age 40.¹ The phase is marked by variability in cycle lengths, with a persistent difference of ≥ 7 days between consecutive menstrual cycles, as defined by clinical criteria of the menopause transition (MT).¹ This early MT gradually transitions into a late transition, and the cycle length increases to 60 days. The term perimenopause covers the early MT, late MT, and the year after menopause. This period is marked by hormonal changes. There is a decrease in the number of primordial follicles. Serum inhibin levels and serum antimüllerian hormone levels decrease, and estradiol levels fall.² A fall in estradiol levels causes an increase in follicle-stimulating hormone (FSH) levels. Low estradiol levels are unable to induce a luteinising hormone (LH) peak, and thus anovulatory cycles occur. The cycles become prolonged and irregular.³ These hormonal changes also lead to increased visceral fat, higher cardiovascular risk, and adverse changes in glucose and lipid metabolism. The risk of coronary artery disease increases, and the incidence of hypertension also rises. Bone loss increases the risk of osteopenia, osteoporosis, and fractures.⁴

Fertility declines during perimenopause beyond 40 years and even lower after 45 years. The annual risk of pregnancy is 10% at 40-44 years, and only 2-3% at 45-49 years.⁵ Though the chances of pregnancy are less, acceptance of unintended pregnancy is low, and therefore, there is a higher percentage of abortions in this age group. Contraception is a must for this age group. As per National Health Service (NHS) data, 5 1,923 (15.87%) pregnancies were unintended in women more than 35 years of age. With a global increase in the number of women in this elderly age group, it is important to address this unmet need. Pregnancies in this age group are associated with a higher risk of abortions, foetal chromosomal anomalies, ectopic pregnancy, foetal growth restriction and prematurity.⁶ There are higher chances of medical problems being present in the mother, like obesity, diabetes mellitus, hypertension, preeclampsia, cardiovascular diseases, dyslipidaemias, which increase maternal morbidity and mortality.^{7,8} Apart from these problems, a woman in the fourth and fifth decades of life has uterine problems like abnormal uterine bleeding (AUB), polyps, endometrial hyperplasia, and fibroids, which affect the reproductive potential and affect contraceptive usage.⁹

At perimenopause, the contraceptive needs are different from those of younger women, but the need for efficacy and safety remains. The annual risk of deaths associated with using no method of contraception far exceeds that for use of any method of contraception among all age groups. Factors to consider when helping a client choose a particular contraceptive method include the user's characteristics and preferences, the baseline risk of disease, the adverse effects profile of different methods, and the costs and availability of these methods. Health benefits of contraceptive use are greatest for women in the 35-44 year old age group because the risk of mortality associated with pregnancy is greatest among this group. Pregnancies in elderly women are associated with high maternal and perinatal mortality and foetal malformations. This has long-lasting social and psychological effects that can be calamitous. Apart from fertility counselling and contraception, this interaction of the woman with the health care providers should evaluate her for metabolic problems, cancer screening, bone health and need for hormone therapy.

CONTRACEPTIVE METHODS

A woman needs to consider her age, health status, menstrual history, medical diseases, sexuality, risk of sexually transmitted infections, past contraception used, lifestyle, obstetric history and attitude toward abortion when choosing a contraceptive method during the perimenopausal years. When evaluating a patient, the health care provider should take a basic history, assess the comorbid conditions, medications she is taking and emerging perimenopausal problems which might benefit from contraception. A detailed systemic and local examination should be performed. Blood pressure measurement should be done. Basic parameters such as haemoglobin, fasting blood sugar, and lipid levels may be checked, especially if other cardiovascular risk factors are present. Screening for cancer and bone health should be conducted. The medical eligibility of contraceptives should be decided. Shared informed consent should be obtained.

SURGICAL STERILISATION

Surgical sterilisation is the most accepted method in India. It is a single procedure resulting in a highly effective, safe method with a case fatality rate of tubectomy being 1-2 /100,000 procedures. It appears to reduce the risk of ovarian cancer. The disadvantages are that it is a permanent method, and the major morbidity with tubal ligation is 1-2%. Vasectomy is even safer except for minor complications. Patients who are willing for a permanent method of contraception and who are at high risk for ovarian cancer may be counselled for bilateral salpingectomy at the time of permanent sterilisation with the understanding that there is no scope for reversal.¹⁰⁻¹² There may be a long-term result of a decrease in ovarian function after this procedure. So, this should be selected as per the needs of the woman, and counselling about the options of other long-term contraceptives should be done.¹³

FERTILITY AWARENESS-BASED METHODS

Fertility awareness-based methods are unreliable during the perimenopause because of unpredictable ovulation and cycles, as described above.

BARRIER METHODS

Condoms may be used by the couple. There is a higher failure rate with typical use. Proper usage should be explained. Whenever counselling for contraception, women should be counselled for sexually transmitted infections (STIs) and human immunodeficiency virus (HIV), and dual protection with barrier methods should be emphasised, irrespective of age.

HORMONAL CONTRACEPTION

All hormonal contraception methods are potentially suitable for medically eligible perimenopausal women, and none are contraindicated by age alone. However, with increasing age, associated medical complications occur, which affect the use and choice of contraceptives. These are diabetes, obesity, hypertension, cancers and dyslipidaemias.¹⁴ Failure rates need to be considered alongside affordability, locally available methods, and the couple's preferences. Refer to Table 1.

COMBINED HORMONAL CONTRACEPTIVES

Combined hormonal contraceptives (CHC) are called combined because they contain components that are estrogens and progestagens. Ethinyl estradiol (EE) is the most common estrogen used in hormonal contraception, but more natural forms, such as estradiol (E2) and estetrol (E4), are now also available in combination. The progesterone component may be natural progesterone, a 19-nor testosterone derivative, or spironolactone.¹⁵ The newer combinations contain low doses of estrogens and progesterones and have less androgenic activity. The delivery system of CHC may be oral, transdermal or vaginal.

Table 1: Percentage of users experiencing an unintended pregnancy within the first year of contraceptive use.

Method	Perfect Use (%)	Typical Use, USA (%)	Typical Use, International (%)
Vas surgery	0.1	0.15	
Fallopian tube surgery	0.5	0.5	
Levonorgestrel (LNG)-releasing IUDs	0.3	0.4	
Copper intrauterine device (Cu-IUD)	0.6	0.8	1
Oral contraceptive pills (combined or progestin-only)	0.3	7	6
Transdermal patches	0.3	7	
Contraceptive vaginal rings (CVRs)	0.3	7	
Implant	0.1	0.3	0.3

COMBINED ORAL CONTRACEPTIVES

Combined oral contraceptives (COC) are orally delivered CHC. They inhibit ovulation, stabilise the endometrium, and thicken cervical mucus.¹⁵

Absolute contraindications: Migraine with aura, current breast cancer, age more than 35 years with smoking > 15 cigarettes per day, history of deep venous thrombosis (DVT) or active DVT, uncontrolled hypertension, Body mass index (BMI) ≥ 35 are absolute contraindications. The medical eligibility criteria (MEC) by World Health Organization (WHO, 2025) is given in Table 2. These would be medical eligibility criteria (MEC) 4, indicating that the risks are unacceptable and the treatment cannot be used. MEC 3 also indicates that the risks outweigh the benefits and that it should not be used.

Table 2: Medical eligibility criterion: WHO 2025¹⁴

Condition	COC	CIC	POP	DMPA	LNG/ETG Implant	Cu-IUD	LNG-IUS
Age	$\geq 40:2$	$\geq 40:2$	$>45:1$	18–45: 1; $>45:2$	18–45: 1; $>45: 1$	$\geq 20: 1$	$\geq 20: 1$
Smoking —age < 35 years	2	2	1	1	1	1	1
Smoking — age ≥ 35 years; < 15 cigarettes/day	3	2	1	1	1	1	1
Smoking — age ≥ 35 years; ≥ 15 cigarettes/day	4	3	1	1	1	1	1
Obesity ≥ 30 kg/m ² BMI	2	2	1	1	1	1	1
Cardiovascular disease — multiple risk factors (older age, hypertension, dyslipidaemia, smoking, diabetes)	3/4	3/4	2	3	2	1	2
Adequately controlled hypertension	3	3	1	2	1	1	1
Elevated BP— systolic 140–159 or diastolic 90–99 mmHg	3	3	1	2	1	1	1
Elevated BP— systolic ≥ 160 or diastolic ≥ 100 mmHg	4	4	2	3	2	1	2
Vascular disease	4	4	2	3	2	1	2
History of DVT/PE	4	4	2	2	2	1	2
Acute DVT/PE	4	4	3	3	3	1	3
Family history of DVT (first-degree relatives)	2	2	1	1	1	1	1
Major surgery — with prolonged immobilisation	4	4	2	2	2	1	2
Major surgery — without prolonged immobilisation	2	2	1	1	1	1	1
Minor surgery without immobilisation	1	1	1	1	1	1	1
Diabetes mellitus — without vascular disease	2	2	2	2	2	1	2
Breast cancer — current	4	4	4	4	4	1	4
Breast cancer — past, no evidence of current disease for 5 years	3	3	3	3	3	1	3
Family history of breast cancer	1	1	1	1	1	1	1

COC = combined oral contraceptive; CIC = combined injectable contraceptive; POP = progestogen-only pill; DMPA = depot medroxyprogesterone acetate; LNG/ETG Implant = levonorgestrel/etonogestrel implant; Cu-IUD = copper intrauterine device; LNG-IUS = levonorgestrel intrauterine system.

Mode of delivery: The CHC are available as oral pills, weekly transdermal patches, vaginal rings to be used for three weeks and one week off and in some countries as monthly injections.

REGIMENS OF COMBINED ORAL CONTRACEPTIVES

- Cyclic regimens, composed of 21 active pills and 7 inactive pills/pill-free interval
- A shortened hormone-free interval (HFI) regimen, composed of 24–26 active pills and 2–4 inactive pills
- An extended regimen, which includes 84 active pills and 7 inactive pills
- A continuous regimen, which is made up of a 365-day active pill regimen

If the pill-free interval is shorter, the symptoms due to estrogen deficiency, such as vasomotor symptoms and menstrual migraines, are less. The lowest dose of the hormones is preferred when prescribing. Those containing 20 mcg of EE and levonorgestrel (LNG) 100 mcg have a reduced risk of venous thromboembolism (VTE), myocardial infarction (MI) and stroke, compared to those with higher doses. However, the lower dose pills have the disadvantage of a higher chance of breakthrough bleeding, which may cause discontinuation.^{16,17}

Failure rate: COCs are highly effective. Ideally, the failure rate is 0.3–0.5%. But the failure rate with typical use in reproductive-age women is higher, 7–9%. This difference is less in perimenopausal women because of decreased fertility in this age group.¹⁸

NON-CONTRACEPTIVE BENEFITS OF COMBINED ORAL CONTRACEPTIVES

- They decrease menstrual blood loss and are useful in treating heavy menstrual bleeding.
- Beneficial in dysmenorrhoea and premenstrual syndrome.
- Acne and hirsutism.
- Improve vasomotor symptoms.
- Improves bone health: decreases bone demineralisation and improves assimilation.
- Protects against ovarian, endometrial and colorectal cancer.
- Beneficial in pain due to endometriosis.

Vasomotor Symptoms

Hot flushes can appear in the premenopausal period and are effectively reduced by CHC use. For women who have already experienced the first symptoms of menopause during this period, COC therapy appears to be a more accepted option than postmenopausal hormone therapy (HT). Those who want contraception along with the COC find it beneficial.

Menstrual Migraines

The menstrual migraines associated with withdrawal of estrogens increase in perimenopause, with an increase in frequency as the cycle length shortens. The COC decrease these headaches. If the pill-free interval is shorter, the improvement in headache is better.¹⁹ The European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESCRH) recommend COCs for women with migraine who require contraception, experience estrogen-withdrawal headaches, or benefit from treatment with COCs for medical reasons.²⁰ Continuous pills or those with shortened hormone-free interval should be used. However, it is important to note that COCs are to be used only for menstrual migraines and not for migraine with aura, as both are individual risks for ischaemic stroke.

Bone Mineral Density

In the general population, the effect of CHC on bone mineral density (BMD) remains unclear. However, in women in perimenopause with a decrease in estrogen levels, it is beneficial for bone health. It decreases bone loss and improves bone density.

RISKS OF COMBINED ORAL CONTRACEPTIVES

Breast Cancer Risk

Breast cancer risk increases with age. It is 1 in 500 at age 35; it is 1 in 100 at age 40. Older COC preparations had higher doses of estrogens and had a higher risk of breast cancer with a relative risk (RR) of 1.24–1.30. The risk gradually declined after discontinuation and became nil after 10 years.²¹ As the risk of usage of contraceptive methods may change over time, the counselling should be personalised. Presently, with the low-dose pills, the risk of breast cancer is minimally high or negligible. A meta-analysis of 5 cohort studies reported a RR of 1.07 (RR 1.07, 95% confidence interval [CI] 1.03–1.11) for every 5 years of use and 1.14 (RR 1.14, 95% CI 1.05–1.23) for every 10 years of use.²² In the Danish study, the RR of developing breast cancer for recent and current users of any hormonal contraceptive (mostly utilising COCs) is 1.20 (95% CI 1.14–1.26, $p = 0.002$). This means one extra breast cancer per 7,690 women using a CHC for one year.²³ For BRCA1/BRCA2 carriers, who themselves have an increased baseline risk, there does not appear to be an additional risk associated with COC use.²⁴ The risk of cervical cancer increase after continuous use for more than five years in women with human papillomavirus, while data about the cumulative risk of breast cancer are conflicting.²⁵

Myocardial Infarction and Stroke

The absolute risk of thrombotic stroke (TS) and MI associated with COC is low in women of reproductive age but increases with age, EE dose and the presence of additional cardiovascular risk factors such as smoking, hypertension, diabetes, obesity and hyperlipidaemia.²⁶ With COC use, the overall risk of stroke increases by 2.2 times and that of MI by 2.3 times.²⁷ A significantly increased risk of thrombotic stroke (TS) in women who use CHCs was also shown in a Cochrane review including 24 observational studies. The dose of EE seems to influence the risk of TS and MI. The Cochrane review found that the relative risk of stroke and MI increased from 1.6 (95% CI 1.4–1.8) for 20 µg EE to 2.0 (95% CI 1.4–3.0) for 30–50 µg EE.²⁸ In recent years, COCs containing E2 rather than EE have been developed.²⁹ A quadriphasic preparation containing E2V+dienogest (DNG) and a monophasic preparation containing micronised E2 + norgestrel acetate (NOMAc) are being used. Both have a short HFI, which results in better menstrual cycle control.²⁹ The estrogenic component resembling the natural one might offer a safer alternative to pills containing EE and may be beneficial for women over 40. However, there is currently insufficient evidence to recommend a specific use for these preparations in women over 40.

Venous Thromboembolism

The incidence of venous thromboembolism (VTE) rises with age. Similarly, the complication of VTE seen in women using COCs is more common in elderly women. A Danish cohort study found that the incidence of VTE in COC users rose from 8.7 per 10,000 women-years for women aged 30–34 to 20.8 per 10,000 women-years for women aged 45–49.³⁰ Another large case-control study found that the incidence rate of VTE in COC users increased by nearly 3-fold between the ages of 20–29 and over 40.¹⁶ Women who have a higher risk of VTE due to other risk factors like obesity, smoking, family history of VTE, or cardiovascular disease should undergo a personal risk assessment and be advised appropriately. In a high-risk scenario, COC should be avoided. Refer to Table 2. VTE is also affected by estrogen dose and the type of progestin used. A study by Sugiura et al. shows that COCs containing 20 µg of EE have a lower risk of pulmonary embolism and serious arterial thromboembolic events than those containing 30–40 µg of EE. The progestin compound in the formulation also affects the risk of VTE. In addition, levonorgestrel-releasing (LNG) COC use is associated with a 50% lower risk of pulmonary embolism (PE) than third-generation COC use.³¹

The INAS SCORE study by Dinger et al. shows that COCs containing E2V and DNG are associated with cardiovascular risk similar to, or even lower than, that of COCs containing LNG or other progestins.³² A similar recent large post-marketing study that includes a total of 101,498 women, with 49,598 using E2-NOMAc and 51,900 using EE-LNG for up to 2 years, has found a risk of VTE and PE in NOMAc-E2, which is similar to or even lower than that of LNG-based COCs users [hazard ratio (HR) adjusted of 0.59 (95% CI 0.25–1.35) (adjusted for age, BMI, family history of VTE and current duration of use)].³³

To summarise, there is a small increase in the risk of cardiovascular disease, including VT, MI and ischaemic stroke, with COC, all of which increase with age. There is an increase in the relative risk of breast cancer by around 20–30 %, and a small increase in risk of cervical cancer in current and recent users, although the attributable risk is likely to be low in countries with universal human papillomavirus vaccination and cervical screening programmes.

COC containing levonorgestrel or norethisterone should be considered first-line COC preparations for women over 40 due to the potentially lower VTE risk compared to formulations containing other progestogens. COC with $\leq 30 \mu\text{g}$ ethinylestradiol should be considered first-line COC preparations for women over 40 due to the potentially lower risks of VTE, cardiovascular disease and stroke compared to formulations containing higher doses of estrogen. A CHC can reduce menstrual bleeding and pain, which may be particularly relevant for women over 40.³⁴⁻³⁶ The quadriphasic estradiol valerate/dienogest pill has been shown to significantly reduce blood loss compared to placebo and is licensed for managing idiopathic heavy menstrual bleeding in women seeking contraception, although there is insufficient evidence to suggest its superiority over other pill formulations.³⁷

VAGINAL RING

Vaginal ring is a combined hormonal contraceptive which can be used vaginally. It can be used in a three-week regimen, with one week off and a replacement, or continuously for four weeks, with immediate replacement upon change. This provides a continuous level of hormones and prevents estrogen withdrawal symptoms.^{38,39} It may cause less nausea and acne, but vaginal itching may be more. Effects on VTE, myocardial infarction and stroke as compared to COC cannot be assessed due to fewer events. A longer study duration will be needed. However, local estrogens provided by the ring improve lubrication and help vaginal changes, which may start at the perimenopausal age. Improvement in vaginal flora and vaginal atrophy was seen after three cycles of use.⁴⁰

TRANSDERMAL PATCH

A transdermal patch is also a CHC and can be applied weekly for three weeks, with one week off. However, few studies showed that patch users were less likely to experience bleeding and spotting than COC users but were more likely to report breast discomfort, nausea, vomiting and menstrual pain.⁴¹ With regard to cardiovascular risk, there seems to be an increased risk of VTE with the contraceptive patch compared to COCs in some studies. There is an absence of long-term safety data; this contraceptive is definitely not the first line for the perimenopausal woman.⁴²

PROGESTERONE-ONLY CONTRACEPTION

These are estrogen-free pills with a low dose of synthetic progestin. The dose of the progesterone component is even less than that in the combined pill. It has been safely used in women with contraindication to estrogen use. Women with obesity, migraines with aura, long-standing diabetes, hypertension, or a history of VTE can safely use POPs. Contraindications to POPs are a personal history of active or recent (within 5 years) breast cancer. They act by thickening cervical mucus, altering the endometrium, and, at times, preventing ovulation.⁴³

The preparations are LNG (30 μg), norethisterone (350 μg) and desogestrel (75 μg). The progestin with the greatest efficacy for ovulation inhibition is desogestrel, which is comparable to CHCs.⁴⁴ A progesterone-only pill containing 4 mg of drospirenone (DRSP) suppresses ovulation and thickens cervical mucus because of its higher doses of progestin. It remains effective even if the schedule is delayed because of its higher dose. Desogestrel and drospirenone pills have a 12-h and 24-h window, respectively. These newer POPs are thought to be more effective than the original pills, although all POPs are highly effective in perimenopausal women due to lower background fertility rates.⁴⁵

POP is not associated with increased risks of VTE, stroke or MI and has not been shown to affect BMD. Side effects of POP are headache, acne, breast tenderness, mood changes and weight gain. A woman 50 years and older using POP who presents with new onset bleeding abnormalities should be investigated to rule out pathologies such as cervical malignancy, endometrial hyperplasia and carcinoma. DRSP has strong anti-mineralocorticoid and antiandrogenic properties. This may lower blood pressure and reduce fluid retention. This will help reduce bloating and weight changes associated with POP. The antiandrogenic properties decrease the cardiovascular risk.⁴⁶ The association with breast cancer may be minimal and decreases after discontinuation.⁴⁷ The use of DRSP-only pills showed higher rates of scheduled bleedings and amenorrhoea rates and much lower rates of unscheduled bleeding/spotting in comparison to the continuous desogestrel regimen of POP.⁴⁸ The effect on bone mineral density has not been reported.

While there is no evidence that POP methods increase the risk of VTE, ischaemic heart disease or stroke, the evidence is not enough to exclude them, and thus a small degree of caution is warranted. Therefore, all POP methods are MEC category 2 if there is a risk of VTE and stroke or MI, and the category becomes MEC 3 if these conditions develop during their use. The pills should be stopped then.

BREAST CANCER

The use of any hormonal method, including all POP methods, in those with current breast cancer is MEC 4, regardless of hormone receptor status. For women with a past history of breast cancer and no evidence of current disease for 5 years, the eligibility criteria are MEC 3.

LONG-ACTING REVERSIBLE CONTRACEPTION

Long-acting reversible contraceptive (LARC) methods can be mechanical, based on inflammatory effects, or progestin-only, so they do not carry the risk of cardiovascular disease or stroke and do not have the other risks and contraindications associated with estrogen use or simple mechanical methods. This group includes progesterone-only methods such as levonorgestrel-releasing intrauterine systems (LNG-IUS) and etonogestrel-releasing subdermal implants. Copper intrauterine devices (Cu-IUDs) also provide long-term contraception and are considered LARC.

LEVONORGESTREL INTRAUTERINE SYSTEM

The LNG IUS is an intrauterine system that releases levonorgestrel in the uterine cavity. It is available in three different dosages (13.5 mg, 19.5 mg and 52 mg). All of them can be used for contraception throughout reproductive life. However, the 52 mg LNG confers endometrial protection if estrogen replacement therapy is prescribed.⁴⁹ If inserted after 45 years, the 52 mg LNG-IUS can be kept for seven years in women with menstrual disorders or till menopause. It can be removed between the ages of 50 and 55. It is an effective contraceptive measure with failure rates of 0.1% per year of typical use. It is effective in abnormal uterine bleeding.⁵⁰ LNG-IUS is a safe & effective option for women in perimenopause suffering from heavy bleeding caused by benign lesions in the uterus or dysmenorrhoea.⁴⁹

It is indicated for the treatment of endometrial hyperplasia and is effective in reversing the changes. It is recommended to be the first-line method.⁵¹ It showed endometrial atrophy after 24 months of LNG-IUS insertion in 100% of women with a documented typical endometrial hyperplasia.⁵⁰ The treatment with LNG-IUS 52 mg has also been used in fertility preservation cases of atypical hyperplasia (endometrial intraepithelial neoplasia), and it has shown significant regression (moderate-quality evidence) compared with no treatment.⁵¹ It can be used for uterine fibroids when the cavity is not distorted, allowing one to avoid hysterectomy in almost 89.5% of cases.⁵²

It has been reported that LNG-IUS may increase the risk of breast cancer; however, though the evidence is not clear, some have reported the risk, and others have not.²¹ Further research is needed to document whether breast cancer risk increases with LNG-IUS use or not. Currently, in women with active breast cancer, its use is category 4, which is unacceptable risk, and those with breast cancer in past, with 5 years of disease-free state, it is category 3.⁵³ In women who are at high risk for breast cancer, such as those with a family history of breast cancer or BRCA1/2 mutation carriers, it can be used.

LNG-IUS 52 mg can be used as hormone therapy for menopausal symptoms along with estrogens.⁵³⁻⁵⁵ Although the IUS has contraceptive efficacy for longer than 5 years, it may not provide adequate endometrial protection from hyperplasia after this time, particularly the IUS with the lower doses.⁵⁶ For endometrial suppression, extended use of the LNG-IUS is not recommended; it should be changed after 4-5 years for this indication.⁵⁶

A higher risk of depression has been reported with LNG-IUS. One should be cautious in women with a background of depression, and the possibility should be known, especially in perimenopause.⁵⁷ Uterine cavity distortion and a subseptate uterus are contraindications to LNG-IUS. However, with fibroids, there may be an increased risk of expulsion.^{14,58,59} NSAIDs and tranexamic acid offer simple and effective therapies and should be considered as first-line therapy options in LNG-IUS-related bleeding/spotting and pain.

IMPLANT

Etonogestrel-containing subdermal implants, Nexplanon or Implanon NXT, are the most commonly available. They contain 68 mg of etonogestrel and have to be inserted and removed by a trained provider. The efficacy is better than tubal ligation. It inhibits ovulation.⁶⁰ The effect of stopping ovarian activity of the implants is beneficial in endometriosis. The only side effect is unpredictable bleeding.⁶¹ Irregular pattern leads to removal in 15% of women who require it.⁶² One in five women complains of prolonged or infrequent bleeding.⁶³ There are no associations with bone density loss or metabolic effects,⁶⁴ and it is recommended in obese women as well.⁶⁵ There is no specific action on the endometrium, so it appears that implants do not protect against endometrial hyperplasia, and breast cancer is a contraindication to its use.⁶⁶

DEPOT MEDROXYPROGESTERONE ACETATE

This is an injectable contraceptive every three months containing 104-400 mg of medroxyprogesterone acetate. It causes a decrease in bone mineral density, and therefore it is not the contraceptive of first choice for women around 45 years, where bone density may be a concern.

MANAGEMENT OF IRREGULAR BLEEDING WITH HORMONAL LONG-ACTING REVERSIBLE CONTRACEPTION

Treatment may be repeated as needed. Options include ant fibrinolytic agents (tranexamic acid), 5 days nonsteroidal anti-inflammatory drugs (NSAIDs) (mefenamic acid and celecoxib), 5–7 days, hormonal treatment (20–30 µg EE COCs or estrogen), short course. SERMs (tamoxifen 10 mg twice daily, 7–10 days) may also be used. For irregular bleeding with implants, the CHC pill or mefenamic acid may be used for the short term. But for problematic bleeding and new onset bleeding after 50 years of age, investigations should be done, and other pathologies should be ruled out.⁶⁷⁻⁷²

COPPER INTRAUTERINE DEVICES

Intrauterine copper devices are nonhormonal methods. They act by creating an inflammatory reaction and macrophage infiltration in the endometrium, thus creating an unfavourable environment for implantation. The copper ions are spermicidal. They are long-acting and available for 3-10 years.⁷³ They can be used in perimenopausal women with contraindications to hormonal therapy.⁶⁶ Copper devices are also used as emergency contraception if inserted within 5 days of unprotected sexual intercourse.⁷⁴ Known or suspected pregnancy, pelvic inflammatory disease, anatomic uterine distortion, such as submucosal fibroid or uterine malformations, and unexplained vaginal bleeding are contraindications to its use. Cu-IUD should not be used in women with heavy menstrual bleeding or dysmenorrhoea, as both can be aggravated.²⁶ Uterine perforation (2/1000) and infections (<1/300) are rare side effects which may be discussed with the woman.⁶⁶

EMERGENCY CONTRACEPTIVE PILLS

Emergency contraceptive pills can be taken after unprotected coitus to prevent pregnancy in all women of reproductive age. A Cu-IUD is the most effective method of emergency contraception.⁷⁴ If needed, the Cu-IUD can be continued to be used as a contraceptive measure. The oral pill with Levonorgestrel 1.5 mg can be used up to 72 hrs of coitus. It is convenient and is available over the counter without a prescription. LNG-IUS has also been recommended for insertion for emergency contraception.⁷⁵ Ulipristal 30 mg can also be used as an emergency contraception pill up to 120 hours after coitus. This delays and prevents ovulation.⁷⁶ The efficacy of both oral LNG and ulipristal may be less in overweight women.⁷⁷

CONTRACEPTION IN OBESE WOMEN

Comorbidities need to be considered when providing contraception in obese women. Obese women, as compared to those with a normal BMI, are at risk of VTE, hypertension, dyslipidaemias, type 2 diabetes, cardiovascular disease, stroke, endometrial cancer, and breast cancer.

CHC is a WHO MEC category 2, meaning the benefit outweighs the harm. However, obese women who use COC are more likely to experience VTE and a small increased risk of MI and stroke than obese women not using hormonal contraception. The absolute risk of VTE in healthy women of reproductive age is small. Limited evidence suggests that obese women who use COCs do not have a higher risk of acute MI or stroke than obese non-users.⁷⁸

It is important to note that in the United Kingdom, CHC use is the United Kingdom Medical Eligibility Criterion (UKMEC) 2 in women with BMI ≥ 30 -34 kg/m² and UKMEC 3 for women with BMI ≥ 35 kg/m². For women with a BMI of 35 kg/m² or greater, the potential risks associated with use of CHC generally outweigh the benefits, as per (UKMEC).⁷⁹ Obese women also do not gain weight with COC in any excess over the normal or overweight group. Evidence suggests that contraceptive effectiveness is maintained among obese CHC users; however, among women with very high BMI using COC, evidence is inconsistent.⁸⁰

POP and implant are in category MEC 1 and can be safely given. There is no need to increase the dose or change the implant early. Intrauterine contraception, both copper devices and LNG-IUS, are highly effective, and efficacy is not affected by body weight. It is a safe option for obese women with MEC 1. ECPs may be less effective in women with BMI ≥ 30 kg/m² than in those with BMI < 25 kg/m². Despite this, there are no safety concerns. Evidence: There is limited

evidence from 1 study that suggests obese women with BMI $\geq 30 \text{ kg/m}^2$ experience an increased risk of pregnancy after use of LNG compared with women with BMI $< 25 \text{ kg/m}^2$.^{79,81}

CONFIRMATION OF MENOPAUSE

Menopause is confirmed if there is amenorrhoea for one year beyond 40 years of age, and most will be menopausal till 55 years, as per the North American Menopause Society. It recommends continuing contraception until the mid-50s.⁸² However, the Faculty of Sexual and Reproductive Healthcare (FSRH) says menopause is confirmed if there is amenorrhoea for two years from 40-50 years of age and for one year beyond 50. Fertility ends in about 90 % of women aged 45–50 years, approaching 100 % by age 50, and is considered ended at 55 years of age.²⁶

WHEN TO STOP CONTRACEPTION

When using hormonal contraception, assessing menopausal status is more challenging. For women using progesterone-only methods, such as POP, implant, or LNG-IUS, FSH levels can be checked once; if they are more than 30 IU/L, the method can be continued for one more year and then stopped. If the level is less than 30 IU/L, the method is to be continued for another year, and FSH is to be checked again.^{83,84} These methods can also be stopped at the age of 55 years without any hormonal evaluation.⁸⁵

In perimenopausal women with DMPA, if FSH is suppressed, the levels generally return to normal before the next injection. FSH levels should be checked on the day of injection and again before the next injection, which is due around 13 weeks later. If both are more than 30 IU/L, then contraception can be stopped. FSH is more suppressed when CHC are used. They can switch to an alternative method at age 50 (progestin-only, Cu-IUD) and follow its specific recommendations. Another option for women aged 50 years and older is to stop their CHCs and use a non-hormonal method for a while. If they do not resume their menses after 6 weeks, they can check their FSH levels twice, 1–2 months apart; if the levels are more than 30 IU/l both times, the contraception can be stopped.⁸⁶ A second option is to check FSH levels twice at the end of the 7-day placebo week, 6–8 weeks apart. If the FSH level is more than 30 IU/l both times, contraception can be discontinued. Once a woman discontinues CHC, she may experience the onset of menopausal symptoms, including vasomotor symptoms, sleep disturbances, vaginal and urinary tract symptoms and changes in sexual function. At this time, postmenopausal HT may be considered on an individual basis.

SYNOPSIS

- Fertility declines after age 40, and declines more after 45. Unintended pregnancies in this age group call for more abortions and social problems.
- Contraception is a must for the perimenopausal age group.
- Pregnancy is associated with higher maternal and foetal complications.
- Low-dose COC containing levonorgestrel is preferred to decrease the risk of stroke, MI and DVT.
- Progesterone-only methods are safe where estrogens are contraindicated and can be used in a diabetic patient or with a history of DVT.
- LNG-IUS provides contraception and is beneficial for AUB and endometrial protection.
- Emergency contraception can be used by women of all reproductive ages.

RESEARCH AGENDA

Abnormal uterine bleeding patterns in women with implant use and their correlation with time of usage.

REFERENCES

1. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. *Climacteric*. 2012 Apr; 15(2): 105-14. <https://doi.org/10.3109/13697137.2011.650656>
2. Bacon JL. The Menopausal Transition. *Obstetrics and gynecology clinics of North America*. 2017 Jun; 44(2): 285-296. <https://doi.org/10.1016/j.ogc.2017.02.008>
3. Shaaban MM. The perimenopause and contraception. *Maturitas*. 1996 Mar; 23(2): 181-92. [https://doi.org/10.1016/0378-5122\(96\)83915-6](https://doi.org/10.1016/0378-5122(96)83915-6)
4. Neer RM. Bone loss across the menopausal transition. *Annals of the New York Academy of Sciences*. 2010 Apr; 1192: 66-71. <https://doi.org/10.1111/j.1749-6632.2009.05233.x>

5. Chandra A, Copen CE, Stephen EH. Infertility and impaired fecundity in the United States, 1982-2010: data from the National Survey of Family Growth. National health statistics reports. 2013 Aug 14; (67): 1-18. Available from: <https://pubmed.ncbi.nlm.nih.gov/24988820/>. Accessed on 7 July 2022.
6. Navot D, Bergh PA, Williams MA, Garrisi GJ, Guzman I, Sandler B, et al. Poor oocyte quality rather than implantation failure as a cause of age-related decline in female fertility. *Lancet*. 1991 Jun 8; 337(8754): 1375-7. [https://doi.org/10.1016/0140-6736\(91\)93060-m](https://doi.org/10.1016/0140-6736(91)93060-m)
7. Antinori S, Gholami GH, Versaci C, Cerusico F, Dani L, Antinori M, et al. Obstetric and prenatal outcome in menopausal women: a 12-year clinical study. *Reproductive biomedicine online*. 2003 Mar; 6(2): 257-61. [https://doi.org/10.1016/s1472-6483\(10\)61718-x](https://doi.org/10.1016/s1472-6483(10)61718-x)
8. Khalil A, Syngelaki A, Maiz N, Zinevich Y, Nicolaides KH. Maternal age and adverse pregnancy outcome: a cohort study. *Ultrasound in Obstetrics & Gynecology*. 2013 Dec; 42(6): 634-43. <https://doi.org/10.1002/uog.12494>
9. Di Bella ZI, Bianchi AM, Araujo FF, Sartori MG, Girao MJ. Contraception and family planning at the extreme of reproductive life - climacteric. *Revista da Associacao Medica Brasileira*. 2016 Sep-Oct; 62(5): 454-7. <https://doi.org/10.1590/1806-9282.62.05.454>
10. Indian Council of Medical Research. Collaborative Study on Sequelae of Tubal Sterilization. New Delhi: Indian Council of Medical Research; 1982. Available from: https://openlibrary.org/books/OL3006889M/Collaborative_study_on_sequelae_of_tubal_sterilization. Accessed on 10 October 2025.
11. Mor-Hadar D, Wilailak S, Berek J, McNally OM. FIGO position statement on opportunistic salpingectomy as an ovarian cancer prevention strategy. *International journal of gynaecology and obstetrics*. 2024 Dec; 167(3): 976-980. <https://doi.org/10.1002/ijgo.15884>
12. Siegler AM, Hulka J, Peretz A. Reversibility of female sterilization. *Fertility and Sterility*. 1985; 43: 499-510. [https://doi.org/10.1016/s0015-0282\(16\)48488-8](https://doi.org/10.1016/s0015-0282(16)48488-8)
13. Qin F, Du DF, Li XL. The Effect of Salpingectomy on Ovarian Reserve and Ovarian Function. *Obstetrical & gynecological survey*. 2016 Jun; 71(6): 369-76. <https://doi.org/10.1097/OGX.0000000000000323>
14. World Health Organization. Medical eligibility criteria for contraceptive use, sixth edition. World Health Organization; 2025. <https://doi.org/10.2471/b09597>
15. Rice C, Killick S, Hickling D, Coelingh Bennink H. Ovarian activity and vaginal bleeding patterns with a desogestrel-only preparation at three different doses. *Human reproduction*. 1996 Apr; 11(4): 737-40. <https://doi.org/10.1093/oxfordjournals.humrep.a019245>
16. Weill A, Dalichampt M, Raguideau F, Ricordeau P, Blotiere PO, Rudant J, et al. Low dose oestrogen combined oral contraception and risk of pulmonary embolism, stroke, and myocardial infarction in five million French women: cohort study. *BMJ*. 2016 May 10; 353: i2002. <https://doi.org/10.1136/bmj.i2002>
17. Gallo MF, Nanda K, Grimes DA, Schulz KF. Twenty micrograms vs. >20 µg estrogen oral contraceptives for contraception: systematic review of randomized controlled trials. *Contraception*. 2005; 71: 162-9. <https://doi.org/10.1016/j.contraception.2004.09.005>
18. Bitzer J. Overview of perimenopausal contraception. *Climacteric*. 2018; 22: 44-50. <https://doi.org/10.1080/13697137.2018.1540566>
19. Blümel JE, Castelo-Branco C, Binfá L, Aparicio R, Mamani L. A scheme of combined oral contraceptives for women more than 40 years old. *Menopause*. 2001 Jul-Aug; 8(4): 286-9. <https://doi.org/10.1097/00042192-200107000-00011>
20. Sacco S, Merki-Feld GS, Egidius KL, Bitzer J, Canonico M, Gantenbein AR, et al. Effect of exogenous estrogens and progestogens on the course of migraine during reproductive age: a consensus statement by the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESCRH). *The journal of headache and pain*. 2018 Aug 31; 19(1): 76. <https://doi.org/10.1186/s10194-018-0896-5>
21. Zhu H, Lei X, Feng J, Wang Y. Oral contraceptive use and risk of breast cancer: a meta-analysis of prospective cohort studies. *The European journal of contraception & reproductive health care*. 2012 Dec; 17(6): 402-14. <https://doi.org/10.3109/13625187.2012.715357>
22. Cibula D, Gompel A, Mueck AO, La Vecchia C, Hannaford PC, Skouby SO, et al. Hormonal contraception and risk of cancer. *Human Reproduction Update*. 2010; 16: 631-50. <https://doi.org/10.1093/humupd/dmq022>
23. Mørch LS, Skovlund CW, Hannaford PC, Iversen L, Fielding S, Lidegaard Ø. Contemporary Hormonal Contraception and the Risk of Breast Cancer. *The New England journal of medicine*. 2017 Dec 7; 377(23): 2228-2239. <https://doi.org/10.1056/NEJMoa1700732>
24. Moorman PG, Havrilesky LJ, Gierisch JM, Coeytaux RR, Lowery WJ, Peragallo Urrutia R et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. *Journal of clinical oncology*. 2013 Nov 20; 31(33): 4188-98. <https://doi.org/10.1200/JCO.2013.48.9021>
25. Mendoza N, Soto E, Sánchez-Borrego R. Do women aged over 40 need different counseling on combined hormonal contraception? *Maturitas*. 2016 May; 87: 79-83. <https://doi.org/10.1016/j.maturitas.2016.02.008>
26. Faculty of Sexual and Reproductive Healthcare. FSRH Clinical Guideline: Contraception for Women Aged over 40 Years. 2017 (Amended 2019). Available from: <https://www.fsrh.org/standards-and-guidance/documents/fsrh-guidancecontraception-for-women-aged-over-40-years-2017/>. Accessed on 7 July 2022.
27. Allen RH, Cwiak CA, Kaunitz AM. Contraception in women over 40 years of age. *CMAJ: Canadian Medical Association journal*. 2013 Apr 16; 185(7): 565-73. <https://doi.org/10.1503/cmaj.121280>
28. Roach REJ, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database of Systematic Reviews*. 2015; (8): Cd011054. <https://doi.org/10.1002/14651858.cd011054.pub2>
29. Grandi G, Napolitano A, Cagnacci A. Metabolic impact of combined hormonal contraceptives containing estradiol. *Expert opinion on drug metabolism & toxicology*. 2016 Jul; 12(7): 779-87. <https://doi.org/10.1080/17425255.2016.1190832>
30. Lidegaard Ø, Nielsen LH, Skovlund CW, Skjeldestad FE, Lokkegaard E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. *BMJ*. 2011; 343: d6423. <https://doi.org/10.1136/bmj.d6423>
31. Sugiura K, Kobayashi T, Ojima T. Risks of thromboembolism associated with hormonal contraceptives related to body mass index and aging in Japanese women. *Thrombosis research*. 2016 Jan; 137: 11-16. <https://doi.org/10.1016/j.thromres.2015.11.038>
32. Dinger J, M ner S, Heinemann K. Combined oral contraceptives containing dienogest and estradiol valerate may carry a lower risk of venous and arterial thromboembolism compared to conventional preparations: Results from the extended INAS-SCORE study. *Frontiers in Women's Health*. 2020; 5. <https://doi.org/10.15761/fwh.1000178>
33. Reed S, Koro C, DiBello J, Becker K, Bauerfeind A, Franke C, et al. Prospective controlled cohort study on the safety of a monophasic oral contraceptive containing norgestrel acetate (2.5mg) and 17 β-oestradiol (1.5mg) (PRO-E2 study): risk of venous and arterial thromboembolism. *The European journal of contraception & reproductive health care*. 2021 Dec; 26(6): 439-446. <https://doi.org/10.1080/13625187.2021.1987410>

34. Lidegaard J. Hormonal contraception, thrombosis and age. Expert opinion on drug safety. 2014 Oct; 13(10): 1353-60. <https://doi.org/10.1517/14740338.2014.950654>
35. Fitzpatrick D, Pirie K, Reeves G, Green J, Beral V. Combined and progestagen-only hormonal contraceptives and breast cancer risk: A UK nested case-control study and meta-analysis. PLOS Medicine. 2023; 20: e1004188. <https://doi.org/10.1371/journal.pmed.1004188>
36. Iversen L, Sivasubramanian S, Lee AJ, Fielding S, Hannaford PC. Lifetime cancer risk and combined oral contraceptives: the Royal College of General Practitioners' Oral Contraception Study. American journal of obstetrics and gynecology. 2017 Jun; 216(6): 580.e1-580.e9. <https://doi.org/10.1016/j.ajog.2017.02.002>
37. Jensen JT, Parke S, Mellinger U, Machlitt A, Fraser IS. Effective treatment of heavy menstrual bleeding with estradiol valerate and dienogest: a randomized controlled trial. Obstetrics and gynecology. 2011 Apr; 117(4): 777-787. <https://doi.org/10.1097/AOG.0b013e3182118ac3>
38. Timmer CJ, Mulders TM. Pharmacokinetics of etonogestrel and ethinylestradiol released from a combined contraceptive vaginal ring. Clinical pharmacokinetics. 2000 Sep; 39(3): 233-42. <https://doi.org/10.2165/00003088-200039030-00005>
39. Algorta J, Diaz M, de Benito R, Lefebvre M, Sicard E, Furtado M, et al. Pharmacokinetic bioequivalence, safety and acceptability of Ornibel[®], a new polymer composition contraceptive vaginal ring (etonogestrel/ethinylestradiol 11.00/3.474 mg) compared with Nuvaring[®] (etonogestrel/ethinylestradiol 11.7/2.7 mg). The European journal of contraception & reproductive health care. 2017 Dec; 22(6): 429-438. <https://doi.org/10.1080/13625187.2017.1413179>
40. Fruzzetti F, Perini D, Fornaciari L, Russo M, Bucci F, Gadducci A. Discontinuation of modern hormonal contraceptives: an Italian survey. The European journal of contraception & reproductive health care. 2016 Dec; 21(6): 449-454. <https://doi.org/10.1080/13625187.2016.1234598>
41. Lopez LM, Grimes DA, Gallo MF, Stockton LL, Schulz KF. Skin patch and vaginal ring versus combined oral contraceptives for contraception. Cochrane Database of Systematic Reviews. 2013; (4): CD003552. <https://doi.org/10.1002/14651858.cd003552.pub4>
42. Cole JA, Norman H, Doherty M, Walker AM. Venous thromboembolism, myocardial infarction, and stroke among transdermal contraceptive system users. Obstetrics and gynecology. 2007 Feb; 109(2 Pt 1): 339-46. <https://doi.org/10.1097/01.AOG.0000250968.82370.04>
43. Tepper NK, Whiteman MK, Marchbanks PA, James AH, Curtis KM. Progestin-only contraception and thromboembolism: a systematic review. Contraception. 2016 Dec; 94(6): 678-700. <https://doi.org/10.1016/j.contraception.2016.04.014>
44. Endrikat J, Gerlinger C, Richard S, Rosenbaum P, Dusterberg B. Ovulation inhibition doses of progestins: a systematic review of the available literature and of marketed preparations worldwide. Contraception. 2011 Dec; 84(6): 549-57. <https://doi.org/10.1016/j.contraception.2011.04.009>
45. Korver T. A double-blind study comparing the contraceptive efficacy, acceptability and safety of two progestogen-only pills containing desogestrel 75 µg/day or levonorgestrel 30 µg/day: Collaborative Study Group on the Desogestrel-containing Progestogen-only Pill. The European Journal of Contraception & Reproductive Health Care. 1998; 3: 169-78. <https://doi.org/10.3109/13625189809167250>
46. Chiara Del Savio M, De Fata R, Facchinetti F, Grandi G. Drospirenone 4 mg-only pill (DOP) in 24+4 regimen: a new option for oral contraception. Expert review of clinical pharmacology. 2020 Jul; 13(7): 685-694. <https://doi.org/10.1080/17512433.2020.1783247>
47. Samson M, Porter N, Orekoya O, Hebert JR, Adams SA, Bennett CL, et al. Progestin and breast cancer risk: a systematic review. Breast cancer research and treatment. 2016 Jan; 155(1): 3-12. <https://doi.org/10.1007/s10549-015-3663-1>
48. Palacios S, Colli E, Regidor PA. A multicenter, double-blind, randomized trial on the bleeding profile of a drospirenone-only pill 4 mg over nine cycles in comparison with desogestrel 0.075 mg. Archives of gynecology and obstetrics. 2019 Dec; 300(6): 1805-1812. <https://doi.org/10.1007/s00404-019-05340-4>
49. Yoo HJ, Lee MA, Ko YB, Yang JB, Kang BH, Lee KH. The efficacy of the levonorgestrel-releasing intrauterine system in perimenopausal women with menorrhagia or dysmenorrhea. Archives of gynecology and obstetrics. 2012 Jan; 285(1): 161-6. <https://doi.org/10.1007/s00404-011-1937-3>
50. Joo JK, Shin JH, Lee JR, Kim MR. Levonorgestrel-Releasing Intrauterine System Use in Perimenopausal Women. Journal of menopausal medicine. 2021 Aug; 27(2): 49-57. <https://doi.org/10.6118/jmm.20038>
51. Mittermeier T, Farrant C, Wise MR. Levonorgestrel-releasing intrauterine system for endometrial hyperplasia. Cochrane Database of Systematic Reviews. 2020 Sep 6; 9(9): CD012658. <https://doi.org/10.1002/14651858.CD012658.pub2>
52. Machado RB, de Souza IM, Beltrame A, Bernardes CR, Morimoto MS, Santana N. The levonorgestrel-releasing intrauterine system: its effect on the number of hysterectomies performed in perimenopausal women with uterine fibroids. Gynecological endocrinology. 2013 May; 29(5): 492-5. <https://doi.org/10.3109/09513590.2013.769517>
53. Varila E, Wahlstrom T, Rauramo I. A 5-year follow-up study on the use of a levonorgestrel intrauterine system in women receiving hormone replacement therapy. Fertility and sterility. 2001 Nov; 76(5): 969-73. [https://doi.org/10.1016/s0015-0282\(01\)02846-1](https://doi.org/10.1016/s0015-0282(01)02846-1)
54. Suvanto-Luukkonen E, Kauppila A. The levonorgestrel intrauterine system in menopausal hormone replacement therapy: five-year experience. Fertility and sterility. 1999 Jul; 72(1): 161-3. [https://doi.org/10.1016/s0015-0282\(99\)00162-4](https://doi.org/10.1016/s0015-0282(99)00162-4)
55. Depypere H, Inki P. The levonorgestrel-releasing intrauterine system for endometrial protection during estrogen replacement therapy: a clinical review. Climacteric. 2015; 18(4): 470-82. <https://doi.org/10.3109/13697137.2014.991302>
56. Grandi G, Farulla A, Sileo FG, Facchinetti F. Levonorgestrel-releasing intra-uterine systems as female contraceptives. Expert opinion on pharmacotherapy. 2018 May; 19(7): 677-686. <https://doi.org/10.1080/14656566.2018.1462337>
57. Skovlund CW, Mørch LS, Kessing LV, Lidegaard J. Association of Hormonal Contraception With Depression. JAMA psychiatry. 2016 Nov 1; 73(11): 1154-1162. <https://doi.org/10.1001/jamapsychiatry.2016.2387>
58. Curtis KM, Tepper NK, Jatlaoui TC, Berry-Bibee E, Horton LG, Zapata LB, et al. U.S. Medical Eligibility Criteria for Contraceptive Use, 2016. MMWR Recommendations and Reports. 2016; 65: 1-103. <https://doi.org/10.15585/mmwr.rr6503a1>
59. Youm J, Lee HJ, Kim SK, Kim H, Jee BC. Factors affecting the spontaneous expulsion of the levonorgestrel-releasing intrauterine system. International journal of gynaecology and obstetrics. 2014 Aug; 126(2): 165-9. <https://doi.org/10.1016/j.ijgo.2014.02.017>
60. Grandi G, Cagnacci A, Volpe A. Pharmacokinetic evaluation of desogestrel as a female contraceptive. Expert opinion on drug metabolism & toxicology. 2014 Jan; 10(1): 1-https://doi.org/10.1517/17425255.2013.844229
61. Mansour D, Korver T, Marintcheva-Petrova M, Fraser IS. The effects of Implanon on menstrual bleeding patterns. The European journal of contraception & reproductive health care. 2008 Jun; 13 Suppl 1: 13-28. <https://doi.org/10.1080/13625180801959931>
62. Casey PM, Long ME, Marnach ML, Bury JE. Bleeding related to etonogestrel subdermal implant in a US population. Contraception. 2011 May; 83(5): 426-30. <https://doi.org/10.1016/j.contraception.2010.09.01263>

63. Bateson D, McNamee K. Perimenopausal contraception: A practice-based approach. *Australian family physician*. 2017 Jun; 46(6): 372-377. Available from: <https://pubmed.ncbi.nlm.nih.gov/28609592/>. Accessed on 7 July 2022.
64. Lopez LM, Grimes DA, Schulz KF, Curtis KM. Steroidal contraceptives: effect on bone fractures in women. *Cochrane Database of Systematic Reviews*. 2006. <https://doi.org/10.1002/14651858.cd006033>
65. Xu H, Wade JA, Peipert JF, Zhao Q, Madden T, Secura GM. Contraceptive failure rates of etonogestrel subdermal implants in overweight and obese women. *Obstetrics and gynecology*. 2012 Jul; 120(1): 21-6. <https://doi.org/10.1097/AOG.0b013e318259565a>
66. Faculty of Sexual and Reproductive Healthcare. UK Medical Eligibility Criteria for Contraceptive Use (UKMEC). 2022. Available from: <https://www.fsrh.org/standards-and-guidance/uk-medical-eligibility-criteria-forcontraceptive-use-ukmec/>. Accessed on 7 July 2022.
67. Lukes AS, Kouides PA, Moore KA. Tranexamic Acid: A Novel Oral Formulation for the Treatment of Heavy Menstrual Bleeding. *Women's Health*. 2011; 7: 151-8. <https://doi.org/10.2217/whe.11.9>
68. Abdel-Aleem H, d'Arcangues C, Vogelsong KM, Gafield ML, Gülmezoglu AM. Treatment of vaginal bleeding irregularities induced by progestin only contraceptives. *The Cochrane database of systematic reviews*. 2013 Oct 21; 2013(10): CD003449. <https://doi.org/10.1002/14651858.CD003449.pub5>
69. Alvarez-Sanchez F, Brache V, Thevenin F, Cochon L, Faundes A. Hormonal treatment for bleeding irregularities in Norplant implant users. *American journal of obstetrics and gynecology*. 1996 Mar; 174(3): 919-22. [https://doi.org/10.1016/s0002-9378\(96\)70326-5](https://doi.org/10.1016/s0002-9378(96)70326-5)
70. Edelman AB, Kaneshiro B, Simmons KB, Hauschildt JL, Bond K, Boniface ER, et al. Treatment of Unfavorable Bleeding Patterns in Contraceptive Implant Users: A Randomized Controlled Trial. *Obstetrics and gynecology*. 2020 Aug; 136(2): 323-332. <https://doi.org/10.1097/AOG.000000000000389671>.
71. Simmons KB, Edelman AB, Fu R, Jensen JT. Tamoxifen for the treatment of breakthrough bleeding with the etonogestrel implant: a randomized controlled trial. *Contraception*. 2017; 95: 198-204. <https://doi.org/10.1016/j.contraception.2016.10.001>
72. Bahamondes L, Brache V, Meirik O, Ali M, Habib N, Landoulsi S. A 3-year multicentre randomized controlled trial of etonogestrel- and levonorgestrel-releasing contraceptive implants, with non-randomized matched copper-intrauterine device controls. *Human reproduction*. 2015 Nov; 30(11): 2527-38. <https://doi.org/10.1093/humrep/dev221>
73. Miller TA, Allen RH, Kaunitz AM, Cwiak CA. Contraception for midlife women: a review. *Menopause*. 2018 Jul; 25(7): 817-827. <https://doi.org/10.1097/GME.0000000000001073>
74. Cleland K, Zhu H, Goldstick N, Cheng L, Trussell J. The efficacy of intrauterine devices for emergency contraception: a systematic review of 35 years of experience. *Human reproduction*. 2012 Jul; 27(7): 1994-2000. <https://doi.org/10.1093/humrep/des140>
75. Turok DK, Gero A, Simmons RG, Kaiser JE, Stoddard GJ, Sexsmith CD, et al. Levonorgestrel vs. Copper Intrauterine Devices for Emergency Contraception. *New England Journal of Medicine*. 2021; 384: 35-44. <https://doi.org/10.1056/nejmoa2022141>
76. Glasier A. The rationale for use of Ulipristal Acetate as first line in emergency contraception: biological and clinical evidence. *Gynecological endocrinology*. 2014 Oct; 30(10): 688-90. <https://doi.org/10.3109/09513590.2014.950645>
77. Jatlaoui TC, Curtis KM. Safety and effectiveness data for emergency contraceptive pills among women with obesity: a systematic review. *Contraception*. 2016 Dec; 94(6): 605-611. <https://doi.org/10.1016/j.contraception.2016.05.002>
78. Horton LG, Simmons KB, Curtis KM. Combined hormonal contraceptive use among obese women and risk for cardiovascular events: A systematic review. *Contraception*. 2016 Dec; 94(6): 590-604. <https://doi.org/10.1016/j.contraception.2016.05.014>
79. Faculty of Sexual and Reproductive Healthcare. FSRH Guideline (April 2019) Overweight, Obesity and Contraception. *BMJ sexual & reproductive health*. 2019 Apr; 45(Suppl 2): 1-69. <https://doi.org/10.1136/bmjsexrh-2019-OOC>
80. Dragoman MV, Simmons KB, Paulen ME, Curtis KM. Combined hormonal contraceptive (CHC) use among obese women and contraceptive effectiveness: a systematic review. *Contraception*. 2017 Feb; 95(2): 117-129. <https://doi.org/10.1016/j.contraception.2016.10.010>
81. Glasier A, Cameron ST, Blithe D, Scherrer B, Mathe H, Levy D, et al. Can we identify women at risk of pregnancy despite using emergency contraception? Data from randomized trials of ulipristal acetate and levonorgestrel. *Contraception*. 2011 Oct; 84(4): 363-7. <https://doi.org/10.1016/j.contraception.2011.02.009>
82. North American Menopause Society. *Menopause Practice: A Clinician's Guide*. 6th Edition. 2022. Available from: <https://www.menopause.org/publications/professional-publications/menopausepractice-a-clinician's-guide>. Accessed on 7 July 2022.
83. Inal MM, Yildirim Y, Ertopcu K, Avci ME, Ozelmas I, Tinar S. Effect of the subdermal contraceptive etonogestrel implant (Implanon) on biochemical and hormonal parameters (three years follow-up). *The European journal of contraception & reproductive health care*. 2008 Sep; 13(3): 238-42. <https://doi.org/10.1080/13625180802075315>
84. Halmesmaki K, Hurskainen R, Tiitinen A, et al. A randomized controlled trial of hysterectomy or levonorgestrel-releasing intrauterine system in the treatment of menopause- effect on FSH levels and menopausal symptoms. *Human reproduction*. 2004; 19(2): 378-382. <https://doi.org/10.1093/humrep/deh055>
85. Baldwin MK, Jensen JT. Contraception during the perimenopause. *Maturitas*. 2013 Nov; 76(3): 235-42. <https://doi.org/10.1016/j.maturitas.2013.07.009>
86. Faculty of Family Planning and Reproductive Health Care Clinical Effectiveness Unit. FFRHC guidance (January 2005) contraception for women aged over 40 years. *The journal of family planning and reproductive health care*. 2005 Jan; 31(1): 51-63. <https://doi.org/10.1783/0000000052973086>

ABNORMAL UTERINE BLEEDING AT MENOPAUSE TRANSITION

Keywords: Causes, investigations and management

07

INTRODUCTION

Menopause transition (MT) is the hormonally dynamic phase preceding the final menstrual period (LMP) and marks the transition from reproductive to post-reproductive life. It is a well-defined stage characterised by progressive menstrual cycle variability (≥ 7 -day difference in cycle length in early MT and ≥ 60 days of amenorrhoea in late MT), fluctuating ovarian function, and the emergence of menopausal symptoms. Twelve months of amenorrhoea define menopause and mark the end of the MT.¹ Abnormal uterine bleeding (AUB) at MT is not uncommon and may be physiological, so physicians need to differentiate between physiological and pathological causes of AUB in this phase.²

ABNORMAL UTERINE BLEEDING

AUB is defined as bleeding from a non-pregnant uterus, with parameters such as volume, frequency, regularity and duration of bleeding abnormal.³ In one-third of women with AUB, irregularities in the menstrual cycle are common at menarche or at MT. In a study by Seltzer, of the 500 perimenopausal patients reviewed, menstrual flow alterations were characterised as follows: 62 women (12%) had sudden amenorrhoea, 347 (70%) had oligomenorrhoea and/or hypomenorrhoea, and 91 (18%) had menorrhagia, metrorrhagia, and/or hypermenorrhoea. This study highlights the high incidence of premalignant and malignant pathology among perimenopausal women presenting with bleeding patterns other than amenorrhoea or oligomenorrhoea/hypomenorrhoea. It underscores the need for thorough evaluation of women with menorrhagia, metrorrhagia, and/or hypermenorrhoea.⁴

Abnormal bleeding may present as heavier than usual bleeding (more than 80 ml), prolonged bleeding lasting more than 7 days, or intermenstrual or postcoital bleeding, which affects patients' quality of life.^{4,5} AUB is a common reason for women to consult their gynaecologist. Approximately 50% of women will experience menstrual abnormalities in their reproductive years, and more than 70% of office visits are among MT and postmenopausal women.⁶ The prevalence of AUB in India, as reported in single-centre studies, is between 17% and 20.5%. The authors of this prevalence study found that 46% of women aged 41-45 years and 26% of those aged 46-50 years suffer from AUB.^{7,8} AUB significantly affects quality of life, causing morbidity in women, such as severe anaemia and fatigue.⁹

The acronym PALM-COEIN (Polyp, Adenomyosis, Leiomyoma, Malignancy and hyperplasia, Coagulopathy, Ovulatory dysfunction, Endometrial, Iatrogenic and Not otherwise classified) was introduced in 2011 by the International Federation of Gynaecology and Obstetrics (FIGO) to provide a common system of nomenclature for uterine bleeding abnormalities in reproductive-aged women. The FIGO system classifies AUB as structural (polyp, adenomyosis, leiomyoma, malignancy/hyperplasia) and non-structural (coagulopathy, ovulatory dysfunction, endometrial, iatrogenic, not otherwise classified) aetiologies.^{10,11} AUB is further classified as acute or chronic. Acute AUB is an episode of excessive bleeding in a non-pregnant woman of reproductive age that requires immediate intervention to prevent further blood loss. Chronic AUB is abnormal in duration, volume, and/or frequency, and has been present for most of the last 6 months.¹² A differential diagnosis for abnormal bleeding is listed in Table 1. A Flowchart for evaluating and managing AUB at MT is provided in Chapter 60.

Women at MT may have ovulatory or anovulatory cycles, leading to menstrual irregularities, such as shortened cycles.¹³ This intermittent anovulation during MT causes recurrent bouts of ovulatory dysfunction (AUB-O). It is associated with physical complaints such as bloating, cramping, water retention, fatigue, decreased mental clarity, diminished concentration, vaginal dryness, hot flushes and night sweats. Anovulatory cycles usually present with spotting, but sporadically can have acute bouts of heavy bleeding.¹⁴ LOOP, defined as luteal - out- of - phase phenomenon, where folliculogenesis may begin during the luteal phase before Menses, causes shortened menstrual cycles.¹⁵ Refer to Chapter 37. The hormonal milieu is characterised by decreased inhibin levels, variable estradiol levels, and normal follicle-stimulating hormone (FSH) concentrations. Antral follicles release estradiol and inhibin. Ultrasound is commonly used to quantify the number of antral follicles, and estradiol and inhibin levels can also be measured. FSH levels are sometimes measured in MT, where elevated FSH indicates fewer antral follicles and diminished negative feedback.¹⁶ Menstrual cycles may be episodically ovulatory and predictable, followed by episodes of erratic menses. This is often frustrating for the patient and physician because the pattern of bleeding changes dramatically.

EVALUATION OF ABNORMAL UTERINE BLEEDING

History

AUB requires a systematic evaluation to determine the underlying cause, assess the severity of bleeding, and manage it appropriately. It is ideal to record not only the last episode of bleeding (length, character, duration, and amount of flow) but also the pattern of bleeding over the previous 6 months to 1 year. This helps establish whether the bleeding is abnormal or a variation of the normal MT pattern, and, further, whether the cause of AUB is ovulatory or anovulatory dysfunction, anatomic, or systemic disease. In a haemodynamically stable woman, a detailed history is obtained as below.

Menstrual history: age at menarche, last menstrual period, intermenstrual or post coital bleeding, and parameters of menstrual cycles are recorded as below -

- *Frequency:* normal (24 to 38 days), infrequent (>38 days), frequent (<24 days) or more than four episodes in 90 days
- *Regularity:* regular with a variation of +/- 2 to 7 days; irregular with a variation >20 days; or absent if there are no periods for more than 90 days
- *Volume:* normal (5 to 80 mL), light (<5 mL of blood loss), and heavy (>80 mL)
- *Duration:* normal (≤8 days), shortened (< 3 days) or prolonged (>8 days)

History also includes obstetric history including number of pregnancies and mode of delivery, fertility treatments, method of contraception used in relation to bleeding like intrauterine device (IUD), depot medroxyprogesterone acetate, use of current medications such as anticoagulants, antidepressants such as selective serotonin reuptake inhibitors and tricyclics, hormonal contraceptives, tamoxifen, antipsychotics first-generation and risperidone, corticosteroids, herbs such as ginseng and chasteberry, use of tobacco, alcohol or recreational drugs which may affect bleeding. A history of polycystic ovarian disease (PCOD), coagulation defects, family history of cancers and co-morbid conditions needs to be elucidated. Take care to exclude pregnancy and cancer.³ Screening tools such as the Menstrual Distress Questionnaire (MEDI-Q) help to evaluate the impact of heavy menstrual bleeding on daily quality of life.¹⁰ Iron deficiency anaemia may overlap with perimenopausal symptoms, such as fatigue, depression, impaired cognition, sleep disturbances and headaches. Women must also be evaluated for iron deficiency anaemia.¹⁷

Table 1: Possible causes of abnormal uterine bleeding in perimenopausal women

- | |
|---|
| <ul style="list-style-type: none"> • ANOVULATION (ABNORMAL UTERINE BLEEDING) • BENIGN REPRODUCTIVE TRACT CONDITIONS <ul style="list-style-type: none"> ➤ Pregnancy ➤ Leiomyomata or endocervical polyps ➤ Adenomyosis ➤ Endometritis ➤ Pelvic inflammatory disease ➤ Vaginal or cervical infection |
| <ul style="list-style-type: none"> • ENDOMETRIAL NEOPLASIA, Refer to Chapter 31 <ul style="list-style-type: none"> ➤ Endometrial hyperplasia (EH) without atypia ➤ EH with atypia ➤ Endometrial carcinoma |
| <ul style="list-style-type: none"> • SYSTEMIC DISEASES <ul style="list-style-type: none"> -Coagulation disorders (thrombocytopenia, von Willebrand's disease, leukaemia) ➤ Hypothyroidism ➤ Liver disease ➤ Hormone therapy ➤ Contraceptive devices or injections |

Source: Kaunitz AM. Gynecologic problems of the perimenopause: evaluation and treatment. Obstet Gynecol Clin North Am. 2002 Sep;29(3):455-73. doi:10.1016/s0889-8545(02)00010-4

Clinical Examination

In cases of acute AUB, initially assess vital signs for haemodynamic stability. A thorough general, physical and gynaecological examination must be performed, even if the woman is experiencing vaginal bleeding. The general examination includes checking vital signs, recording the body mass index, looking for signs of anaemia and thyroid dysfunction, and performing the breast and abdominal examinations.

A thorough gynecologic examination includes a systematic evaluation of the urogenital and anal area. It is important to visualise the cervix and exclude cervicitis, ectropion, sexually transmitted ulcerations and cervical polyps. The speculum should be rotated to fully visualise the vaginal fornices and to establish the absence of ulcerations or foreign bodies. An empty bladder facilitates bimanual evaluation of the adnexae, uterine contour, size, and the presence of uterine tenderness. Rectal examination is done if anorectal pathology is suspected.³

Tests for Evaluation of AUB

The evaluation of AUB includes laboratory studies, imaging, endometrial evaluation and biopsy.

Laboratory Tests

Laboratory studies are conducted based on the findings from history and physical examination. Pregnancy testing should always be performed in sexually active women, even in those who have had a tubal ligation.

- *Thyroid function tests* - mainly thyroid-stimulating hormone.
- *Hormonal tests* - prolactin, estrogen or androgen levels are reserved only for high suspicion of endocrine dysfunction.
- Complete blood count, ferritin levels and coagulation profile
- The other tests are the Pap smear, HPV and, if indicated, liver and renal function tests, which should be checked in women with signs or symptoms of systemic disease.⁵
- *Antimüllerian hormone (AMH)* may be used to predict menopause in a select group, mainly to offer and discuss treatment options. AMH levels have a positive predictive value for the onset of menopause within the next year, ranging from 51% at <48 years to 79% at 51 years of age.^{13,18,19} In the past, medical therapy was instituted for 3 months in hemodynamically stable patients; if this failed, further evaluation of the endometrium was undertaken. Today, with the easy availability of ultrasound, management is based on imaging the pelvic organs.

Transvaginal Ultrasound (TVS) & Trans Abdominal Ultrasound (TAS)

TVS and TAS are the first-line imaging modalities in women with AUB. They are very useful for diagnosing structural abnormalities such as polyps, fibroids, and adenomyosis, as well as for evaluating the endometrium.^{5,10,20}

TVS is used to assess uterine size, myometrial echotexture, the endomyometrial junction, endometrial thickness, adnexa, and Doppler studies. Women at MT with intermenstrual bleeding and prolonged heavy menstrual bleeding require further evaluation.²¹

It is difficult to define a cut-off endometrial thickness in women at MT, as endometrial stroma and glands vary due to persistent stimulation.^{22,23} In premenopausal women, endometrial thickness varies between the proliferative phase (4–8 mm) and the secretory phase (8–14 mm), and TVS should be scheduled between days 4 and 6 of the menstrual cycle, when the endometrium is the thinnest. TAS is preferred if the uterine size is greater than 12 gestational weeks.

Three-dimensional ultrasonography may be more accurate than two-dimensional sonohysterography in determining the size and depth of myometrial invasion of submucosal leiomyomas, which may help predict the success of hysteroscopic resection. However, there is insufficient evidence to recommend routine three-dimensional ultrasonography (USG) in the evaluation of AUB.¹³

Saline Infusion Sonography (SIS)

In SIS, 5–15 mL of saline is infused into the uterine cavity, leading to distention of the uterine cavity. This helps to evaluate the uterus for intracavitary lesions more accurately than TVS. The causes of endometrial thickness can be clearly differentiated with saline infusion. Three-dimensional SIS may be more accurate than two-dimensional SIS in determining the size and depth of myometrial invasion of submucosal leiomyomas, which may help predict the

success of hysteroscopic resection. SIS is comparable to hysteroscopy and has a sensitivity of 95% (95% CI, 93–97%) and specificity of 88% (95% CI, 85–91%) for diagnosing focal lesions.²⁴

If the endometrium is not clearly visualised on initial assessment by two-dimensional ultrasound, the SIS is not very useful in defining the endometrium.²⁰ SIS is usually performed in the first few days of the menstrual cycle, as it carries a 27% risk of false positives when performed in the latter half of the menstrual cycle.²⁴

The indications for SIS are given in Table 2.

Table 2: Indications for saline infusion ultrasound

- Abnormal bleeding in premenopausal or postmenopausal patients
- Evaluation of an endometrium that is thickened, irregular, immeasurable, or poorly defined by conventional TVS
- Irregular endometrial appearance by TVS in women using tamoxifen
- The need to differentiate between sessile and pedunculated masses of the endometrium
- Presurgical evaluation of intracavitary fibroids

TVS: Transvaginal ultrasound

Magnetic Resonance Imaging (MRI)

MRI is infrequently used in cases of AUB. It may be useful in fibroids and adenomyomas before planning for conservative surgery. MRI may be useful for evaluating uterine anomalies when the ultrasound results are ambiguous.^{5,10,20}

Endometrial Biopsy (EB)

Why do we need it before planning management?

Endometrial sampling is important before definitive management of AUB because it can diagnose endometrial cancer (EC) or premalignant disease and guide treatment. EC is among the most common female cancers globally, and GLOBOCAN 2022 estimates 17,420 new corpus uteri cancers and 6,845 deaths in India in 2022. India is ranked fifth in the world for new cases of EC in 2022 and third in the world for the number of deaths reported in 2022.²⁵

The risk of EC in women aged 20–34 years is 1.6%. In women aged 35–44 years, the rate increases to 6.2%.²⁶ Therefore, women in this age group who do not respond to medical therapy or who have prolonged periods of unopposed estrogen stimulation should be considered for endometrial assessment. Among women aged 40–50 years, the incidence of EC ranges from 13.6 to 24 cases per 100,000 women-years. Compared with women aged ≤44 years, those aged ≥45 years with EC are more likely to present with advanced-stage disease, have lower tumour differentiation, and experience poorer prognosis. Consequently, international guidelines recommend endometrial sampling as a first-line investigation in women aged ≥45 years presenting with abnormal uterine bleeding, irrespective of other risk factors.²⁷

Given the high prevalence of EH (25%) and carcinoma (4–6%) among Indian women and the high prevalence of metabolic risk factors such as obesity, polycystic ovarian syndrome, diabetes, and hypertension along with earlier onset of anovulatory bleeding and endometrial pathology, a lower age threshold for endometrial biopsy (≥40 years) may be justified in women presenting with AUB, especially in the presence of additional risk factors or failure of medical therapy. This approach aligns with risk-based evaluation principles and may facilitate earlier detection of premalignant and malignant endometrial disease in the Indian population. Hospital-based studies from India suggest that EB in women ≥40 years with AUB identifies a substantial burden of premalignant pathology, though the absolute yield of carcinoma is lower and heterogeneous. These findings support a risk-adapted biopsy strategy rather than reliance on age alone.^{28,29}

Endometrial pathology may diagnose EC or determine the likelihood of coexistent or future cancer. In a recent study, the cumulative 20-year progression rate among women is less than 5% for benign EH, but is 28% for atypical EH. The rate of progression to carcinoma is higher in women with atypical EH.³⁰ Endometrial sampling should also be performed in patients younger than 40 years with a history of unopposed estrogen exposure, such as obesity or PCOS, failed medical management, and persistent AUB.³¹ A literature review including 2572 patients reported that 37% of

women with a diagnosis of atypical endometrial hyperplasia on endometrial sampling were found to have endometrial carcinoma on subsequent biopsy or hysterectomy.³²

Methods of endometrial biopsy: There are three methods for endometrial sampling: office blind biopsy by Pipelle, Karman's cannula, dilation and curettage (D&C); (blind biopsy under general anaesthesia (G.A), and directed biopsy by hysteroscopy (in-office or under G.A).³³ Blind endometrial sampling techniques like the Pipelle, Karman's cannula, other aspirational devices, have an accuracy of 91-99 % in detecting EC in pre and postmenopausal women. A retrospective cross-sectional study of 1677 hysterectomy specimens revealed a post-test probability of EC or endometrial intraepithelial neoplasia. (EIN) In a negative endometrial sample, the rate was 0.74 %. This emphasises the importance of an adequate endometrial biopsy.³⁴ A 2025 review examined direct diagnostic algorithms for endometrial cancer screening and found that the Pipelle endometrial biopsy has a significant false-negative rate (10%-20%) and may fail to yield adequate diagnostic material in up to 30% of cases. D & C is a blind procedure performed under anaesthesia with a higher risk of complications.³⁵ A retrospective study comparing preoperative histology with hysterectomy specimens found a discrepancy of 38% and upgrades of 26% for Pipelle biopsy, and a discrepancy of 27% and upgrades of 23% for D&C in FIGO grades 1 and 2 adenocarcinoma of the uterus.³⁶

Despite this, in low-resource settings, Pipelle biopsy and D&C are acceptable alternatives to endometrial sampling.³⁷ A retrospective study of 895 women analysed the failure rates of Pipelle versus D&C. Neither technique provided an adequate endometrial sample. The failure rates were 60/339 (17.3%) versus 88/556 (15.8%) for the Pipelle and D&C groups, respectively. Although the rates were comparable between groups, D&C was slightly better.³⁸ Compared with D&C, Pipelle is less expensive, safer, more accurate, and performed in the office without anaesthesia.³⁹

Hysteroscopy : Hysteroscopy allows complete visualisation of the endometrial cavity and endocervix, and is helpful in diagnosing focal lesions that are missed with blind endometrial sampling. A magnified visual inspection helps in accurate diagnosis of atrophy, endometrial hyperplasia, polyps, fibroids, retained products of conception and endometrial cancer. Directed endometrial biopsies yield better histopathology specimens. Hysteroscopy's targeted biopsy has a 95% sensitivity for endometrial cancer and 90%–95% accuracy for polyps.⁴⁰ A meta-analysis of 1295 patients showed that hysteroscopic biopsy diagnostic failure rates for endometrial cancer and hyperplasia are 82% lower than those with blind sampling, whereas Pipelle's sensitivity for polyps remains low (12.5%).^{41,42} In-office hysteroscopy offers the advantage of targeted biopsy with the highest diagnostic accuracy.⁴³ The drawbacks are limited availability, delayed diagnosis, and associated pain in up to 65% of patients.³⁵

THERAPY FOR AUB

Factors that are considered to decide the treatment of AUB are the underlying cause, severity of bleeding, desire for fertility, co-morbidities, desire for contraception, efficacy of the treatment, its adverse effects, and the cost. Medical treatment should be considered as the first-line therapeutic option for AUB in the absence of pelvic pathology, endometrial hyperplasia and cancers. Correction of anaemia and thyroid dysfunction is done prior to instituting targeted medical therapy. Abnormal uterine bleeding due to anovulatory cycles is best treated medically; surgery is suggested when medical therapy fails or is contraindicated. Medical therapy with oral contraceptive pills or progesterone therapy is the mainstay for the treatment of anovulatory menstrual cycles. Patients with ovulatory AUB must be evaluated for structural intracavitary uterine pathology, since hormonal dysfunction is not the likely cause of bleeding. Patients with anatomic causes associated with abnormal bleeding can be treated surgically. Finally, management depends on the cause, the cost-benefit analysis of therapy and the patient's choice.³

Non-Hormonal Medical Therapy

Nonsteroidal Anti-Inflammatory Drugs: Nonsteroidal anti-inflammatory drugs (NSAIDs) reduce dysmenorrhoea rates and blood loss by 10-52%. Mefenamic acid 500 mg three times daily with food. Naproxen 500 mg initially, then repeat in 8 hours, then 250 to 500 mg twice daily. Ibuprofen, diclofenac, indomethacin and aspirin (ASA) alone have all been shown to be effective when taken during menses. Ibuprofen 600 mg every 6 hours or 800 mg every 8 hours.^{5,10,44} Significant differences in efficacy between different NSAIDs have not been demonstrated. Therapy ideally begins the day before menses and continues for 3-5 days or until bleeding ceases. In a Cochrane review including 17 randomised trials, NSAIDs reduced menstrual blood loss by 33-55% when compared with placebo, without a significant difference in adverse effects.⁴⁵ NSAIDs also have the added benefit of improving dysmenorrhoea for up to 70% of patients. Contraindications to NSAID therapy include hypersensitivity, pre-existing gastritis, and peptic ulcer disease. Side effects, such as gastrointestinal upset, are unlikely to be significant or cause discontinuation since therapy continues only for a few days each month. Clinical trials comparing NSAIDs to other medical agents have found them to be less

effective in objectively reducing menstrual blood loss than tranexamic acid, the combined oral contraceptive pill (COCP), danazol, or the levonorgestrel-releasing intrauterine system (LNG-IUS). NSAIDs can be combined with oral contraceptive pills (OCP) if needed. Patients with bleeding disorders and platelet abnormalities should avoid the use of all NSAIDs.⁴⁶

Antifibrinolytic Agents: Plasminogen activators are a group of enzymes that cause fibrinolysis, the degradation of blood clots. There is an increase in plasminogen activators in the endometrium of women with heavy menstrual bleeding. Tranexamic acid is an antifibrinolytic agent or plasminogen activator inhibitor that reversibly binds to plasminogen to reduce local fibrin degradation without changing blood coagulation parameters, hence significantly reducing menstrual bleeding. Adverse effects occur in up to one-third of patients and include muscle cramps and nausea. Tranexamic acid does not treat dysmenorrhoea. Tranexamic acid is given in a dose of 500 mg to 1 g taken orally every 6 hours during menstruation, but a single daily dose of 4 g has also been found to be effective. In acute conditions, intravenous tranexamic acid with a dose of 10 mg/kg every 6 hours is given. With tranexamic acid, there is a 40-50 % reduction in the menstrual blood loss per menstrual cycle. A Cochrane review and subsequent clinical trials found no significant increase in thromboembolic events in the general population. Tranexamic acid should be used with caution in women with a personal history or active risk of venous or arterial thrombosis. It is contraindicated in women with current or past venous thromboembolism (VTE)/arterial thromboembolism or known thrombophilia, such as Factor V Leiden and antiphospholipid syndrome.⁴⁷ Ethamsylate is an alternative for excessive bleeding when antifibrinolytics are contraindicated or unavailable. Taken from the onset of menses for 4–5 days, it provides a modest 20%–30% reduction in blood loss by improving platelet adhesiveness and capillary stability. However, it is less effective than tranexamic acid.

Hormonal Medical Therapy

LNG-IUS: The LNG-IUS is the first-line treatment for reducing menstrual blood loss. It also acts like a contraceptive and relieves dysmenorrhoea. This IUD produces a decline in menstrual blood loss by 65-98% within 12 months of use. Concentrations of levonorgestrel absorbed into the systemic circulation are minimal (0.4-0.6 nmol/L), reducing the likelihood of systemic hormonal side effects. Both the contraceptive effect and the control of uterine bleeding have been shown to last up to 5 years. The device containing 20 mcg of levonorgestrel causes pseudodecidual changes and amenorrhoea, with minimal systemic progesterone absorption. The most commonly experienced side effects after LNG insertion include irregular bleeding and spotting, cramping, and hormonal side effects such as breast tenderness, mood changes and acne. Irregular spotting is common for the first 3–6 months after LNG-IUS insertion and usually improves with time. By 6–12 months, most women experience markedly reduced bleeding or amenorrhoea, which is a normal and benign effect. These symptoms are usually mild and dissipate with time, with only 1-2/100 women discontinuing therapy at 1 year due to these symptoms. Contraindications to LNG-IUS insertion include pregnancy, active pelvic infection, including purulent cervicitis or untreated gonorrhoea or chlamydia, unexplained abnormal uterine bleeding, known or suspected endometrial or cervical malignancy, and significant distortion of the endometrial cavity that precludes correct device placement. A uterine cavity length of approximately 6–9 cm is considered suitable for insertion, whereas marked cavity distortion or very small uterine cavities may increase the risk of malposition or expulsion.^{48,49} A Cochrane meta-analysis of 8 trials comparing medical treatment with all surgical methods found that endometrial ablation techniques and hysterectomy are more effective than medical treatment at reducing menstrual blood loss; yet LNG-IUS provides an equivalent improvement in quality of life.⁵⁰

COCP: The COCP pill is an ideal treatment choice for women with abnormal bleeding who need a reliable contraceptive method and for women suffering from vasomotor symptoms. Combined estrogen-progesterone therapy reduces menstrual blood flow; progesterone suppresses ovulation and causes endometrial atrophy. Estrogen raises levels of both factors VIII and stabilises the endometrium, preventing the breakthrough bleeding. COCPs are prescribed in a dosage identical to that used for contraception, 21 days of hormonally active pills followed by 7 days of placebo, during which time withdrawal bleeding occurs. Extended-cycle and continuous use of COCPs and the hormonal ring reduces both the amount of blood loss per cycle and the number of bleeding episodes per year compared with traditional COCP regimens. This regimen, with prolonged ovarian suppression, is particularly indicated for women with dysmenorrhea and pelvic pain associated with AUB. Contraindications for oral COCPs are the same as with their use in contraception. COCP reduces heavy menstrual bleeding from 12 to 77 % over six months (compared to 3% in women taking a placebo).⁵¹

Progesterone: Progesterone therapy is effective in women with anovulatory menstrual cycles. It stabilises the

proliferative endometrium and creates a regular sloughing of the endometrium. Cyclic progesterone is also useful in women with contraindications to estrogen therapy, women older than the age of 35 years who smoke, have a history of DVT or have higher risk cardiovascular factors. Cyclic luteal phase supplementation of progestins, such as medroxyprogesterone acetate, norethindrone or norethisterone acetate, is taken for 12-14 days in the luteal phase each month. With this regimen, about 50% of women with irregular cycles will achieve menstrual regularity. However, luteal phase progestin alone is not an effective treatment for regular heavy menstrual bleeding. A Cochrane meta-analysis including 7 randomised trials concluded that cyclic luteal phase progestin therapy is significantly less effective in treating “menorrhagia” than NSAIDs, tranexamic acid or danazol, and it does not provide contraception. Common side effects from oral progestins include breast tenderness, water retention, weight gain, headaches and acne.

An extended regimen of cyclic oral norethisterone acetate 5 mg taken 3 times daily for 21 days (days 5-26) was compared with the LNG-1US in one trial of 44 women with regular cycles. Both groups had a significant reduction in mean blood loss from baseline (87%), but the reduction was greater still for those randomised to the LNG-IUS. Extended cyclical regimens of oral progesterone reduce heavy blood flow better compared to luteal phase supplement. Adverse effects include weight gain, irregular bleeding and depression.⁴⁶

Intravenous conjugated equine estrogen (IV CEE): IV CEE may be used for short-term control of severe acute abnormal uterine bleeding in selected, haemodynamically stable women. IV CEE promotes rapid endometrial re-epithelialisation and vascular stabilisation, resulting in prompt haemostasis. Owing to the risk of thromboembolism, its use should be limited to brief courses (≤ 24 –48 hours) and followed by appropriate progestogen or combined hormonal therapy.^{4,12,52}

Gonadotropin-releasing hormone (GnRH): It may be offered for women in the late perimenopausal stage suffering from AUB and dysmenorrhoea with adenomyosis and fibroids, and who have contraindications to other medical therapies. These women may spontaneously enter into menopause while amenorrhoeic from GnRH therapy.

GnRH agonists induce a reversible hypogonadal state, causing endometrial atrophy and amenorrhoea, and are usually achieved in a 3- to 4-week period. Long-term use of GnRH agonists is limited by significant adverse effects, including bone pain, loss of bone density, and hypoestrogenic effects, including hot flushes, night sweats and vaginal dryness. Add-back therapy with low-dose estrogen and progestins will minimise adverse effects and should be administered if therapy is to extend beyond 6 months. GnRH agonists have been shown to reduce uterine and leiomyoma volume by up to 60%, and thus are often used for short-term preoperative therapy, but the effects are reversed once treatment ceases.^{46,53,54} GnRH agonists are effective for endometriosis-associated pain; when used with concurrent add-back estrogen with progestogen to prevent bone loss, vasomotor, and urogenital symptoms, without compromising, 6-12 months courses are appropriate.⁵⁵

Oral GnRH antagonists, including elagolix and relugolix, provide effective medical therapy for estrogen-dependent gynecologic disorders such as endometriosis and fibroid-associated symptoms, offering rapid suppression of gonadotropins and ovarian steroid hormones with predictable, reversible hypoestrogenism.^{56,57} Elagolix has demonstrated sustained efficacy in reducing endometriosis-associated pain, improving quality of life, & maintaining an acceptable safety profile in long-term extension studies. When used with appropriate add-back therapy, elagolix can be safely continued for up to 24 months, with bone loss and vasomotor symptoms mitigated without compromising efficacy.⁵⁷⁻⁶⁰ Elagolix is contraindicated in women with known osteoporosis, severe hepatic impairment, or hormone-dependent malignancy. Baseline and follow-up bone mineral density (BMD) assessment (at 12 months) should be considered when treatment extends beyond short courses or in women with additional osteoporosis risk factors. Adequate calcium and vitamin D intake, weight-bearing exercise, and other bone-protective lifestyle measures should be ensured. Relugolix combination therapy (relugolix 40 mg with estradiol 1 mg and norethindrone acetate 0.5 mg daily) has shown robust and sustained efficacy for endometriosis-associated pain and fibroid-related heavy menstrual bleeding, with maintenance of symptom control over two years off follow up. Long-term data demonstrate improvement in quality of life, reduction in opioid use, and a favourable bone safety profile, supporting its use as a longer-term medical option in appropriately selected women.^{61, 62} With combination therapy, routine BMD monitoring is not required in women without additional osteoporosis risk factors.

Systematic reviews confirm that both elagolix and relugolix, administered either as monotherapy or with hormonal add-back, effectively reduce pelvic pain, improve patient-reported outcomes, and are generally well tolerated, with minimal clinically significant loss of bone mineral density when add-back therapy is employed. Among available

sustained efficacy with improved long-term tolerability compared with antagonist monotherapy.^{63,64} GnRH antagonists may be considered as a short-to medium-term medical option for symptom control or surgical deferral in selected women with adenomyosis, with add-back therapy recommended to minimise hypoestrogenic adverse effects and bone loss.^{58,65,66}

SURGICAL THERAPY

Surgical management of AUB is an option for cases in which medical therapy fails or is contraindicated, or there is an existing pelvic pathology. Surgical options depend on the aetiology of the AUB and the patient's and physician's preferences.

- *Therapeutic D&C* may be used as a temporary measure to manage severe acute abnormal uterine bleeding, primarily to achieve short-term haemostasis and obtain endometrial tissue for diagnostic evaluation. Although D&C can result in a transient reduction in menstrual blood loss during the index cycle, this effect is not sustained, and bleeding commonly recurs or increases in subsequent cycles, limiting its role as a definitive therapeutic option.⁶⁷
- *Operative hysteroscopy*: Outpatient operative hysteroscopy for local causes such as submucosal fibroids and polyps is quick, safe and effective. Both are associated with high rates of patient satisfaction. It is indicated for directed biopsies.^{4,68}
- *Myomectomy*: The type of therapy offered is dependent on the patient's desire for pregnancy or her personal wish to preserve the uterus. When fertility is desired, the patient should be counseled for abdominal or laparoscopic myomectomy. The surgical approach for myomectomy depends on the number, size, and location of fibroids, as well as the surgeon's skill.^{69,70}
- *Uterine fibroid embolisation*: When pregnancy is not desired, and fibroids contribute to heavy menstrual bleeding, the patient can be offered uterine fibroid embolisation.⁷¹
- *Endometrial ablation*: an alternative to hysterectomy for women with AUB. It may be offered after failed medical therapy in women with a normal uterine cavity, negative laboratory workup results, and completed childbearing. The choices are hysteroscopic ablation, which destroys the endometrium under direct vision, or non-hysteroscopic techniques, which include a range of modalities that destroy the endometrium without direct visualisation. These vary in the type of energy used, the time required, and the outcomes. Both first- and second-generation techniques are equally effective.^{72,73}
- *Hysterectomy*: Hysterectomy is for women with failed medical management or who are contraindicated, and the family is complete. It improves quality of life and enhances patient satisfaction. The approach depends on the patient's profile and the surgeon's expertise. The dictum to follow is patient safety, minimally invasive and minimal morbidity.⁷⁴

SYNOPSIS

- Menstrual irregularity and dysfunctional bleeding are the hallmarks of menopause transition.
- It is suggested to use the PALM-COEIN classification for AUB.
- Common causes are anovulatory bleeding, leiomyoma, endometrial polyp, endometrial hyperplasia and endometrial cancer.
- A detailed medical history and complete physical examination are necessary in the evaluation of AUB.
- Substantial evidence indicates that sonohysterography is superior to TVS for detecting intracavitary lesions, such as polyps and submucosal leiomyomas.
- Endometrial tissue sampling is advisable in patients with AUB who are older than 40 years and in women with a high risk of endometrial cancer.
- TVS is the primary screening test for AUB, and MRI should be considered only when the diagnosis is inconclusive. Management depends on the cause, cost-benefit analysis of therapy and the patient's choice
- Endometrial ablation should be offered only after a failed trial of medical therapy.

- The LNG-IUS effectively treats menorrhagia in the majority of women but may be associated with erratic bleeding during the initial months.
- Fertility continues in a significant number of women during perimenopause. OCPs, if not contraindicated, are ideal therapy for perimenopausal symptoms of irregular menses, hot flushes and residual fertility, and may be continued until early menopause.
- Perimenopause may be an ideal time to reinforce the importance of healthy habits, periodic medical screening, and disease prevention.

RESEARCH AGENDA

Study of patterns and causes of menstrual irregularities at menopause transition.

REFERENCES

1. Santoro N. Perimenopause: From Research to Practice. *J Womens Health*. 2016 Apr 1;25(4):332–9. doi: 10.1089/jwh.2015.5556.
2. Dreisler E, Frandsen CS, Ulrich L. Perimenopausal abnormal uterine bleeding. *Maturitas*. 2024 Jun;184:107944. doi: 10.1016/j.maturitas.2024.107944
3. Mikes BA, Vadakekut ES, Sparzak PB. Abnormal Uterine Bleeding. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2026 Feb 4]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK532913/>
4. Seltzer VL, Benjamin F, Deutsch S. Perimenopausal bleeding patterns and pathologic findings. *J Am Med Womens Assoc* 1972. 1990;45(4):132–4.
5. Wouk N, Helton M. Abnormal Uterine Bleeding in Premenopausal Women. *Am Fam Physician*. 2019 Apr 1;99(7):435–443
6. Matthews ML. Abnormal uterine bleeding in reproductive-aged women. *Obstet Gynecol Clin North Am*. 2015;42(1):103–15.
7. Sharma A, Dogra Y. Trends of AUB in tertiary centre of Shimla hills. *J-Life Health*. 2013;4(1):67–8.
8. Choudhury SA, Nath P. Abnormal uterine bleeding; its prevalence, causes and management in a tertiary care hospital. *N Indian J OBGYN*. 2020;7(1):52–7.
9. Fraser IS, Langham S, Uhl-Hochgraeber K. Health-related quality of life and economic burden of abnormal uterine bleeding. *Expert Rev Obstet Gynecol*. 2009 Mar;4(2):179–89. doi: 10.1586/17474108.4.2.179.
10. Leal CR, Vannuccini S, Jain V, Dolmans MM, Sardo ADS, Al-Hendy A, et al. Abnormal uterine bleeding: The well-known and the hidden face. *J Endometr Uterine Disord*. 2024;6:100071.
11. Marnach ML, Laughlin-Tommaso SK. Evaluation and management of abnormal uterine bleeding. In: *Mayo Clinic Proceedings*. Elsevier; 2019. p. 326–35.
12. ACOG committee opinion no. 557: Management of acute abnormal uterine bleeding in nonpregnant reproductive-aged women. *Obstet Gynecol*. 2013 Apr;121(4):891–896. doi: 10.1097/01.AOG.0000428646.67925.9a. PMID: 23635706.
13. Van Voorhis BJ, Santoro N, Harlow S, Crawford SL, Randolph J. The Relationship of Bleeding Patterns to Daily Reproductive Hormones in Women Approaching Menopause. *Obstet Gynecol*. 2008 July;112(1):101–8. doi: 10.1097/AOG.0b013e31817d452b.
14. Santoro N, Clain E. Perimenopausal abnormal uterine bleeding. *Contemp OBGYN*. 2021;66(2):26–32.
15. Hale GE, Hughes CL, Burger HG, Robertson DM, Fraser IS. Atypical estradiol secretion and ovulation patterns caused by luteal out-of-phase (LOOP) events underlying irregular ovulatory menstrual cycles in the menopausal transition. *Menopause*. 2009 Jan-Feb;16(1):50–9. doi: 10.1097/GME.0b013e31817ee0c2
16. Santoro N, Johnson J. Diagnosing the Onset of Menopause. *JAMA*. 2019 Aug 27;322(8):775–6. doi: 10.1001/jama.2019.6250.
17. Gandhi A, Pandit S, Malhotra J, Joshi M, Desai J, Biniwale P, et al. Iron deficiency in peri-menopausal women: Clinical considerations from an expert consensus. *Indian J Obstet Gynecol Res*. 2023;9(2):153–61. doi: 10.18231/j.ijogr.2022.032
18. Finkelstein JS, Lee H, Karlamangla A, Neer RM, Sluss PM, Burnett-Bowie SAM, et al. Antimüllerian hormone and impending menopause in late reproductive age: the study of women's health across the nation. *J Clin Endocrinol Metab*. 2020 Apr 1;105(4):e1862–71. doi: 10.1210/clinem/dgz283.
19. Santoro N. Using Antimüllerian Hormone to Predict Fertility. *JAMA*. 2017 Oct 10;318(14):1333–1334. doi: 10.1001/jama.2017
20. Robbins JB, Sadowski EA, Maturen KE, Akin EA, Ascher SM, Brook OR et al ACR Appropriateness Criteria: Abnormal Uterine Bleeding. *J Am Coll Radiol*. 2020 Nov;17(11S):S336–S345. doi: 10.1016/j.jacr.2020.09.008. PMID: 33153547
21. Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, Clark TJ, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. *Obstet Gynecol*. 2010 Jul;116(1):160–167. doi: 10.1097/AOG.0b013e3181e3e7e8
22. Thoprasert P, Phaliwong P, Smachat B, Prommas S, Bhamarapravata K, Suwannarurk K. Endometrial thickness measurement as predictor of endometrial hyperplasia and cancer in perimenopausal uterine bleeding: Cross-sectional study. *Asian Pac J Cancer Prev*. 2023 Feb 1;24(2):693–699. doi: 10.31557/APJCP.2023.24.2.693
23. Jha S, Singh A, Sinha HH, Bhadani P, Anant M, Agarwal M. Rate of premalignant and malignant endometrial lesion in “low-risk” premenopausal women with abnormal uterine bleeding undergoing endometrial biopsy. *Obstet Gynecol Sci*. 2021 Nov;64(6):517–23. doi: 10.5468/ogs.21150.
24. Wolman I, Groutz A, Gordon D, Kupferminc MJ, Lessing JB, Jaffa AJ. Timing of Sonohysterography in Menstruating Women. *Gynecol Obstet Invest*. 1999 Dec 1;48(4):254–8. doi: 10.1159/000010194.
25. Endometrial cancer statistics [Internet]. World Cancer Research Fund. Available from: <https://www.wcrf.org/preventing-cancer/cancer-statistics/endometrial-cancer-statistics/>. Accessed on 10/01/2026
26. Arora V, Quinn MA. Endometrial cancer. *Best Pract Res Clin Obstet Gynaecol*. 2012 June 1;26(3):311–24. doi: 10.1016/j.bpobgyn.2011.12.007.

27. Pennant M, Mehta R, Moody P, Hackett G, Prentice A, Sharp S, et al. Premenopausal abnormal uterine bleeding and risk of endometrial cancer. *Bjog*. 2017 Feb;124(3):404–11. doi: 10.1111/1471-0528.14385.
28. Amin R, Kazmi J, Jeelani B, Khursheed R. Prevalence of Endometrial Hyperplasia among Patients with Abnormal Uterine Bleeding: An Analysis from a Single Centre. *J Adv Med Med Res*. 2024;36(12):231–5. doi: 10.9734/jamr/2024/v36i125671
29. Vaidya R, Vinayachandran S, Devi S, Prejisha B, Lekshminath G, Sreedharan S, et al. Prevalence of abnormal uterine bleeding and its associated risk factors in women of perimenopausal age group-a retrospective study. *J Clin Diagn Res*. 2022;16(12):9–13. doi: 10.7860/JCDR/2022/59994.17252
30. Lacey JV, Ioffe OB, Ronnett BM, Rush BB, Richesson DA, Chatterjee N, et al. Endometrial carcinoma risk among women diagnosed with endometrial hyperplasia: the 34-year experience in a large health plan. *Br J Cancer*. 2008 Jan 15;98(1):45–53. doi: 10.1038/sj.bjc.6604102.
31. Abdol Manap N, Ng BK, Phon SE, Abdul Karim AK, Lim PS, Fadhil M. Endometrial Cancer in Pre-Menopausal Women and Younger: Risk Factors and Outcome. *Int J Environ Res Public Health*. 2022 July 25;19(15):9059. doi: 10.3390/ijerph19159059.
32. Rakha E, Wong SC, Soomro I, Chaudry Z, Sharma A, Deen S, et al. Clinical outcome of atypical endometrial hyperplasia diagnosed on an endometrial biopsy: institutional experience and review of literature. *Am J Surg Pathol*. 2012;36(11):1683–90.
33. Papakonstantinou E, Adonakis G. Management of pre-, peri-, and post-menopausal abnormal uterine bleeding: When to perform endometrial sampling? *Int J Gynecol Obstet*. 2022 Aug;158(2):252–9. doi: 10.1002/ijgo.13988.
34. Taraboanta C, Britton H, Plotkin A, Azordegan N, Clement PB, Gilks CB. Performance characteristics of endometrial sampling in diagnosis of endometrial carcinoma. *Int J Gynecol Pathol*. 2020 Jan;39(1):19–25. doi: 10.1097/PGP.0000000000000569.
35. Aznar AL, Canton R, Loren G, Carvajal J, de la Calle I, Masferrer-Ferragutcasas C, et al. Current challenges and emerging tools in endometrial cancer diagnosis. *Int J Gynecol Cancer*. 2025 Apr;35(4):100056. doi: 10.1016/j.ijgc.2024.100056
36. Frumovitz M, Singh DK, Meyer L, Smith DH, Wertheim I, Resnik E, et al. Predictors of final histology in patients with endometrial cancer. *Gynecol Oncol*. 2004 Dec;95(3):463–8. doi: 10.1016/j.ygyno.2004.07.016
37. Senturk S, Aydin G, Bayrak CC, Hatirnaz S, Stojković M, Sparic R, et al. Endometrial sampling in the absence of hysteroscopy: Insights from more than 1000 dilatation and curettage cases. *Int J Gynecol Obstet*. 2025 Aug 28;ijgo.70459. doi: 10.1002/ijgo.70459.
38. Piatek S, Warzecha D, Kisielewski F, Szymusik I, Panek G, Wielgos M. Pipelle biopsy and dilatation and curettage in clinical practice: are factors affecting their effectiveness the same? *J Obstet Gynaecol Res*. 2019;45(3):645–51. doi: 10.1111/jog.13882.
39. Terzic MM, Aimagambetova G, Terzic S, Norton M, Bapayeva G, Garzon S. Current role of Pipelle endometrial sampling in early diagnosis of endometrial cancer. *Transl Cancer Res*. 2020 Dec;9(12):7716–24. doi: 10.21037/tcr.2020.04.20.
40. Di Spiezo Sardo A, Saccone G, Carugno J, Pacheco LA, Zizo i B, Haimovich S, et al. Endometrial biopsy under direct hysteroscopic visualisation versus blind endometrial sampling for the diagnosis of endometrial hyperplasia and cancer: Systematic review and meta-analysis. *Facts Views Vis ObGyn*. 14(2):103–10. doi: 10.52054/FVVO.14.2.023.
41. Su H, Huang L, Huang KG, Yen CF, Han CM, Lee CL. Accuracy of hysteroscopic biopsy, compared to dilation and curettage, as a predictor of final pathology in patients with endometrial cancer. *Taiwan J Obstet Gynecol*. 2015 Dec 1;54(6):757–60. doi: 10.1016/j.tjog.2015.10.013.
42. Terzic M, Norton M, Terzic S, Bapayeva G, Aimagambetova G. Fertility preservation in endometrial cancer patients: options, challenges and perspectives. *ecancermedscience*. 2020 May 6;14:1030. doi: 10.3332/ecancer.2020.1030.
43. Vitale SG, Buzzaccarini G, Riemma G, Pacheco LA, Sardo ADS, Carugno J, et al. Endometrial biopsy: Indications, techniques and recommendations. An evidence-based guideline for clinical practice. *J Gynecol Obstet Hum Reprod*. 2023;52(6):102588. doi: 10.1016/j.jogoh.2023.102588
44. Marnach ML, Laughlin-Tommaso SK. Evaluation and Management of Abnormal Uterine Bleeding. *Mayo Clin Proc*. 2019 Feb;94(2):326–335. doi: 10.1016/j.mayocp.2018.12.012
45. Rodriguez MB, Lethaby A, Farquhar C. Non-steroidal anti-inflammatory drugs for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2019;(9). *Cochrane Database Syst Rev*. 2019 Sep 19;9(9):CD000400. doi: 10.1002/14651858.CD000400.pub4.
46. Singh S, Best C, Dunn S, Leyland N, Wolfman WL, Leyland N, et al. Abnormal Uterine Bleeding in Pre-Menopausal Women. *J Obstet Gynaecol Can*. 2013 May;35(5):473–475. English, French. doi: 10.1016/S1701-2163(15)30939-7
47. Bryant-Smith AC, Lethaby A, Farquhar C, Hickey M. Ant fibrinolytics for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2018 Apr 15;2018(4):CD000249. doi: 10.1002/14651858.CD000249.pub2.
48. Petta CA, Ferriani RA, Abrao MS, Hassan D, Rosa e Silva JC, Podgaec S, et al. Randomized clinical trial of a levonorgestrel-releasing intrauterine system and a depot GnRH analogue for the treatment of chronic pelvic pain in women with endometriosis. *Hum Reprod*. 2005;20(7):1993–8. *Hum Reprod*. 2005 Jul;20(7):1993–8. doi: 10.1093/humrep/deh869
49. Mansour D. Modern management of abnormal uterine bleeding – the levonorgestrel intra-uterine system. *Best Pract Res Clin Obstet Gynaecol*. 2007 Dec 1;21(6):1007–21. doi: 10.1016/j.bpobgyn.2007.03.023.
50. Marjoribanks J, Lethaby A, Farquhar C. Surgery versus medical therapy for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2016 Jan 29;(1):CD003855. doi: 10.1002/14651858.CD003855
51. Lethaby A, Wise MR, Weterings MA, Bill Rodriguez M, Brown J. Combined hormonal contraceptives for heavy menstrual bleeding. *Cochrane Database Syst Rev*. 2019 Feb 11;2019(2):CD000154. doi: 10.1002/14651858.CD000154.pub3.
52. DeVORE GR, OWENS O, KASE N. Use of intravenous Premarin in the treatment of dysfunctional uterine bleeding: a double-blind randomized control study. *Obstet Gynecol Surv*. 1982;37(7):478–80.
53. Thomas EJ. Add-back therapy for long-term use in dysfunctional uterine bleeding and uterine fibroids. *Br J Obstet Gynaecol*. 1996;103:18–21.
54. Friedman AJ, Hoffman DI, Comite F, Browneller RW, Miller JD. Treatment of leiomyomata uteri with leuprolide acetate depot: a double-blind, placebo-controlled, multicenter study. The Leuprolide Study Group. *Obstet Gynecol*. 1991 May;77(5):720–5.
55. Veth VB, de Kar MM, McDonnell R, Julania S, Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. *Cochrane Database Syst Rev*. 2010 Dec 8;2010(12):CD008475. doi: 10.1002/14651858.CD008475.pub2.
56. Schlaff WD, Ackerman RT, Al-Hendy A, Archer DF, Barnhart KT, Bradley LD, et al. Elagolix for Heavy Menstrual Bleeding in Women with Uterine Fibroids. *N Engl J Med*. 2020 Jan 23;382(4):328–40. doi: 10.1056/NEJMoa1904351.
57. Taylor HS, Giudice LC, Lessey BA, Abrao MS, Kotarski J, Archer DF, et al. Treatment of Endometriosis-Associated Pain with Elagolix, an Oral GnRH Antagonist. *N Engl J Med*. 2017 July 6;377(1):28–40. doi: 10.1056/NEJMoa1700089.

58. Muneeyirci-Delale O, Archer DF, Owens CD, Barnhart KT, Bradley LD, Feinberg E, et al. Efficacy and safety of elagolix with add-back therapy in women with uterine fibroids and coexisting adenomyosis. *FS Rep.* 2(3):338–46. doi: 10.1016/j.xfre.2021.05.004.
59. U.S. Food and Drug Administration. Orilissa[®] (elagolix) Prescribing Information. Silver Spring (MD): FDA; 2018 [Internet]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/210450s000lbl.pdf. Accessed on 12/01/2026
60. Surrey E, Taylor HS, Giudice L, Lessey BA, Abrao MS, Archer DF, et al. Long-term outcomes of elagolix in women with endometriosis: results from two extension studies. *Obstet Gynecol.* 2018 Dec;132(6):1507–1508. doi: 10.1097/AOG.0000000000003038.
61. Al-Hendy A, Lukes AS, Poindexter AN, Venturella R, Villarroel C, McKain L, et al. Long-term Relugolix Combination Therapy for Symptomatic Uterine Leiomyomas. *Obstet Gynecol.* 2022 Dec;140(6):920–30. doi: 10.1097/AOG.0000000000004988.
62. Becker CM, Johnson NP, As-Sanie S, Arjona Ferreira JC, Abrao MS, Wilk K, et al. Two-year efficacy and safety of relugolix combination therapy in women with endometriosis-associated pain: SPIRIT open-label extension study. *Hum Reprod Oxf Engl.* 2024 Jan 18;39(3):526–37. doi: 10.1093/humrep/dead263.
63. Wang X, Li J, Liu Y, Zheng Y, Wang X, Liu G. A systematic review and meta-analysis comparing the use of elagolix therapy alone or in combination with add-back therapy to treat women with uterine fibroid associated heavy menstrual bleeding. *Gland Surg.* 2025 Jan 24;14(1):60–73. doi: 10.21037/ggs-24-386.
64. Quishpe M, Endara-Mina J, Caizapanta J, Guzmán A, Tenesaca D, Asto D, et al. Efficacy of Elagolix and Relugolix for the Treatment of Pelvic Pain in Patients With Endometriosis: A Systematic Review. *Cureus.* 17(9):e92149. doi: 10.7759/cureus.92149.
65. Yamanaka K, Washio K, Uchida A, Sasagawa Y, Nishimoto M, Yamasaki Y, et al. Rapid reduction of adenomyosis coexisting with leiomyoma volume during treatment with Relugolix. *Gynecol Endocrinol.* 2023 Dec 14;39(1):2237121. doi: 10.1080/09513590.2023.2237121.
66. Etrusco A, Barra F, Chiantera V, Ferrero S, Bogliolo S, Evangelisti G, et al. Current Medical Therapy for Adenomyosis: From Bench to Bedside. *Drugs.* 2023;83(17):1595–611. doi: 10.1007/s40265-023-01957-7.
67. Speroff L, Fritz MA. Clinical gynecologic endocrinology and infertility. 7th Edition. lippincott Williams & wilkins; 2005.
68. Clark TJ, Middleton LJ, Cooper NA, Diwakar L, Denny E, Smith P, et al. A randomised controlled trial of Outpatient versus inpatient Polyp Treatment (OPT) for abnormal uterine bleeding. *Health Technol Assess Winch Engl.* 2015 July;19(61):1–194. doi: 10.3310/hta19610.
69. Stewart EA. Uterine fibroids. *Lancet.* 2001 Jan 27;357(9252):293–8. doi: 10.1016/S0140-6736(00)03622-9
70. Vitale SG, Riemma G, Ciebiera M, Cianci S. Hysteroscopic treatment of submucosal fibroids in perimenopausal women: when, why, and how? *Climacteric.* 2020 July 3;23(4):355–9. doi: 10.1080/13697137.2020.1754390.
71. Gupta JK, Sinha A, Lumsden MA, Hickey M. Uterine artery embolization for symptomatic uterine fibroids. *Cochrane Database Syst Rev.* 2014 Dec 26;(12):CD005073. doi: 10.1002/14651858.CD005073
72. Vitale SG, Della Corte L, Ciebiera M, Carugno J, Riemma G, Lasmar RB, et al. Hysteroscopic Endometrial Ablation: From Indications to Instrumentation and Techniques—A Call to Action. *Diagnostics.* 2023 Jan 17;13(3):339. doi: 10.3390/diagnostics13030339.
73. Boffill Rodriguez M, Lethaby A, Grigore M, Brown J, Hickey M, Farquhar C. Endometrial resection and ablation techniques for heavy menstrual bleeding. *Cochrane Database Syst Rev.* 2019 Jan 22;2019(1):CD001501. doi: 10.1002/14651858.CD001501.pub5.
74. Kuppermann M, Varner RE, Summitt J, Robert L, Learman LA, Ireland C, Vittinghoff E, et al. Effect of Hysterectomy vs Medical Treatment on Health-Related Quality of Life and Sexual Functioning The Medicine or Surgery (Ms) Randomized Trial. *JAMA.* 2004 Mar 24;291(12):1447–55. doi: 10.1001/jama.291.12.1447.

POSTMENOPAUSAL BLEEDING

Keywords: Definition, differential diagnosis, investigations.

08

INTRODUCTION

Postmenopausal bleeding (PMB) is a common clinical presentation in gynaecological practice, accounting for 5 % of the visits.¹ Contributory factors include perhaps increasing longevity, obesity, and hormone therapy (HT), both supervised and unsupervised.² An increasing number of women seeking help or reassurance for this problem, due to greater awareness, would also contribute to this increase. PMB occurs in 4-11% of postmenopausal women.³⁻⁶

DEFINITION

The menopause is defined by the World Health Organisation (WHO) as the permanent cessation of menstruation resulting from the loss of ovarian follicular activity.⁷ However, the definition of PMB and what is clinically significant varies. By definition, PMB is bleeding that occurs 12 months after the last normal period in women who do not receive HT. However, it is recommended that any vaginal bleeding occurring 6 months after the last period (presumed menopause) should be investigated.⁸ Approximately 5% of PMB cases will have endometrial cancer.⁹

SIGNIFICANCE OF PMB

In postmenopausal women, endometrial thickness (ET) is substantially lower than in premenopausal women, and increasing thickness is directly associated with a higher likelihood of endometrial pathology. PMB is most frequent in the early postmenopausal years and becomes progressively less common with increasing time since the final menstrual period. In population-based data, the estimated incidence decreases from approximately 409 per 1000 person-years soon after menopause to around 42 per 1000 person-years more than 3 years after menopause (4%/year).³

The likelihood of endometrial carcinoma (EC) among women presenting with PMB increases with advancing age. Population-based studies show that while the risk is low in younger postmenopausal women, it rises substantially in older women, reaching approximately 20–25% in women aged ≥ 75 –80 years.¹⁰ Although the occurrence of bleeding decreases with age, the probability of malignancy as an underlying cause increases; therefore, any PMB warrants evaluation.¹¹ Despite this age-related increase in cancer risk, most cases of PMB are attributable to benign causes, and clinically significant endometrial pathology, including malignancy, endometrial intraepithelial neoplasia (EIN), or polyps. It is identified in only about one fifth of women evaluated for PMB.^{11,12} Overall, approximately 5–10% of women presenting with PMB are found to have EC, with risk increasing substantially with advancing age and other risk factors.¹³ Conversely, the majority, around 80–90% of endometrial cancers in postmenopausal women, present with abnormal uterine bleeding, including PMB, underscoring the need for prompt and systematic evaluation.¹³ The global burden of endometrial cancer is rising steadily and is projected to increase substantially over the coming decades, driven largely by increasing obesity, metabolic dysfunction, and later age at menopause.¹⁴ Among postmenopausal women using menopausal hormone therapy (MHT), vaginal bleeding is relatively common, occurring in approximately 20–30% during the initial months of therapy and declining to about 10% by one year.¹⁵ Such women should be evaluated according to standard PMB protocols, as validated ET thresholds specific to MHT users are currently lacking. Recurrent PMB is defined as a new episode of vaginal bleeding occurring after a symptom-free interval of at least 6 weeks following resolution of an initial PMB episode.¹² Reassessment is warranted in such cases, as approximately 3–5% of women with recurrent PMB may subsequently be diagnosed with EC or premalignant pathology, even after an initially negative evaluation. Endometrial polyps are a common underlying cause, accounting for approximately 20–30% of PMB cases.¹⁰

CAUSES OF PMB

Excess estrogen

- *Exogenous estrogen*: Estrogen supplements (ET).

- *Endogenous estrogen:* Peripheral conversion of androstenedione, estrogen-producing tumours, such as granulosa cell tumour or theca cell tumours of the ovary.
- *Atrophic endometritis or vaginitis.*
- *Benign conditions:* Cervical polyp, endometrial polyp, endometrial hyperplasia, submucous fibroid, cervicitis, vaginitis.
- *Malignancy:* Endometrial cancer, cervical cancer, vaginal wall cancer, fallopian tube cancer, uterine sarcoma, ovarian malignancy.
- *Genetic predisposition* of endometrial cancer, such as Lynch syndrome and Cowden disease, and more recently, the BRCA1 mutation gene also seems to carry an increased risk of endometrial cancer.¹⁶
- *Miscellaneous:* Direct trauma, forgotten intrauterine contraceptive device, pessary or tampon, coitus, decubitus ulcer of prolapse, anticoagulant therapy.

Table 1: Causes of abnormal uterine bleeding in perimenopausal and postmenopausal women in order of occurrence¹⁶

Perimenopausal women	Postmenopausal women
Anovulation	Endometrial atrophy
Endometrial polyps	Vaginal atrophy
Uterine fibroids	Endometrial hyperplasia and cancer
Adenomyosis	Endometrial polyp
Endometrial hyperplasia	Hormonal
Vulvar, vaginal, and cervical lesions	Vulvar, vaginal, or cervical lesions
	Others - genital tuberculosis (rare)
	Post-radiation vaginal bleeding

Table 2: Frequency of different causes of PMB¹⁶

Etiology	Frequency
Exogenous estrogen	30%
Atrophic endometritis, vaginitis	30.8%
Endometrial polyp/hyperplasia	37.7%/15%
Endometrial cancer	6.6%
Miscellaneous (cervical cancer, uterine sarcoma, local trauma, others)	10%
Fibroid	6.2%
Hyperplasia without atypia	2%
Hyperplasia with atypia	0.2%
Proliferative/secretory	14.5%

EVALUATION OF PMB

The principal aim of the initial evaluation of PMB is to exclude malignancy, and the secondary evaluation is to determine the cause of PMB. A detailed history is essential to understand the underlying aetiology of PMB.¹⁷ Refer to Chapter 60 for the evaluation of PMB.

History

The nature of the current bleeding should be carefully documented, including whether it is a first episode, persistent bleeding, or recurrent PMB, and any changes in the pattern or severity of bleeding. A prior history of perimenopausal dysfunctional uterine bleeding and/or endometrial hyperplasia should be specifically enquired about. Characteristics of PMB, including onset, duration, frequency, heaviness, precipitating factors, post-coital bleeding, and any associated symptoms such as fever, pelvic pain, dysuria, vaginal dryness, or dyspareunia, should be elicited.^{11,12,18,19} The presence of co-morbid risk factors known to increase the likelihood of endometrial pathology, such as diabetes mellitus, hypertension, obesity, nulliparity, and use of unopposed estrogen therapy, should be recorded.^{17,20} A detailed treatment history is mandatory and should include prior or current use of tamoxifen, tibolone, cyclical or continuous combined MHT,^{15,21} herbal or complementary medications, and any recent pelvic procedures. Treatment history should be explicitly obtained, as several over-the-counter herbal agents, including ginseng, soy products, and red clover, may cause vaginal bleeding through phytoestrogenic effects.^{22,23} Reproductive factors such as early menarche and late menopause, which increase cumulative estrogen exposure, are associated with a higher risk of endometrial hyperplasia and carcinoma. A family history of malignancy, particularly breast, gynecologic, urologic, or gastrointestinal cancers, should be sought, along with an enquiry into hereditary cancer syndromes, such as Lynch syndrome or Cowden syndrome, which confer an increased risk of endometrial cancer.²²

Examination

A thorough general and local examination is mandatory. The difficulty of this in postmenopausal women should be borne in mind. The primary aim of this is to rule out vulval, vaginal, cervical and pelvic pathology, mainly cancer. A general examination must also include a woman's body mass index (BMI). A per speculum and per vaginal examination should be done. Atrophic vaginitis, cervical polyps, and growth and ulceration associated with ring-shaped pessaries can be identified. Examine for genital lacerations or urethral prolapse. Hematuria and bleeding per rectum (haemorrhoids) should be considered. Bimanual examination may reveal pelvic masses or enlarged lymph nodes.^{14,18,24} Conventional Pap smear and liquid-based cervical cytology may detect abnormal endometrial cells in a minority of women with EC, with reported detection rates of approximately 10–20% and higher yields in high-grade or advanced disease. Cervical cytology is therefore not a reliable screening test for endometrial cancer, and a normal Pap smear does not exclude endometrial pathology.²⁵ The reporting of benign-appearing endometrial cells on a Pap smear warrants clinical correlation. Current evidence supports endometrial evaluation in women aged ≥ 40 years when benign endometrial cells are identified on cervical cytology, particularly in the presence of additional clinical indicators, such as PMB, abnormal uterine bleeding, or other risk factors for endometrial pathology.^{26–29}

Investigations

The principal aim of investigating PMB is to identify or exclude endometrial pathology, particularly EC, while avoiding unnecessary invasive procedures in low-risk women. A structured, stepwise approach based on individual risk factors and imaging findings is recommended.¹¹ In women presenting with spontaneous PMB, transvaginal sonography (TVS) is recommended as the first-line investigation, as it is non-invasive, widely available, and has a high sensitivity for detecting endometrial pathology. TVS allows measurement of the endometrial echo complex (EEC) and provides additional information regarding endometrial morphology, myometrial interface, intracavitary lesions, and adnexal pathology.^{11,30} In low-risk women with a first episode of PMB, an initial TVS-based triage strategy is appropriate. When the ET exceeds 4 mm, outpatient endometrial sampling should be performed. In contrast, an $ET \leq 4$ mm has a negative predictive value of approximately 99% for EC, allowing conservative management in the absence of persistent or recurrent bleeding.^{31–33} The commonly used ET thresholds of 3–5 mm provide high sensitivity for excluding malignancy, and the choice of cut-off should be individualised to the clinical context.³³

Measurement of the endometrium on ultrasound (USG) should include the full double thickness from anterior to posterior on the long axis of the uterine view of the endometrium, with any content within the endometrial cavity. However, TVS assessment should not rely solely on ET. Endometrial morphology, including heterogeneous

echotexture, focal thickening, cystic areas, an irregular endometrial-myometrial junction, intracavitary fluid, and abnormal vascular patterns on power Doppler, should be carefully evaluated, as these features may indicate focal pathology even when ET is within normal limits.³³

Women presenting with a first episode of PMB and additional risk factors such as obesity, diabetes mellitus, hypertension, tamoxifen use, increasing years since menopause, prior endometrial polyps, smoking, family history of EC, poor image quality, focal echogenicity, diffuse heterogeneity, or persistent bleeding should undergo both TVS and endometrial sampling, rather than sequential testing, to minimise missed pathology.^{11,32}

Adjunctive imaging modalities may be useful in selected situations. Saline infusion sonography (SIS) improves visualisation of the endometrial cavity and has high diagnostic accuracy for focal intrauterine lesions, such as polyps and submucous fibroids, while three-dimensional TVS may assist in volumetric assessment. However, neither SIS nor 3D-TVS replaces ET-based triage for EC, nor can they substitute for histological sampling when malignancy is suspected. Evidence from large meta-analyses supports the diagnostic performance of ET measurement in PMB. A meta-analysis of 90 studies demonstrated that a 3-mm ET cutoff yields a sensitivity of approximately 98%, whereas 4-mm and 5-mm cutoffs yield sensitivities of approximately 95% and 90%, respectively, for EC detection.^{31,34} Despite this, clinicians should be aware that certain molecular subtypes of EC, particularly p53-abnormal (p53abn) tumours, may present with a thin endometrium, and relying on a standard ET threshold of ≤ 4 mm may result in a false-negative rate of up to 25%, especially in women with persistent symptoms.³⁵

In women with recurrent PMB following an initially negative evaluation, further investigation is mandatory. Outpatient hysteroscopy, which has high accuracy for detecting focal intrauterine disease, is preferred in this setting. Observational studies indicate that approximately 20% of such women have endometrial polyps, while 4–5% may subsequently be diagnosed with EC or premalignant pathology, despite earlier reassuring findings.^{34,36} The approach differs in asymptomatic postmenopausal women with incidentally detected endometrial thickening. In this group, there is no universally accepted ET threshold that reliably predicts malignant transformation.^{41,43} Conversely, an ET > 11 mm should prompt an endometrial biopsy. For ET values between 3/4 mm and 11 mm, decisions regarding biopsy should be individualised, taking into account clinical risk factors, endometrial morphology, and Doppler findings.^{5,37} Recent evidence supports a “one-stop” diagnostic approach combining TVS with endometrial aspiration for the evaluation of endometrial neoplasia. In postmenopausal women, the combined use of sonographic assessment of endometrial morphology and thickness, along with endometrial sampling, improves diagnostic accuracy compared with either modality alone and enables efficient risk stratification and timely identification of clinically significant endometrial pathology.³⁸

Magnetic resonance imaging (MRI)

Pelvic MRI is not a first-line test in PMB, but it is useful when malignancy remains suspected despite equivocal/poor-quality TVS, when the endometrium cannot be adequately assessed, or when imaging suggests complex disease requiring local staging. MRI is particularly valuable in cases of confirmed or strongly suspected EC for assessing the depth of myometrial invasion, cervical stromal involvement, and suspicious lymph nodes and extra-uterine spread, thereby informing surgical planning and risk stratification.³⁹

Endometrial biopsy in PMB

Histological assessment is the definitive test for excluding premalignant and malignant endometrial disease in PMB.^{11,40} Yet, in women with PMB, the sensitivity of endometrial sampling to detect endometrial cancer, especially atypical hyperplasia and endometrial disease, including endometrial polyps, is lower than previously thought. Therefore, further diagnostic workup for focal pathology is warranted after a benign endometrial sampling result.¹² In women with an isolated episode of PMB who are low risk and have a thin, well-visualised endometrium (≤ 4 mm) on TVS, endometrial atrophy is the most likely cause, and immediate biopsy may be deferred if bleeding resolves; however, ongoing clinical vigilance is essential, and persistent or recurrent bleeding warrants tissue diagnosis regardless of ET.

Indications for endometrial sampling in PMB include: (i) ET > 4 mm (or suspicious morphology) on TVS; (ii) persistent or recurrent PMB, even with ET ≤ 4 mm; (iii) presence of clinical risk factors for endometrial cancer (such as obesity, diabetes, unopposed estrogen exposure/tamoxifen, increasing years since menopause, relevant family history); and (iv) inadequate visualisation of the endometrial stripe or non-diagnostic initial sampling.

Methods of endometrial sampling: Three commonly used methods are outpatient/office biopsy (Pipelle), dilatation and curettage (D&C), and hysteroscopy with directed biopsy. Importantly, no blind sampling technique is perfect: sampling may be insufficient or may miss focal lesions such as polyps or focal neoplasia, especially when pathology does not involve a substantial portion of the cavity. However, when the endometrium is thickened without a focal lesion, an office biopsy is reasonable. Any method of sampling the endometrial cavity misses a proportion of endometrial cancers. If endometrial cancer occupies less than 50% of the endometrial cavity surface area, it can be missed by a blind endometrial biopsy. In low-resource areas, initial evaluation may be done with a blind biopsy, but further evaluation is needed if bleeding persists, and the results do not indicate cancer or atypical hyperplasia, or if the evaluation was not adequate. Thus, distinguishing global from focal pathologies is important before a biopsy.¹²

Office biopsy: Outpatient suction endometrial biopsy is generally well tolerated and an appropriate first-line sampling method in women with PMB when TVS suggests diffuse or global endometrial thickening without a clear focal lesion. Sampling is typically performed using flexible plastic devices, such as the Pipelle endometrial curette, as an office procedure without anaesthesia.¹¹ As a blind technique, the Pipelle biopsy retrieves tissue from a limited, non-uniform portion of the endometrial cavity. Although the procedure is convenient and acceptable to most patients, sampling adequacy is variable in postmenopausal women, and insufficient or failed sampling is common, particularly in the presence of endometrial atrophy, focal intracavitary pathology, or cervical stenosis. Reported rates of inadequate or failed sampling vary widely in the literature, ranging from approximately 10% to over 50% in some series, highlighting the limitations of blind outpatient techniques.^{11,12,41} Systematic reviews demonstrate that blind outpatient endometrial sampling has high specificity and good sensitivity for diffuse endometrial pathology, including EC and atypical hyperplasia. However, its performance is substantially lower for focal lesions, such as polyps or localised neoplasia. Consequently, a benign or insufficient office biopsy does not conclude the evaluation when bleeding persists or recurs, or when imaging or clinical suspicion remains high; further assessment, preferably with hysteroscopy-directed biopsy, is warranted.^{12,41} Overall, for diffuse endometrial disease, the diagnostic accuracy of blind outpatient sampling is comparable to that of hysteroscopy-directed biopsy. In contrast, hysteroscopy offers superior accuracy for detecting focal intrauterine lesions and allows targeted sampling under direct vision.⁴²

Dilatation And Curettage(D&C): D&C should no longer be considered the preferred first-line test for PMB evaluation because it is blind and can miss focal lesions. Classic prospective data in PMB with a thick endometrium showed that D&C left focal pathology behind in many cases and missed a substantial proportion of polyps and hyperplasia, as well as a smaller proportion of cancers, supporting the superiority of hysteroscopy when focal disease is possible.⁴³ D&C is also invasive, often requires anaesthesia, and carries risks such as uterine perforation, bleeding, and infection. Rare, but clinically relevant, especially in women with comorbidities.^{8,11,13}

Hysteroscopy: Hysteroscopy with directed endometrial biopsy is considered the gold standard for evaluating PMB, particularly when focal endometrial pathology is suspected. Direct visualisation of the uterine cavity enhances detection of polyps, submucous fibroids, and localised neoplasia, and allows simultaneous treatment of benign lesions. Several observational studies and meta-analytic evidence support have demonstrated very high specificity and positive predictive value (often >95%) for hysteroscopy in identifying benign and malignant pathology in women with PMB.^{12,44,45} Current evidence indicates that diagnostic hysteroscopy does not compromise short- or long-term oncologic outcomes in women with EC. While hysteroscopy has been associated with higher rates of positive peritoneal cytology, this finding has not been associated with increased recurrence or reduced survival. Accordingly, hysteroscopy is not contraindicated in the evaluation of PMB, even when malignancy is suspected. Meta-analytic data to date support the absence of an adverse prognostic effect; further evidence from ongoing studies will help refine these conclusions.

Tumor Markers

Many authors have studied the use of tumour markers for diagnosing endometrial cancer. These include the cancer antigens 125, 19-9, 50, and 15-3, as well as carcinoembryonic antigen, alpha-fetoprotein, placental-type alkaline phosphatase, and the core fragment of urinary beta-human chorionic gonadotropin. To date, these tumour markers have proved to be of little value in the screening of women with PMB for endometrial cancer.^{11,17}

MANAGEMENT

Management of PMB is directed primarily at treating the underlying cause, once appropriate evaluation has excluded or confirmed endometrial and extra-uterine pathology. In addition to aetiology, symptom severity, comorbid medical

conditions, and the woman's preferences, should be taken into account when planning treatment. All cases of PMB should be managed only after adequate investigation and diagnosis, including exclusion of bleeding sources arising outside the uterine cavity.

General Measures and Long-Term Care

Optimal management of PMB also includes control of associated medical comorbidities, such as diabetes, hypertension, and obesity, and addressing long-term menopausal health issues, including cardiovascular disease and osteoporosis. Lifestyle interventions, regular physical activity, a healthy diet, weight reduction, and avoidance of smoking and alcohol should be strongly encouraged.

Endometrial Polyps: Endometrial polyps are frequently asymptomatic but account for approximately 30% of PMB cases. Malignancy within endometrial polyps occurs in about 1% of cases in postmenopausal women.⁴⁶ Hysteroscopic polypectomy is the treatment of choice, allowing complete excision and histological assessment.³³ The surrounding endometrium should also be sampled, as endometrial hyperplasia may coexist in approximately 3% of cases.⁴⁴ Cervical polyps should be managed by simple excision followed by histopathological examination.

Submucous Myomas: Submucous fibroids account for a smaller proportion of PMB. Approximately 10–20% of submucous myomas may be symptomatic in the postmenopausal period and carry an increased concern for sarcomatous change. Uterine fibroids are present in 30–40% of women over 40 years, and typically regress after menopause due to estrogen withdrawal. However, fibroids may persist, become symptomatic, or enlarge after menopause, particularly in obese women, owing to peripheral estrogen conversion in adipose tissue.⁴⁷ Symptomatic or enlarging fibroids after menopause require careful evaluation and management.

Conservative Management in Low-Risk Women

A first episode of PMB in the absence of identifiable pathology may be managed conservatively. Low-risk women defined by an ET ≤ 3 –4 mm, homogeneous echotexture, normal morphology and Doppler findings, and good-quality imaging whose bleeding has resolved may be observed with shared decision-making. Repeat TVS or endometrial biopsy is indicated only if bleeding recurs.¹¹ All women should receive documented counselling regarding the importance of follow-up and should be advised to promptly report red flag symptoms, including recurrent bleeding, abnormal vaginal discharge, pelvic pain, or unexplained weight loss.¹¹

Management of PMB Based on Histopathological Report

Refer to Flowchart 1. The management of PMB (PMB) should be guided by the histopathological findings of endometrial sampling, in conjunction with clinical presentation, imaging findings, and individual risk factors. Refer to flow chart 1.

Atrophic Endometrium

Endometrial atrophy is the most common cause of PMB, accounting for approximately 60–80% of cases. In women with a histopathological diagnosis of atrophic endometrium and no additional risk factors, reassurance is appropriate, as the risk of underlying malignancy is extremely low. Local measures such as vaginal moisturisers or low-dose vaginal estrogen therapy may be offered for associated genitourinary syndrome of menopause, provided there are no contraindications. However, persistent or recurrent bleeding despite an atrophic biopsy warrants re-evaluation, as blind sampling may miss focal lesions. In such cases, further assessment with hysteroscopy and directed biopsy should be considered.

Inadequate or Insufficient Endometrial Sample

An inadequate or insufficient endometrial sample is a common outcome of outpatient biopsy in postmenopausal women, particularly in the presence of endometrial atrophy, cervical stenosis, or focal pathology. An insufficient sample does not exclude EC or premalignant disease. Management depends on the clinical context. In women with persistent or recurrent PMB, risk factors for endometrial cancer, or abnormal imaging, further evaluation is mandatory. This should include repeat endometrial sampling, preferably under hysteroscopic guidance, or alternative diagnostic modalities such as SIS to identify focal lesions. In low-risk women with a single self-limited episode of PMB and reassuring imaging, short-term observation with clear safety-netting may be acceptable.

Proliferative Endometrium

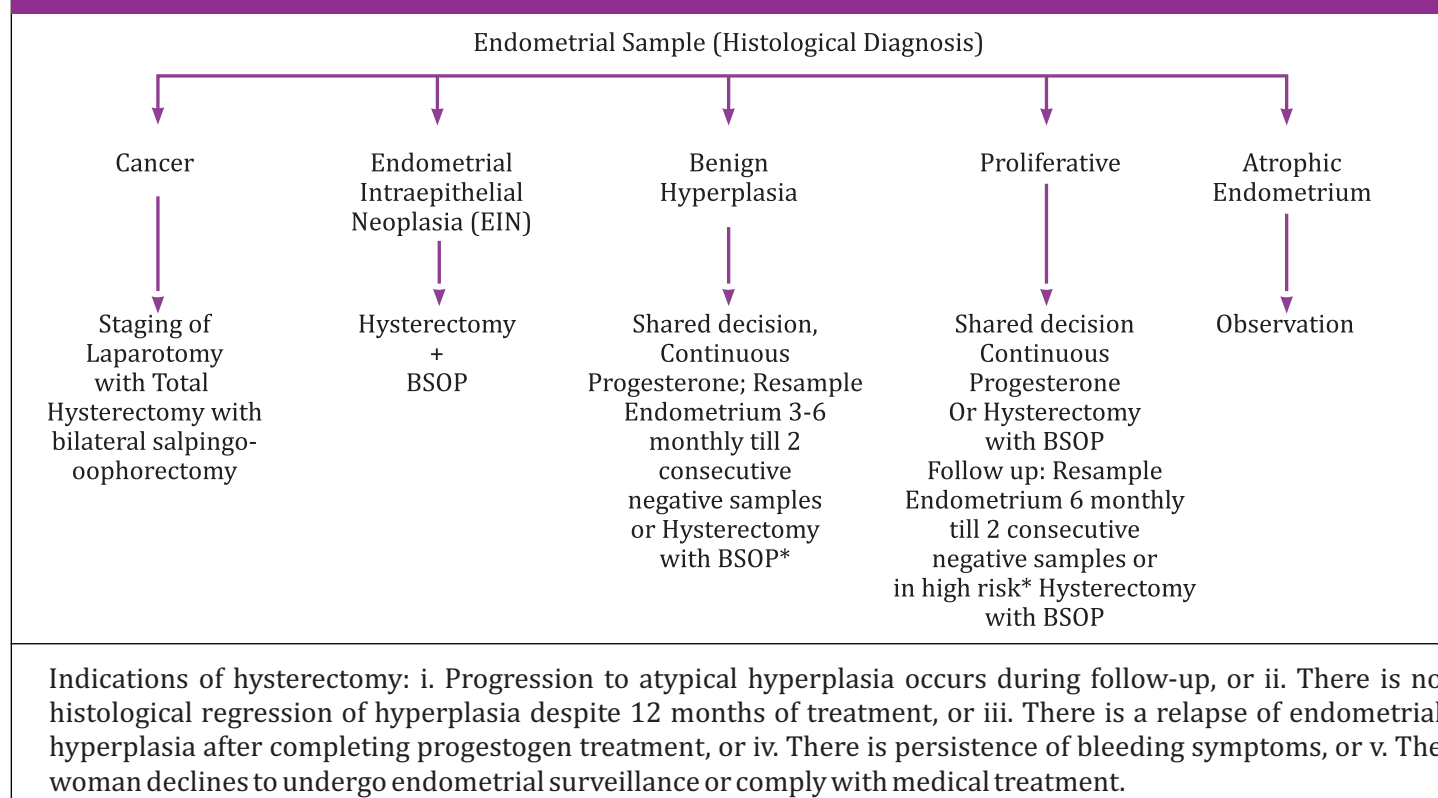
A proliferative endometrium in a postmenopausal woman is an abnormal finding and usually reflects unopposed estrogen exposure. Common causes include peripheral aromatisation of androgens in adipose tissue, particularly in obese women, as well as exogenous estrogen exposure or estrogen-producing ovarian tumours.⁴⁸ Management should focus on identifying and correcting the source of estrogen excess. Women should undergo evaluation for metabolic risk factors, review of medications and supplements, and assessment for ovarian pathology where clinically indicated. Although the immediate risk of malignancy is low, women with a proliferative endometrium are at increased long-term risk of developing endometrial hyperplasia or carcinoma, and therefore require close clinical follow-up. We should perform surveillance endometrial sampling every 3-6 months after initiating progestin treatment. If such sampling reveals benign, but not proliferative, endometrial changes, progestin therapy can be stopped and endometrial biopsy repeated if bleeding recurs.

The management suggestions included shared decision-making on surveillance versus intervention. The options are the levonorgestrel-releasing intrauterine (LNG) system and oral progesterone therapy. Further research is needed to develop evidence-based management guidelines for proliferative endometrium in women with PMB.⁴⁹ Definitive surgery with hysterectomy and bilateral salpingo-oophorectomy is not routinely indicated but may be considered in selected women with recurrent bleeding, high-risk features for endometrial cancer, unwilling for a regular follow up and persistent diagnostic uncertainty after appropriate reassessment.⁴⁸

Endometrial Hyperplasia

Endometrial hyperplasia may cause recurrent bleeding; the risk of progression to carcinoma is low in non-atypical hyperplasia but significantly higher in EIN. Management typically involves progestogen therapy, either systemic or via a LNG system, with interval endometrial surveillance. The regression rate for simple hyperplasia between progestin routes are 89% for oral progestins, 96% for the LNG-IUS. Progestin concentrations in the endometrium have been shown to be 100-fold higher after LNG-IUD placement compared with oral progestin use. In addition, adverse effects, including bloating, unpleasant mood changes, and increased appetite, are more common with oral than intrauterine progestin therapy. Hysterectomy is generally not required unless medical management fails or bleeding persists.^{50,51} Refer to chapter 60 for the flowchart on management.

Flowchart 1: Management based on histological diagnosis



Endometrial Intraepithelial Neoplasia (EIN): Refer to Chapter 31

Endometrial Carcinoma: Refer to Chapter 31

NON-ENDOMETRIAL CANCERS

PMB is also associated with other non-endometrial cancers. The most common of these is carcinoma of the cervix, with a reported incidence in women with PMB of 0.8-13%. Other associated tumour sites of the female reproductive tract include the fallopian tubes, vagina and vulva. In addition, postmenopausal women who complain of vaginal bleeding have a small but significant risk of having ovarian, breast or colorectal carcinomas.⁵² Unlike Western countries, remember carcinoma cervix is still an equally important cause of PMB.⁵³

RISK OF RECURRENT BLEEDING

Recurrent PMB following an initial benign endometrial tissue diagnosis continues to warrant clinical concern. Subsequent evaluation may reveal EC or EIN, either due to disease progression or missed focal pathology at the initial assessment.^{53,54} Accordingly, all women with recurrent PMB should undergo repeat investigation. Repeat investigation should prioritise modalities with high accuracy for detecting focal intrauterine disease, particularly outpatient hysteroscopy and/or SIS, alongside transvaginal ultrasound and endometrial sampling.^{51,55} While an ET $\leq$ 4 mm on TVUS has a high negative predictive value for malignancy, persistent or recurrent bleeding warrants further assessment regardless of ET.⁵³

Evidence from a five-year follow-up cohort of women presenting with recurrent PMB after an initial benign histological diagnosis demonstrated that a clinically meaningful proportion were subsequently diagnosed with EC or complex hyperplasia, with the risk being substantially higher in women aged ≥ 65 years.⁵³ Based on these findings, the authors suggested that definitive surgical management, in the form of total hysterectomy with bilateral salpingo-oophorectomy, may be considered in selected women with troublesome recurrent PMB when repeated multimodal evaluation remains negative, after individualised counselling on potential benefits, risks, and alternative management options. In another cohort, older age, nulliparity, a history of endometrial polyps, and a short interval (<12 months) between bleeding episodes or endometrial sampling were predictive of subsequent endometrial hyperplasia or carcinoma.⁵⁶

PERSISTENT PMB

In women with persistent PMB lasting six months or longer, diagnostic hysteroscopy with operative treatment is often effective, as benign structural causes, particularly endometrial polyps and submucous fibroids, are common. In one clinical series of 110 women with prolonged PMB, hysteroscopic management successfully controlled bleeding in nearly 90% of cases, while only a small number of early-stage endometrial cancers were identified.³⁴

PMB AFTER ENDOMETRIAL ABLATION

There may be a small segment of women who present with PMB after endometrial ablation. The challenges in investigations vary because standard diagnostic pathways may be less straightforward. Post-ablation cavity distortion and intrauterine synechiae can make ET assessment unreliable or unmeasurable on transvaginal ultrasound. It may also limit the feasibility or adequacy of blind endometrial biopsy and even hysteroscopic access in some cases.^{57,58} Although endometrial cancer after ablation appears uncommon, a contemporary systematic review (11 studies; 29,102 women) reported an incidence ranging from 0.0% to 1.6%; among 38 reported cancers, vaginal bleeding was the presenting symptom in 71%, and diagnostic work-up is not a challenge because of previous endometrial ablation.⁵⁹ Earlier systematic review data similarly suggest that cancer after ablation is rare but can occur across a wide interval following the procedure and often in women with baseline risk factors.⁶⁰ Importantly, despite technical limitations, most reported cancers are diagnosed at an early stage, supporting the principle that symptom-triggered evaluation remains essential. Similarly, population-based data demonstrate that endometrial resection or ablation does not increase the long-term incidence of endometrial cancer; however, malignancy may still occur years after the procedure, most commonly presenting with PMB, underscoring the need for symptom-driven evaluation in this population.⁶¹

In the absence of universally accepted evidence-based thresholds for imaging or sampling in the post-ablation uterus, investigation and management should be individualised, guided by the severity/persistence of bleeding, cancer risk profile, feasibility of obtaining histology, and multidisciplinary judgement.

TAMOXIFEN AND ENDOMETRIUM: Refer to Chapter 40

HORMONE THERAPY AND PMB: Refer to Chapter 37

SYNOPSIS

- PMB is defined as uterine bleeding occurring after at least 1 year of amenorrhea. Its incidence is about 10-15%.
- Women with PMB have a 10-15% chance of having endometrial cancer. Conversely, 90% of the endometrial cancer in the postmenopausal period presents with PMB. Hence, immediate evaluation is required.
- A common cause of PMB is due to atrophic changes in the vagina and the endometrium.
- A detailed clinical and drug history is important as some over-the-counter drugs like “Ginseng” can cause PMB.
- A thorough clinical examination is carried out to rule out cervical, vulval and vaginal cancer, atrophic vaginitis, urinary and anal causes for bleeding.
- Women with PMB may be assessed initially with TVS and an endometrial biopsy.
- A thorough clinical examination is carried out to rule out cervical, vulval and vaginal cancer, atrophic vaginitis, urinary and anal causes for bleeding. Women with PMB may be assessed initially with TVS and an endometrial biopsy.
- ET is measured as the maximum anteroposterior thickness of the EEC on a long-axis transvaginal view of the uterus.
- Women with PMB with an ET of less than or equal to 3-4 mm in transvaginal scan do not require endometrial sampling unless they are at a high risk for EC or bleeding is episodic.
- If ET is greater than 3-4 mm on TVS, endometrial sampling should be considered. In women with homogeneous and normal morphology, women on HT and hypertensive medication, the acceptable combined thickness is 6mm.
- A focal increased echogenicity or a diffuse heterogeneity in the endometrium, even in a thin endometrium, warrants further investigations.
- Outpatient hysteroscopy-directed biopsy is the gold standard; Pipelle is a simple procedure for global pathology in a low-risk woman.
- If the endometrial biopsy is reported as insufficient for diagnosis and the ET on transvaginal USG is less than 4 mm, follow-up is sufficient. Recurrent episodes warrant further investigations.
- D&C and fractional curettage are useful in low-resource settings. SIS and 3D USG play a limited role in PMB evaluation.

RESEARCH AGENDA

Comparison of the adequacy of the endometrial sample, pain score by D&C versus Pipelle’s biopsy.

REFERENCE

1. Moodley M, Roberts C. Clinical pathway for the evaluation of postmenopausal bleeding with an emphasis on endometrial cancer detection. *J Obstet Gynaecol*. 2004 Jan 24(7):736–41. doi: 10.1080/014436104100009394. doi/full/10.1080/014436104100009394
2. Approach to the patient with postmenopausal uterine bleeding - UpToDate [Internet]. [cited 2026 Feb 11]. Available from: <https://www.uptodate.cn/contents/approach-to-the-patient-with-postmenopausal-uterine-bleeding>. Accessed on 10/11/2025
3. Astrup K, Olivarius NDF. Frequency of spontaneously occurring postmenopausal bleeding in the general population. *Acta Obstet Gynecol Scand*. 2004 Feb;83(2):203–7. doi: 10.1111/j.0001-6349.2004.00400.x.
4. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women’s Health Initiative randomized controlled trial. *JAMA*. 2002 Jul 17;288(3):321–33. doi: 10.1001/jama.288.3.321
5. Smith-Bindman R, Weiss E, Feldstein V. How thick is too thick? When endometrial thickness should prompt biopsy in postmenopausal women without vaginal bleeding. *Ultrasound Obstet Gynecol*. 2004 Oct;24(5):558–65. doi: 10.1002/uog.1704.
6. Mirkin S, Archer DF, Taylor HS, Pickar JH, Komm BS. Differential effects of menopausal therapies on the endometrium. *Menopause* [Internet]. 2014 [cited 2026 Feb 11];21(8):899–908. doi: 10.1097/GME.0000000000000186

7. WHO SG. Research on the Menopause in the 1990's: A Report of the WHO Scientific Group. Geneva World Health Organ. 1996; 866,1:07.
8. Munro MG. Investigation of Women with Postmenopausal Uterine Bleeding: Clinical Practice Recommendations. Perm J [Internet]. 2014;18(1):55–70. doi: 10.7812/TPP/13-072. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3951032/> Accessed on 01/01/2026
9. Goldstein S. Evaluation of postmenopausal bleeding. Menopause. 2025;32(3):275–7. doi: 10.1097/GME.0000000000002522.
10. Gredmark T, Kvint S, Havel G, Mattsson LÅ. Histopathological findings in women with postmenopausal bleeding. BJOG Int J Obstet Gynaecol. 1995;102(2):133–6. doi:10.1111/j.1471-0528.1995.tb09066.x
11. Obstetricians ACO. ACOG committee opinion no. 734: the role of transvaginal ultrasonography in evaluating the endometrium of women with postmenopausal bleeding. Obstet Gynecol. 2018;131(5):e124–9. doi: 10.1097/AOG.0000000000002631
12. Van Hanegem N, Breijer MC, Khan KS, Clark TJ, Burger MPM, Mol BWJ, Timmermans A. Diagnostic evaluation of the endometrium in postmenopausal bleeding: an evidence-based approach. Maturitas. 2011 Feb;68(2):155–64. doi: 10.1016/j.maturitas.2010.11.010.
13. Clarke MA, Long BJ, Del Mar Morillo A, Arbyn M, Bakkum-Gamez JN, Wentzensen N. Association of Endometrial Cancer Risk With Postmenopausal Bleeding in Women. JAMA Intern Med. 2018 Sept;178(9):1210–22. doi: 10.1001/jamainternmed.2018.2820.
14. Makker V, MacKay H, Ray-Coquard I, Levine DA, Westin SN, Aoki D, et al. Endometrial cancer. Nat Rev Dis Primers. 2021 Dec 9;7(1):88. doi: 10.1038/s41572-021-00324-8.
15. Hickey M, Higham JM, Fraser I. Progestogens with or without oestrogen for irregular uterine bleeding associated with anovulation. Cochrane Database Syst Rev 2012 Sept 12;2012(9):CD001895. doi: 10.1002/14651858.CD001895.pub3.
16. Matanes E, Volodarsky-Perel A, Eisenberg N, Rottenstreich M, Yasmeen A, Mitric C, et al. Endometrial Cancer in Germline BRCA Mutation Carriers: A Systematic Review and Meta-analysis. J Minim Invasive Gynecol. 2021 May;28(5):947–956. doi: 10.1016/j.jmig.2020.11.023
17. Sung S, Carlson K, Abramovitz A. Postmenopausal Bleeding. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2026 Feb 11]. Available from: <http://www.ncbi.nlm.nih.gov/books/NBK562188/> Accessed on 12/01/2026
18. Nappi RE, Martini E, Cucinella L, Martella S, Tiranini L, Inzoli A, et al. Addressing Vulvovaginal Atrophy (VVA)/Genitourinary Syndrome of Menopause (GSM) for Healthy Aging in Women. Front Endocrinol. 2019 Aug 21;10:561. doi: 10.3389/fendo.2019.00561.
19. Gibson CJ, Huang AJ, McCaw B, Subak LL, Thom DH, Van Den Eeden SK. Associations of Intimate Partner Violence, Sexual Assault, and Posttraumatic Stress Disorder With Menopause Symptoms Among Midlife and Older Women. JAMA Intern Med 2019 Jan;179(1):80–7. doi: 10.1001/jamainternmed.2018.5233.
20. Van den Bosch T, Ameye L, Van Schoubroeck D, Bourne T, Timmerman D. Intra-cavitary uterine pathology in women with abnormal uterine bleeding: a prospective study of 1220 women. Facts Views Vis ObGyn [Internet]. 2015 7(1):17–24. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC4402439/> Accessed on 01/02/2026
21. Kagan R, Goldstein SR, Pickar JH, Komm BS. Patient considerations in the management of menopausal symptoms: role of conjugated estrogens with bazedoxifene. Ther Clin Risk Manag [Internet]. 2016 Apr 7;12:549–62. doi: 10.2147/TCRM.S63833. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC4827910/> Accessed on 10/02/2026
22. Van Hunsel FP, Kampschöer P. Postmenopausal bleeding and dietary supplements: a possible causal relationship with hop-and soy-containing preparations. Ned Tijdschr Geneesk 2012 [;156(41):A5095–A5095. Available from: <https://europepmc.org/article/med/23062258> Accessed on 10/02/2026
23. Unfer V, Casini ML, Costabile L, Mignosa M, Gerli S, Renzo GCD. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. Fertil Steril. 2004 Jul;82(1):145–8, quiz 265. doi:10.1016/j.fertnstert.2003.11.041.
24. Braun MM, Overbeek-Wager EA, Grumbo RJ. Diagnosis and management of endometrial cancer. Am Fam Physician 2016;93(6):468–74. Available from: <https://www.aafp.org/pubs/afp/issues/2016/0315/p468.html> Am
25. Nadaf A, Rani H, SS P, Rao R, Shastri D. Pap Smears in Endometrial Adenocarcinoma: Does It Have a Role? Asian Pac J Cancer Prev APJCP [; 2017;18(4):1145–50. doi: 10.22034/APJCP.2017.18.4.1145.
26. Jones AC, Irvin MR, Claas SA, Arnett DK. Lipid Phenotypes and DNA Methylation: A Review of the Literature. Curr Atheroscler Rep 2021 Sept 1 23(11):71. doi: 10.1007/s11883-021-00965-w
27. Colletti SM, Tranesh GA, Nassar A. Significance of finding benign endometrial cells in women 40–45 versus 46 years or older on Papanicolaou tests and histologic follow-up. Cytojournal. 2017 Sep 25;14:22. doi: 10.4103/cytojournal.cytojournal_16_17
28. Hernandez A, Schatz-Siemers N, Zhou F, Brandler TC, Negron R, Modi L, et al. Reporting of Benign Endometrial Cells in Papanicolaou Tests: Quest for Defining the Right Age Cutoff. Am J Clin Pathol. 2020 Aug 5;154(3):381–386. doi: 10.1093/ajcp/aqaa041.
29. Nayar R, Wilbur DC. The Bethesda System for Reporting Cervical Cytology: A Historical Perspective. Acta Cytol. 2017;61(4-5):359–372. doi: 10.1159/000477556
30. Manchanda R, Thapa S. An overview of the main intrauterine pathologies in the postmenopausal period. Climacteric. 2020 July 3 23(4):384–7. doi: 10.1080/13697137.2020.1776694.
31. Timmermans A, Opmeer BC, Khan KS, Bachmann LM, Epstein E, Clark TJ, et al. Endometrial thickness measurement for detecting endometrial cancer in women with postmenopausal bleeding: a systematic review and meta-analysis. Obstet Gynecol. 2010 Jul;116(1):160–167. doi: 10.1097/AOG.0b013e3181e3e7e8
32. Kumari K, Paswan MK, Kundan M, Ambedkar SN. A prospective study of endometrial histopathology in post-menopausal women in Jharkhand. J Fam Med Prim Care. 2024 May;13(5):1696–700. doi: 10.4103/jfmpc.jfmpc_1331_23.
33. Singh P, Dwivedi P, Mendiratta S. Correlation of Endometrial Thickness with the Histopathological Pattern of Endometrium in Postmenopausal Bleeding. J Obstet Gynecol India. 2016 Feb 66(1):42–6. doi: 10.1007/s13224-014-0627-z.
34. Ghoubara A, Sundar S, Ewies AAA. Endometrial pathology in recurrent postmenopausal bleeding: observational study of 385 women. Climacteric 2018 July 4 11;21(4):391–6. doi: 10.1080/13697137.2018.1461825.
35. Wagar MK, Mojdehbakhsh RP, Reetz E, Huang D, Kao MJ, Al-Niimi AN, et al. Ultrasonography-based measurements of endometrial thickness in patients with p53 abnormal endometrial carcinomas. Obstet Gynecol. 2025 Dec 1;146(6):881–887. doi: 10.1097/AOG.0000000000006074.

36. Zhang L, Guo Y, Qian G, Su T, Xu H. Value of endometrial thickness for the detection of endometrial cancer and atypical hyperplasia in asymptomatic postmenopausal women. *BMC Womens Health* 2022 Dec 12 [22:517. doi: 10.1186/s12905-022-02089-y
37. Li JXL, Chan F, Johansson CYM. Can a higher endometrial thickness threshold exclude endometrial cancer and atypical hyperplasia in asymptomatic postmenopausal women? A systematic review. *Aust N Z J Obstet Gynaecol*. 2022 Apr 62(2):190–7. doi:10.1111/ajo.13472
38. Li Z, Li L. Risk of malignancies among asymptomatic postmenopausal women with thickened endometrium. *Medicine (Baltimore)*. 2019 Feb 8;98(6):e14464. doi: 10.1097/MD.00000000000014464
39. Concin N, Matias-Guiu X, Cibula D, Colombo N, Creutzberg CL, Ledermann J, et al. ESGO-ESTRO-ESP guidelines for the management of patients with endometrial carcinoma: update 2025. *Lancet Oncol*. 2025 Oct;26(10):e522. doi: 10.1016/S1470-2045(25)00560-1.
40. Sakna NA, Elgendi M, Salama MH, Zeinhom A, Labib S, Nabhan AF. Diagnostic accuracy of endometrial sampling tests for detecting endometrial cancer: a systematic review and meta-analysis. *BMJ Open* 2023 June 23;13(6):e072124. doi: 10.1136/bmjopen-2023-072124
41. Epstein E, Ramirez A, Skoog L, Valentin L. Dilatation and curettage fails to detect most focal lesions in the uterine cavity in women with postmenopausal bleeding. *Acta Obstet Gynecol Scand* [2001 Dec;80(12):1131–6. doi: 10.1034/j.1600-0412.2001.801210.x
42. Dijkhuizen FPHLJ, Mol BWJ, Brilman HAM, Heintz APM. The accuracy of endometrial sampling in the diagnosis of patients with endometrial carcinoma and hyperplasia: A meta-analysis. *Cancer*. 2000 Oct 15;89(8):1765–72. doi: 10.1002/1097-0142(20001015)89
43. Wang X, Huang Z, Di W, Lin Q. Comparison of D&C and hysterectomy pathologic findings in endometrial cancer patients. *Arch Gynecol Obstet*. 2005 Aug;272(2):136–41. doi:10.1007/s00404-004-0712-0
44. Sasaki LMP, Andrade KRC, Figueiredo ACMG, Wanderley M da S, Pereira MG. Factors Associated with Malignancy in Hysteroscopically Resected Endometrial Polyps: A Systematic Review and Meta-Analysis. *Journal of minimally invasive gynecology*. 2018 Jul 1;25(5):777-85.
45. Trojano G, Damiani GR, Casavola VC, Loiacono R, Malvasi A, Pellegrino A, et al. The Role of Hysteroscopy in Evaluating Postmenopausal Asymptomatic Women with Thickened Endometrium. *Gynecol Minim Invasive Ther*. 2018;7(1):6–9. doi: 10.4103/GMIT.GMIT_10_17
46. Nijkang NP, Anderson L, Markham R, Manconi F. Endometrial polyps: Pathogenesis, sequelae and treatment. *SAGE Open Med*. 2019 May 2;7:2050312119848247. doi: 10.1177/2050312119848247
47. Ulin M, Ali M, Chaudhry ZT, Al-Hendy A, Yang Q. Uterine Fibroids in Menopause and Perimenopause. *Menopause N Y N*. 2020 Feb 27(2):238–42. doi: 10.1097/GME.0000000000001438
48. Rotenberg O, Doulaveris G, Fridman D, Renz M, Kaplan J, Xie X, et al. Long-term outcome of postmenopausal women with proliferative endometrium on endometrial sampling. *Am J Obstet Gynecol*. 2020 Dec;223(6):896.e1-896.e7. doi: 10.1016/j.ajog.2020.06.045
49. Srinivas S, Maiti S, Jothilakshmi P. Management of proliferative endometrium on biopsy in post-menopausal women. *J Gynecol Obstet*. 2016 [4(6):38–43.
50. Visser NCM, Sparidaens EM, van den Brink J, Breijer MC, Boss EA, Veersema S, et al. Long-term risk of endometrial cancer following postmenopausal bleeding and reassuring endometrial biopsy. *Acta Obstet Gynecol Scand* [Internet]. 2016 Dec;95(12):1418–24. doi: 10.1111/aogs.13022
51. Ring KL, Mills AM, Modesitt SC. Endometrial Hyperplasia. *Obstet Gynecol*. 2022 Dec 1;140(6):1061-1075. doi: 10.1097/AOG.0000000000004989.
52. Small W, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, et al. Cervical cancer: A global health crisis. *Cancer* 2017 July ;123(13):2404–12. doi: 10.1002/cncr.30667
53. Twu NF, Chen SS. Five-year follow-up of patients with recurrent postmenopausal bleeding. *Zhonghua Yi Xue Za Zhi (Taipei)*. 2000 Aug;63(8):628-33.
54. Van Doorn HC, Timmermans A, Opmeer BC, Kruitwagen RFMP, Dijkhuizen FPHLJ, Kooi GS, et al. What is the recurrence rate of postmenopausal bleeding in women who have a thin endometrium during a first episode of postmenopausal bleeding? *Acta Obstet Gynecol Scand*. 2008 Jan;87(1):89–93. doi: 10.1080/00016340701763130.
55. Veeranaraphanit U, Saeai N, Srisintorn W. Predicting Endometrial Hyperplasia and Endometrial Cancer on Recurrent Abnormal Uterine Bleeding. *Obstet Gynecol*. 2024 Aug 1;144(2):259-265. doi: 10.1097/AOG.0000000000005641
56. Johns DA, Garza-Leal JG, Diamond MP, Harris M. Post-ablation cavity evaluation: a prospective multicenter observational clinical study to evaluate hysteroscopic access to the uterine cavity 4 years after water vapor endometrial ablation for the treatment of heavy menstrual bleeding. *J Minim Invasive Gynecol*. 2020 Sep-Oct;27(6):1273-1280. doi:10.1016/j.jmig.2019.09.775.
57. Daub CA, Sepmeyer JA, Hathuc V, Sakala MD, Caserta MP, Clingan MJ, et al. Endometrial Ablation: Normal Imaging Appearance and Delayed Complications. *Am J Roentgenol* 2015 Oct;205(4):W451–60. doi: 10.2214/AJR.14.13960.
58. Oderkerk TJ, van de Kar MR, Cornel KM, Bongers MY, Geomini PM. Endometrial cancer after endometrial ablation: a systematic review. *Int J Gynecol Cancer* 2022 32(12):1555–60. doi: 10.1136/ijgc-2022-003866
59. AlHilli MM, Hopkins MR, Famuyide AO. Endometrial cancer after endometrial ablation: systematic review of medical literature. *J Minim Invasive Gynecol*. 2011;18(3):393–400. doi: 10.1016/j.jmig.2011.02.004
60. Floer Radestad A, Dahm-Kahler P, Holmberg E, Bjurberg M, Hellman K, Hellberg T, et al. Long-term incidence of endometrial cancer after endometrial resection and ablation: A population based Swedish gynecologic cancer group (SweGCG) study. *Acta Obstet Gynecol Scand* 2022 May 27 [;101(8):923–30. doi: 10.1111/aogs.14385.
61. Jhingran A. Updates in the treatment of vaginal cancer. *Int J Gynecol Cancer*. 2022;32(3):344–51. doi: 10.1136/ijgc-2021-002517

MENOPAUSE TRANSITION AND SYMPTOMS

Keywords: Vasomotor symptoms, physiology, variability, management

09

INTRODUCTION

The menopausal transition (MT) typically begins four years before the final menstrual period (FMP) and is characterised by irregular menstrual cycles, endocrine changes, and symptoms such as hot flushes that may affect a woman's quality of life (QoL).¹ Perimenopause includes MT and covers the period one year after the FMP. It may be considered a biological marker for chronic diseases. The biology and symptomatology of menopause are blurred by its relationship to the underlying ageing process and associated comorbidities.^{2,3} The critical question is who, when and how to treat it, and the answer lies in the impact of symptoms on patient-related outcomes (bothersome or not) and the long-term effects of estrogen deprivation on systems. The categorisation of menopausal symptoms into vasomotor (hot flushes, night sweats), somatic (muscle aches, headaches, joint pain), genitourinary (urogenital vaginal dryness, urinary issues and sexual - decreased libido, painful sex), and neuropsychiatric (mood changes, insomnia, concentration problems, "brain fog") is widely recognised and validated by both analytical studies and clinical assessment tools in the literature.^{2,3} At all stages of menopause, vasomotor and urogenital symptoms are directly linked to estrogen deficiency.

However, many other symptoms, like muscle and joint pain, vertigo, palpitation, paraesthesia, mood change, depression, insomnia, nervousness, formication, and decline in sexuality, are multifactorial and can be influenced by chronic diseases.^{4,5} The symptoms do not necessarily correlate with estrogen levels. The woman's perception of her health is crucial to her presentations.^{6,7} This distinction is crucial for personalised management of menopausal symptoms. The Penn Ovarian Aging Study found that the MT /perimenopause, characterised by fluctuations in estradiol rather than absolute low levels, is a strong predictor of hot flushes, joint pain/stiffness, and depressed mood.⁸ However, the study, similar to others, also found that poor sleep, decreased libido, and vaginal dryness were not strongly predicted by these estradiol fluctuations, suggesting additional non-hormonal, psychosocial, and local tissue factors contribute to these manifestations.⁹⁻¹¹

MENOPAUSE TRANSITION - A WINDOW OF OPPORTUNITY

Evidence from the robust, long-term, well-designed Study of Women's Health Across the Nation (SWAN) has clearly differentiated the effects of the MT from those of chronological midlife ageing across multiple physiological systems and health domains.¹² Other landmark longitudinal cohorts, including the Melbourne Women's Midlife Health Project and the Penn Ovarian Aging Study, have further refined our understanding of the temporal sequence of menopausal symptoms and their associations with QoL, sexual function, bone density, and reproductive hormone dynamics during the MT.^{13,14} The immediate changes are symptom clusters, menstrual irregularity, and exaggeration of estrogen-dominant diseases. The study showed that the MT uniquely accelerates adverse changes in cardiovascular (lipid abnormalities, vascular remodelling, and visceral fat deposition), musculoskeletal (bone density and physical function declines), cognitive (brain fog), sleep disturbances, and sexual health (decreased desire and vaginal dryness). Changes accelerated by midlife are increased blood pressure and body mass index (BMI) rather than the MT. Many chronic conditions and general physical decline are more related to ageing processes than to the hormonal changes of the MT.¹⁵⁻¹⁷

PREVALENCE OF MENOPAUSAL SYMPTOMS: INDIA AND GLOBAL

Table 1 presents data on the prevalence of menopausal symptoms in India from 1995 to 2011¹⁸, and Table 2 from 2012 to 2025.¹⁹⁻⁴³ Refer to Table 3 for the prevalence of menopausal symptoms in Caucasians vs nonresident Indians.^{45,46}

Table 1: Prevalence of Symptoms - Studies from India from 1995 to 2011

Symptoms in %	Ankleasaria B 1995	Krishna U 1995	Sparc Maitreyi 2000	Shah R 2004	Bagga 2004	Bipasa Sen 2006	Meeta 2008	S Sharma 2011
Number (total)		500	150		500		500	
Vasomotor	30	33	27	40	54	24	24	54
Psychological	36	20	46					60
Physical				58	28	64	64	78
Genitourinary	70	35	35	20			32	
Weight gain							17	43

Source: Meeta Menopause Management Simplified. New Delhi: Jagsonpal; 2012¹⁸

Table 2: Prevalence of Symptoms - Studies from India from 2012-2025¹⁹⁻⁴³

Author (Year)	Number of Participants	Vasomotor Symptoms (%)	Psychological Symptoms (%)	Physical Symptoms (%)	Genitourinary Symptoms (%)
Meeta et al. (2012) ¹⁹	1800	75	62	32	16
Borker et al. (2013) ²⁰	106		90.7 (emotional problems)	53.3 (Musculo-skeletal), 72.9 (headache), 65.4 (lethargy)	9.3 (genital), 31.8 (sexual), 58.9 (dysuria)
Singh A, Pradhan (2014) ²¹	252	46.4 (hot flushes), 45.6 (night sweats)	21 (anxiety), 32.1 (depression)	59.1 (joint/muscle pain), 62.7 (sleep disturbance)	
Garg et al. (2015) ²²	218	45 (hot flushes/sweating)	11 (anxiety/irritability), 65 (mood swings)	70 (muscle/joint pain), 46.7 (backache)	44 (change in sexual desire), 41 (vaginal dryness), 35 (urinary symptoms)
Kulkarni et al. (2016) ²³	100	65 (hot flushes/night sweats)	76 (depression), 73 (irritability)	92 (joint/muscle pain), 84 (exhaustion)	
Joseph, Varghese (2017) ²⁴	100	Not specified	Not specified	Not specified	Not specified

Karmakar, N. (2017) ²⁵	100	60	55	81	50
Shukla et al. (2018) ²⁶	100	21.3	4.7	91.5	
Khatoon et al. (2018) ²⁷	300	53.3 (hot flushes)	70 (depressive mood), 40.3 (anxiety), 46.6 (irritability)	87 (joint/muscle), 60.3 (heart discomfort), 60 (exhaustion), 56 (sleep problems)	26 (bladder), 23 (vaginal dryness), 20 (sexual problems)
Thakur et al. (2019) ²⁸	351	Not specified	Not specified	Not specified	Not specified
Patil, Deshmukh (2019) ²⁹	288	Not specified	Not specified	77.8 (joint/muscle), 54.5 (exhaustion)	Not specified
Anuradha et al. (2020) ³⁰	200	16.5 (hot flushes)	44.5 (anxiety), 43 (depression), 66.5 (irritability)	90.5 (joint/muscle), 57.5 (sleep problems), 40 (exhaustion), 35 (heart discomfort)	54 (vaginal dryness), 51 (bladder), 4.5 (sexual problems)
Armo & Sainik (2020) ³¹	199	Not specified	73.3	75.6 (somatic)	76.9
Kalhan et al. (2020) ³²	400	36.7 (hot flushes)	88.2 (anxiety 80)	79 (exhaustion 71.5, joint/ muscle 56)	32.7
Nagaraj et al. (2021) ³³	200	Not specified	Not specified	Not specified	Not specified
S. S RK et al. (2022) ³⁴	650	88.15 (hot flushes /night sweats)	93.38 depressive mood)	97.07 (muscle/ joint pain), 94.15 (sleep problems), 92.61 (tiredness)	Not specified
Sundararajan, Srinivasan (2023) ³⁵	264	Not specified	68.5 (irritability)	66.2 (joint/muscle pain), 66.1 (exhaustion), 70.2 (sleep problems)	Not specified
Mangasuli, Sherkhane (2023) ³⁶	334	Not specified	85.33	93.11(somatic))	33.53
Natarajan et al. (2024) ³⁷	148	Not specified	Not specified	93.2 (physical), backache 62.3	Not specified

Nath & Jain (2024) ³⁸	100	Not specified	Not specified	Physical exhaustion, joint/muscle pain (not quantified)	Not specified
Umamaheswari & Anitha (2024) ³⁹ (2018) ²⁶	100	85 (hot flushes)	Not specified	80 (mental/physical exhaustion), 70 (joint/muscle pain)	Not specified
Mediboina et al. (2024) ⁴⁰	100	25 (heat discomfort)	57 (anxiety)	82 (joint/muscle pain), 64 (sleep problems)	Not specified
Mathew et al. (2024) ⁴¹	86	45.5 (hot flushes)	38.6 (mood swings)	52.3 (pain on extremities), 34.1 (sleeplessness)	23.9 (cervical dryness)
Shah & Prajapati (2024) ⁴²	23 studies (systematic review)	Hot flushes (average not specified)	63.03 (average, psychological)	73.66 (average, somatic) epleteness)	51.40 (average, urogenital, 13 studies)
Shobhana M, et al. (2025) ⁴³	1479	38%	Not specified	Not specified	Not specified

Table 3 Menopausal symptoms-Caucasians vs nonresident Indians

Country	Vasomotor	Somatic	Sleep disturbance
UK Caucasians	86%	29%	68%
UK Asians	71%	50%	32%
Delhi Asians	30%	18%	12%
NRI Australia	33%	50%	

Indian Data

Studies from India (cross-sectional designs with sample sizes ranging from 86 to 1800 women) report a high prevalence of menopausal symptoms but a wide variation in reporting. Somatic symptoms are the most common (32%-97%), followed by psychological symptoms (4.7% -93%), and urogenital symptoms are the least prevalent (9.3%-76%). Vasomotor symptoms (VMS) have a wide prevalence, ranging from 16.5% to over 88% across regions and study populations. and indicate a need for more stringent criteria for reporting VMS.¹⁹⁻⁴³ Night sweats were reported in 58% of women in the Kerala study and in 88.15% when combined with hot flushes in the Telangana study.^{20,34} The finding that 96.6% of women in rural Puducherry experienced some menopausal symptoms highlights the near-universal nature of this health transition and the need for comprehensive healthcare planning.³⁷

Data from the 2024 Indian Menopause Society Registry showed that the overall prevalence of genitourinary syndrome of menopause (GSM) across all stages was 48.5%. The most prevalent symptoms were lower urinary tract symptoms (LUTS) (38.2%) and vaginal dryness (26.4%). The Vaginal Health Index (VHI) score was ≤ 15 in 42.1% of women. Prevalence increased from 28% at MT to 60% at early postmenopause and 71% at late menopause, as defined by the Stages of Reproductive Ageing Workshop (STRAW).⁴⁴ The prevalence of VMS in the United Kingdom (UK) Asians was reported as 71%⁴⁵ and in the Australian Indians as 33%.⁴⁶

Global Data

Globally, menopausal symptoms show marked regional and ethnic variation, with VMS being universal but differing greatly in prevalence. Moderate-to-severe VMS affect about 40% of European, 34% of United States (US), and only 16% of Japanese postmenopausal women.⁴⁷ Large multi-ethnic cohort and meta-analytic data involving over 480,000 women confirm that somatic and psychosomatic symptoms such as fatigue, musculoskeletal aches, sleep disturbance, depression, and weight gain are often more prevalent and more bothersome than hot flushes. Joint and muscular discomfort is the most common global symptom (>65%), while symptoms such as formication are the least frequent (>20%).⁴⁸ Multi-ethnic cohort data demonstrate that vasomotor and psychosomatic symptoms form distinct clusters and that symptom burden varies significantly by ethnicity, independent of age, education, health status, and socioeconomic factors, arguing against a single universal “menopausal syndrome.”⁴⁹ Postmenopausal symptom trajectories also differ by ethnicity, with Australian women showing a decline in vasomotor, psychological, and somatic symptoms after menopause, whereas Japanese women experience persistence of these symptoms.⁵⁰ Importantly, hot flushes and night sweats disproportionately impair daily functioning compared with work productivity, underscoring their clinical and QoL impact worldwide.⁵¹ Attitudes toward HT vary widely, with a high proportion of women remaining hormone-averse or cautious despite eligibility, particularly in East Asian populations. Tang R highlights important East-West differences in menopause symptomatology, rooted in both biological and sociocultural determinants, and advocates tailored clinical awareness and research that reflect these global diversities.⁵²

MENOPAUSAL SYMPTOMS

Changes in the menstrual cycle pattern: Refer to Chapter 2

Vasomotor Symptoms or Hot Flushes

The most common symptoms during the MT and menopause are hot flushes: details are given below.

Early Genitourinary Syndrome of Menopause

A slight decrease in vaginal lubrication upon sexual arousal is often one of the first signs of estrogen insufficiency. As the hypoestrogenic state becomes chronic, additional symptoms of GSM are reported. Sexual desire may decrease.⁵³ Refer to Chapter 10.

Somatic Symptoms

Refer to Chapter 1. In 1926, Cecil and Archer described “Arthritis of the menopause, a subset of degenerative arthritis affecting women around the age of 53.”⁵⁴

Midlife is a critical window for the development of poor physical functioning. Symptoms presenting at MT include joint and muscle pain (musculoskeletal pain, MSP), fatigue and exhaustion, backache, numbness and tingling of extremities, gastrointestinal complaints (such as bloating, constipation), headaches, palpitations, and sleep disturbances, and poor balance, which often cluster with psychological symptoms. A systematic review demonstrated a high prevalence of MSP among perimenopausal women (71%), with a significantly higher likelihood compared to premenopausal women (odds ratio [OR]: 1.63). The risk of moderate/severe MSP increases linearly from premenopause to postmenopause, highlighting the progressive nature of pain severity with advancing menopausal stage. The analysis may not fully account for confounding factors such as mood disorders, physical activity, BMI, comorbidities, and self-perception of health, which are known to influence MSP risk. Future research should address mechanistic pathways, confounding factors, and longitudinal outcomes to formulate targeted interventions.^{48,55}

The aetiology of these symptoms is multifactorial, involving hormonal changes (estrogen deficiency), psychosocial factors, and systemic inflammation. In the SWAN study, inflammation, as indicated by elevated levels of C-reactive protein and haemostatic markers, including plasminogen-activator inhibitor 1, tissue plasminogen activator antigen,

and factor VIIc, predicted poor physical functioning outcomes.^{17:56-58} In the Women's Health Initiative (WHI), women with baseline joint pain or stiffness were more likely to experience relief with either combined estrogen-progestin therapy or unopposed estrogen than with placebo.⁵⁹ The Melbourne Women's Mid-life Health Project found that postmenopausal women were more than twice as likely to experience aches and stiff joints compared with the premenopausal group. High severity and frequency of arthralgias correlated with higher BMI, negative mood, and unemployment.⁶⁰

Dalbergia sissoo, called *Shisham* or Indian rosewood, is a medicinal plant that has demonstrated antiosteoporotic and anti-inflammatory activities, as indicated by a decline in circulating tumour necrosis factor alpha (TNF α) (raised due to estrogen deficiency) at menopause, with concurrent reduction in alkaline phosphatase (ALP).⁶¹

Fibromyalgia is 10 times more common in women than in men, with the onset of symptoms occurring after menopause in as many as 58% of females. Women who had early menopause or hysterectomy are more likely to develop symptoms of fibromyalgia within the first year of menopause compared to females who had natural menopause.⁶²

Women on aromatase inhibitors (AIs) complain of joint pains along with the symptoms of VMS and GSM. The Arimidex Tamoxifen Alone or in Combination Trial (ATAC) reported that a third of women who were free of joint symptoms before treatment developed joint pain within the first few months of therapy, 35% in the Arimidex group and 30% in the Tamoxifen group.⁶³ Other studies report AI-induced arthralgia in up to 47% of women.^{64:65}

Diagnosis is primarily clinical, utilising validated symptom scales, and requires careful differentiation from other medical or psychiatric conditions. Understanding the presentation and diagnostic approach to somatic symptoms at menopause is crucial for effective management and improved women's health outcomes. However, the subjective nature of symptom reporting and the overlap with symptoms of ageing, comorbidities, and psychosocial stressors complicate diagnosis. The differential diagnosis should include Vitamin D deficiency, hypothyroidism, hyperparathyroidism, chronic infections, inflammatory rheumatic diseases and non-inflammatory rheumatic diseases like osteoarthritis, spondylolysis, and fibromyalgia.

Neuropsychiatric Symptoms and Sleep

Refer to Chapters 14, 15 and 16.

Early MT shows subtle changes in brain function and increased mood symptoms, linked to estradiol variability. Sleep complaints begin before the FMP, worsen around menopause, and persist after; vasomotor-related nocturnal arousals partly mediate mood-sleep links.

Breast Pain

Breast pain and tenderness are common in early MT and diminish by late MT, likely due to fluctuations in serum estradiol levels.⁶⁶

LONG-TERM CONSEQUENCES OF ESTROGEN DEFICIENCY

There are long-term effects of estrogen deficiency, including osteoporosis, cardiovascular disease (CVD), GSM and dementia.²

Skeletal and Muscular Changes: Refer to Chapters 17, 18, and 19

Cardiovascular Disease: Refer to Chapter 12

Late Genitourinary Syndrome of Menopause: Refer to Chapter 10

Dementia: Refer to Chapters 14, 15

Body Composition: Refer to Chapter 42

Skin and Hair Changes: Refer to Chapter 21

VASOMOTOR SYMPTOMS

VMS include hot flushes, cold sweats and night sweats.¹⁶ Such vasomotor events are part of a normal physiological response to fever. However, during menopausal flushes, the body's core temperature is not elevated. A hot flush is a subjective heat sensation associated with objective signs of cutaneous vasodilatation and a subsequent drop in core 107

temperature.^{67,68} Withdrawal of gonadal steroids induces flushes in a variety of patients: women treated with tamoxifen for breast cancer, women with premature ovarian failure, ageing men with diminished testosterone, and men with prostate carcinoma undergoing androgen ablation therapy.^{69,70}

Physiological Changes

The subjective sensation of heat is the predominant feature of the hot flush. Biophysical studies have supported the changes that occur during flushes.⁷¹ Hot flushes are characterised by an abrupt onset of warmth that usually begins in the upper chest and neck and spreads to the face, driven by cutaneous vasodilatation, an increased heart rate, lower blood pressure, and dizziness.⁷² These may be associated with redness and sweating that lasts for a few seconds to several minutes, with an average flush lasting about 3-6 minutes. Skin temperature may rise by 1-3°F during the flush, while core temperature falls slightly.^{71,73} The sensation is due to rapid vasodilatation of the skin blood vessels, which is associated with an increase in metabolic rate and heart rate (7-15 beats/min), a reduction in skin resistance, and a decrease in blood flow to the brain.^{71,72} Heart rate and skin blood flow peak approximately 3 minutes after the onset of a hot flush, triggering vasodilatation and a decrease in internal temperature (0.1-0.9°C), resulting in a feeling of chill.⁷³ The increase in skin temperature results from sudden peripheral vasodilatation, which is well demonstrated by plethysmography in the fingers, hands, or arms. This increased blood flow precedes the subjective sensation of the flush by at least 1 minute and persists for many minutes afterwards, gradually declining along with the temperature.⁷¹

Sweats have similar features, but are common at night and tend to be more prolonged. Night sweats can be more upsetting than daytime flushes because they disrupt sleep. Some women find that as a result they have insomnia, which leads to irritability, tiredness, forgetfulness and inability to concentrate. It is not the absolute level of estrogens, but the rate of estrogen withdrawal and fluctuations that determines the onset of flushes.⁷⁴ Flushes often begin during the MT, when serum estrogen levels fluctuate widely.⁷⁵ Eventually, most postmenopausal women will acclimatise to the low estrogen level, and the flushes will disappear.⁶⁷ However, even in these women, hot flushes may recur if estrogens are administered and then withdrawn.⁷⁶

Pathophysiology of Hot Flushes

Hot flushes are primarily linked to the decline in estrogen levels during menopause, which disrupts the hypothalamic regulation of body temperature.^{77,78} Several observations support the role of estrogen withdrawal in triggering hot flushes. Hot flushes occur most commonly during periods of estrogen withdrawal. Estrogen replacement therapy effectively treats hot flushes, and hot flushes can be induced by antiestrogens.^{70,79} The exact pathophysiology of hot flushes is not entirely understood and involves complex interactions between estrogen's fluctuating levels and withdrawal, thermoregulatory dysfunction, and central nervous system adaptations.

Thermoregulatory Dysfunction

The fundamental mechanism underlying hot flushes involves dysfunction of the hypothalamic thermoregulatory centre, located in the preoptic area, which appears to control the vasodilatation and sweating associated with hot flushes. The thermoregulatory nucleus regulates core body temperature and maintains it within a homeostatic range called the thermoregulatory zone. Core body temperature in homeotherms is regulated between an upper threshold for sweating and a lower threshold for shivering. Between these thresholds lies a neutral zone in which significant thermoregulatory responses (sweating, shivering) do not occur. Hot flushes are triggered when body temperature rises or when sweating thresholds are lowered. In normal women, heat-loss mechanisms are initiated once core body temperature rises by 0.4°C. In menopausal women, the thermoregulatory zone is narrowed; therefore, body temperature changes of as little as 0.1°C can trigger a hot flush.⁷¹

Core body temperature (T_c) also rises before hot flushes. These elevations may be caused by increased metabolic rate (heat production) and/or peripheral vasoconstriction (decreased heat loss).⁶⁸ Basic science investigations showed that the upper and lower thresholds of the thermoneutral zone in menopausal women were 0.0°C in symptomatic women and 0.4°C in asymptomatic women, indicating a narrow thermoneutral zone.^{80,81}

Autonomic Dysfunction and Neurotransmitter Changes: Central sympathetic dominance leads to alterations in monoaminergic tone (the balance and activity of monoamine neurotransmitters, primarily serotonin and norepinephrine), which play key roles in regulating mood, thermoregulation, and autonomic function. Estrogen withdrawal increases hypothalamic norepinephrine activity, narrowing the thermoregulatory zone and making the body more sensitive to slight changes in temperature.^{81,82} Estrogen influences serotonin (5-HT) synthesis, degradation, and receptor signalling. However, recent evidence questions the primary role of serotonin, as increasing

5-HT alone may not be adequate to alleviate hot flushes. Data indicate altered (often reduced) serotonergic tone or receptor/transporter dysfunction.^{83,84}

Thermoregulatory Instability: A slight increase in core body temperature triggers a hot flush, a rapid, exaggerated heat-dissipation response involving sweating and peripheral vasodilatation. In animal models, intrahypothalamic norepinephrine narrows the thermoregulatory zone, and in humans, an α 2-adrenergic antagonist (yohimbine) can provoke flushes, whereas an α -adrenergic agonist (clonidine) can reduce them, supporting a role for altered adrenergic signalling in symptomatic women.⁸²

Kisspeptin, Neurokinin B, and Dynorphin (KNDy) Neuron Signalling: The arcuate nucleus of the hypothalamus (thermoregulatory centre) is innervated by the Kisspeptin, Neurokinin B (NKB), and Dynorphin (KNDy neurons), involved in the generation of the gonadotropin-releasing hormone (GnRH) pulse. Kisspeptin and neurokinin B act as stimulatory signals, while dynorphin has an inhibitory effect within the KNDy circuit.⁶⁹ These are inhibited by estrogens and stimulated by neurokinin B (NKB) via neurokinin-3 receptors (NK3R). During menopause, declining estrogen leads to hypertrophy and overactivation of KNDy neurons. The unopposed neurokinin B (NKB) signalling via its receptor (NK3R) is a primary cause of hot flushes.⁸³ Alterations in their signalling, alongside changes in the monoaminergic system, can lead to autonomic and vascular changes. Furthermore, recent research highlights the involvement of the NK3R and nitric oxide-heat shock protein 70 (NO-HSP70) system in the physiology of these processes.

Autonomic and Vascular Changes: The blood vessels in the skin rapidly dilate to release heat, causing a sensation of warmth and flushing. The sweat glands are activated to cool the body.⁸⁴ Women with hot flushes show altered heart rate responses, particularly during stress tests such as the Valsalva manoeuvre, indicating autonomic imbalance. This imbalance may increase cardiovascular risk and exacerbate hot flush symptoms.^{85,86}

Vascular and Inflammatory Mechanisms

Nitric Oxide and Heat Shock Protein 70: Research also indicates a link between nitric oxide (NO) and heat shock protein 70 (HSP70) in the development of VMS. Estrogen withdrawal during menopause reduces HSP70, a cytoprotective protein involved in the anti-inflammatory heat shock response. These neuroendocrine alterations provide another potential pathway for understanding how estrogen deficiency contributes to menopausal hot flushes and increases the risk of chronic inflammatory diseases.⁸⁷

Elevated Inflammatory Markers: Early menopausal women with moderate to severe hot flushes have higher levels of vascular inflammatory markers, such as P-selectin and soluble CD40 ligand (sCD40L), than those with mild or no hot flushes and premenopausal controls.^{88,89}

Endothelial Dysfunction: Severity of hot flushes is the strongest independent predictor of impaired endothelial function (measured by flow-mediated dilation), linking hot flushes to early vascular changes and increased atherosclerotic risk.⁸⁹

Proinflammatory State: Chronic low-grade inflammation, characterised by increased cytokines and adhesion molecules are associated with hot flushes and vascular dysfunction, further amplifying symptom severity.⁸⁹

In conclusion, hot flushes result from a complex cascade involving estrogen withdrawal, a narrowed thermoneutral zone, altered neurotransmitter signalling, and KNDy neuron activation. This cascade ultimately leads to exaggerated heat dissipation responses that characterise this cardinal symptom of menopause. Vascular inflammation further amplifies symptoms and cardiovascular risk in menopausal women.

Brain Adaptation

The pathophysiology includes an important adaptive component.⁹⁰ The thermoregulatory system appears to adjust gradually to the new, hypoestrogenic state. Most women experience symptom resolution 2-7 years post-menopause, suggesting the brain undergoes "resetting" or "adaptation" to the hypoestrogenic state.⁹¹

Therapy Targets

Most Effective Therapy

Restoring estrogenic signalling (hormone therapy) reverses many of the central and peripheral changes and remains the most effective treatment for VMS.⁷⁶

Non-Hormonal Targets

Factors that modulate noradrenergic or serotonergic tone (α 2-agonists, Selective Serotonin Reuptake Inhibitors/Serotonin-Norepinephrine Reuptake Inhibitors [SSRIs/SNRIs]) and novel NK3R antagonists (targeting neurokinin B signalling) validate distinct nodes in the proposed pathway and provide effective non-estrogen options.⁹²

Therapies that reduce this activation, such as paced breathing, have been shown to reduce hot flushes. The efficacy of clonidine and certain antidepressants (SSRIs and SNRIs) in reducing hot flushes provides indirect evidence for the involvement of these pathways. The discovery of NK3R's central role in hot flushes led to the development of NK3R antagonists, such as fezolinetant, a groundbreaking non-hormonal treatment approved by the U.S. Food and Drug Administration (FDA). These drugs work by blocking overactive NKB signalling.⁹²

Broader Physiology

Recognising the autonomic and NO/HSP70 pathways links hot flushes to systemic vascular and inflammatory biology. This motivates research into whether VMS are biomarkers of later cardiometabolic risk or contributors via chronic neurovascular dysregulation.⁹³

Variability in Presentation

Timing

These symptoms often commence in the MT. The frequency and intensity of symptoms vary between women, and over time, the incidence of hot flushes typically increases during the MT, reaches a peak during the first 2 years of postmenopause, and then declines.¹⁷ Most women experience hot flushes for 6 months to 2 years, although some may experience them for 10 years or longer, with an average of 7.4 years.^{1,10} SWAN studied the most diverse racial and ethnic groups with a follow-up of more than 10 years. They found the peak occurrence of VMS in the late MT and early menopause, but VMS may present in women with regular cycles and extend into the 60s and 70s.^{10,17} A Swedish study found that about 9% of 72-year-old women have hot flushes.⁹⁴ An Australian study found a high prevalence of untreated moderate-to-severe VMS and sexual symptoms, even in women aged 60 to 65 years.⁹⁵

Frequent VMS lasted more than 7 years during the MT for more than half of women and persisted for 4.5 years after the FMP. According to the Massachusetts Women's Health Study, the incidence in the United States of America (USA) is 75% during the MT, with a median duration of 3.8 years.⁹⁶ Individual characteristics, including being premenopausal and having greater negative affective factors at the onset of VMS, were associated with longer-lasting VMS. Health care professionals should counsel women to expect that frequent VMS could last more than 7 years, and that they may last longer for African American women, as per the conclusions from SWAN.¹

Intensity

Hot flushes and night sweats have been graded as mild, moderate, and severe for ease of documentation, reproducibility, and management.⁹⁷⁻⁹⁹ A flush lasts for a few seconds to several minutes, with an average flush lasting about 3-6 minutes.

Frequency

The frequency of hot flushes varies widely among women. Some women may experience several episodes per hour, while others may have only occasional episodes. The frequency often increases during the late MT and early postmenopause.

Mild: Feeling of heat without sweating / 1-2 per day or <7 per week

Moderate: Feeling of heat with sweating / 3-4 per day or 7-14 per week

Severe: Feeling of heat with sweating and palpitations that disrupt usual activity $\geq$ 5 per day or >14 per week

Hot flush grading in research and clinical practice typically considers frequency and severity, with moderate/severe grades often defined as $\geq$ 4-5 hot flushes per day. However, subjective impact and severity ratings remain central to most validated scales and trial endpoints. Patient perception of bother and interference with QoL is also important and may not always correlate with frequency.^{100,101} Findings suggest that hot flush interference may be the most appropriate single measure to include in clinical trials of VMS therapies. Measuring and ameliorating patients' perceptions of hot flush interference with life activities and subjective sleep quality may be the most direct routes to improving QoL.

Hot Flush Index

Some studies use a composite "hot flush index" multiplying frequency by severity to quantify overall burden.^{102,103} However, subjective impact severity ratings remain central to most validated scales and trial endpoints.¹⁰⁴

Vasomotor Symptoms Following Induced Menopause

Abrupt menopause can result from surgical castration, radiation, chemotherapy, or drug-induced causes.⁷⁰ Flushes following surgical menopause can be particularly problematic. Surgical removal of the ovaries causes a dramatic drop in circulating estradiol within hours.¹³ Surgical menopause, a sudden transition, is associated with a particularly high risk of flushes. A follow-up study has shown that most women undergoing surgical menopause develop particularly distressing flushes, but the full extent of the problem is often not established at discharge from the hospital or even at follow-up 6 weeks later.^{105,106} The risk is the same for women close to the menopause and those who had a full reproductive function before surgery.¹⁰⁷ Menopause induced by surgery is associated with about a 90% probability of hot flushes during the first year. Symptoms associated with surgical menopause are often more abrupt and severe.¹⁰⁸ They can last longer than those associated with a non-surgical menopause. Over time, they become similar to those of natural menopause.^{109,110}

Other Factors Influencing the Experience of Menopause Transition

The age at menopause and the transition experience are likely influenced by genetic and environmental factors. Genetic variants, particularly in the TACR3 gene, are modestly associated with VMSs in midlife women, with reported odds ratios of 0.78-1.3, suggesting a small but significant contribution to symptom risk.¹¹¹ In a study by Grub, estrogen receptor (ER) gene polymorphisms emerged as key factors that modulate the effect of E2 fluctuations on the trajectory of menopausal symptoms.¹¹² Menopausal hot flushes were significantly associated with age, menopausal stage, education level, race, ethnicity, and cigarette smoking.^{10,102,110,113-115}

The prevalence of menopausal symptoms ranges from 0.1% in the Mayan population to 80% in the Dutch population. These variations are questionable because reporting, characterisation, and grading of symptoms have not been standardised in many studies.¹¹⁶ More African American and Hispanic women and fewer Chinese and Japanese women than White women will report VMS, but the magnitude of change in VMS as women progress from one MT stage to the next will not differ by race/ethnicity. Ethnic differences in VMS reporting, similar to those found here, have been reported previously.¹¹⁴

Higher BMI is independently associated with increased frequency, severity and persistence of VMS, both directly and through related chronic conditions and behavioural factors.^{1,117,118} Obesity worsens hot flushes by impairing heat dissipation, increasing hypothalamic thermoregulatory instability, and amplifying inflammatory and metabolic signalling, overriding any protective effect of peripheral estrone production. Longitudinal studies are needed to establish temporal and causal inferences. Past and current smoking can increase the risk of hot flushes.¹¹⁵ A unique contribution of the Midlife Women's Health Study (MWHs) is the observation that some personal interventions, such as quitting smoking, may reduce the odds of hot flushes. Low education and negative mood increase the risk.¹¹⁹ Warm ambient air temperature and low physical activity may also increase the risk. Moderate physical activity may reduce the risk.¹²⁰ No relationship was found between hot flushes and emotional stress. Likewise, eating hot, spicy foods, consuming alcohol, and caffeine were not found to increase the risk.¹²¹

DIAGNOSIS OF VASOMOTOR SYMPTOMS

VMS are primarily diagnosed clinically, based on a detailed history. The STRAW staging system may help identify the menopausal stage and correlate symptom presentation with age and menstrual patterns. The typical presentation includes a sudden sensation of heat involving the face, neck, and chest, often accompanied by flushing, sweating, and palpitations, followed by chills. Physical examination has a limited role in diagnosis but may help exclude alternative causes. Assessment of vaginal pH and vaginal cytology may provide supportive evidence of hypoestrogenism by indicating associated GSM, rather than directly contributing to the diagnosis of VMS.

Routine laboratory evaluation is not recommended for diagnosing VMS. Although follicle-stimulating hormone (FSH) levels may be elevated during the MT, significant variability limits their diagnostic utility. Low estradiol levels support a hypoestrogenic state but are not required for diagnosis, and inhibin B declines early in the MT but is not routinely used in clinical practice. Hormonal testing is therefore reserved for cases with diagnostic uncertainty, suspected premature ovarian insufficiency, or atypical clinical presentations.

A therapeutic trial of hormone therapy (HT) may be considered in selected cases; however, it is primarily used for management rather than diagnosis.

ASSESSMENT AND MEASUREMENT

Subjective and objective methods can be used to measure the intensity of hot flushes. Individual perceptions may vary across daily activities or during sleep, limiting the reliability of subjective measures. Nonetheless, women reliably describe their hot flushes as mild, moderate, or severe. A diary of hot flush frequency and severity used by Mayo Clinic investigators in seven clinical trials with 968 patients was consistent and reliable. Various scoring systems are available to document and clarify symptom severity. These scoring systems help evaluate symptom severity, assess the effectiveness of different therapies, build confidence in the woman, and support everyday communication in research. The commonly used scores are the Menopause Rating Scale, the Utian Scale, and the Cervantes Short-Form Scale.¹²²⁻¹²⁴ Objective assessment methods include finger and core temperature, skin conductance, body temperature, and sternal conductance monitoring. Although most objective measures of hot flushes are accurate, they require close observation and monitoring, and many are invasive. Objective monitoring is more resource-intensive and may not be feasible for routine clinical use, but it is valuable in research and complex diagnostic cases.¹²⁵

DIFFERENTIAL DIAGNOSIS¹²⁶

The clinical situation most often points to a diagnosis of menopausal flushing. Flushing can also be caused by other pathological conditions and medications. FSH levels are measured only if there is a suspicion of other causes of flushing.

Medications: Nicotinic acid, Selective Estrogen Receptor Modulators (SERMs) (such as tamoxifen, raloxifene), Gonadotropin-Releasing Hormone (GnRH) analogues, Als (such as anastrozole, letrozole), bromocriptine, opiates, alcohol, alpha-2 adrenergic antagonists (such as yohimbine) *Systemic Diseases:* Thyroid diseases, carcinoid syndrome, mastocytosis, medullary thyroid carcinoma, pancreatic carcinoma, pheochromocytoma, renal cell carcinoma, mealtime anxiety, migraine, Parkinson's disease, spinal cord lesions.¹¹⁴

Associated with Eating and Food Additives: Auriculotemporal dumping syndrome, hot beverages, monosodium glutamate, and sodium nitrite.

Infections: Tuberculosis, autoimmune deficiency syndrome, and recurrent urinary tract infections.

MANAGEMENT OF PALPITATIONS

Avoid smoking, caffeinated drinks, and tobacco. Restore hormonal balance with HT in patients with palpitations as part of the postmenopausal syndrome. Treat any other underlying cause if detected. Eliminate or reduce drugs known to precipitate palpitations. Breathing exercises, stress management, morning and evening meditation, and beta-blockers such as propranolol may be used.

MANAGEMENT OF VASOMOTOR SYMPTOMS

Management should be guided by symptom severity, the woman's most bothersome complaint, and her expected outcomes. An individualised approach must emphasise the pattern of symptom presentation, whether isolated or clustered, comorbidities, and patient-specific priorities to target interventions more effectively. Optimal care integrates hormonal therapy, non-hormonal pharmacological options, and evidence-based lifestyle and dietary strategies.

Placebo Effect

Interpretation of treatment efficacy in VMS trials is substantially influenced by a robust placebo effect. In randomised, placebo-controlled studies, placebo alone produces approximately 20-50% reductions in hot flush frequency and severity, with clinically meaningful improvement often observed within 4-12 weeks. This high placebo response underscores the need for rigorously designed, placebo-controlled randomised trials to accurately distinguish true therapeutic effects from non-specific symptom improvement.^{127,128}

Hormone Therapy

Menopausal Hormone Therapy

112 Estrogen therapy is the treatment of choice for VMS and reduces both the weekly frequency and the severity of these

symptoms, and addresses all menopausal symptoms with long-term benefits.¹²⁹ Progestin therapy at high doses, including depot medroxyprogesterone acetate (DMPA) and megestrol, also decreases hot flushes but is not nearly as effective as estrogen. The indication for progesterone use in Menopausal Hormone Therapy (MHT) is to suppress estrogen-induced endometrial proliferation.¹³⁰ For hot flush relief, hormone treatment lasts 3 to 5 years, and discontinuation may lead to recurrence in up to 50% of cases.^{131,132} Considering the benefits of HT for osteoporosis prevention and QoL improvement, and for the treatment of persistent VMS, there is a current trend to extend therapy until age 60 or 65. Refer to Chapter 37.

Tibolone

Tibolone has estrogenic, progestogenic, and androgenic properties. Refer to Chapter 39.

Selective Estrogen Receptor Modulators

Refer to Chapter 40

Bazedoxifene

This combination of bazedoxifene and conjugated estrogens is approved for treating vasomotor symptoms and preventing osteoporosis. Refer to Chapter 40.

Non-Hormonal Therapy

For women who are unable to or choose not to use MHT to treat VMS, there are several alternative pharmacologic and non-pharmacologic therapy options, but the efficacy is generally lower than that of MHT.

Non-pharmacological interventions such as weight reduction, exercise, yoga, acupuncture, paced respiration, diet-based therapies, tai chi, nutraceuticals, vitamins, phytoestrogens, and alternative and complementary therapies have been evaluated for VMS but show inconsistent and limited evidence of efficacy. In contrast, mind-body interventions, including cognitive behavioural therapy (CBT), clinical hypnosis, and mindfulness-based stress reduction, demonstrate more consistent benefits and are therefore recommended as effective non-pharmacological treatment options.

Counselling: has an important role to play: encourage lifestyle modification, engage in regular exercise, especially if overweight, use cooling methods such as handheld fans, drink cold water, wear layered clothing, try relaxation methods such as paced, deep breathing daily and during the attack, avoid triggers such as caffeine, spicy food, alcohol, tobacco, and learn or seek help to handle stressful situations.

Dietary Modifications and Weight Loss: Maintaining a healthy weight is associated with a greater likelihood of eliminating VMS; weight loss as part of a healthy diet can help reduce hot flushes.^{133,134} Eating regular meals and staying hydrated are general healthy lifestyle recommendations often included in dietary guidance for managing hot flushes. However, direct clinical trial evidence for these behaviours is less robust. A randomised controlled trial (RCT) found that a low-fat, plant-based diet with daily soybeans reduced moderate-to-severe hot flushes by 88%, compared with 34% in controls.^{79,135}

Avoiding Triggers: Multiple studies confirm that hot flushes are spontaneous and can be triggered by both internal and external factors. Thermal stimuli, such as increased ambient temperature or the consumption of hot beverages, chemical triggers, such as caffeine and spicy foods, and psychological factors, such as stress or anxiety, have all been shown to precipitate hot flushes in susceptible individuals.^{69,136-138}

Environmental Modifications: include keeping cool with fans or air conditioning; layering clothing for easy removal with moisture-wicking fabrics.

Mind-Body Techniques

Cognitive-behavioural Therapy: CBT has robust evidence from RCTs demonstrating clinically meaningful reductions in the bothersomeness of VMS in women with and without a history of breast cancer, with an average 50% reduction after 8 hours of group CBT; weekly group sessions over 4-6 weeks, with benefits maintained at six months.^{139,140} A brief, unguided self-help cognitive behaviour therapy (SHCBT) booklet is a potentially effective management option for working women experiencing problematic issues.¹⁴¹ For women with induced VMS after breast cancer therapy, internet-based CBT (with or without therapist guidance) has demonstrated clinically meaningful reductions in the perceived impact and frequency of hot flushes and night sweats (HF/NS) and improved sleep quality in a large RCT.

CBT is therefore recommended as a first-line non-pharmacological treatment for VMS, particularly in women who cannot or do not wish to use HT.

Clinical Hypnosis: Clinical hypnosis is a structured mind-body therapy that uses deep relaxation, individualised imagery, and therapeutic suggestion. It produces clinically significant reductions in both subjective and objectively measured vasomotor symptoms, with additional improvements in sleep and mood, and effects that are independent of expectancy. It is a recommended non-pharmacological therapy for hot flushes.^{142,143}

Stress Management: Stress-reduction techniques may help manage menopausal symptoms. Shifting the focus from an individual symptom, such as hot flushes, to a symptom cluster, including hot flushes, mood and sleep symptoms, may prompt clinicians to redesign therapies to target interventions more effectively and maximise treatment effects. At the early MT stage, the late MT stage, and the early PM, the symptom factor structure of the previous stage best predicted the symptom clusters. Education level was the only demographic variable that showed a significant relationship to the symptom factor structure at any stage.¹⁴⁴

Mindfulness-Based Interventions (MBIs): Evidence for MBIs in the management of VMS is limited and inconsistent. Mindfulness-Based Stress Reduction (MBSR) may be a clinically significant resource for reducing the degree of bother and distress women experience from hot flushes and night sweats.¹⁴⁵

Exercise, Yoga, Tai Chi: Refer to Chapter 35.

Nutraceuticals, Vitamins, Phytoestrogens, Alternative and Complementary Therapies:

Refer to Chapter 41.

NON-HORMONAL PRESCRIPTION-BASED THERAPIES

These comprise a diverse group of centrally acting medications that modulate hypothalamic thermoregulation and related neurochemical pathways to reduce menopausal VMS. All of them are second-line therapies. These include antidepressants, such as SSRIs paroxetine, escitalopram, citalopram, fluoxetine, and SNRIs venlafaxine, desvenlafaxine, and duloxetine; anticonvulsant neuromodulators such as the gabapentinoids gabapentin and pregabalin; centrally acting alpha-adrenergic agents, principally the alpha-2 agonist clonidine; anticholinergic antimuscarinic agents such as oxybutynin; and hypothalamic thermoregulatory pathway modulators, notably neurokinin-3 receptor (NK3R) antagonists fezolinetant and a dual NK1/NK3 receptor antagonist elinzanetant.

Non-hormonal VMS therapy must be individualised based on symptom clustering, comorbidities and safety profile; NK3 antagonists represent the most targeted and rapidly effective option. Refer to Table 4.

Neurokinin B Receptor Antagonist

Neurokinin-B receptor antagonists were initially investigated in the 1980s-1990s for central nervous system indications, including schizophrenia and affective disorders. Although early psychiatric development was discontinued, subsequent elucidation of hypothalamic KNDy neuron pathways led to their repositioning as targeted non-hormonal therapies for menopausal VMS.

Fezolinetant, approved by the FDA in 2023, and elinzanetant, approved by the FDA in 2025, represent important non-hormonal therapies for VMS. Fezolinetant, a selective neurokinin-3 (NK-3) receptor antagonist, has demonstrated superiority over placebo within and up to 12 weeks of use.¹⁴⁶ The FDA has approved the use of fezolinetant in postmenopausal women. In meta-analyses, fezolinetant 45 mg once daily was significantly more effective than other non-HTs in reducing the frequency and severity of moderate-to-severe VMS and in improving QoL measures, with effects on symptom severity that were comparable or superior.^{147,148} Across all fezolinetant dose groups, more than 80% of participants experienced a $\geq 50\%$ reduction in moderate or severe VMS, and more than half of women achieved a $\geq 90\%$ reduction.¹⁴⁹ Results from the SKYLIGHT-4 trial confirm the 52-week safety and tolerability of fezolinetant, with no clinically significant adverse effects on endometrial, breast, or bone health, thereby supporting its continued use as a non-hormonal therapy for VMS. Overall, 98.2% of participants receiving fezolinetant had liver function test results within the normal range, compared with 99.0% in the placebo group. Improvement in VMS is seen within a week, with maximal benefit by 2-4 weeks and sustained efficacy over long-term use.¹⁵⁰

Elinzanetant 120 mg/day, a dual neurokinin B receptor-1 and receptor-3 (NK-1/NK-3) antagonist, has demonstrated significant reductions in the frequency and severity of moderate-to-severe VMS and related sleep disturbances in postmenopausal women.^{151,152}

A recent analysis comparing SSRI/SNRI and NK3R antagonists found that SSRI/SNRI efficacy ranged from 48% to 67% reductions in VMS frequency from baseline at 8-12 weeks, with efficacy broadly comparable to NK3R antagonists.¹⁵³

Neurokinin-3 receptor antagonists have a comparatively favourable adverse-effect profile, enhancing tolerability. In contrast, commonly used SSRIs and SNRIs are frequently associated with gastrointestinal and neurovegetative adverse effects, including nausea, dry mouth, insomnia, dizziness, constipation, and weight gain, which may limit long-term adherence and clinical acceptance. NK-3 receptor antagonists are usually not associated with classical withdrawal phenomena, but dose reduction rather than sudden cessation is reasonable until longer-term post-marketing data are available. There are currently no head-to-head trials directly comparing the efficacy of fezolinetant with MHT. Fezolinetant is a non-hormonal therapy and therefore does not provide the systemic benefits of MHT on bone, collagen, or cardiometabolic health; available clinical trial data suggest it is broadly neutral for these outcomes over the studied durations, with efficacy limited to VMS control.

Prerequisites and Monitoring

Before initiating NK3, confirm and document the indication of moderate to severe VMS, and exclude secondary causes of flushing. Baseline assessment of general health must include liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], ALP and total bilirubin), renal function, review of concomitant medications (avoiding strong cytochrome P450 1A2 [CYP1A2] inhibitors), and exclusion of pregnancy in perimenopausal women. These agents are contraindicated in women with active liver disease or baseline transaminases greater than twice the upper limit of normal. Liver function tests should be repeated at 4, 8 and 12 weeks after initiation and thereafter every six months if stable, with immediate discontinuation recommended if ALT or AST rise to ≥ 3 times the upper limit of normal or to ≥ 2 times the upper limit of normal with associated symptoms.¹⁵⁴

Other Non-hormonal Prescription Therapies

SSRIs/SNRIs, gabapentinoids, and clonidine produce mild to moderate reductions in VMS. RCTs report approximately 25-69% reductions in hot flush frequency and severity compared with placebo in women with natural or surgical menopause, including cancer survivors.¹⁵⁵⁻¹⁵⁷

Selective Serotonin Reuptake Inhibitors and Serotonin-Norepinephrine Reuptake Inhibitors

SSRIs and SNRIs are widely used to treat a broad range of psychiatric and functional disorders beyond major depression, including panic disorder, obsessive-compulsive disorder, generalised and social anxiety disorders, post-traumatic stress disorder, body dysmorphic disorder, bulimia nervosa, binge-eating disorder, premenstrual syndrome, and somatoform disorders. Menopausal VMS and vulvodynia also respond to these agents, typically at lower doses than those used for the treatment of major depressive disorder.¹⁵⁸⁻¹⁶³

The use of SSRIs and SNRIs is contraindicated in individuals with neuroleptic malignant syndrome or serotonin syndrome, and in those receiving monoamine oxidase inhibitors (MAOIs) due to the risk of life-threatening serotonin toxicity. Caution is required when prescribing SSRIs and SNRIs in patients with uncontrolled seizure disorders, bipolar disorder, renal or hepatic impairment, uncontrolled hypertension, hyponatraemia, and in those currently using another SSRI or SNRI. Genetic polymorphisms affecting cytochrome P450 metabolism may also alter drug levels and increase adverse effects, warranting dose individualisation.

Oxybutynin

Oxybutynin, an antimuscarinic used for overactive bladder, significantly improves moderate to severe VMS in postmenopausal women at doses of 2.5-5 mg twice daily up to 15 mg extended-release daily.¹⁶⁴ Long-term use may be associated with cognitive decline in older women.^{164,165}

Duloxetine

Duloxetine is a dual SNRI.¹⁶⁶ It is understood to enhance the activity of the striated muscle of the external urethral sphincter during the urine storage phase and is recommended as a second-line therapy for stress urinary incontinence, only if a patient prefers medication over surgery or is medically unsuitable for surgical intervention. It has been shown to relieve VMS.¹⁶⁶ Duloxetine has been found to reduce VMS in smaller studies. Hot flush reductions vary from 25% to 69% with these treatments, with improvements in composite hot flush severity and frequency from 27% to 61%.¹⁶⁷ Escitalopram and duloxetine are both effective treatments for relieving hot flushes in breast cancer survivors with similar beneficial effects. In an RCT, significant improvement in depression was observed at the end of

the study period in both groups, with no major side effects.¹⁶⁸ Duloxetine should be initiated and discontinued with gradual dose titration to minimise withdrawal effects. The most common adverse event reported with duloxetine is nausea. Duloxetine should not be used in individuals with liver issues or when combined with certain medications, such as CYP1A2 inhibitors (such as ciprofloxacin) or monoamine oxidase inhibitors. Maund et al. reported that the harmful effects of duloxetine outweigh its beneficial effects.¹⁶⁹

Gabapentin

Gabapentin is a gamma-aminobutyric acid (GABA) analogue and antiepileptic agent that is effective in reducing VMS.^{155,170} RCTs show that gabapentin 900 mg/day (300 mg three times daily) significantly reduces the frequency and severity of hot flushes compared with placebo,^{170,171} and higher doses (up to 2,400 mg/day) show efficacy comparable to estradiol (conjugated equine estrogens [CEE] 0.625 mg/day) but are limited by adverse effects.¹⁷² Bedtime dosing may be beneficial for women with sleep disturbances. Gabapentin carries a class warning for suicidal thoughts and can lead to dependence. Long-term data are limited.

Duration of Treatment and Follow-Up

Refer to Table 4. Most non-hormonal therapies for vasomotor symptoms, including SSRIs/SNRIs, gabapentin, pregabalin, clonidine, and oxybutynin, produce clinically meaningful improvement within 1-2 weeks, with maximal benefit typically achieved by 4-6 weeks. An adequate therapeutic trial is generally considered to be 6-8 weeks at an effective dose before response is assessed. These medications should not be co-administered with other antidepressants or with preparations containing St John's Wort.¹⁵⁴ If effective and well-tolerated, therapy may be continued for several months with periodic reassessment, as vasomotor symptoms often diminish over time. Discontinuation should be gradual rather than abrupt, particularly for SSRIs/SNRIs, gabapentinoids, and clonidine, to minimise withdrawal or rebound effects such as dizziness, insomnia, anxiety, nausea, or rebound hypertension (with clonidine). For most agents, stepwise dose tapering over 1-2 weeks is sufficient; longer tapering schedules may be required after prolonged use or higher doses. International consensus further recommends considering antidepressant discontinuation after approximately 6-18 months following remission of anxiety symptoms and 4-12 months following remission of depressive disorders.^{173,174} The duration of use for VMS relief is not defined.¹⁵⁷ Follow-up is suggested at 1 month, 3 months, 6 months, and 1 year to evaluate treatment response, tolerability, and adverse effects.

Drug Interaction and Comorbidities

The selection of non-hormonal therapy must account for its drug interactions and other effects on the body. Potent cytochrome P450 2D6 (CYP2D6) inhibitors, such as paroxetine and fluoxetine, may reduce the conversion of tamoxifen to its active metabolite, endoxifen, and should generally be avoided in breast cancer survivors receiving tamoxifen. Weak or minimal CYP2D6 inhibitors, such as venlafaxine (37.5 mg-75 mg/day), desvenlafaxine (50-100 mg/day), escitalopram (10-20 mg/day), or citalopram (10-20 mg/day), are preferred alternatives in this setting.^{175,176} Both venlafaxine (75 mg/day) and low-dose oral estradiol (0.5 mg/day) effectively reduce VMS in midlife women, with only a small and clinically uncertain advantage for estradiol.¹⁷⁷ Low-dose paroxetine (7.5 mg/day) is the only SSRI approved by the United States Food and Drug Administration (US FDA) for moderate to severe VMS and has shown sustained improvements in hot flush frequency, severity, and sleep disruption. It is well-tolerated and maintains efficacy for up to 24 weeks.¹⁵⁸ Low-dose paroxetine (7.5 mg/day) is not available in India; only higher doses (10 mg, 12.5 mg controlled-release (CR), 20 mg) are available, which are antidepressant doses and not menopause-specific. In Indian clinical practice, venlafaxine, desvenlafaxine, or escitalopram are preferred non-hormonal options. Venlafaxine was associated with the most adverse lipid profile, with the highest total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and total cholesterol to high-density lipoprotein (TC: HDL) ratio. Citalopram/escitalopram had the least detrimental lipid profile.¹⁷⁸ Citalopram and escitalopram also appear to exert beneficial effects on glycaemic control, as evidenced by reductions in glycated haemoglobin (HbA1c) and fasting blood glucose.¹⁷⁹ High-dose citalopram should be avoided in women with baseline QT (electrocardiogram interval) prolongation. Oxybutynin should be avoided in women at increased risk of cognitive impairment, and gabapentinoids should be used cautiously or avoided in women at high risk of falls.¹⁸⁰⁻¹⁸²

Effect on Cardiovascular Disease

SSRIs seem to be the safest option, as they may have beneficial effects on the cardiovascular system. However, they must be administered cautiously to patients with a history of cardiac arrhythmia, coronary heart disease (CHD), and

carotid atherosclerosis, as the latter may be exacerbated by SSRIs. SNRIs are the second safest drugs in this category; nevertheless, their use is associated with elevated blood pressure and tachycardia due to their noradrenergic effects. Clonidine may help hypertensive women with perimenopausal symptoms, but it has considerable adverse effects on the cardiovascular system. Phytoestrogens, pregabalin and gabapentin seem to have no adverse effects on the cardiovascular system. Gabapentin appears to be safe in terms of cardiovascular effects.¹⁸³

Effect on Bone

Among non-hormonal prescription therapies for menopausal symptoms, SSRIs (and to a lesser extent SNRIs) are associated with lower BMD and higher fracture risk, whereas gabapentinoids primarily increase fracture risk through falls. In women at high fracture risk, use the lowest effective dose, reassess need, optimise calcium/vitamin D and exercise, and ensure osteoporosis screening and treatment as appropriate.¹⁸⁴

Refer to Table 5 for Non-hormonal medication, dose and side effects.

Non-Hormonal Therapies — Not Routinely Recommended

Pregabalin

Pregabalin is FDA-approved for neuropathic pain and seizure disorders. Evidence for its use in VMS is limited to a single phase 3 RCT, in which pregabalin 75 mg or 150 mg twice daily significantly reduced hot flush frequency compared with placebo. Its use is restricted by dizziness, cognitive effects, and weight gain, and it is a controlled substance with abuse potential. No studies have compared the effectiveness of pregabalin with HRT or other non-hormonal drugs such as antidepressants, clonidine, or gabapentin.¹⁸⁵ Due to limited efficacy data and safety concerns, pregabalin is not recommended for routine management of VMS, and gabapentin is the treatment of choice.^{171,185,186}

Clonidine

Clonidine, a centrally acting α_2 -adrenergic agonist, provides modest benefit over placebo for VMS but is less effective than SSRIs, SNRIs, and gabapentin. Its use is limited by dose-dependent adverse effects and the risk of rebound hypertension on abrupt withdrawal. Due to its limited efficacy and unfavourable tolerability, clonidine is not recommended for routine management of VMS.^{154,156}

Table 4: Selection of Non-hormonal Medication for VMS based on symptom cluster/comorbidity

Indications	Options
VMS	Fezolinetant / Elinzanetant
VMS + Insomnia	Gabapentin
VMS + Mood disorder	Escitalopram, Fluoxetine/Paroxetine
VMS + Dyslipidemia	Citalopram/Escitalopram/Fluoxetine
VMS + Hypertension	Clonidine
VMS + overactive bladder	Oxybutynin
VMS + stress urinary incontinence	Duloxetine
VMS in Tamoxifen users	Citalopram, Venlafaxine, Desvenlafaxine, Gabapentin, Oxybutynin

Table 5: Nonhormonal medication, dose and side effects

Drug	Dose for VMS (oral)	Common adverse effects	Important notes
Venlafaxine	37.5-75 mg/day	Nausea, dry mouth, insomnia, drowsiness, sexual dysfunction, ↑blood pressure (BP) at higher doses	Safe with Tamoxifen. Avoid in dyslipidaemia
Desvenlafaxine	100-150 mg/day	Nausea, dizziness, constipation, sexual dysfunction	Safe with Tamoxifen
Paroxetine	10, 12.5 CR, 20 mg/day	Sexual dysfunction, weight gain, nausea, restless legs, muscle cramps	Avoid in tamoxifen users
Fluoxetine	20 mg/day	Sexual dysfunction, nausea, drowsiness, insomnia, anxiety, gastrointestinal (GI) upset	Avoid in tamoxifen users
Citalopram	10-20 mg/day	QT prolongation (dose related), nausea, withdrawal, sexual dysfunction	Use lower doses in older women
Escitalopram	10-20 mg/day	Headache, nausea, fatigue, sexual dysfunction, withdrawal	Minimal CYP2D6 interaction. Least lipid effects
Gabapentin	100-300 mg at night, increase to 900 mg-2,400 mg/day	Drowsiness, dizziness, oedema. Class warning for suicidal thoughts and can lead to dependence	Taper gradually to avoid withdrawal
Duloxetine	20 mg twice daily	Dry mouth, hypotension, constipation	Useful when VMS is present with stress incontinence
Oxybutynin	2.5-5 mg twice daily	Dry mouth, difficulty urinating, abdominal pain, constipation, cognitive decline in the elderly	Useful when VMS is present with urge incontinence/overactive bladder

EMERGING THERAPIES

Several emerging non-hormonal, non-traditional options for bothersome VMS are increasingly supported by clinical trials. Stellate ganglion block (SGB) is a sympathetically mediated intervention. A randomised, placebo-controlled trial in perimenopausal women reported significant improvements in hot flash scores and sleep outcomes with repeated SGB compared with saline.¹⁸⁷

Transcutaneous vagus nerve stimulation (tVNS) is a non-invasive neuromodulation technique that enhances parasympathetic tone and reduces sympathetic overactivity.¹⁸⁸

Thermoregulatory cooling devices and wearables (cooling pads, phase-change cooling garments, and bedside cooling technologies) did not show a beneficial effect in an RCT.¹⁸⁹

Hypothesis

Gut microbiome modulation has emerged as a novel mechanistic target for VMS via the “oestrobolome,” a group of intestinal microbes that regulate estrogen metabolism and enterohepatic recycling.¹⁹⁰

RATIONALE FOR TREATING VASOMOTOR SYMPTOMS IN MIDLIFE WOMEN

Untreated moderate-to-severe vasomotor symptoms significantly impair QoL, reduce functional capacity and work productivity at home and in the workplace, and are associated with increased healthcare utilisation and medical costs. Beyond symptomatic distress, accumulating evidence indicates that persistent and severe VMS are linked to adverse cardiometabolic profiles, accelerated bone loss, and dysfunction of multiple estrogen-dependent systems. Vasomotor symptoms, therefore, represent not only a treatable cause of morbidity but also an early clinical marker of long-term health vulnerability, underscoring the importance of timely recognition and appropriate management.^{47,191}

VASOMOTOR SYMPTOMS AND LINK TO CHRONIC DISEASES

VMS signals neurovascular and autonomic changes associated with higher cardiovascular risk, but does not reliably predict fracture risk. Hence, recommendations centre on individualised risk assessment and symptom-directed HT.

Vasomotor Symptoms and Cardiovascular Risk

VMS were traditionally regarded as benign QoL manifestations of the MT. However, accumulating epidemiological, imaging, and mechanistic evidence now supports the view that VMS represent a female-specific cardiovascular risk phenotype rather than merely a transient climacteric complaint. Large prospective cohort studies consistently demonstrate that frequent, persistent, late-onset, or severe VMS are associated with increased future CVD events and mortality. Data from the SWAN showed that women experiencing frequent VMS had a significantly higher incidence of CVD and stroke over long-term follow-up, independent of traditional risk factors.¹⁹² Similarly, analyses from the WHI reported that women with late-onset VMS had higher risks of coronary events and all-cause mortality compared with asymptomatic women, even after adjustment for traditional CVD risk factors, whereas early transient VMS did not confer excess risk.¹⁹³ Severity of symptoms and late onset appear important; women with moderate-to-severe VMS have higher CVD risk than those with mild symptoms.¹⁹⁴ Additionally, data indicate that the association between VMS and incident CVD events differs with age, and VMS increases the incidence of CVD only in women under 60 years of age at baseline.¹⁹⁴ Meta-analytical evidence confirms these associations. A large systematic review and meta-analysis involving over 100,000 women demonstrated that VMS were significantly associated with a higher risk of coronary heart disease, stroke, and composite cardiovascular outcomes.¹⁹⁵ More recent reviews reaffirm these findings and highlight persistent VMS as the phenotype most strongly linked to vascular risk.^{196,197}

VMS have been associated with unfavourable CVD risk factors, including hypertension, a higher Homoeostatic Model Assessment (HOMA) index, insulin resistance, incident diabetes, Metabolic Syndrome (MetS), and an adverse lipid profile.¹⁹⁸⁻²⁰⁴ Women reporting frequent VMS exhibit higher coronary artery calcium scores and adverse cardiometabolic profiles, suggesting accelerated atherosclerosis even before overt cardiovascular events occur.^{205,206} After menopause, a relative androgen predominance develops, and an increased testosterone-to-estradiol ratio is independently associated with higher cardiovascular risk, even when estradiol levels appear normal, indicating that hormonal imbalance rather than estrogen deficiency alone contributes to cardiovascular vulnerability.²⁰⁷

Sympathetic nervous system activity increases with age, but rises more steeply in women after menopause, resulting in impaired blood pressure regulation and exaggerated sympathetic cardiovascular responses. Vasomotor symptoms further amplify this risk by promoting sleep disruption and heightened sympathetic neural drive, potentially leading to sustained autonomic dysfunction and increased long-term cardiovascular disease risk.²⁰⁸⁻²¹⁰ VMS are associated with endothelial dysfunction, increased sympathetic activation, impaired thermoregulatory vasodilatation, elevated blood pressure variability, and arterial stiffness, all of which contribute to vascular injury. These findings support the concept that VMS represent a vascular vulnerability phenotype rather than isolated neuroendocrine symptoms.²¹¹

The emerging body of robust evidence indicates that women experiencing vasomotor symptoms during the MT should be closely monitored for cardiovascular disease risk factors. Conventional cardiometabolic risk factors should be identified early and managed aggressively in women with troublesome VMS, and referral for comprehensive cardiometabolic evaluation should be considered when VMS coexist with other risk signals. At present, menopausal hormone therapy is appropriate for symptomatic relief in eligible women without contraindications, but it is not indicated for the primary prevention of cardiovascular disease.

Vasomotor Symptoms and Breast Cancer

No primary observational or trial data directly demonstrate that women who experience VMS have a lower incidence

of breast cancer. Prospective studies are needed to evaluate whether VMS phenotypes independently predict breast cancer risk.²¹²

Vasomotor Symptoms and Biological Ageing

In the Women's Health Initiative integrative genomics cohort, postmenopausal women not on HT with severe or late-onset vasomotor symptoms showed accelerated DNA methylation-based epigenetic ageing independent of chronological age, suggesting greater underlying biological ageing.²¹³

Vasomotor Symptoms and Bone Health

Fracture risk is multifactorial, involving many extraosseous factors. VMS and bone loss are both linked to estrogen deficiency. Women with moderate-to-severe VMS have lower bone mineral density (BMD) and higher hip fracture rates.²¹⁴ A systematic review in 2024 found that VMS is associated with low BMD in postmenopausal women, although it does not appear to increase fracture risk.²¹⁵ In a study by Crandall CJ, additional variables such as diabetes, frequent falls, vasomotor symptoms, physical function score, or lumbar spine BMD did not yield meaningful improvements in Fracture Risk Assessment Tool (FRAX) discrimination for fracture interventions. Hence, women with moderate-to-severe or persistent VMS may remain under-classified for fracture risk using FRAX alone and should undergo early skeletal risk assessment and preventive intervention even when FRAX estimates appear low.²¹⁶ When VMS and bone risk coexist: In symptomatic women at elevated fracture risk, MHT may simultaneously relieve VMS and reduce fracture risk. Optimal duration and dosing of estrogen to balance symptomatic relief versus long-term skeletal and non-skeletal risks remain individualised questions, influenced by age and time since menopause.²¹⁶⁻²¹⁸

SYNOPSIS

- The MT typically begins approximately four years before the FMP and is characterised by irregular menstrual cycles, endocrine fluctuations, and vasomotor symptoms, which may significantly affect QoL.
- The main clinical questions, who to treat, when to treat, and how to treat, should be guided by the severity and impact of symptoms on patient-reported outcomes, as well as the potential long-term consequences of estrogen deprivation across organ systems.
- Across all stages of menopause, VMS and GSM are directly attributable to estrogen deficiency. In contrast, symptoms such as poor sleep, reduced libido, and vaginal dryness are not consistently predicted by circulating estradiol fluctuations, suggesting important contributions from non-hormonal, psychosocial, and local tissue factors.
- Hot flushes arise from a complex neuroendocrine cascade involving estrogen withdrawal, narrowing of the thermoneutral zone, altered central neurotransmitter signalling, and activation of hypothalamic KNDy neurons.
- The age at menopause and the individual experience of the MT are influenced by an interplay of genetic susceptibility and environmental exposures.
- Estrogen therapy remains the most effective treatment for VMS, while non-hormonal interventions are appropriate for women who have contraindications to, or prefer not to use, MHT.
- Growing epidemiological, imaging, and mechanistic evidence supports the concept that vasomotor symptoms represent a female-specific cardiovascular risk phenotype, rather than merely a transient climacteric complaint.

RESEARCH AGENDA

Efficacy and safety of fezolinetant 45 mg once daily in the Indian population

EDITOR'S NOTE

This chapter is dedicated to the late Dr Mandakini Parihar.

REFERENCES

1. Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, et al. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med.* 2015 Apr;175(4):531–9. <https://doi.org/10.1001/jamainternmed.2014.8063>
2. Podfigurna A, Szeliga A, Męczekalski B. Climacteric syndrome. In: *Female Reproductive Dysfunction*. 2020:1–26. https://doi.org/10.1007/978-3-030-03594-5_16-1
3. Sourouni M, Zangger M, Honermann L, Foth D, Stute P. Assessment of the climacteric syndrome: a narrative review. *Arch Gynecol Obstet.* 2021 Oct;304(4):855–862. <https://doi.org/10.1007/s00404-021-06139-y>
4. Yao Y, Pei Q, Tian X. Meta-analysis of the correlation between chronic diseases and climacteric syndrome. *Practical Medical Research.* 2024;2(2). <https://doi.org/10.18686/pmr.v2i2.4443>
5. Katainen RE, Engblom JR, Siirtola TJ, Erkkola RU, Polo-Kantola P. Climacteric symptoms in middle-aged women with chronic somatic diseases. *Maturitas.* 2016 Apr;86:17–24. <https://doi.org/10.1016/j.maturitas.2016.01.005>
6. Katainen RE, Engblom JR, Siirtola TJ, Erkkola RU, Polo-Kantola P. The role of self-rated health in the association between chronic somatic diseases and climacteric-related symptoms. *Climacteric.* 2017 Feb;20(1):80–82. <https://doi.org/10.1080/13697137.2016.1264935>
7. Wang Y, Xu X, Lv Q, Zhao Y, Zhang X, Zang X. Network analysis of symptoms, physiological, psychological and environmental risk factors based on unpleasant symptom theory in patients with chronic heart failure. *Int J Nurs Pract.* 2024 Apr;30(2):e13246. <https://doi.org/10.1111/ijn.13246>
8. Freeman EW, Sammel MD, Lin H, Gracia CR, Pien GW, Nelson DB, et al. Symptoms associated with menopausal transition and reproductive hormones in midlife women. *Obstet Gynecol.* 2007 Aug;110(2 Pt 1):230–40. <https://doi.org/10.1097/01.aog.0000270153.59102.40>
9. Lui-Filho JF, Pedro AO, Baccaro LF, Costa-Paiva L. Risk factors associated with intensity of climacteric symptoms in Brazilian middle-aged women: a population-based household survey. *Menopause.* 2018 Apr;25(4):415–422. <https://doi.org/10.1097/gme.0000000000001022>
10. Thurston RC, Joffe H. Vasomotor symptoms and menopause: findings from the Study of Women's Health across the Nation. *Obstet Gynecol Clin North Am.* 2011 Sep;38(3):489–501. <https://doi.org/10.1016/j.ogc.2011.05.006>
11. Yang JL, Hodara E, Sriprasert I, Shoupe D, Stanczyk FZ. Estrogen deficiency in the menopause and the role of hormone therapy: integrating the findings of basic science research with clinical trials. *Menopause.* 2024 Oct 1;31(10):926–939. <https://doi.org/10.1097/gme.0000000000002407>
12. Santoro N, Randolph JF Jr. Reproductive hormones and the menopause transition. *Obstet Gynecol Clin North Am.* 2011 Sep;38(3):455–66. <https://doi.org/10.1016/j.ogc.2011.05.004>
13. Burger HG, Dudley E, Marnett P, Groome N, Robertson DM. Early follicular phase serum FSH as a function of age: the roles of inhibin B, inhibin A and estradiol. *Climacteric.* 2000 Mar;3(1):17–24. <https://doi.org/10.3109/13697130009167595>
14. Freeman EW, Sammel MD, Lin H. Temporal associations of hot flashes and depression in the transition to menopause. *Menopause.* 2009 Jul-Aug;16(4):728–34. <https://doi.org/10.1097/gme.0b013e3181967e16>
15. Karvonen-Gutierrez C, Woods NF. Health and function from mid life to late adulthood: findings from the Study of Women's Health Across the Nation (SWAN). *Innov Aging.* 2023;7(Suppl 1):622. <https://doi.org/10.1093/geronl/igad104.2029>
16. Harlow SD, Burnett-Bowie SM, Greendale GA, Avis NE, Reeves AN, Richards TR, et al. Disparities in reproductive ageing and midlife health between Black and White women: the Study of Women's Health Across the Nation (SWAN). *Women's Midlife Health.* 2022 Feb 8;8(1):3. <https://doi.org/10.1186/s40695-022-00073-y>
17. El Khoudary SR, Greendale G, Crawford SL, Avis NE, Brooks MM, Thurston RC, et al. The menopause transition and women's health at midlife: a progress report from the Study of Women's Health Across the Nation (SWAN). *Menopause.* 2019 Oct;26(10):1213–1227. <https://doi.org/10.1097/gme.0000000000001424>
18. Meeta. *Menopause Management Simplified*. New Delhi: Jagsonpal; 2012.
19. Singh M. Early age of natural menopause in India, a biological marker for early preventive health programs. *Climacteric.* 2012 Dec;15(6):581–6. <https://doi.org/10.3109/13697137.2011.643514>
20. Borker SA, Venugopalan PP, Bhat SN. Study of menopausal symptoms, and perceptions about menopause among women at a rural community in Kerala. *J Midlife Health.* 2013 Jul;4(3):182–7. <https://doi.org/10.4103/0976-7800.118997>
21. Singh A, Pradhan SK. Menopausal symptoms of postmenopausal women in a rural community of Delhi, India: a cross-sectional study. *J Midlife Health.* 2014 Apr;5(2):62–7. <https://doi.org/10.4103/0976-7800.133989>
22. Garg R, Rawat R, Pathak M, Lalitha G, Rajwanshi R, Mazhar SB. Menopausal symptoms among postmenopausal women of north India: a cross-sectional study. *J South Asian Feder Menopause Soc.* 2015;3(1):3–5. <https://doi.org/10.5005/jp-journals-10032-1060>
23. Kulkarni P, Savitha Rani BB, Kumar DS, Manjunath R. Burgeoning menopausal symptoms: an urgent public health concern. *J Midlife Health.* 2016 Apr-Jun;7(2):83–7. <https://doi.org/10.4103/0976-7800.185329>
24. Joseph LA, Varghese AP. Prevalence of menopausal symptoms and perceptions about menopause among postmenopausal women attending gynaecology OPD at GMC Idukki, India. *Int J Reprod Contracept Obstet Gynecol.* 2017;6(2):413. <https://doi.org/10.18203/2320-1770.ijrcog20170065>
25. Karmakar N, Majumdar S, Dasgupta A, Das S. Quality of life among menopausal women: a community-based study in a rural area of West Bengal. *J Midlife Health.* 2017 Jan-Mar;8(1):21–27. https://doi.org/10.4103/jmh.jmh_78_16
26. Shukla R, Ganjiwale J, Patel R. Prevalence of postmenopausal symptoms, its effect on quality of life and coping in rural couple. *J Midlife Health.* 2018 Jan-Mar;9(1):14–20. https://doi.org/10.4103/jmh.jmh_34_16
27. Khatoon F, Sinha P, Shahid S, Gupta U. Assessment of menopausal symptoms using modified menopause rating scale (MRS) in women of northern India. *Int J Reprod Contracept Obstet Gynecol.* 2018;7(3):947. <https://doi.org/10.18203/2320-1770.ijrcog20180871>
28. Thakur M, Kaur M, Sinha AK. Assessment of menopausal symptoms in different transition phases using the Greene Climacteric Scale among rural women of north India. *Ann Hum Biol.* 2019 Feb;46(1):46–55. <https://doi.org/10.1080/03014460.2019.1587508>
29. Patil SD, Deshmukh J. Prevalence and pattern of menopausal symptoms among menopausal women in central India: a community based cross sectional study. *Galore Int J Health Sci Res.* 2019;4(3):61–67.

30. Anuradha S, Priyadarsini MS, Sumithra P. A study to assess the menopausal symptoms among women in selected villages at Chandragiri Mandal, Andhra Pradesh. *Int J Obstet Perinat Neonatal Nurs.* 2020;6(1):14–19.
31. Armo M, Sainik S. Assessment of menopausal symptom using modified Menopause Rating Scale among rural women of Rajnandgaon in Chhattisgarh, a central India region. *J South Asian Feder Obstet Gynaecol.* 2020;12(4):209–214. <https://doi.org/10.5005/jp-journals-10006-1797>
32. Kalhan M, Singhanika K, Choudhary P, Verma S, Kaushal P, Singh T. Prevalence of menopausal symptoms and its effect on quality of life among rural middle aged women (40–60 years) of Haryana, India. *Int J Appl Basic Med Res.* 2020 Jul-Sep;10(3):183–188. https://doi.org/10.4103/ijabmr.IJABMR_428_19
33. Nagaraj D, Ramesh N, Devraj D, Umman M, John AK, Johnson AR. Experience and perceptions regarding menopause among rural women: a cross-sectional hospital-based study in south Karnataka. *J Midlife Health.* 2021 Jul-Sep;12(3):199–205. https://doi.org/10.4103/jmh.jmh_196_20
34. Sivaprasad S, Ravi Kumar V, Murali Krishna PV, Sadakvali C, Md Y, Srikanth A. A cross-sectional study on prevalence of menopausal symptoms in a tertiary care hospital, Telangana, India. *Int J Pharm Sci Rev Res.* 2022;73(2):129–133. <https://doi.org/10.47583/ijpsrr.2022.v73i02.024>
35. Sundararajan M, Srinivasan V. Prevalence of menopausal symptoms and health-seeking behaviour of school teachers with menopausal symptoms in Kumbakonam, South India. *Int J Community Med Public Health.* 2023;10(3):1224–1231. <https://doi.org/10.18203/2394-6040.ijcmph20230644>
36. Mangasuli V, Sherkhane MS. Assessment of postmenopausal symptoms among women residing in urban slums. *J Community Health Res.* 2023;11(4). <https://doi.org/10.18502/jchr.v11i4.11642>
37. Natarajan N, Nandi P, Ka N, S L. Investigating the prevalence of menopausal symptoms and medico-social dimensions of menopause in rural Puducherry, India: a cross-sectional analytical study. *Cureus.* 2024 Mar;16(3):e55841. <https://doi.org/10.7759/cureus.55841>
38. Nath J, Jain NG. A study of menopausal symptoms using the Menopause Rating Scale (MRS) in the rural women of Gurugram District of Haryana, North India. *Int J Sci Res.* 2024 May;13(5):35–37. <https://doi.org/10.36106/ijsr/8901207>
39. Umamaheswari V, Anitha J. A study to assess the prevalence of menopausal symptoms among perimenopausal women in urban community Coimbatore, Tamilnadu. *Glob J Res Anal.* 2024;13(6):15–17. <https://doi.org/10.36106/gira/7300672>
40. Mediboina A, Pratyusha P, Kumar GS. Determining the prevalence and severity of menopausal symptoms in post-menopausal women of Eluru, Andhra Pradesh, India, using the Menopause Rating Scale (MRS). *Int J Med Stud.* 2024;12(2):152–160. <https://doi.org/10.5195/ijms.2024.2116>
41. Mathew J, George J, Pa A, K S. Prevalence of menopausal symptoms among women in selected areas of Malappuram District. *Int J Multidiscip Res.* 2024;6(1). <https://doi.org/10.36948/ijfmr.2024.v06i01.14360>
42. Shah A, Prajapati H. Menopause symptoms experienced by women in India: a systematic review. *Int J Res Rev.* 2024;11(8):45–53. <https://doi.org/10.52403/ijrr.2024080643>
43. Shobhana M, Chandran JR, Aggarwal N, Sharma S, Jankiram R, Soni A, et al. Incidence of hot flashes among peri- and postmenopausal women in India: a clinico-demographic analysis. *J Midlife Health.* 2025 Jan-Mar;16(1):32–37. https://doi.org/10.4103/jmh.jmh_47_24
44. Gupta P, Sturdee DW, Hunter MS. Mid-age health in women from the Indian subcontinent (MAHWIS): general health and the experience of menopause in women. *Climacteric.* 2006 Feb;9(1):13–22. <https://doi.org/10.1080/13697130500515776>
45. Hafiz I, Liu J, Eden J. A quantitative analysis of the menopause experience of Indian women living in Sydney. *Aust N Z J Obstet Gynaecol.* 2007 Aug;47(4):329–34.
46. Ashraf AB, Meeta M, Chitra AB, Pahwa S, Shah J, Mohi M, et al. Genitourinary syndrome of menopause: a multicenter study from the Indian Midlife Registry. *Climacteric.* 2025 Jun;28(3):329–336. <https://doi.org/10.1080/13697137.2025.2496681>
47. Nappi RE, Kroll R, Siddiqui E, Stoykova B, Rea C, Gemmen E, et al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. *Menopause.* 2021 May 24;28(8):875–882. <https://doi.org/10.1097/gme.0000000000001793>
48. Fang Y, Liu F, Zhang X, Chen L, Liu Y, Yang L, et al. Mapping global prevalence of menopausal symptoms among middle-aged women: a systematic review and meta-analysis. *BMC Public Health.* 2024 Jul 2;24(1):1767. <https://doi.org/10.1186/s12889-024-19280-5>
49. Avis NE, Stellato R, Crawford S, Bromberger J, Ganz P, Cain V, et al. Is there a menopausal syndrome? Menopausal status and symptoms across racial/ethnic groups. *Soc Sci Med.* 2001 Feb;52(3):345–356. [https://doi.org/10.1016/s0277-9536\(00\)00147-7](https://doi.org/10.1016/s0277-9536(00)00147-7)
50. Anderson D, Yoshizawa T, Gollschewski S, Atogami F, Courtney M. Menopause in Australia and Japan: effects of country of residence on menopausal status and menopausal symptoms. *Climacteric.* 2004 Jun;7(2):165–74. <https://doi.org/10.1080/13697130410001713760>
51. Im EO, Ko Y, Chee W. Ethnic differences in the clusters of menopausal symptoms. *Health Care Women Int.* 2014 May;35(5):549–65. <https://doi.org/10.1080/07399332.2013.815752>
52. Tang R, Liu Q, Yu Q. Menopausal symptoms: what are the differences between the West and the East? *Climacteric.* 2025 Oct;28(5):510–515. <https://doi.org/10.1080/13697137.2025.2503880>
53. Nappi RE, Kokot-Kierepa M. Vaginal Health: Insights, Views & Attitudes (VIVA) - results from an international survey. *Climacteric.* 2012 Feb;15(1):36–44. <https://doi.org/10.3109/13697137.2011.647840>
54. Cecil RL, Archer BH. Arthritis of the menopause. *JAMA.* 1925 Jan 10;84(2):75. <https://doi.org/10.1001/jama.1925.02660280001001>
55. Lu CB, Liu PF, Zhou YS, Meng FC, Qiao TY, Yang XJ, et al. Musculoskeletal pain during the menopausal transition: a systematic review and meta-analysis. *Neural Plast.* 2020;2020:8842110. <https://doi.org/10.1155/2020/8842110>
56. Wright VJ, Schwartzman JD, Itinchoe R, Wittstein J. The musculoskeletal syndrome of menopause. *Climacteric.* 2024 Oct;27(5):466–472. <https://doi.org/10.1080/13697137.2024.2380363>
57. Sriramaneni N, Selvan C, Kumar S N, Kalra P, P GY, R MP, et al. Quality of life in postmenopausal women and its association with sarcopenia. *Menopause.* 2024 Aug 1;31(8):679–685. <https://doi.org/10.1097/GME.0000000000002378>
58. Das A, Sunny AM, Paul A, Anto A, Abraham BT. A research to spot the association between menopausal symptoms and metabolic syndrome in post-menopausal women in a tertiary care hospital. *Curr Med Res Pract.* 2021 May;11(3):113–7. https://doi.org/10.4103/cmrrp.cmrrp_33_21
59. Chlebowski RT, Cirillo DJ, Eaton CB, Stefanick ML, Pettinger M, Carbone LD, et al. Estrogen alone and joint symptoms in the Women's Health Initiative randomized trial. *Menopause.* 2013 Jun;20(6):600–8. <https://doi.org/10.1097/GME.0b013e31828392c4>
60. Szoek CE, Cicuttini FM, Guthrie JR, Dennerstein L. The relationship of reports of aches and joint pains to the menopausal transition: a longitudinal study. *Climacteric.* 2008 Feb;11(1):55–62. <https://doi.org/10.1080/13697130701746006>

61. Meeta, Raut AA, Agashe SV, Wajahat A, Sarada CV, Vaidya ADB, et al. A clinical study of a standardized extract of leaves of *Dalbergia sissoo* (Roxb ex DC) in postmenopausal osteoporosis. *J Midlife Health*. 2019 Jan-Mar;10(1):37–42. https://doi.org/10.4103/jmh.JMH_22_19
62. Pamuk ON, D mez S, Cakir N. Increased frequencies of hysterectomy and early menopause in fibromyalgia patients: a comparative study. *Clin Rheumatol*. 2009 May;28(5):561–4. <https://doi.org/10.1007/s10067-009-1087-1>
63. Sestak I, Cuzick J, Sapunar F, Eastell R, Forbes JF, Bianco AR, et al. Risk factors for joint symptoms in patients enrolled in the ATAC trial: a retrospective, exploratory analysis. *Lancet Oncol*. 2008 Sep;9(9):866–872. [https://doi.org/10.1016/s1470-2045\(08\)70182-7](https://doi.org/10.1016/s1470-2045(08)70182-7)
64. Crew KD, Greenlee H, Capodice J, Raptis G, Brafman L, Fuentes D, et al. Prevalence of joint symptoms in postmenopausal women taking aromatase inhibitors for early-stage breast cancer. *J Clin Oncol*. 2007 Sep 1;25(25):3877–83. <https://doi.org/10.1200/JCO.2007.10.7573>
65. Morales L, Pans S, Paridaens R, Westhovens R, Timmerman D, Verhaeghe J, et al. Debilitating musculoskeletal pain and stiffness with letrozole and exemestane: associated tenosynovial changes on magnetic resonance imaging. *Breast Cancer Res Treat*. 2007 Jul;104(1):87–91. <https://doi.org/10.1007/s10549-006-9394-6>
66. Burger HG, Hale GE, Robertson DM, Dennerstein L. A review of hormonal changes during the menopausal transition: focus on findings from the Melbourne Women's Midlife Health Project. *Hum Reprod Update*. 2007 Nov-Dec;13(6):559–65. <https://doi.org/10.1093/humupd/dmm020>
67. Kronenberg F. Hot flashes: epidemiology and physiology. *Ann N Y Acad Sci*. 1990;592:52–86; discussion 123–33. <https://doi.org/10.1111/j.1749-6632.1990.tb03031.x>
68. Freedman RR. Physiology of hot flashes. *Am J Hum Biol*. 2001 Jul-Aug;13(4):453–64. <https://doi.org/10.1002/ajhb.1077>
69. Padilla SL, Johnson CW, Barker FD, Patterson MA, Palmiter RD. A neural circuit underlying the generation of hot flushes. *Cell Rep*. 2018 Jul 10;24(2):271–277. <https://doi.org/10.1016/j.celrep.2018.06.037>
70. Mom CH, Buijs C, Willemse PH, Mourits MJ, de Vries EG. Hot fushes in breast cancer patients. *Crit Rev Oncol Hematol*. 2006 Jan;57(1):63–77. <https://doi.org/10.1016/j.critrevonc.2005.04.009>
71. Freedman RR. Biochemical, metabolic, and vascular mechanisms in menopausal hot flashes. *Fertil Steril*. 1998 Aug;70(2):332–7. [https://doi.org/10.1016/s0015-0282\(98\)00137-x](https://doi.org/10.1016/s0015-0282(98)00137-x)
72. Ginsburg J, Swinhoe J, O'Reilly B. Cardiovascular responses during the menopausal hot flush. *Br J Obstet Gynaecol*. 1981 Sep;88(9):925–30. <https://doi.org/10.1111/j.1471-0528.1981.tb02230.x>
73. Freedman RR, Woodward S. Core body temperature during menopausal hot luses. *Fertil Steril*. 1996 Jun;65(6):1141–4. [https://doi.org/10.1016/s0015-0282\(16\)58328-9](https://doi.org/10.1016/s0015-0282(16)58328-9)
74. Rebar RW, Spitzer IB. The physiology and measurement of hot luses. *Am J Obstet Gynecol*. 1987 May;156(5):1284–8. [https://doi.org/10.1016/0002-9378\(87\)90165-7](https://doi.org/10.1016/0002-9378(87)90165-7)
75. Burger HG, Dudley EC, Robertson DM, Dennerstein L. Hormonal changes in the menopause transition. *Recent Prog Horm Res*. 2002;57:257–75. <https://doi.org/10.1210/rp.57.1.257>
76. Jensen J, Christiansen C. Dose-response and withdrawal effects on climacteric symptoms after hormonal replacement therapy. A placebo-controlled therapeutic trial. *Maturitas*. 1983 Aug;5(2):125–33. [https://doi.org/10.1016/0378-5122\(83\)90008-7](https://doi.org/10.1016/0378-5122(83)90008-7)
77. Deecher DC, Dorries K. Understanding the pathophysiology of vasomotor symptoms (hot flushes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages. *Arch Womens Ment Health*. 2007;10(6):247–57. <https://doi.org/10.1007/s00737-007-0209-5>
78. Prokai-Tatrai K, Prokai L. The impact of 17 β -estradiol on the estrogen-deficient female brain: from mechanisms to therapy with hot flushes as target symptoms. *Front Endocrinol (Lausanne)*. 2023;14:1310432. <https://doi.org/10.3389/fendo.2023.1310432>
79. Stearns V, Ullmer L, López JF, Smith Y, Isaacs C, Hayes D. Hot luses. *Lancet*. 2002 Dec 7;360(9348):1851–61. [https://doi.org/10.1016/s0140-6736\(02\)11774-0](https://doi.org/10.1016/s0140-6736(02)11774-0)
80. Sturdee DW. The menopausal hot lush—anything new? *Maturitas*. 2008 May 20;60(1):42–9. <https://doi.org/10.1016/j.maturitas.2008.02.006>
81. Brück K, Zeisberger E. Adaptive changes in thermoregulation and their neuropharmacological basis. *Pharmacol Ther*. 1987;35(1-2):163–215. [https://doi.org/10.1016/0163-7258\(87\)90106-9](https://doi.org/10.1016/0163-7258(87)90106-9)
82. Freedman RR. Menopausal hot flashes: mechanisms, endocrinology, treatment. *J Steroid Biochem Mol Biol*. 2014 Jul;142:115–20. <https://doi.org/10.1016/j.jsbmb.2013.08.010>
83. Rance NE, Dacks PA, Mittelman-Smith MA, Romanovsky AA, Krajewski-Hall SJ. Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: a novel hypothesis on the mechanism of hot flushes. *Front Neuroendocrinol*. 2013 Aug;34(3):211–27. <https://doi.org/10.1016/j.yfrne.2013.07.003>
84. Miller VM, Kling JM, Files JA, Joyner MJ, Kapoor E, Moyer AM, et al. What's in a name: are menopausal “hot flashes” a symptom of menopause or a manifestation of neurovascular dysregulation? *Menopause*. 2018 Jun;25(6):700–703. <https://doi.org/10.1097/gme.0000000000001065>
85. Hautamäki H, Piirilä P, Haapalahti P, Tuomikoski P, Sovijärvi AR, Ylikorkala O, et al. Cardiovascular autonomic responsiveness in postmenopausal women with and without hot luses. *Maturitas*. 2011 Apr;68(4):368–73. <https://doi.org/10.1016/j.maturitas.2011.01.004>
86. Rohini NS, Bhanupriya, Anusuya SK, Ravishankar SN, Atre AS, Shettannavar P, et al. A comparative study of autonomic nervous system dysfunction in post menopausal women with diabetes and without diabetes as a predictor of cardiovascular events. *Indian J Obstet Gynecol Res*. 2020;7(2):182–186. <https://doi.org/10.18231/j.ijogr.2020.038>
87. Miragem AA, Homem de Bittencourt PI Jr. Nitric oxide-heat shock protein axis in menopausal hot flushes: neglected metabolic issues of chronic inflammatory diseases associated with deranged heat shock response. *Hum Reprod Update*. 2017 Sep 1;23(5):600–628. <https://doi.org/10.1093/humupd/dmx020>
88. Bechlioulis A, Naka KK, Kalantaridou SN, Kaponis A, Papanikolaou O, Vezyraki P, et al. Increased vascular i lammation in early menopausal women is associated with hot flush severity. *J Clin Endocrinol Metab*. 2012 May;97(5):E760–4. <https://doi.org/10.1210/jc.2011-3151>
89. Figueroa-Vega N, Moreno-Frías C, Malacara JM. Alterations in adhesion molecules, pro-inflammatory cytokines and cell-derived microparticles contribute to intima-media thickness and symptoms in postmenopausal women. *PLoS One*. 2015;10(5):e0120990. <https://doi.org/10.1371/journal.pone.0120990>
90. Sassarini J. Investigating the aetiology of hot flushing in postmenopausal women and hypogonadal men [PhD thesis]. Glasgow: University of Glasgow; 2013. Available from: <https://theses.gla.ac.uk/5436/>

91. Mosconi L, Berti V, Dyke J, Schelbaum E, Jett S, Loughlin L, et al. Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid-beta deposition. *Sci Rep*. 2021 Jun 9;11(1):10867. <https://doi.org/10.1038/s41598-021-90084-y>
92. Patel B, Dhillon WS. Menopause review: emerging treatments for menopausal symptoms. *Best Pract Res Clin Obstet Gynaecol*. 2022 May;81:134–144. <https://doi.org/10.1016/j.bpobgyn.2021.10.010>
93. Lee E, Anselmo M, Tahsin CT, Vanden Noven M, Stokes W, Carter JR, et al. Vasomotor symptoms of menopause, autonomic dysfunction, and cardiovascular disease. *Am J Physiol Heart Circ Physiol*. 2022 Dec 1;323(6):H1270–H1280. <https://doi.org/10.1152/ajpheart.00477.2022>
94. Rödrström K, Bengtsson C, Lissner L, Milsom I, Sundh V, Björkelund C. A longitudinal study of the treatment of hot flushes: the population study of women in Gothenburg during a quarter of a century. *Menopause*. 2002 May-Jun;9(3):156–61. <https://doi.org/10.1097/00042192-200205000-00003>
95. Gartoulla P, Worsley R, Bell RJ, Davis SR. Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60 to 65 years. *Menopause*. 2015 Jul;22(7):694–701. <https://doi.org/10.1097/GME.0000000000000383>
96. Avis NE, McKinlay SM. The Massachusetts Women's Health Study: an epidemiologic investigation of the menopause. *J Am Med Womens Assoc* (1972). 1995 Mar-Apr;50(2):45–9, 63. PMID: 7722206.
97. National Institutes of Health State-of-the-Science Conference statement: management of menopause-related symptoms. *Ann Intern Med*. 2005 Jun 21;142(12 Pt 1):1003–13. https://doi.org/10.7326/0003-4819-142-12_Part_1-200506210-00117
98. Ferreira-Valente MA, Pais-Ribeiro JL, Jensen MP. Validity of four pain intensity rating scales. *Pain*. 2011 Oct;152(10):2399–2404. <https://doi.org/10.1016/j.pain.2011.07.005>
99. Schneider HP, Rosemeier HP, Schnitker J, Gerbsch S, Turck R. Application and factor analysis of the menopause rating scale [MRS] in a post-marketing surveillance study of Climen. *Maturitas*. 2000 Dec 29;37(2):113–24. [https://doi.org/10.1016/s0378-5122\(00\)00177-8](https://doi.org/10.1016/s0378-5122(00)00177-8)
100. Hunter MS, Liao KL. A psychological analysis of menopausal hot flushes. *Br J Clin Psychol*. 1995 Nov;34(4):589–99. <https://doi.org/10.1111/j.2044-8260.1995.tb01493.x>
101. Rand KL, Otte JL, Flockhart D, Hayes D, Storniolo AM, Stearns V, et al. Modeling hot flushes and quality of life in breast cancer survivors. *Climacteric*. 2011 Feb;14(1):171–80 <https://doi.org/10.3109/13697131003717070>
102. Guthrie JR, Dennerstein L, Taffe JR, Leher P, Burger HG. Hot flushes during the menopause transition: a longitudinal study in Australian-born women. *Menopause*. 2005 Jul-Aug;12(4):460–7. <https://doi.org/10.1097/01.GME.0000155200.80687.BE>
103. Pan Y, Meister R, Löwe B, Kaptchuk TJ, Buhling KJ, Nestoriuc Y. Open-label placebos for menopausal hot flushes: a randomized controlled trial. *Sci Rep*. 2020 Nov 18;10(1):20090. <https://doi.org/10.1038/s41598-020-77255-z>
104. Shanafelt TD, Barton DL, Adjei AA, Loprinzi CL. Pathophysiology and treatment of hot flashes. *Mayo Clin Proc*. 2002 Nov;77(11):1207–18. <https://doi.org/10.4065/77.11.1207>
105. Haines CJ, Chung TK, Leung DH. A prospective study of the frequency of acute menopausal symptoms in Hong Kong Chinese women. *Maturitas*. 1994 Mar;18(3):175–81. [https://doi.org/10.1016/0378-5122\(94\)90123-6](https://doi.org/10.1016/0378-5122(94)90123-6)
106. Matsuo K, Gualtieri MR, Cahoon SS, Toboni MD, Machida H, Moeini A, et al. Contributing factors for menopausal symptoms after surgical staging for endometrial cancer. *Menopause*. 2016 May;23(5):535–43. <https://doi.org/10.1097/GME.0000000000000576>
107. Price SAL, Maki PM, El Khoudary SR, Brand A, Islam RM, Domchek SM, et al. What happens after menopause (WHAM)? A progress report of a prospective controlled study of women after pre-menopausal risk-reducing bilateral salpingo-oophorectomy. *BJOG*. 2025 Jul 23. <https://doi.org/10.1111/1471-0528.18304>
108. Kaur H, Kaur S, Gupta N, Garg S, Sharda K. A comparative study of effects of surgical and natural menopause on menopausal symptoms and musculoskeletal complaints in menopausal women. *Natl J Physiol Pharm Pharmacol*. 2021;11(1):1. <https://doi.org/10.5455/njppp.2022.12.03081202102082021>
109. Page CE, Soreth B, Metcalf CA, Johnson RL, Duffy KA, Sammel MD, et al. Natural vs. surgical postmenopause and psychological symptoms confound the effect of menopause on executive functioning domains of cognitive experience. *Maturitas*. 2023 Apr;170:64–73. <https://doi.org/10.1016/j.maturitas.2023.01.007>
110. Gjelsvik B, Rosvold EO, Straand J, Dalen I, Hunskaar S. Symptom prevalence during menopause and factors associated with symptoms and menopausal age. Results from the Norwegian Hordaland Women's Cohort study. *Maturitas*. 2011 Dec;70(4):383–90. <https://doi.org/10.1016/j.maturitas.2011.09.011>
111. Ruth KS, Beaumont RN, Locke JM, Tyrrell J, Crandall CJ, Hawkes G, et al. Insights into the genetics of menopausal vasomotor symptoms: genome-wide analyses of routinely-collected primary care health records. *BMC Med Genomics*. 2023 Oct 2;16(1):231. <https://doi.org/10.1186/s12920-023-01658-w>
112. Grub J, Willi J, Süß H, Ehlert U. The role of estrogen receptor gene polymorphisms in menopausal symptoms and estradiol levels in perimenopausal women - findings from the Swiss Perimenopause Study. *Maturitas*. 2024 May;183:107942. <https://doi.org/10.1016/j.maturitas.2024.107942>
113. Freeman EW, Sammel MD, Sanders RJ. Risk of long-term hot flashes after natural menopause: evidence from the Penn Ovarian Aging Study cohort. *Menopause*. 2014 Sep;21(9):924–32. <https://doi.org/10.1097/GME.0000000000000196>
114. Gold EB, Colvin A, Avis N, Bromberger J, Greendale GA, Powell L, et al. Longitudinal analysis of the association between vasomotor symptoms and race/ethnicity across the menopausal transition: study of women's health across the nation. *Am J Public Health*. 2006 Jul;96(7):1226–35. <https://doi.org/10.2105/ajph.2005.066936>
115. Jenabi E, Poorolajal J. The association between hot flushes and smoking in midlife women: a meta-analysis. *Climacteric*. 2015;18(6):797–801. <https://doi.org/10.3109/13697137.2015.1080236>
116. Beyene Y. Cultural significance and physiological manifestations of menopause. A biocultural analysis. *Cult Med Psychiatry*. 1986 Mar;10(1):47–71. <https://doi.org/10.1007/BF00053262>
117. Shobeiri F, Jenabi E, Poorolajal J, Hazavehei SM. The association between body mass index and hot flash in midlife women: a meta-analysis. *J Menopausal Med*. 2016 Apr;22(1):14–9. <https://doi.org/10.6118/jmm.2016.22.1.14>
118. Thurston RC, Sowers MR, Sutton-Tyrrell K, Everson-Rose SA, Lewis TT, Edmundowicz D, et al. Abdominal adiposity and hot flashes among midlife women. *Menopause*. 2008 May-Jun;15(3):429–34. <https://doi.org/10.1097/gme.0b013e31815879cf>
119. Ziv-Gal A, Smith RL, Gallicchio L, Miller SR, Zacur HA, Flaws JA. The Midlife Women's Health Study - a study protocol of a longitudinal prospective study on predictors of menopausal hot flashes. *Womens Midlife Health*. 2017;3:4. <https://doi.org/10.1186/s40695-017-0024-8>

120. Gama-Pinto J, Mielke GI. Cumulative adult physical activity and vasomotor symptoms in pre-, peri-, and postmenopausal women aged 40-48. *Maturitas*. 2025 May;196:108245. <https://doi.org/10.1016/j.maturitas.2025.108245>
121. Ziv-Gal A, Flaws JA. Factors that may influence the experience of hot flashes by healthy middle-aged women. *J Womens Health (Larchmt)*. 2010 Oct;19(10):1905-14. <https://doi.org/10.1089/jwh.2009.1852>
122. Heinemann K, Ruebig A, Potthoff P, Schneider HP, Strelow F, Heinemann LA, et al. The Menopause Rating Scale (MRS) scale: a methodological review. *Health Qual Life Outcomes*. 2004 Sep 2;2:45. <https://doi.org/10.1186/1477-7525-2-45>
123. Utian WH, Janata JW, Kingsberg SA, Schluchter M, Hamilton JC. The Utian Quality of Life (UQOL) Scale: development and validation of an instrument to quantify quality of life through and beyond menopause. *Menopause*. 2002 Nov-Dec;9(6):402-10. <https://doi.org/10.1097/00042192-200211000-00005>
124. Coronado PJ, Borrego RS, Palacios S, Ruiz MA, Rejas J. Structural validity of a 16- item abridged version of the Cervantes Health-Related Quality of Life scale for menopause: the Cervantes Short-Form Scale. *Menopause*. 2015 Mar;22(3):325-36. <https://doi.org/10.1097/GME.0000000000000321>
125. Carpenter JS, Monahan PO, Azzouz F. Accuracy of subjective hot flush reports compared with continuous sternal skin conductance monitoring. *Obstet Gynecol*. 2004 Dec;104(6):1322-6. <https://doi.org/10.1097/01.AOG.0000143891.79482.ee>
126. Lugo T, Tetrokashvili M. Hot flashes. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK539827/>
127. Zhou T. Estimation of placebo effect in randomized placebo-controlled trials for moderate or severe vasomotor symptoms: a meta-analysis. *Menopause*. 2023 Jan 1;30(1):5-10. <https://doi.org/10.1097/GME.0000000000002094>
128. Sloan JA, Loprinzi CL, Novotny PJ, Barton DL, Lavasseur BI, Windschitl H. Methodologic lessons learnt from hot flash studies. *J Clin Oncol*. 2001 Dec 1;19(23):4280-90. <https://doi.org/10.1200/JCO.2001.19.23.4280>
129. MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flashes. *Cochrane Database Syst Rev*. 2004 Oct 18;2004(4):CD002978. <https://doi.org/10.1002/14651858.CD002978.pub2>
130. Nelson HD. Menopause. *Lancet*. 2008 Mar 8;371(9614):760-770. [https://doi.org/10.1016/s0140-6736\(08\)60346-3](https://doi.org/10.1016/s0140-6736(08)60346-3)
131. Ockene JK, Barad DH, Cochrane BB, Larson JC, Gass M, Wassertheil-Smoller S, et al. Symptom experience after discontinuing use of estrogen plus progestin. *JAMA*. 2005 Jul 13;294(2):183-93. <https://doi.org/10.1001/jama.294.2.183>
132. Brunner RL, Aragaki A, Barnabei V, Cochrane BB, Gass M, Hendrix S, et al. Menopausal symptom experience before and after stopping estrogen therapy in the Women's Health Initiative randomized, placebo-controlled trial. *Menopause*. 2010 Sep-Oct;17(5):946-54. <https://doi.org/10.1097/gme.0b013e3181d76953>
133. Kroenke CH, Caan BJ, Stefanick ML, Anderson G, Brzyski R, Johnson KC, et al. Effects of a dietary intervention and weight change on vasomotor symptoms in the Women's Health Initiative. *Menopause*. 2012 Sep;19(9):980-8. <https://doi.org/10.1097/gme.0b013e31824f606e>
134. Brennan H, Znayenko-Miller T, Sutton M, Holubkov R, Barnard ND, Kahleova H. Diet quality, body weight, and postmenopausal hot flashes: a secondary analysis of a randomized clinical trial. *BMC Womens Health*. 2024 Nov 23;24(1):620. <https://doi.org/10.1186/s12905-024-03467-4>
135. Barnard ND, Kahleova H, Holtz DN, Znayenko-Miller T, Sutton M, Holubkov R, et al. A dietary intervention for vasomotor symptoms of menopause: a randomized, controlled trial. *Menopause*. 2023 Jan 1;30(1):80-87. <https://doi.org/10.1097/GME.0000000000002080>
136. McCallum KA, Reading C. Hot flashes are induced by thermogenic stimuli. *Br J Urol*. 1989 Nov;64(5):507-10. <https://doi.org/10.1111/j.1464-410x.1989.tb05288.x>
137. Sturdee DW, Hunter MS, Maki PM, Gupta P, Sassarini J, Stevenson JC, et al. The menopausal hot flush: a review. *Climacteric*. 2017 Aug;20(4):296-305. <https://doi.org/10.1080/13697137.2017.1306507>
138. Swartzman LC, Edelberg R, Kemmann E. Impact of stress on objectively recorded menopausal hot flashes and on flush report bias. *Health Psychol*. 1990;9(5):529-45. <https://doi.org/10.1037//0278-6133.9.5.529>
139. Mann E, Smith MJ, Hellier J, Balabanovic JA, Hamed H, Grunfeld EA, et al. Cognitive behavioural treatment for women who have menopausal symptoms after breast cancer treatment (MENOS 1): a randomised controlled trial. *Lancet Oncol*. 2012 Mar;13(3):309-18. [https://doi.org/10.1016/S1470-2045\(11\)70364-3](https://doi.org/10.1016/S1470-2045(11)70364-3)
140. Hunter MS, Coventry S, Hamed H, Fentiman I, Grunfeld EA. Evaluation of a group cognitive behavioural intervention for women suffering from menopausal symptoms following breast cancer treatment. *Psychooncology*. 2009 May;18(5):560-3. <https://doi.org/10.1002/pon.1414>
141. Hardy C, Griffiths A, Norton S, Hunter MS. Self-help cognitive behaviour therapy for working women with problematic hot flashes and night sweats (MENOS@Work): a multicenter randomized controlled trial. *Menopause*. 2018 May;25(5):508-519. <https://doi.org/10.1097/GME.0000000000001048>
142. Elkins GR, Fisher WI, Johnson AK, Carpenter JS, Keith TZ. Clinical hypnosis in the treatment of postmenopausal hot flashes: a randomized controlled trial. *Menopause*. 2013 Mar;20(3):291-8. <https://doi.org/10.1097/gme.0b013e31826ce3ed>
143. Elkins G, Marcus J, Stearns V, Perfect M, Rajab MH, Ruud C, et al. Randomized trial of a hypnosis intervention for treatment of hot flashes among breast cancer survivors. *J Clin Oncol*. 2008 Nov 1;26(31):5022-6. <https://doi.org/10.1200/JCO.2008.16.6389>
144. Cray LA, Woods NF, Mitchell ES. Identifying symptom clusters during the menopausal transition: observations from the Seattle Midlife Women's Health Study. *Climacteric*. 2013 Oct;16(5):539-49. <https://doi.org/10.3109/13697137.2012.746657>
145. Carmody JF, Crawford S, Salmoirago-Blotcher E, Leung K, Churchill L, Olendzki N. Mindfulness training for coping with hot flashes: results of a randomized trial. *Menopause*. 2011 Jun;18(6):611-20. <https://doi.org/10.1097/gme.0b013e318204a05c>
146. Johnson KA, Martin N, Nappi RE, Neal-Perry G, Shapiro M, Stute P, et al. Efficacy and safety of fezolinetant in moderate to severe vasomotor symptoms associated with menopause: a phase 3 RCT. *J Clin Endocrinol Metab*. 2023 Jul 14;108(8):1981-1997. <https://doi.org/10.1210/clinem/dgad058>
147. Morga A, Ajmera M, Gao E, Patterson-Lomba O, Zhao A, Mancuso S, et al. Systematic review and network meta-analysis comparing the efficacy of fezolinetant with hormone and nonhormone therapies for treatment of vasomotor symptoms due to menopause. *Menopause*. 2024 Jan 1;31(1):68-76. <https://doi.org/10.1097/GME.0000000000002281>
148. Lederman S, Ottery FD, Cano A, Santoro N, Shapiro M, Stute P, et al. Fezolinetant for treatment of moderate-to-severe vasomotor symptoms associated with menopause (SKYLIGHT 1): a phase 3 randomised controlled study. *Lancet*. 2023;401(10382):1091-1102. [https://doi.org/10.1016/s0140-6736\(23\)00085-5](https://doi.org/10.1016/s0140-6736(23)00085-5)

149. Santoro N, Waldbaum A, Lederman S, Kroll R, Fraser GL, Lademacher C, et al. Effect of the neurokinin 3 receptor antagonist fezolinetant on patient-reported outcomes in postmenopausal women with vasomotor symptoms: results of a randomized, placebo-controlled, double-blind, dose-ranging study (VESTA). *Menopause*. 2020 Dec;27(12):1350–1356. <https://doi.org/10.1097/GME.0000000000001621>
150. Neal-Perry G, Cano A, Lederman S, Nappi RE, Santoro N, Wolfman W, et al. Safety of fezolinetant for vasomotor symptoms associated with menopause: a randomized controlled trial. *Obstet Gynecol*. 2023 Apr 1;141(4):737–747. <https://doi.org/10.1097/AOG.0000000000005114>
151. Trower M, Anderson RA, Ballantyne E, Joffe H, Kerr M, Pawsey S. Effects of NT-814, a dual neurokinin 1 and 3 receptor antagonist, on vasomotor symptoms in postmenopausal women: a placebo-controlled, randomized trial. *Menopause*. 2020 May;27(5):498–505. <https://doi.org/10.1097/gme.0000000000001500>
152. Pinkerton JV, Simon JA, Joffe H, Maki PM, Nappi RE, Panay N, et al. Elinzanetant for the treatment of vasomotor symptoms associated with menopause: OASIS 1 and 2 randomized clinical trials. *JAMA*. 2024 Aug 22;332(16):1343–54. <https://doi.org/10.1001/jama.2024.14618>
153. Menown SJ, Tello JA. Neurokinin 3 receptor antagonists compared with serotonin norepinephrine reuptake inhibitors for non-hormonal treatment of menopausal hot flushes: a systematic qualitative review. *Adv Ther*. 2021 Oct;38(10):5025–5045. <https://doi.org/10.1007/s12325-021-01900-w>
154. The 2023 nonhormone therapy position statement of The North American Menopause Society. *Menopause*. 2023 Jun 1;30(6):573–590. <https://doi.org/10.1097/GME.0000000000002200>
155. Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA*. 2006 May 3;295(17):2057–71. <https://doi.org/10.1001/jama.295.17.2057>
156. Rada G, Capurro D, Pantoja T, Corbalán J, Moreno G, Letelier LM, et al. Non-hormonal interventions for hot flushes in women with a history of breast cancer. *Cochrane Database Syst Rev*. 2010 Sep 8;(9):CD004923. <https://doi.org/10.1002/14651858.CD004923.pub2>
157. Shams T, Firwana B, Habib F, Alshahrani A, Alnough B, Murad MH, et al. SSRIs for hot flushes: a systematic review and meta-analysis of randomized trials. *J Gen Intern Med*. 2014 Jan;29(1):204–13. <https://doi.org/10.1007/s11606-013-2535-9>
158. Simon JA, Portman DJ, Kaunitz AM, Mekonnen H, Kazempour K, Bhaskar S, et al. Low-dose paroxetine 7.5 mg for menopausal vasomotor symptoms: two randomized controlled trials. *Menopause*. 2013 Oct;20(10):1027–35. <https://doi.org/10.1097/GME.0b013e3182a66aa7>
159. Loprinzi CL, Sloan JA, Perez EA, Quella SK, Stella PJ, Mailliard JA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. *J Clin Oncol*. 2002 Mar 15;20(6):1578–83. <https://doi.org/10.1200/JCO.2002.20.6.1578>
160. Freeman EW, Guthrie KA, Caan B, Sternfeld B, Cohen LS, Joffe H, et al. Efficacy of escitalopram for hot flashes in healthy menopausal women: a randomized controlled trial. *JAMA*. 2011 Jan 19;305(3):267–74. <https://doi.org/10.1001/jama.2010.2016>
161. Davari-Tanha F, Soleymani-Farsani M, Asadi M, Shariat M, Shirazi M, Hadizadeh H. Comparison of citalopram and venlafaxine's role in treating sleep disturbances in menopausal women, a randomized, double-blind, placebo-controlled trial. *Arch Gynecol Obstet*. 2016 May;293(5):1007–13. <https://doi.org/10.1007/s00404-015-3900-1>
162. Loprinzi CL, Kugler JW, Sloan JA, Mailliard JA, LaVasseur BI, Barton DL, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised controlled trial. *Lancet*. 2000 Dec 16;356(9247):2059–63. [https://doi.org/10.1016/S0140-6736\(00\)03403-6](https://doi.org/10.1016/S0140-6736(00)03403-6)
163. Speroff L, Gass M, Constantine G, Olivier S. Efficacy and tolerability of desvenlafaxine succinate treatment for menopausal vasomotor symptoms: a randomized controlled trial. *Obstet Gynecol*. 2008 Jan;111(1):77–87. <https://doi.org/10.1097/01.AOG.0000297371.89129.b3>
164. Leon-Ferre RA, Novotny PJ, Wolfe EG, Faubion SS, Ruddy KJ, Flora D, et al. Oxybutynin vs placebo for hot flashes in women with or without breast cancer: a randomized, double-blind clinical trial (ACCRU SC-1603). *JNCI Cancer Spectr*. 2020 Feb;4(1):pkz088. <https://doi.org/10.1093/jncics/pkz088>
165. Duong V, Iwamoto A, Pennycuff J, Kudish B, Iglesia C. A systematic review of neurocognitive dysfunction with overactive bladder medications. *Int Urogynecol J*. 2021 Oct;32(10):2693–2702. <https://doi.org/10.1007/s00192-021-04909-5>
166. Nambiar AK, Bosch R, Cruz F, Lemack GE, Thiruchelvam N, Tubaro A, et al. EAU guidelines on assessment and nonsurgical management of urinary incontinence. *Eur Urol*. 2018 Apr;73(4):596–609. <https://doi.org/10.1016/j.eururo.2017.12.031>
167. Freeman MP, Hirschberg AM, Wang B, Petrillo LF, Connors S, Regan S, et al. Duloxetine for major depressive disorder and daytime and nighttime hot flashes associated with the menopausal transition. *Maturitas*. 2013 Jun;75(2):170–4. <https://doi.org/10.1016/j.maturitas.2013.03.007>
168. Biglia N, Bounous VE, Susini T, Pecchio S, Sgro LG, Tuninetti V, et al. Duloxetine and escitalopram for hot flushes: efficacy and compliance in breast cancer survivors. *Eur J Cancer Care (Engl)*. 2018 Jan;27(1):e12484. <https://doi.org/10.1111/ecc.12484>
169. Maund E, Guski LS, Gøtzsche PC. Considering benefits and harms of duloxetine for treatment of stress urinary incontinence: a meta-analysis of clinical study reports. *CMAJ*. 2017 Feb 6;189(5):E194–E203. <https://doi.org/10.1503/cmaj.151104>
170. Yoon SH, Lee JY, Lee C, Lee H, Kim SN. Gabapentin for the treatment of hot flushes in menopause: a meta-analysis. *Menopause*. 2020 Apr;27(4):485–493. <https://doi.org/10.1097/GME.0000000000001491>
171. Pandya KJ, Morrow GR, Roscoe JA, Zhao H, Hickok JT, Pajon E, et al. Gabapentin for hot flashes in 420 women with breast cancer: a randomised double-blind placebo-controlled trial. *Lancet*. 2005 Sep 3-9;366(9488):818–24. doi: 10.1016/S0140-6736(05)67215-7.
172. Reddy SY, Warner H, Guttuso T Jr, Messing S, DiGrazio W, Thornburg L, et al. Gabapentin, estrogen, and placebo for treating hot flushes: a randomized controlled trial. *Obstet Gynecol*. 2006 Jul;108(1):41–8. <https://doi.org/10.1097/01.AOG.0000222383.43913.ed>
173. Bandelow B, Zohar J, Hollander E, Kasper S, Möller HJ, Zohar J, et al. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for the pharmacological treatment of anxiety, obsessive-compulsive and post-traumatic stress disorders – first revision. *World J Biol Psychiatry*. 2008;9(4):248–312. <https://doi.org/10.1080/15622970802465807>
174. Cleare A, Pariante CM, Young AH, Anderson IM, Christmas D, Cowen PJ, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2008 British Association for Psychopharmacology guidelines. *J Psychopharmacol*. 2015 May;29(5):459–525. <https://doi.org/10.1177/0269881115581093>
175. Desmarais JE, Looper KJ. Managing menopausal symptoms and depression in tamoxifen users: implications of drug and medicinal interactions. *Maturitas*. 2010 Dec;67(4):296–308. <https://doi.org/10.1016/j.maturitas.2010.08.005>
176. Kelly CM, Juurlink DN, Gomes T, Duong-Hua M, Pritchard KI, Austin PC, et al. Selective serotonin reuptake inhibitors and breast cancer mortality in women receiving tamoxifen: a population based cohort study. *BMJ*. 2010 Feb 8;340:c693. <https://doi.org/10.1136/bmj.c693>

177. Joffe H, Guthrie KA, LaCroix AZ, Reed SD, Ensrud KE, Manson JE, et al. Low-dose estradiol and the serotonin-norepinephrine reuptake inhibitor venlafaxine for vasomotor symptoms: a randomized clinical trial. *JAMA Intern Med.* 2014 Jul;174(7):1058–66. <https://doi.org/10.1001/jamainternmed.2014.1891>
178. Richards-Belle A, Austin-Zimmerman I, Wang B, Zartaloudi E, Cotic M, Gracie C, et al. Associations of antidepressants and antipsychotics with lipid parameters: do CYP2C19/CYP2D6 genes play a role? A UK population-based study. *J Psychopharmacol.* 2023 Apr;37(4):396–407. <https://doi.org/10.1177/02698811231152748>
179. Dai Y, Zhao M, Li M, Ding J, Ye M, Tan Z, et al. Effects of the selective serotonin reuptake inhibitors citalopram and escitalopram on glucolipid metabolism: a systematic review. *Front Endocrinol (Lausanne).* 2025;16:1578326. <https://doi.org/10.3389/fendo.2025.1578326>
180. Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med.* 2015 Mar;175(3):401–7. <https://doi.org/10.1001/jamainternmed.2014.7663>
181. Center for Drug Evaluation and Research. FDA Drug Safety Communication: Abnormal heart rhythms associated with high doses of Celexa (citalopram hydrobromide). FDA [Internet]. 2021 Jan 7 [cited 2026 Feb 5]; Available from: <https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safetycommunication-abnormal-heart-rhythms-associated-high-doses-celexa-citalopram>
182. Leung MTY, Turner JP, Marquina C, Ilomäki J, Tran T, Bykov K, et al. Gabapentinoids and risk of hip fracture. *JAMA Netw Open.* 2024 Nov 4;7(11):e2444488. <https://doi.org/10.1001/jamanetworkopen.2024.44488>
183. Mareti E, Ampatzi C, Paschou SA, Voziki E, Goulis DG. Non-hormonal replacement therapy regimens: do they have an effect on cardiovascular risk? *Curr Vasc Pharmacol.* 2019;17(6):573–578. <https://doi.org/10.2174/1570161116666180911104942>
184. Hu J, Xie K, Wu S, Chen Y. Osteoporosis and fracture risk associated with novel antidepressants: a systematic review and meta-analysis. *Actas Esp Psiquiatr.* 2024 Jun;52(3):334–346. <https://doi.org/10.62641/aep.v52i3.1560>
185. Loprinzi CL, Qin R, Balcueva EP, Flynn KA, Rowland KM Jr, Graham DL, et al. Phase III, randomized, double-blind, placebo-controlled evaluation of pregabalin for alleviating hot flashes, N07C1. *J Clin Oncol.* 2010 Feb 1;28(4):641–7. <https://doi.org/10.1200/JCO.2009.24.5647>
186. Nguyen ML. The use of pregabalin in the treatment of hot flashes. *Can Pharm J (Ott).* 2013 Jul;146(4):193–6. <https://doi.org/10.1177/1715163513490636>
187. Li Y, Chang J, Shi G, Zhang W, Wang H, Wei L, et al. Effects of stellate ganglion block on perimenopausal hot flashes: a randomized controlled trial. *Front Endocrinol (Lausanne).* 2023;14:1293358. <https://doi.org/10.3389/fendo.2023.1293358>
188. Lerman I, Hauger R, Sorkin L, Proudfoot J, Davis B, Huang A, et al. Noninvasive transcutaneous vagus nerve stimulation decreases whole blood culture-derived cytokines and chemokines: a randomized, blinded, healthy control pilot trial. *Neuromodulation.* 2016 Apr;19(3):283–90. <https://doi.org/10.1111/ner.12398>
189. Reid RL, Magee B, Trueman J, Hahn PM, Pudwell J. Randomized clinical trial of a handheld cooling device (Menopod®) for relief of menopausal vasomotor symptoms. *Climacteric.* 2015 Oct;18(5):743–9. <https://doi.org/10.3109/13697137.2015.1042856>
190. Flores R, Shi J, Fuhrman B, Xu X, Veenstra TD, Gail MH, et al. Fecal microbial determinants of fecal and systemic estrogens and estrogen metabolites: a cross-sectional study. *J Transl Med.* 2012 Dec 21;10:253. <https://doi.org/10.1186/1479-5876-10-253>
191. Sarrel P, Portman D, Lefebvre P, Lafeuille MH, Grittner AM, Fortier J, et al. Incremental direct and indirect costs of untreated vasomotor symptoms. *Menopause.* 2015 Mar;22(3):260–6. <https://doi.org/10.1097/GME.0000000000000320>
192. Thurston RC, Aslanidou Vlachos HE, Derby CA, Jackson EA, Brooks MM, Matthews KA, et al. Menopausal vasomotor symptoms and risk of incident cardiovascular disease events in SWAN. *J Am Heart Assoc.* 2021 Feb 2;10(3):e017416. <https://doi.org/10.1161/JAHA.120.017416>
193. Szmuiłowicz ED, Manson JE, Rossouw JE, Howard BV, Margolis KL, Greep NC, et al. Vasomotor symptoms and cardiovascular events in postmenopausal women. *Menopause.* 2011 Jun;18(6):603–10. <https://doi.org/10.1097/gme.0b013e3182014849>
194. Nudy M, Aragaki AK, Jiang X, Manson JE, Allison MA, Shadyab AH, et al. The severity of individual menopausal symptoms, cardiovascular disease, and all-cause mortality in the Women's Health Initiative Observational Cohort. *Menopause.* 2022 Dec 1;29(12):1365–1374. <https://doi.org/10.1097/GME.0000000000002089>
195. Franco OH, Muka T, Colpani V, Kunutsor S, Chowdhury S, Chowdhury R, et al. Vasomotor symptoms in women and cardiovascular risk markers: systematic review and meta-analysis. *Maturitas.* 2015 Jul;81(3):353–61. <https://doi.org/10.1016/j.maturitas.2015.04.016>
196. Armeni A, Agnostos P, Armeni E, Mili N, Goulis D, Lambrinoudaki I. Vasomotor symptoms and risk of cardiovascular disease in peri- and postmenopausal women: a systematic review and meta-analysis. *Maturitas.* 2023 May;171:13–20. <https://doi.org/10.1016/j.maturitas.2023.02.004>
197. Zhu D, Chung HF, Dobson AJ, Pandeya N, Anderson DJ, Kuh D, et al. Vasomotor menopausal symptoms and risk of cardiovascular disease: a pooled analysis of six prospective studies. *Am J Obstet Gynecol.* 2020 Dec;223(6):898.e1–898.e16. <https://doi.org/10.1016/j.ajog.2020.06.039>
198. Samargandy S, Matthews KA, Brooks MM, Barinas-Mitchell E, Magnani JW, Thurston RC, et al. Trajectories of blood pressure in midlife women: does menopause matter? *Circ Res.* 2022 Feb 4;130(3):312–322. <https://doi.org/10.1161/CIRCRESAHA.121.319424>
199. Carpenter JS, Cortés YI, Tisdale JE, Sheng Y, Jackson EA, Barinas-Mitchell E, et al. Palpitations across the menopause transition in SWAN: trajectories, characteristics, and associations with subclinical cardiovascular disease. *Menopause.* 2023 Jan 1;30(1):18–27. <https://doi.org/10.1097/GME.0000000000002082>
200. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, Crandall CJ, Sternfeld B, Joffe H, et al. Vasomotor symptoms and insulin resistance in the study of women's health across the nation. *J Clin Endocrinol Metab.* 2012 Oct;97(10):3487–94. <https://doi.org/10.1210/jc.2012-1410>
201. Gray KE, Katon JG, LeBlanc ES, Woods NF, Bastian LA, Reiber GE, et al. Vasomotor symptom characteristics: are they risk factors for incident diabetes? *Menopause.* 2018 May;25(5):520–530. <https://doi.org/10.1097/GME.0000000000001033>
202. Reeves AN, Elliott MR, Brooks MM, Karvonen-Gutierrez CA, Bondarenko I, Hood MM, et al. Symptom clusters predict risk of metabolic-syndrome and diabetes in midlife: the Study of Women's Health Across the Nation. *Ann Epidemiol.* 2021 Jun;58:48–55. <https://doi.org/10.1016/j.annepidem.2021.02.011>
203. Nudy M, Jiang X, Aragaki AK, Manson JE, Shadyab AH, Foy AJ, et al. The severity of vasomotor symptoms and number of menopausal symptoms in postmenopausal women and select clinical health outcomes in the Women's Health Initiative Calcium and Vitamin D randomized clinical trial. *Menopause.* 2020 Nov;27(11):1265–1273. <https://doi.org/10.1097/GME.0000000000001667>

204. Thurston RC, El Khoudary SR, Sutton-Tyrrell K, Crandall CJ, Gold EB, Sternfeld B, et al. Vasomotor symptoms and lipid profiles in women transitioning through menopause. *Obstet Gynecol*. 2012 Apr;119(4):753–61. <https://doi.org/10.1097/AOG.0b013e31824a09ec>
205. Thurston RC, El Khoudary SR, Tepper PG, Jackson EA, Joffe H, Chen HY, et al. Trajectories of vasomotor symptoms and carotid intima media thickness in the Study of Women's Health Across the Nation. *Stroke*. 2016 Jan;47(1):12–7. <https://doi.org/10.1161/STROKEAHA.115.010600>
206. Mishra T, Pasnoor DS, Gandhi M, Mohamed N, Chauhan S, Adompreh-Fia K, et al. Interplay of menopause, coronary artery calcium score and cardiovascular disease risk. *World J Cardiol*. 2025 Nov 26;17(11):109627. <https://doi.org/10.4330/wjc.v17.i11.109627>
207. Subramanya V, Zhao D, Ouyang P, Ying W, Vaidya D, Ndumele CE, et al. Association of endogenous sex hormone levels with coronary artery calcium progression among post-menopausal women in the Multi-Ethnic Study of Atherosclerosis (MESA). *J Cardiovasc Comput Tomogr*. 2019 Jan-Feb;13(1):41–47. <https://doi.org/10.1016/j.jcct.2018.09.010>
208. Keir DA, Badrov MB, Tomlinson G, Notarius CF, Kimmerly DS, Millar PJ, et al. Influence of sex and age on muscle sympathetic nerve activity of healthy normotensive adults. *Hypertension*. 2020 Sep;76(3):997–1005. <https://doi.org/10.1161/HYPERTENSIONAHA.120.15208>
209. Hart EC, Charkoudian N, Wallin BG, Curry TB, Eisenach J, Joyner MJ. Sex and ageing differences in resting arterial pressure regulation: the role of the β -adrenergic receptors. *J Physiol*. 2011 Nov 1;589(Pt 21):5285–97. <https://doi.org/10.1113/jphysiol.2011.212753>
210. Keller-Ross ML, Cunningham HA, Carter JR. Impact of age and sex on neural cardiovascular responsiveness to cold pressor test in humans. *Am J Physiol Regul Integr Comp Physiol*. 2020 Sep 1;319(3):R288–R295. <https://doi.org/10.1152/ajpregu.00045.2020>
211. Carson MY, Thurston RC. Vasomotor symptoms and their links to cardiovascular disease risk. *Curr Opin Endocr Metab Res*. 2023 Jun;30:100448. <https://doi.org/10.1016/j.coemr.2023.100448>
212. Johanneke van den Berg M, Mishra GD, van der Schouw YT, Herber-Gast GC. Vasomotor menopausal symptoms are not associated with incidence of breast cancer in a population-based cohort of mid-aged women. *Eur J Cancer*. 2014 Mar;50(4):824–30. <https://doi.org/10.1016/j.ejca.2013.11.033>
213. Thurston RC, Carroll JE, Levine M, Chang Y, Crandall C, Manson JE, et al. Vasomotor symptoms and accelerated epigenetic ageing in the Women's Health Initiative (WHI). *J Clin Endocrinol Metab*. 2020 Apr 1;105(4):1221–7. <https://doi.org/10.1210/clinem/dgaa081>
214. Crandall CJ, Aragaki A, Cauley JA, Manson JE, LeBlanc E, Wallace R, et al. Associations of menopausal vasomotor symptoms with fracture incidence. *J Clin Endocrinol Metab*. 2015 Feb;100(2):524–34. <https://doi.org/10.1210/jc.2014-3062>
215. Anagnostis P, Lallas K, Pappa A, Avgeris G, Beta K, Damakis D, et al. The association of vasomotor symptoms with fracture risk and bone mineral density in postmenopausal women: a systematic review and meta-analysis of observational studies. *Osteoporos Int*. 2024 Aug;35(8):1329–1336. <https://doi.org/10.1007/s00198-024-07075-8>
216. Crandall CJ, Larson J, Cauley JA, Schousboe JT, LaCroix AZ, Robbins JA, et al. Do additional clinical risk factors improve the performance of Fracture Risk Assessment Tool (FRAX) among postmenopausal women? Findings from the Women's Health Initiative Observational Study and clinical trials. *JBMR Plus*. 2019 Dec;3(12):e10239. <https://doi.org/10.1002/jbm4.10239>
217. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. *JAMA*. 2003 Oct 1;290(13):1729–38. <https://doi.org/10.1001/jama.290.13.1729>
218. Meeta M, Harinarayan CV, Marwah R, Sahay R, Kalra S, Babhulkar S. Clinical practice guidelines on postmenopausal osteoporosis: *an executive summary and recommendations – update 2019-2020. *J Midlife Health*. 2020 Apr-Jun;11(2):96–112. https://doi.org/10.4103/jmh.JMH_143_20

GENITOURINARY SYNDROME OF MENOPAUSE

Keywords: Genitourinary syndrome, vulvovaginal atrophy, recurrent urinary tract infections, urinary incontinence, genital prolapse

10

INTRODUCTION

Genitourinary atrophy is one of the inevitable changes among postmenopausal women, which may cause vaginal dryness, irritation, dyspareunia, recurrent urinary tract infections (RUTIs) and sexual dysfunction affecting quality of life (QoL).¹⁻³ Pelvic floor dysfunction, which includes five types of dysfunction (that is, dysfunctions of micturition, defecation, prolapse, sex and pain), is known to increase with age.^{3,4} Women may present with urinary or bowel incontinence, pelvic organ prolapse (POP), and pelvic pain during this transition phase.²

TERMINOLOGY

The International Society for the Study of Women's Sexual Health and the North American Menopause Society, together after consensus, have coined the term genitourinary syndrome of menopause (GSM) for the urogenital and vulvovaginal atrophy (VVA) that occurs at menopause.¹ Genitourinary syndrome of menopause is defined as a collection of symptoms and signs associated with a decrease in estrogen and other sex steroids involving changes of the labia majora/minora, clitoris, vestibule/ introitus, vagina, urethra and bladder. The syndrome may include, but is not limited to, genital symptoms of dryness, burning, and irritation; sexual symptoms of lack of lubrication, discomfort or pain, and impaired function; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections (RUTIs).¹

The onset of symptoms is often insidious and can occur long after the resolution of other menopausal symptoms, such as hot flashes and may persist for years.⁴ Vaginal atrophy becomes clinically apparent generally after 1-6 years of menopause.^{4,5} Although it is not a serious condition, vaginal atrophy is progressive and typically does not resolve on its own and has an effect on the QoL.^{6,7} GSM requires treatment, unlike vasomotor symptoms, which improve as age advances, in most women, irrespective of treatment.⁸⁻¹¹

PATHOPHYSIOLOGY

Estrogen plays a fundamental role in maintaining the integrity and function of genitourinary tissues, which express robust estrogen receptors (ER). The urogenital tract is susceptible to estrogen deficiency; consequently, approximately 50% of postmenopausal women experience symptoms of urogenital atrophy.¹² Before menopause, circulating serum estradiol levels typically range from 40 to 400 pg/mL, but these levels decline sharply to 5–20 pg/mL postmenopause in the later stages of menopause.¹³ Early data showed that untreated postmenopausal women displaying <50 pg/ml of circulating estradiol suffer more from symptoms associated with VVA.¹⁴ This reduction in systemic estrogen levels leads to a cascade of physiological alterations in the genitourinary system, contributing to a spectrum of urinary and genital symptoms. However, symptom manifestation varies, and not all women are clinically affected.¹⁵

The female genital and lower urinary tracts share a common embryological origin and are highly responsive to sex steroid hormones.¹⁶⁻¹⁸ Structures such as the distal urethra, bladder trigone, vulvar vestibule, and upper vagina all derive from the urogenital sinus, which is rich in ER. The external vulva, including the labia majora, arises from ectodermal tissue, whereas the vestibule remains urogenital in origin.¹⁹ Anatomically, the vagina comprises four layers: an inner stratified squamous epithelial layer, the lamina propria, the muscular layer, and the adventitia. It serves as a practical site for assessing estrogenic status, particularly in postmenopausal women. Estrogen maintains the multilayered squamous epithelium, ensuring its pink hue, moisture, and rugae. It also promotes the synthesis of acid mucopolysaccharides and hyaluronic acid, which are essential for epithelial hydration. Furthermore, estrogen stimulates glycogen deposition in the vaginal epithelium. Döderlein's lactobacilli metabolise this glycogen into lactic acid, maintaining a vaginal pH of less than 4.5 in premenopausal women.²⁰ In estrogen-deficient states, epithelial cell turnover declines, resulting in an increased proportion of parabasal cells and thinning of the epithelium. Vaginal secretions decrease markedly, from approximately 3–4 g per 4 hours to 1.7 g per 4 hours.¹⁹ This reduction leads to diminished glycogen availability and impaired microbial defence. Consequently, lactobacilli populations decline, pH

increases (>5), and the microbiota shifts toward diverse species such as *Gardnerella*, *Streptococcus*, and *Sneathia*. These changes are strongly associated with higher risks of infection and inflammation.²¹ Postmenopausal changes also affect fibroblast function. Fibroblasts, the primary collagen-producing cells in the vaginal connective tissue, become quiescent and differentiate into fibrocytes. Collagen fibres in the dermis undergo hyalinisation and fusion. This, combined with elastin fragmentation, leads to decreased vaginal elasticity and loss of rugae, typically evident 2–3 years after menopause. Local estrogen replacement therapy increased collagen degradation and replacement, as found with histological evidence, but it did not have a beneficial effect on stress incontinence.²²

After treatment with DHEA, a precursor for estrogen and testosterone, a higher collagen density was observed in oophorectomised rats.^{23,24} The distal one-third of the urethra shares structural similarity with the vagina and is lined by non-keratinised stratified squamous epithelium. It is equally estrogen-sensitive. With hypoestrogenism, this tissue becomes thin and poorly vascularised, leading to glycogen depletion, loss of lactobacilli, elevated pH, and symptoms such as dysuria, urethral burning, and meatal discomfort. Additionally, atrophy of the periurethral vascular plexus and submucosa compromises urethral closure pressure, exacerbating urinary incontinence. ER in the bladder trigone also influence detrusor muscle function by modulating muscarinic receptors, further contributing to lower urinary tract symptoms (LUTS) and increased susceptibility to recurrent urinary tract infections (rUTIs).^{25–27}

Hormone Receptor Distribution in Genitourinary Tissues

ERs are distributed throughout the genitourinary system, including the epidermis, stroma, and fibroblasts of the vulva, vagina, bladder, urethra, pelvic floor, and endopelvic fascia. Hodgins' research demonstrated that ERs are absent in cutaneous blood vessels, lymphatics, and most skin appendages, except for the luminal epithelium of apocrine sweat glands.²⁸ Notably, this may explain the observed efficacy of estrogen-based therapies in conditions such as hidradenitis suppurativa. ER- α is consistently expressed in the vaginal tissue of both pre- and postmenopausal women. At the same time, ER- β is significantly reduced or absent in postmenopausal vaginal tissues and does not respond to estrogen therapy. ER density is highest in the vagina and diminishes progressively toward the vulva and surrounding skin.^{29–31} Postmenopausal vaginal tissue expresses the enzyme 17 β -hydroxysteroid dehydrogenase type 2, which converts estradiol to the less potent estrone. Estrone is further inactivated via estrone sulfotransferase.

These enzymatic processes contribute to variability in symptom severity and treatment response, underscoring that local estrogen metabolism can occur independently of systemic hormone levels.^{25,32}

Androgen receptors (ARs) are distributed throughout the vulvovaginal region, including the labia majora, labia minora, and suprapubic skin. AR density is highest in external genital tissues and lowest in vaginal tissues, an inverse pattern to ERs. High AR expression is found in epidermal keratinocytes, dermal fibroblasts, and sebaceous glands.^{29,33–35} Serum androgen levels, including dehydroepiandrosterone (DHEA), decline significantly with age, with approximately 60% lost by the time menopause is reached. DHEA has demonstrated dual androgenic and estrogenic effects in animal models, enhancing all layers of the vaginal wall, including epithelial mucification and collagen fibre organisation. Pessina's work also indicates that testosterone increases adrenergic nerve fibre density, suggesting a neural mechanism for androgen-mediated benefits.^{36–39}

Progesterone receptors (PRs) are present throughout the vaginal wall & lower urinary tract, but their expression varies and is generally reduced postmenopause. Progesterone's direct role in GSM is limited.^{16,40} Clinically, progestogens are primarily used in combination with estrogen to protect the endometrium.⁴¹ Tibolone, a synthetic steroid with mixed hormonal effects, has shown some benefit in improving vaginal maturation index, although it is not considered first-line therapy for GSM.^{42,43}

Neuroanatomy and Hormonal Effects on Innervation

Embryologically, the external vulva is ectodermal in origin, while the vestibule arises from the urogenital sinus and is innervated by the pudendal nerve. The hymen marks the junction between the endodermally derived vestibule and the mesodermal, Müllerian-derived vaginal canal, innervated by the pelvic nerve. Immunohistochemical studies reveal that free small fibre nerve endings are concentrated in the vestibular epithelium and the anterior vaginal wall's lamina propria and muscle layers. The submucosal vaginal nerve plexus is composed primarily of autonomic fibres, with fewer sensory fibres. In contrast, the vestibule contains a dense network of superficial sensory fibres, contributing to its heightened sensitivity.^{44,45} This neural distribution explains why symptoms such as burning, dyspareunia, and irritation are more intense in the vulvar vestibule and anterior vaginal wall in GSM and vulvodynia.⁴⁶ Hormonal deprivation leads to epithelial thinning, reducing the barrier between nerve endings and the vaginal lumen. Estrogen also modulates neurotransmitter expression in these tissues.³⁷

Emerging evidence shows that ERs influence epithelial and stromal compartments and neural architecture. Estrogen deficiency is associated with reduced nerve density and altered sensory processing. While the direct presence of ERs in nerve fibres remains under investigation, ER- α is thought to predominate in smooth muscle and vascular nerve tissues.

Neural Remodelling in Hormonal Deficiency

Estrogen deprivation is associated with enhanced sympathetic activity, which may increase vasoconstriction and contribute to vaginal dryness. Concurrently, sensory nerve proliferation may result in burning, pain, and pruritus. Animal studies show that ovariectomy leads to variable changes in vaginal innervation, which are reversed by estradiol supplementation. Continuous 17 β -estradiol treatment restores nerve density to levels observed in the oestrus phase, indicating estrogen's pivotal role in neural remodelling.^{44,47}

Therapeutic Implications

Topical estrogen therapy in postmenopausal women has been shown to reduce sympathetic, parasympathetic, and nociceptive innervation in the vagina. This neurological remodelling is likely a key mechanism by which hormonal therapies alleviate symptoms of GSM.⁴⁸ Menopausal estrogen deficiency disrupts the genitourinary system via multiple interrelated mechanisms: altered epithelial structure, reduced lactobacilli, elevated pH, impaired vascular and neural function, and diminished fluid secretion. These changes underpin the clinical presentation of GSM and highlight the central role of sex steroids, particularly estrogen, in maintaining urogenital health.

PREVALENCE OF GENITOURINARY SYNDROME OF MENOPAUSE

Global: Vulvar and vaginal atrophy (VVA) is a chronic and progressive condition experienced by almost 40–60% of postmenopausal women.^{49–51} A 2020 review stated that, as many as 64.7% of women at 1 year and 84.2% at 6 years after menopause had developed GSM.⁵² Meta-analysis of seven key studies indicates a prevalence of 50%.^{4,51,53–58} Range across countries/studies: Individual studies report 13%–87% prevalence, reflecting heterogeneity by design, case definition, and sampling frame.⁵⁹ The prevalence of vaginal dryness as the most bothersome symptom (MBS) increased with years since menopause, while that of itching, dysuria and burning remained approximately constant over time. The prevalence of dyspareunia as the MBS was 26.2% in the first 6 years after menopause and declined thereafter to 8.8%.^{5,10,60–6}

A systematic review reported wide variation in treatment use (13%–78%); OTC lubricants/moisturisers were most commonly used (24–85.5%); and low-dose vaginal estrogens were used by 4.8–35% across studies.⁵⁹ The conclusion from the meta-analysis was that far fewer women seek treatment, often because they are uninformed about hypoestrogenic postmenopausal vulvovaginal changes and the availability of safe, effective, and well-tolerated treatments. Because women hesitate to seek help for symptoms, a proactive approach to conversations about vulvovaginal discomfort would improve diagnosis and treatment.⁵³

Indian Context: Indian women tend to be reserved in expressing their feelings and needs, particularly when addressing concerns related to genital health and sexual function, compared to Western women. Not only rural women but also educated urban women may be culturally inhibited in this context. However, these women, while hesitant in discussing their sexual problems, are relieved if their doctor initiates a discussion and offers help. It needs no emphasis that Indian women need greater awareness of the implications of vaginal atrophy and the benefits of early treatment.

Two studies from the Indian Menopause Society reported similar findings. The first study in 2012, with a sample of 1800, found that dryness of the vagina was higher in menopausal women (31.8%) compared to perimenopausal women (26.7%). Itchiness was also higher among menopausal women (16.3%) than among perimenopausal women (11.6%).⁶⁴ The second study from the IMS Registry, with a sample size of 1781 women, reported a GSM prevalence of 48.5%, increasing significantly across menopause stages: 28.5% in the menopause transition, 57.9% in early postmenopause, and 71.7% in late postmenopause. Moreover, the most prevalent symptoms were lower urinary tract symptoms (LUTS) (38.2%) and vaginal dryness (26.4%). The Vaginal Health Index (VHI) score was ≤ 15 in 69% of women.⁶⁵ In a study on 100 rural women in central India, the most common symptom was vaginal dryness (77%), followed by vaginal discharge (74%), and 79% showed a VHI score of less than 15. The incidence of VVA was 79%.⁶⁶

RISK FACTORS FOR GENITOURINARY SYNDROME OF MENOPAUSE

The primary driver of GSM is estrogen deficiency, whether from natural menopause, surgical menopause, premature ovarian insufficiency (POI), or hypothalamic–pituitary disorders. Earlier menopause (EM) is associated with longer and more severe GSM symptoms. Other risk factors for developing GSM include alcohol abuse, cigarette smoking, lack of exercise, and lack of sexual activity.⁶⁷⁻⁶⁹ Any condition leading to estrogen decline in the absence of menopause (hormonal therapies and chemotherapy treatment) can cause estrogen deficiency and produce symptoms of GSM. Women undergoing cancer treatment, including radiation, chemotherapy and on adjuvant endocrine therapies, are particularly affected. Studies have reported that more than 70% of breast cancer patients on adjuvant therapy experience symptoms of VVA, and aromatase inhibitors are associated with more severe symptoms of VVA than tamoxifen.⁷⁰ The duration of hypoestrogenism is a significant factor in the development and severity of GSM.

Aggravating Factors

Sociocultural barriers, including stigma, embarrassment, and lack of awareness, contribute to underreporting and delayed diagnosis of GSM. The European Vulvovaginal Epidemiological Survey (EVES) highlighted the significant impact of GSM on QoL and sexual function.⁷¹ Older age, late postmenopausal status, poor sleep quality, and lower educational status have been shown to significantly increase the likelihood of experiencing GSM, as demonstrated in data from the Indian Midlife Registry.⁶⁵

DIAGNOSIS

Currently, no universally accepted diagnostic criteria exist for GSM. Clinical diagnosis relies primarily on characteristic symptom presentation, with or without supporting physical findings, after excluding alternative conditions or concurrent pathologies. For research purposes, the U.S. Food and Drug Administration (FDA) mandates standardised assessment using three core parameters: vaginal pH measurement, vaginal maturation index (VMI), and identification of the patient's most bothersome symptom (MBS).⁷² However, routine clinical practice often lacks access to pH measurement tools or VMI assessment capabilities, necessitating a practical minimum diagnostic approach.

International Consensus Development to Establish Standardised Outcome Measures for Clinical Trials

The Core Outcome Set (COMMA) initiative represents an international consensus effort spanning 21 countries and incorporates perspectives from women with lived menopausal experience and their healthcare providers. This collaborative approach aims to establish standardised outcome measures for clinical trials evaluating treatments for GSM. Notably, participants in the COMMA consensus voted against incorporating objective measures, determining that clinician assessments of genital appearance do not reliably correlate with symptoms or women's lived experiences and should therefore be excluded from core outcome sets.⁷³ In the Women's Health Initiative, it was found that more than two-thirds (69%) of women had physical evidence of VVA at enrolment, only 10% of the same population, however, reported moderate to severe vaginal or genital dryness.⁷⁴ Nevertheless, a GSM measurement scale is under development but may still include "objective measures" such as vaginal pH.⁶⁷

Diagnostic Challenges and Controversies

Recent 2023 literature questions GSM terminology and raises concern regarding the lack of standardised diagnostic criteria, which may lead to over-pathologising and over-treatment. Conversely, women experiencing troublesome symptoms who could benefit from intervention might not be clearly identified using current GSM criteria.

Proposed Minimum Diagnostic Criteria

Pérez-López and colleagues (2021) have proposed a practical minimum diagnostic framework incorporating⁷⁶:

- Symptomatic presentation: Characteristic symptoms include vaginal dryness, pruritus, irritation, and dyspareunia.
- Objective clinical findings: Pale, smooth, lustrous, dry vaginal epithelium with loss of rugae
Differential diagnosis: Exclusion of alternative conditions, particularly infectious etiologies
- Vaginal Health Index (VHI) assessment: Scores ≤ 15 in hypoestrogenic contexts may support GSM diagnosis

The Role of Objective Measurements

Clinical debate continues over whether diagnosis should rely solely on symptomatic presentation or incorporate at least one objective finding, with vaginal pH measurement the most accessible option.

Notelovitz (1995) demonstrated that postmenopausal women with estrogen deficiency exhibit elevated vaginal and urethral pH levels associated with atrophic changes. In a double-blind study of 67 women, topical vaginal conjugated estrogen therapy normalised both parameters, establishing vaginal pH testing as valuable for both diagnostic and monitoring purposes.²⁵ Looking at GSM severity assessment methods, the currently best standardised tools are VMI, clinical evaluation scales, patient-reported outcomes, and symptoms. Urogenital symptoms and signs progress over time based on primary longitudinal studies,^{77,78} treatment response studies with temporal data,^{79,80} natural history and progression reviews,^{81,82} short-term progression studies,⁸³ and objective measure progression.⁸⁴ Table 1 shows the pattern of symptoms and signs that have been prevalent throughout the lifespan.

Table 1: Prevalence pattern of symptoms and signs of GSM over the life span.

Symptom/Sign	1 Year Post-Menopause	Mid-Menopause (6+ years)	Late Menopause
Dyspareunia	67.5%	~75% (peak)	~41%
Dysuria	~15%	20-25%	~30%
pH >5	~78%	85%	~90%
Mucosal Pallor/Thinning	~60%	75%	~90%
Mucosal Fragility	~35%	60%	~80%
Petechiae	15-20%	35%	~51%

APPROACH TO CLINICAL ASSESSMENT

Comprehensive clinical evaluation begins with detailed history taking and pelvic examination to assess GSM's impact on QoL and exclude other conditions causing urogenital symptoms. Given that GSM is significantly underreported, clinicians should employ leading questions when women do not spontaneously report relevant symptoms.

Symptomatic women may present with:

- Genital dryness and inadequate lubrication
- Sexual activity-related pain and postcoital spotting or bleeding
- Decreased arousal, orgasm, and desire
- Vulvovaginal irritation, burning, or pruritus
- Urinary symptoms, including a sense of urgency, lower abdominal pressure, and involuntary urine loss. This condition is differentiated from cystitis by the absence of dysuria and a normal urine culture. Pressure on the trigone through the anterior vaginal wall replicates the symptoms.
- Significant QoL impairment

Validated Assessment Tools for Patient-Reported Outcome Measures

Multiple validated patient-reported outcome measures are available for clinical documentation of symptom severity and quality of life impact:

- Vulvovaginal Symptoms Questionnaire (VSQ).⁸⁵
- Day-to-Day Impact of Vaginal Ageing (DIVA) questionnaire.⁸⁶

- Most Bothersome Symptoms assessment.⁸⁷
- Vaginal and Vulvar Assessment Scale.⁸⁸
- Vulvar Pain Assessment Questionnaire (VPAQ).⁸⁹
- Female Sexual Function Index (FSFI).⁹⁰
- Female Sexual Distress Scale-Revised (FSDS-R).⁹¹
- Vestibular level, named Vestibular Trophic Health (VeTH), is a morphological descriptor and a functional index of GSM.⁹²
- Urinary symptoms can be studied with the three-item International Consultation on Incontinence Questionnaire.⁹³

Clinical consideration: While comprehensive, these assessment tools may be time-consuming in routine clinical settings.

Physical Examination

Vulvar Assessment: Vulvar examination may reveal loss of connective tissue substance with consequent shrinkage of labia majora and minora, often accompanied by decreased introital opening. Clinicians should assess for:

- Tissue fragility, fissures, or petechiae at the introitus
- Prominent urethral meatus or urethral eversion/prolapse
- Advanced GSM changes, including labial fusion, introital stenosis, labial and clitoral atrophy, prepuce
- phimosis, and urethral caruncles, polyps, eversion, or prolapse

Vestibular Sensitivity Assessment: Physical examination should include cotton swab testing with a 0-3 pain scale to identify sites of surface tenderness, particularly in the six vestibular areas. Vestibular tenderness typically occurs just distal to the hymenal ring in the cryptlike fold surrounding the hymen and may be associated with erythema.

Pelvic Floor Evaluation: The standardised pelvic floor dysfunction examination⁹⁴ begins with palpation of the mid-thigh muscles to provide the patient with a reference point and to demonstrate that the palpation typically feels like “pressure, not pain.” Vaginal examination involves bilateral palpation of the obturator and levator ani muscles, with patients reporting and scoring the pain elicited on a scale of 1 (mild discomfort) to 10 (severe pain).

Vaginal Examination Considerations: When vestibular tenderness is present, topical lidocaine application before vaginal examination is recommended. Gynaecological examination using a small-sized speculum often reveals maximum pain at the vestibule, decreasing along the vaginal wall. Important sensitivity differences exist between the vestibule and vaginal epithelium. Severe erosive lichen planus affecting only vaginal epithelium may be asymptomatic despite marked atrophy and scarring, whereas vestibular involvement can cause intense pain. This phenomenon is exemplified during childbirth, where the vaginal canal remains largely insensitive to stretching. However, intense pain occurs as the foetal head distends the richly innervated vestibule at the crowning stage.

Progressive Pain Patterns: Observational studies document that women in late menopause may initially experience provoked intercourse pain, which can progress to constant, severe vestibular pain. Management with nightly estradiol cream applied directly to the vestibule has demonstrated gradual symptom improvement; severe cases may require an adjunctive topical anaesthetic to tolerate therapy. Early intervention before pain becomes severe is crucial for maintaining QoL, with therapeutic success depending more on treatment duration than dose.^{95,96}

Objective Assessment Parameters

Vaginal Appearance: Classic vaginal atrophy presentation includes:

- Loss of rugae with pale, thin, flattened vaginal epithelium
- Tenderness to palpation and reduced vaginal elasticity
- Vaginal narrowing with increased susceptibility to trauma and irritation

- Friable epithelial tissues with potential submucosal petechial haemorrhages
- Reduced posterior fornix fluid content
- Fluid colour change from normal white flocculent to thin white/yellow or absent fluid

Microscopic Findings: Wet-mount microscopy typically demonstrates:

- Immature vaginal epithelial cells with large nuclei (parabasal cells)
- Minimal or absent lactobacilli
- More than one white blood cell per epithelial cell
- Vaginal pH is typically >5.0

Diagnostic Testing

In healthy reproductive age women,, vaginal pH is 3.8–4.5.⁹⁷

Vaginal pH Measurement: Technique: Apply pH test stick to vaginal sidewall for several seconds, avoiding contamination from blood, semen, or cervical mucus pooled in the posterior fornix. Alternatively, swab the vaginal sidewall with a dry swab and roll onto pH paper. The pH remains stable at room temperature for approximately 2-5 minutes.⁸¹

Technical considerations:

- Avoid premoistening swabs, as liquids can alter pH.
- Narrow range pH paper (4.0-5.5) is easier to interpret than broad range (4.5-7.5).
- Elevated pH in premenopausal women suggests infections (Bacterial vaginosis:pH >4.5; trichomoniasis: pH 5-6) and helps exclude candidial vulvovaginitis (pH 4-4.5)
- Lubricating gels, semen, blood, douches, and intravaginal medications may alter vaginal pH.

The vaginal pH is an excellent surrogate test of the vagina and urethra's hormonal status.

Standardised Clinical validation²⁵:

Vaginal Health Index: The VHI provides a comprehensive scoring system for assessing the severity of genitourinary tract atrophy. Each parameter is scored from 1 (worst) to 5 (best), and the sum of the scores provides the overall score. Scores ≤15 indicate vaginal atrophy.⁸¹

Vaginal Maturation Index^{98,99} :The VMI quantifies vaginal epithelium estrogen status by analysing parabasal, intermediate, and superficial cell ratios. The index is calculated as a weighted average: $(0 \times \% \text{ parabasal}) + (0.5 \times \% \text{ intermediate}) + (1 \times \% \text{ superficial})$.

Normal values: Premenopausal women: >15% superficial cells are considered normal. Postmenopausal women with VVA: Typically, <5% superficial cells are seen.

Interpretation: Low VMI (such as 0/0/100): High superficial cell percentage indicates normal/high estrogen levels ; High VMI (such as 90/10/0): High parabasal cell percentage with absent superficial cells indicates low estrogen levels and vaginal atrophy.

Intermediate VMI: Mixed parabasal and intermediate cells suggest moderate estrogen levels.

Cellular characteristics: Normal: Superficial cells predominate with a low nuclear/cytoplasmic ratio and pyknotic nuclei; Atrophic: More parabasal cells with a high nuclear/cytoplasmic ratio and inflammatory exudate.

Finally, a few authors have attempted to objectively evaluate transvaginal ultrasound for measuring vaginal wall thickness in GSM, suggesting that it could be an effective histological measure. This is a promising line of investigation, as it would bring objectivity through noninvasive exploration.¹⁰⁰

Standardised Clinical Assessment

The basis of good treatment is a correct and complete diagnosis. Most physicians rely on medical history, clinical examination, and investigations. Atrophic changes observed on examination do not necessarily require treatment, though women should be informed that these changes may worsen over time. During the late menopausal transition, early symptoms such as vaginal dryness and provoked dyspareunia, after excluding other causes, may herald the onset of GSM. Based on the available evidence,^{77-93,95-102} we propose the following criteria for diagnosing GSM.

- At least two genital or urinary symptoms, rate their severity on a four-point scale after excluding non-estrogen deficiency causes, or
- One symptom accompanied by a Vaginal pH of > 5 and /or a VHI score ≤15

Therapeutic Endpoints

Accepted therapeutic benefit requires significant improvement in three co-primary endpoints, including MBS, vaginal pH, and VMI.

DIFFERENTIAL DIAGNOSIS

Vulvo vaginal atrophy: A range of conditions should be considered in women presenting with symptoms such as vaginal dryness, burning, itching, dyspareunia, reduced arousal or orgasm, rUTIs, or urge incontinence.

Causes other than menopause leading to atrophic vaginitis are oophorectomy, decreased ovarian function, chemotherapy, immune disorder, hypothalamic disorder, elevated prolactin, as in postpartum, breastfeeding, pituitary adenoma; medications like tamoxifen, danazol, progestins, gonadotropin-releasing hormone (GnRH) agonists (leuprolide, nafarelin), aromatase inhibitors (AIs) and use of tobacco.

Symptoms of VVA can result from dermatologic disorders like lichen sclerosus, lichen planus, eczema, or psoriasis. Desquamative inflammatory vaginitis can produce discharge, burning, itching, and dyspareunia and is characterised visually by small vaginal blotches and petechiae. It reflects inflammatory disturbances in the vaginal microbiome. Less common causes include infections such as candidal vulvovaginitis, bacterial vaginosis, trichomoniasis, herpes simplex, or other sexually transmitted infections; allergic or irritant reactions to hygiene products, soaps, spermicides, condoms, and lubricants. Other co-morbidities like diabetes mellitus, chronic pelvic pain, vulvodynia, and vaginismus have to be checked.

Apart from atrophic vaginitis, vaginal dryness may be seen due to the use of anticholinergics, antihistamines, tricyclic antidepressants, antipsychotics, antibiotics, corticosteroids, immunosuppression, douches, detergents, deodorants, perfumes, sanitary products, synthetic clothing, nulliparity and cessation of coital activity, endocrine treatment-induced vulvovaginal symptoms.

Postcoital bleeding should be evaluated for cervical cancer. Rule out vulvar intraepithelial neoplasia, vulvar cancer, malignant melanoma and extramammary Paget disease.

Sexual symptoms: Dyspareunia is considered a cardinal symptom when other causes have been excluded, and clinical examination confirms GSM. Reduced sexual arousal or orgasm might be associated with hormonal deficiency, psychosocial or relationship factors, psychological conditions like depression or anxiety, medication side effects, or neurological conditions.¹⁰³

Recurrent urinary symptoms: May be caused by repeated bacterial urinary tract infections, interstitial cystitis, overactive bladder syndrome, bladder malignancy, urolithiasis, urethral diverticulum, pelvic organ prolapse, or neurologic disorders. A thorough assessment is required to differentiate among these causes and to guide appropriate management.

Urgency Urge incontinence: GSM is diagnosed after excluding other causes of urge incontinence and overactive bladder. It may coexist with other causes of incontinence.

LONG-TERM SEQUELAE OF GENITOURINARY SYNDROME OF MENOPAUSE

There is strong evidence that untreated GSM can lead to significant long-term consequences for urogenital health, sexual function, psychological well-being, and overall quality of life, including rare but severe anatomical complications such as partial or complete labial adhesions (fusion of the labia minora).¹⁰⁴⁻¹⁰⁹ These adhesions can

cause urinary retention, pseudo-incontinence, recurrent urinary tract infections, and sexual dysfunction. They may also hinder adequate cytological sampling and colposcopic evaluation, and cause difficult access to the uterine cavity after postmenopausal bleeding. Retraction of the urethra into the anterior vaginal wall is another, though uncommon, presentation in GSM.¹⁰⁴⁻¹⁰⁹

Complete labial agglutination has been associated with complications such as persistent genital and urinary tract inflammation, recurrent urinary tract infections, urinary retention, apareunia, acute renal failure, urocolpos, pyosalpinx, and even peritonitis.¹¹⁰⁻¹¹²

Etiologies other than estrogen deficiency, such as chronic inflammatory skin conditions (lichen sclerosus, erosive lichen planus), autoimmune diseases (mucous membrane pemphigoid, Behcet syndrome, Stevens-Johnson syndrome, toxic epidermal necrolysis), or prior vulvar cancer surgery and trauma, may also lead to labial adhesions.¹¹³

Management is usually surgical, involving division of the labial fusion under anaesthesia to restore normal vaginal anatomy. Postoperative care typically includes topical estrogen and antibiotics to promote healing. Surgical release is highly effective, with a low risk of recurrence in postmenopausal women when followed by appropriate medical therapy.¹¹⁴

MANAGEMENT OF GENITOURINARY SYNDROME OF MENOPAUSE

The management of GSM is fundamentally patient-centered, aiming to relieve symptoms and, where possible, restore urogenital physiology. Notably, there is often a disconnect between the clinical signs of urogenital atrophy and the symptoms reported by patients, necessitating individualised, need-based shared decision-making and regular reassessment.^{12,69,115-122} Treatment selection should be tailored to the type and severity of symptoms and to each woman's risk factors, preferences, and expectations.^{116-120,123,124} Early initiation of therapy, ideally at symptom onset, may optimise long-term outcomes, as severe GSM becomes more challenging to treat with increasing age and time since menopause.^{116,124}

First-line therapy for mild GSM consists of nonhormonal vaginal moisturisers and lubricants, which provide symptomatic relief but do not reverse atrophic changes.^{67,118} For moderate to severe GSM, vaginal low-dose estrogen therapy (LET) is the gold standard, with robust evidence supporting its efficacy for vulvovaginal, urinary, and sexual symptoms.^{26,125}

The use of both systemic and local vaginal estrogen therapies for the treatment of GSM is widespread, with several studies indicating that topical estrogen application is more efficacious than systemic administration.^{80,100} The difference in efficacy by route of administration may be because topical estrogens lead to a greater ER increase in vaginal epithelium, compared with systemic preparations.¹²⁰ Both routes decrease the vaginal innervation density, but the response is greater with LET.¹²¹ A recent review of studies assessing the sustainability of vaginal estrogens evidenced that atrophic changes in vaginal epithelium present as early as four weeks after LET discontinuation, while subjective GSM symptoms recur after 3-6 months.¹²² In line with the 2016 Cochrane review, a systematic review concluded that a lack of level 1 long-term data assessing the efficacy, tolerability, and safety of GSM treatments leaves postmenopausal women and clinicians without evidence to guide treatment for longer than 1 year. The lacunae are that few studies enrolled women with a history of breast or gynaecologic cancers.^{126,127} Overall, vaginal estrogen, vaginal dehydroepiandrosterone (DHEA), vaginal moisturisers, and oral ospemifene may all improve at least some GSM symptoms. At the same time, evidence does not demonstrate the efficacy of energy-based therapies, vaginal or systemic testosterone, vaginal oxytocin, or oral raloxifene or bazedoxifene for any GSM symptoms.¹²⁷

Lifestyle Modifications

Lifestyle modifications such as smoking cessation, regular sexual activity, and pelvic floor exercises can help maintain urogenital health and may delay or reduce the severity of GSM symptoms.

Smoking fastens the estrogen metabolism and is associated with higher rates of vaginal atrophy. Smoking cessation would delay/prevent vaginal atrophy, but smoking cessation should be encouraged for many other benefits too.¹²⁸

Sexual Activity and Masturbation: Regular vaginal intercourse and masturbation increase genital blood flow, which may help sustain urogenital health and protect against atrophy. The SWAN study showed that pain during intercourse, rather than frequency, was most associated with impaired sexual function, and that reducing pain improved sexual

function.¹²³ Women who have contraindications to estrogen therapy and who desire vaginal intercourse may improve vaginal function with the use of vaginal dilators. Regular cranberry juice consumption reduced the risk of UTI recurrence.

Probiotics: There is an inverse correlation between the absence of *Lactobacillus* (especially *L. iners* and *L. crispatus*) and increased bacterial diversity, as well as moderate to severe vaginal dryness.¹²⁹ The current evidence base for probiotics in the management of GSM is promising but remains preliminary, with probiotics considered a potential adjunct rather than a replacement. Nonetheless, the heterogeneity of probiotic strains, dosages, and study populations limits the generalisability of findings.¹³⁰

Nonhormonal Treatments

Nonhormonal treatments, including vaginal moisturisers, lubricants, hyaluronic acid preparations, physical therapy, and energy-based therapies (such as laser), have demonstrated varying degrees of efficacy in symptom relief and QoL improvement. Nonhormonal options are for women with mild GSM and or wishing to avoid hormonal therapy or in high-risk individuals with a history of hormone-sensitive malignancy such as breast or endometrial cancer. Topical lubricants or moisturisers are contraindicated only in women with an allergic or adverse reaction to a particular product. Regular use of vaginal moisturisers and lubricants helps restore vaginal moisture, improve comfort, and relieve symptoms such as dryness and irritation, especially in women with mild symptoms.¹³¹ Additional nonhormonal options with evidence of benefit include hyaluronic acid preparations, physical therapy, and energy-based therapies (such as laser), all of which can improve vaginal health and quality of life without the use of hormones.

Vaginal lubricants: Lubricants are generally used during sexual intercourse to give temporary relief from vaginal dryness and dyspareunia. There are two basic types: water and silicone-based. While they can be used to decrease immediate irritation during intercourse, there is no evidence that they have any long-term therapeutic effect.¹³² They might lead to vaginal irritation later, and importantly, vaseline can break the latex of condoms. Women prone to yeast infections should avoid glycerine-based lubricants.

Vaginal moisturisers: Moisturisers are used on a chronic maintenance basis to replace normal vaginal secretions, whereas lubricants are specifically designed to reduce friction associated with sexual activity. Moisturisers are hydrophilic, insoluble, cross-linked polymers, and hyaluronic acid is often used as a key ingredient in vaginal moisturisers. They are bioadhesives; they connect to mucin and epithelial cells on the vaginal wall, retaining water. Their buffering properties, which reduce vaginal pH, are the mainstay of their symptom-relieving effects. Their efficacy is much longer lasting than that of lubricants, and they can typically provide relief for up to 2–3 days and can be used 2–3 times per week.¹³³ The efficacy of moisturisers on vaginal symptoms is lower than that of topical estrogen therapy.¹³⁴ A study found that while low-dose vaginal estradiol may have some benefits for overall quality of life, neither it nor vaginal moisturiser provided additional relief for vulvovaginal symptoms compared to placebo. However, women receiving vaginal estradiol had a greater abundance of *Lactobacillus* species and lower vaginal pH at the end of treatment.¹³⁵

It is important to understand that several water-based moisturisers and lubricants are hyperosmolar, associated with epithelial cell toxicity, and exhibit epithelial damage in vitro. Near iso-osmolar and silicone-based lubricants did not have this effect. The World Health Organisation recommends an osmolarity of less than 380 mOsm/kg, with an osmolality range of 200–600 mOsm/kg or lower, and not beyond the 1200 mOsm/kg range.¹³⁶ The products must be free of parabens, chlorhexidine polyquaternium-15, sorbic acid and sorbates, phenoxyethanol, benzoic acid and domiphen bromide. Glycols should not exceed a mass fraction of 9.9% to maintain osmolality.^{116,117} The final message is that the product for menopausal VVA should be chosen that is body-similar in terms of pH (that is, around 3.5, with a range of 3–5) and osmolality (around 380 mOsmol/kg, with a range of 200–600 mOsmol/kg) to reduce the chances of endothelial irritation and side effects.¹³⁶ Natural oils such as olive, coconut, and mineral oil can also be used for vaginal moisturisation; however, further clinical trials are necessary.¹³⁷

Hyaluronic acid: Hyaluronic acid supports epidermal function and reepithelialisation and can form an extracellular water film in the vaginal epithelium, thereby maintaining water balance.¹³⁸ Hyaluronic acid has the properties to be an efficient moisturiser for women suffering from VVA who have contraindications for estrogen therapy and for vulvovaginal signs and symptoms affecting sexual well-being.¹³⁹ However, a well-designed randomised controlled trial is needed to clarify its efficacy and safety profile.

The conclusion from the above comparative studies indicates that there is no evidence to show the superiority of HA to estrogen in the treatment of postmenopausal vaginal atrophy. However, the therapeutic efficacy of HA is comparable to estrogen, and considering its safety, HA can be used as an alternative to estrogen in patients who do not want to use estrogen.¹²⁹

Colostrum gel: Colostrum contains immunoglobulins, lactoferrin and cytokines, which help to modulate the immune response and promote antibacterial action in the neonate. However, it also contains transforming and epidermal growth factors that promote normal cell growth and proliferation.¹⁴⁰ Based on this, local treatment with a gel product based on purified bovine colostrum showed improved vaginal haemodynamics and thickness of vaginal epithelium in ovariectomised rats. Vaginal gel applied twice daily for 8 weeks significantly improved both the VHI and the maturation index in the vagina of postmenopausal women.¹⁴¹

Oxytocin: A peptide hormone, oxytocin has been shown to increase wound-healing rates, mucosal blood flow, and the secretion of several growth factors. Larger studies are currently in progress to further evaluate oxytocin as a clinical treatment for vaginal atrophy. The meta-analysis of 2023 results indicates that vaginal oxytocin does not have a significant effect on GSM patients for VMI, vaginal pH, histological evaluation, endometrial thickness, or dyspareunia.¹⁴²

Phytoestrogens: Phytoestrogens, plant-derived compounds with estrogen-like activity, have been explored as alternatives to hormone therapy for managing GSM and related symptoms. While oral phytoestrogen supplementation (such as soy isoflavones and flaxseed) increases circulating phytoestrogen levels, most high-quality studies show little to no effect on the vaginal epithelium or GSM symptoms when administered orally.^{143,144} In contrast, intravaginal application of phytoestrogens, such as isoflavone or genistein gels, has shown promise in improving vaginal maturation indices (VMI), genital symptoms, and colposcopic scores, with efficacy comparable to low-dose vaginal estrogen and no significant systemic effects. Long-term safety data are limited, but some studies raise concerns about endometrial hyperplasia with prolonged high-dose oral phytoestrogen use. In a double-blind, randomised, placebo-controlled study, the efficacy of isoflavone vaginal gel was compared with the effectiveness of CEE and placebo in treating VVA. In this study, 90 postmenopausal women were treated for 12 weeks with either 4% isoflavone vaginal gel (1 g/day), CEE cream (0.3 mg/day), or placebo gel. Women treated with isoflavone gel showed a similar improvement to the estrogen group for vaginal dryness and dyspareunia, both of which differed significantly from the placebo group. There was also a significant increase in VMI with isoflavone gel treatment.¹⁴⁴ No changes in endometrial thickness or estradiol levels were observed in the study group.¹⁴⁵ Accordingly, the authors concluded that isoflavone vaginal gel is effective in the treatment and management of VVA and may be a viable option for women who have contraindications or decline hormone therapy.

Vitamins: Several vitamins, including vitamins E, D and alpha-tocopherol, have been used to treat some menopausal disorders and atrophy of the vaginal mucosa. Vitamin E, either in daily oral doses of 100-600 IU or administered locally, has been found to increase vaginal lubrication and to relieve the dryness and irritation that accompany atrophic and other forms of vaginitis.¹⁴⁶ This review of 2022 highlights the need for additional high-quality RCTs to further explore different doses of vitamin E in terms of tolerability and benefit, as well as the efficacy and safety of vaginal vitamin E.¹⁴⁷ Vitamin D and analogues have been used to prevent and treat postmenopausal osteoporosis. However, it has been shown that vitamin D also regulates the growth and differentiation of the stratified squamous epithelium in the vagina.¹⁴⁸⁻¹⁵⁰ In one double-blind, placebo-controlled study, the use of vaginal vitamin D improved VCMi and reduced pH and dryness in women with VVA.¹⁵¹

Laser therapy: Fractional CO₂ laser therapy and erbium:yttrium-aluminium-garnet (Er: YAG) and neodymium-doped:yttrium-aluminium-garnet (Nd: YAG) lasers have been proposed as nonhormonal therapies for GSM since 2013.^{152,153} The principle of its treatment is to destroy parts of the lamina propria by drilling small holes with fractional CO₂ or YAG laser energy, resulting in neocollagenesis and neovascularisation, with an increase in vaginal epithelial morphology, and subsequently relieving symptoms of atrophic vaginitis.¹⁵⁴ Several small studies have shown that fractional CO₂ laser therapy can restore the vaginal epithelium to a premenopausal-like state, increase Lactobacillus and other premenopausal flora, and improve the VHI score and subjective GSM symptoms, including LUTS. The treatment is delivered every 4 to 6 weeks, with 3 treatments initially, followed by a single annual treatment. Although invasive, laser therapy offers choice, with treatment delivered much less frequently than with other options and independent of sexual intercourse. The non-ablative ErYAG laser therapy improves the symptoms of GSM and

affects the QoL and sexual function in pre- and post menopausal women.¹⁵⁵ A systematic review of the efficacy and safety of intravaginal laser therapy concluded that evidence is needed on the safety and efficacy of energy-based devices.¹⁵⁶⁻¹⁵⁸ A systematic review from 2024, following Cochrane guidelines, evaluated vaginal laser treatments for breast cancer survivors with VVA, concluding that more high-quality RCTs are needed to confirm benefits and assess long-term effects.¹⁵⁹ The European Urogynaecological Association (EUGA) FDA Working Group stated that Er:YAG and CO₂ vaginal lasers are safe energy-based therapeutic options for the management of VVA and/or GSM symptoms in postmenopausal women and BC survivors.¹⁵⁶⁻¹⁶⁰⁻¹⁶² Other reviews highlight mixed results for stress urinary incontinence (SUI) and suggest caution due to a lack of robust, long-term data for many applications.¹⁵³

All the reviews have a common conclusion: updated evidence from randomised trials is needed to better guide health professionals on the efficacy and safety of vaginal laser therapy for various gynaecological conditions. Moreover, in women with contraindications to hormonal therapy, several efficacious alternatives, such as hyaluronic acid and ultra-low-dose local estriol, have been demonstrated to be safe for use in such patients.^{125,152}

Injectables: Injection treatments have recently been proposed as novel options. They include hyaluronic acid fillers (cross-linked, non-cross-linked, thermally stabilised, associated with calcium hydroxyapatite) injection, lipofilling (both nanofat and microfat grafting), platelet-rich plasma (PRP) injection, and a combination of PRP injection with lipofilling for urogenital atrophy. Larger and randomised studies are necessary to confirm and further investigate this field.¹⁶³

Pelvic floor muscle training (PFMT) aims to improve strength, endurance, power, and/or relaxation. A physiotherapist guides it and incorporates various modalities, including education, lifestyle modifications, PFMT, manual techniques, electrostimulation, and biofeedback therapy. Its role in GSM needs to be established, but it is important in pelvic pain and urinary dysfunction.¹⁶⁴

Hormonal Treatments

Local estrogen therapy (LET): LET includes a range of vaginally administered estrogen products approved with the indication to treat symptomatic VVA. A systematic review with evidence from clinical trials as well as from prospective observational studies concluded that vaginal estrogen therapy is superior to nonhormonal treatments in improving symptoms of VVA.^{126,165} There is a need for extensive randomised, long-term studies to assess long-term safety. For GSM, vaginal preparations are usually more potent at alleviating symptoms of atrophic vaginitis than oral or transdermal preparations.¹⁶⁶ The reported efficacy rate is approximately 80 to 90 per cent for vaginal estrogen therapy and 75 per cent for systemic therapy, based upon observational data.^{167,168} It is observed that 10-25% of women receiving systemic hormone therapy still experience symptoms of urogenital atrophy; LET preparations may have an additional beneficial effect.¹⁶⁹ Estrogen is readily absorbed through the atrophic vaginal epithelium; as the epithelium matures with therapy, absorption decreases.^{170,171} Smaller doses are needed to maintain vaginal health. Treatment early, before irreversible atrophic changes have occurred¹⁷² is equally important.

Type and dose of estrogen (potency): Among estrogen preparations, estradiol was found to be most effective in reducing patients' symptoms. However, conjugated equine estrogen (CEE) produced the greatest cytological change and the most significant increase in serum estradiol levels. Estriol is a low-potency estrogen and is not converted to the highly potent estradiol.¹⁷³ Vaginal estradiol was found to have a negligible effect on serum estrogen, although not as great as systemic preparations. The peak plasma estradiol levels with local estradiol at a 10-25 mcg dose were between 5-10 pg/mL.¹⁷⁴ With doses of 0.3-2.5 mg/day, CEE produced a mean estradiol plasma concentration of 12-62 pg/mL.¹⁷⁵ Vaginal estriol did not affect the serum levels of estradiol or estrone, while oral estriol had minimal effect.¹⁷⁶

The various doses for local therapy are: CEE, 0.3-1.25 mg/day; estradiol, 25 mcg/day; estriol cream, 0.5 mg/day; estriol tablets, 4-8 mg/day for 2 weeks, followed by maintenance therapy.¹⁷⁷ Low-dose vaginal estrogen is considered ≤50 mcg estradiol or ≤0.3 mg conjugated estrogens (in ≤0.5 g cream). Doses of conjugated estrogens cream (≥0.625 mg in 1 g of cream) and estradiol vaginal cream (>100 mcg in >1 g of cream) are considered higher dose preparations. An ultra-low dose is four µg-10 µg of vaginal estradiol, 30 µg of estriol.¹⁷⁸

Low-dose vaginal estradiol was found to be effective for treating GSM. A study demonstrated that ultra-low-dose vaginal estradiol (10 mcg) compared with placebo, increased vaginal maturation, improved vaginal health, restored vaginal pH and reduced vaginal symptoms.¹⁷⁴ The total administered vaginal dose per year of a preparation

containing 10 microgrammes of estradiol used twice weekly is similar to one single daily dose of systemic oral therapy (that is, 1 milligramme). Only 10- 30% of the dose used to treat vasomotor symptoms may effectively manage urogenital symptoms.¹⁷⁹

An ultra-low-dose vaginal estriol 0.03 mg/day with viable *Lactobacillus* was superior to placebo in treating VVA.¹⁸⁰ Clinical data revealed that vaginal 0.03 mg-E3/L is comparable in efficacy to the 16-fold higher dose of 0.5 mg.¹⁸¹ Furthermore, the equivalent efficacy of ultra-low-dose E3 in treating vagina atrophy has been demonstrated in clinical studies using E3 mono-preparations. Doses as high as 0.5 mg E3 twice weekly are not associated with a significant increase in serum estrogen levels after short-term (weeks) or long-term (12 months) treatments.^{182,183} A meta-analysis of all published studies concluded that once-daily intravaginal E3 (0.5 mg) is safe and does not increase the risk of endometrial proliferation or hyperplasia.¹⁸⁴ Estriol bioavailability is higher than estradiol because of its lower affinity for the sex hormone-binding protein.¹⁸⁵ Estriol has lower estrogenic potency than estradiol (ranging from 1:10 to 1:100)¹⁸⁵ and greater relative affinity for estrogen receptor- β than for estrogen receptor- α , thus minimising extravasational effects.¹⁸⁵ For this reason, a sequential progesterone for endometrial protection can be omitted even with oral estriol for GSM.¹⁸⁵

Serum estradiol levels and LET: Considering all published studies with any estradiol level, using assays with varying sensitivities and methodologies, the mean circulating estradiol level in normal, untreated women ranges from undetectable to 10.7 pg/mL. Estradiol absorption is dose-dependent and may be influenced by dose, formulation, and positioning in the vagina. Very low systemic estradiol absorption is observed with low/ultra-low-dose vaginal estrogens. It may potentially prevent any adverse events that may be associated with higher doses of vaginal estrogens used for treating moderate to severe VVA due to less estradiol exposure. Higher absorption was reported with higher vaginal estradiol doses, 25 μ g: 7.1-22.7 pg/mL, 10 μ g: 4.6-14.8 pg/mL, compared with the lowest available dose of 4 μ g (3.6-3.9 pg/mL). With doses of 0.3-2.5 mg/day, CEE produced a mean estradiol plasma concentration of 12-62 pg/mL. Most studies indicate that the rise in circulating estradiol levels is most pronounced during the first 12 weeks of treatment, and then subsides as vaginal epithelium thickness and systemic absorption decrease.¹⁷⁴

Estetrol (E4) demonstrated estrogenic effects in the vagina and reduced signs of atrophy. E4 15 mg is a promising treatment option also for important menopausal symptoms other than VMS.¹⁸⁶

Formulations: Vaginal estrogens are available as creams, tablets and rings. The CEE (Premarin) and estriol (Evalon) creams are available in India. Creams should be inserted in the vagina at bedtime to aid in retention, but some women may find them messy. The vaginal estrogen tablet is administered with an applicator and gradually dissolves, releasing estrogen to the vaginal wall. Compared with vaginal estrogen creams, the vaginal tablet provides a more consistent dose of estrogen and reduces the potential for leakage. Vaginal estrogen cream can be underdosed or overdosed because the various formulations are not available in prepackaged doses. The creams are also associated with poor patient adherence rates, possibly because of their messiness and relative inconvenience. A vaginal ring is impregnated with estrogen; the absorbed daily dose is low, and the ring does not interfere with coitus. The ring needs to be replaced every 3 months.

Regime: A daily application in the lower part of the vaginal for 2-4 weeks, followed by a maintenance of two or three applications per week for 2-6 months. The effectiveness of therapy may take two or more weeks, and noticeable results are expected by the end of four to 12 weeks. A pea-sized estradiol cream applied to the vulvar vestibule, paired with pre-coital silicone lubricant, is an alternative to vaginal therapy for dyspareunia.⁹⁶

A Cochrane systematic review of 30 RCTs found no evidence of a difference in efficacy among intravaginal estrogenic preparations. All preparations improved the symptoms of VVA in postmenopausal women compared with placebo, similar to A 2006 Cochrane review.

Duration of treatment: Although it is believed to be acceptable to continue treatment indefinitely, safety data beyond 1 year are not yet available for use with any vaginal products.¹¹⁸ Evidence indicates that the smallest effective dose should be utilised for long-term therapy, with eventual tapering of estrogen to maintain once urogenital function has improved. Although the benefits of LET in preventing vaginal atrophy are well established, such treatment may still be contraindicated in women with undiagnosed vaginal/ uterine bleeding or known or suspected endometrial cancer. All cases of postmenopausal bleeding should be evaluated with ultrasound examination of endometrial thickness and endometrial sampling.¹⁸⁷

Absorption by sexual partners: Clinical implications of the absorption of vaginal estrogen by a sexual partner are generally unknown, and there are no data to support refraining from coital activity for a specific period of time after 141

use of a vaginal estrogen.¹⁸⁸

Adverse effects: Patients may complain of vaginal irritation or itching, vaginal bleeding, or breast tenderness; headaches or hot flashes are rare, messiness with cream, compliance/difficulty (due to restricted mobility or joint problems) for vaginal use.

Contraindications: The absolute contraindications are undiagnosed vaginal or uterine bleeding (known, suspected, or history of estrogen-dependent malignancy, active or recent stroke, myocardial infarction (Grade A) and relative contraindications are history of breast cancer, severe liver dysfunction and known hypersensitivity to estrogen preparations or excipients.

Role of Sequential and/or Combination Treatment for Urogenital Atrophy

Sequential treatment involves designing a strategy that uses one or more¹⁸⁹ medications for a long enough period to achieve the desired benefits with minimal risk and maximum adherence as a first option. We should consider prescribing treatments that work on ERs for physiological, preventive, and efficacy reasons. As a second option, there are vaginal moisturisers, which are effective on symptoms but do not prevent or improve conditions. Finally, techniques using heat, although they represent a clearer alternative each time, are also costly and have limited long-term safety data. Of course, we consider that vulvar moisturisers and lubricants can be used at any time.¹⁹⁰

Safety

A Cochrane review of 19 studies evaluating different LET formulations reported no cases of venous thromboembolism (VTE).¹²⁶ The increased risks of coronary heart disease, stroke and VTE, which have been reported with oral systemic hormone therapy, have not been reported with LET.¹⁹¹⁻¹⁹³ Moreover, long-term follow-up of women in the Women's Health Initiative (WHI) trial of unopposed estrogen showed no increased risk of coronary events or all-cause mortality, indicating that LET is unlikely to affect these outcomes.¹⁹⁴

In a nested case-control study, use of vaginal estradiol tablets was not associated with an increased rate of recurrent ischaemic stroke in women with a history of ischaemic stroke.¹⁹⁵

Endometrial safety: Systematic reviews based on RCTs and observational studies confirm the endometrial safety of topical estradiol for up to 52 weeks of follow-up.¹⁹⁴ In the prescribed dose and duration of treatment with estradiol, CEE and estriol, there is no incidence of endometrial hyperplasia.^{192,196} A systematic review concludes that no studies provide evidence of endometrial proliferation after 6-24 months of use. Ultrasound studies have not shown any change in endometrial stripe thickness, and endometrial histopathology has been reassuring.¹⁹² Hence, progesterone supplementation is not needed for endometrial protection in asymptomatic, low-risk women receiving LET. Longer observational follow-up data, for example, from the WHI Observational Study (45,663 women, median follow-up of 7.2 years), also confirm endometrial safety, as no increased risk of endometrial cancer was observed among vaginal estrogen users compared with non-users.¹⁹⁰ This was also found in the Nurses' Health Study, with 18 years of follow-up.¹⁹⁷ However, a Danish national cohort study found that compared to never users, users of vaginal estrogen therapy had a nearly two-fold risk of endometrial cancer (RR 1.96, 95% CI 1.77-2.17). It was realised there were limitations in the analysis, which included potential confounders by concomitant use of systemic hormone therapy in the Danish cohort, as a substantial proportion of women were using unopposed systemic estrogen.¹⁹⁸

Breast: A meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer (2019), based on 58 studies involving 568,814 women, found no increased risk of breast cancer with vaginal estrogens.^{197,199}

Use of Local Vaginal Estrogen in Asymptomatic Women

- *Vulvovaginal surgery:* LET may be given before the procedure. This helps convert the atrophic vaginal epithelium to a better vascularised multilayered vaginal epithelium, thus helping to identify the tissue planes and promote wound healing.
- *Pelvic organ prolapse or urinary incontinence:* Women with symptomatic pelvic organ prolapse or urinary incontinence are treated with LET, although the benefit of this approach is uncertain. However, when pessary use is employed in the management of these conditions, estrogen therapy is beneficial to prevent vaginal abrasions.
- *Prior to Pap smear:* Prior to doing a Pap smear in a postmenopausal woman with atrophic vaginitis, it may be helpful to give a short course of vaginal estrogen therapy. This helps prevent erroneous diagnoses of dysplasia due to an

atrophic endometrium.

Systemic Hormone Therapy

Estrogen: Urogenital symptoms, when associated with other symptoms of menopause, are an indication for systemic hormone therapy. It is estimated that approximately 25% of women taking oral hormone replacement have persistent vaginal dryness and other urogenital symptoms. In such situations, additional local estrogen therapy can be prescribed. Daily oral estriol, decreasing from 8 mg/day to 2 mg/day, was effective in postmenopausal women aged 60. In elderly patients aged 80-89 years, estriol 3 mg/day for 1 month, followed by 1 mg/day for 1 month, relieved bothersome symptoms.²⁰⁰ Estriol is given as a single dose/day, taken before a meal. Transdermal microdose of 0.014 mg/day estradiol (the primary endpoint was the effect on vasomotor symptoms) was studied as the secondary endpoint in VVA. It was well tolerated and effective.

Tibolone: A steroid with a tissue-specific mode of action, which displays weak estrogenic, androgenic and progestogenic action, also significantly improved vaginal atrophy and cytology in comparison with placebo. It is not used as first-line therapy for GSM.²⁰¹

Selective estrogen receptor modulators: Specific selective estrogen receptor modulators (SERMs) that act as estrogen agonists/antagonists are effective in treating VVA. Ospemifene, a triphenylethylene SERM, was initially developed as a treatment for postmenopausal osteoporosis, but was found to have favourable estrogenic effects on the vaginal epithelium in phase I and II clinical trials.²⁰² It was approved by the U.S. FDA in early 2013 for the treatment of moderate-to-severe dyspareunia.²⁰³ It may be used in women who are not suitable candidates for estrogen therapy.²⁰⁴ After 12 weeks of treatment with 60 mg of ospemifene, the percentage of patients with detrusor overactivity decreased from 39% to 13%, along with reductions in detrusor pressure and improvements in peak flow, initial voiding urge, and maximum cystometric capacity.²⁰⁵ The incidence of headaches, deep vein thrombosis, coronary artery disease, cardiovascular events, severe adverse events, vaginal bleeding, endometrial cancer and breast cancer did not differ significantly from other therapies.²⁰⁶ There was no difference in the incidence and recurrence of breast cancer between ospemifene users and untreated VVA patients. The combined evidence from clinical trials and the post-authorisation safety study (PASS) suggests that the SERM-associated elevated risk of VTE does not apply to ospemifene.²⁰⁷ The CRETA (Cross-sectional European Study on adherence), conducted in 29 hospitals and centres across Spain and enrolling 831 postmenopausal women with VVA, reported higher satisfaction and adherence with ospemifene than with vaginal estrogen therapy, as well as fewer missed doses in the treatment of moderate to severe VVA.²⁰⁸

Dehydroepiandrosterone: DHEA, a sex steroid precursor, has been shown to have sound effects on sexual function. However, like estrogen, DHEA levels decline with age.²⁰⁹ Intravaginal DHEA has been found to act on all three layers of the vagina, inducing mucification of the epithelium, increasing density of collagen fibres in the vaginal wall and stimulating the muscle layer. DHEA can be administered either orally or vaginally, with dosages varying accordingly.²¹⁰ Several randomised controlled trials (RCTs) have demonstrated the efficacy of DHEA (prasterone) in treating GSM, particularly in reducing postmenopausal symptoms like dyspareunia and vaginal dryness. Daily vaginal DHEA use for two weeks, followed by a biweekly regimen or a 12-week dosing schedule, was shown to have positive effects on vaginal atrophy, sexual function and other genitourinary symptoms. DHEA is administered as a vaginal insert once daily at bedtime. When applied intravaginally, DHEA is converted into estrogens and androgens such as testosterone, androstenedione, and dihydrotestosterone (DHT).²¹¹

Larger studies employing more accurate symptom assessment tools are needed, as well as studies investigating the long-term safety of the drug in women with a history of hormone-sensitive malignancies, who particularly could benefit from local androgen therapy.

FOLLOW-UP

A follow-up visit is scheduled after 1 and 3 months. Monitor the response by repeating the vaginal pH test 3 months later and then annually. If, in 3 months, she shows improvement in her signs and symptoms, the patient will be advised to try discontinuing. She is counselled that she will likely require long-term vaginal estrogen therapy to ease the vulvovaginal irritation and frequent urinary infection. In the absence of contraindications, therapy may be continued as long as needed for symptom management, as symptoms will recur upon discontinuation. Routine endometrial surveillance is not recommended in low-risk women using LET. Any spotting or bleeding requires a thorough

evaluation that may include a transvaginal ultrasound (TVU) and/or an endometrial biopsy.

Adherence must be assessed in nonresponders. Women who remain symptomatic despite the use of LET should be reevaluated, with consideration given to alternative or concomitant diagnoses, such as infection, inflammatory or autoimmune diseases, dermatoses, allergic conditions, neoplasia, vulvodynia, or other medical or psychological contributors.

RECURRENT URINARY TRACT INFECTIONS

Prevalence

UTIs are common in women, and almost 50% are affected at least once in their lifetime. 2-3% of these experience a recurrence within 6-12 months. Postmenopausal women are disproportionately affected by rUTI.²¹² Women who were 55 years and above had a 53 % risk of rUTI in a primary care setting.²¹³

Definition

Recurrent urinary tract infection (rUTI) refers to ≥ 2 infections within 6 months or ≥ 3 infections within 12 months, with resolution demonstrated prior to a subsequent infection.²¹⁴

Re-infection: refers to a new infection, caused by a different pathogen, which occurs > 2 weeks after the eradication of prior infection.²¹⁵

Persistent UTI: refers to the presence of the same pathogen which fails to respond to antibiotic treatment after 48 hours of treatment. The most common causes are struvite calculi and nonadherence to antibiotics, which can lead to inadequate bacterial therapy, malabsorption, abnormal drug metabolism, and the emergence of resistant organisms. They require further imaging and cystoscopy.²¹⁶

Relapse UTI: refers to recurring infection with the presence of the prior pathogen, due to incomplete eradication of the infection, occurring in ≤ 2 weeks after initial treatment.^{215,217}

Uncomplicated versus Complicated Urinary Tract Infection

Uncomplicated UTI: An uncomplicated UTI is an infection in a healthy patient with an anatomically and functionally normal urinary tract²¹⁸

Complicated UTI: A complicated urinary tract infection is one that occurs in the presence of factors that increase bacterial colonisation and reduce treatment efficacy, such as anatomical or functional urinary tract abnormalities, immunocompromised status, or infection with multidrug-resistant organisms.²¹⁹

Factors Predisposing Postmenopausal Women to Recurrent Urinary Tract Infection

Estrogen deficiency (increased vaginal pH and loss of lactobacilli, leading to increased colonisation of Enterobacteriaceae),²¹⁰

- Urinary incontinence,
- Urogenital surgery,
- Cystocele,
- Increased post-void residual urine and
- Genetic factors such as nonsecretor (of histo-blood group antigens) status
- History of UTI
- Diabetes and
- Sexual activity.
- In elderly institutionalised women aged > 70 years, functional status and catheterisation are the most important risk factors.

The incidence of both UTI and asymptomatic bacteriuria increases with age.²²⁰

Signs and Symptoms

Recurrent UTI typically presents with urinary urgency, increased frequency, dysuria, or suprapubic pain, while the presence of fever, chills, rigours, marked fatigue, or malaise suggests a complicated urinary tract infection.²²¹

Microbiome and Urinary Tract Infection

The Human Microbiome Project, a population-based study of human microbiomes from 18 sites, excluded the bladder because they considered urine sterile. The theory is disproved by the identification of the urinary microbiome in the healthy bladder. The female urinary microbiome (FUM) was discovered in 2011.²²²

The healthy microbiome maintains bladder homeostasis by protecting against infection, promoting normal immune function, regulating neurotransmitters, and maintaining urothelial integrity.²²³ Dysbiosis is defined as an imbalance between the healthy microbiota and communities lacking the above-mentioned functions. This spectrum of urinary dysbiosis may help us understand the risk of clinical conditions, such as UTI, UUI, and perhaps some forms of bladder pain syndromes.²²⁴

Unlike in premenopausal women, where lactobacilli are abundant in the urine and vagina, they are less abundant in postmenopausal women, making them more susceptible to infections.²²⁵ Recent research emphasised that estrogen deficiency alone cannot explain the occurrence of GSM or urinary symptoms in some women, whereas others have no symptoms.^{225,226}

Diagnosis and Investigations

Evaluation includes detailed history taking and clinical examination, along with investigations such as urine analysis for protein, nitrites, leukocyte esterase, and blood, urine culture, and screening for diabetes; imaging with renal ultrasonography or CT scan of the abdomen and pelvis is advised in cases of haematuria, urinary calculi, or repeated *Proteus* infections, while diagnostic cystoscopy is rarely indicated.^{227,228}

Management

Although there is no clear evidence that lack of estrogen per se causes an increase in UTI in postmenopausal women, studies have revealed a significant reduction of UTI by using vaginal estrogens over placebo, especially where there is evidence of vaginal atrophy.²²⁰

Estrogen therapy: A 2023 systematic review concluded that LET may decrease the risk of rUTI in postmenopausal women.²²⁹ The 2008 Cochrane review, based on two small studies, concluded that vaginal estrogen reduces episodes of rUTI in postmenopausal women, but the treatment protocols varied, including the type of estrogen used and the treatment duration.²³⁰ Oral estrogen did not reduce the risk of rUTI in postmenopausal women.²³¹ The authors suggest that the vaginal cream appears to be the most cost-effective way of delivering the estrogen.

Cranberry: Cranberry products have been widely used as a preventive measure against recurrent UTI. Although no definite mechanism of action is known, research suggests that cranberries prevent bacterial adhesion to uroepithelium. Currently, the Cochrane review, 2023, does not support the use of cranberries in the elderly.²³²

D- mannose: A 2021 RCT compared a dose of 2g/day in postmenopausal women on vaginal estrogen with uncomplicated rUTI with controls and found it to be well tolerated, but the study lacked statistical power to detect a difference in the incidence of rUTI. Further research, exploring the benefits, is needed.²³³

Probiotics: A combination of probiotics, D-mannose and cranberry reduced UTIs by 76% and antibiotic use by >90% in a small study.²³⁴

Table. 1 Antibiotic use for uncomplicated recurrent UTI

First-line		
Nitrofurantoin (first line)	50-100 mg nightly	Avoid if GFR <30 ml/min; first line agent
SMX -TMP (first line)	40/200 mg nightly	Monitor for sulfa allergy and renal function
Trimethoprim (first line)	100 mg nightly	Useful when sulfa combination is contraindicated
Second-line		
Fosfomycin	3 g every 10 days	Alternative for resistant organisms; limited data
Pivmecillinam	185 mg daily	Effective against ESBL-producing E. coli; dose reduction if GFR <30 ml/min
Cephalexin	125 - 250 mg nightly	
Norfloxacin	400 mg nightly	
Cefaclor	250 mg nightly	

Despite the frequent use of antibiotics, the antibiotic choice for postmenopausal / older women has a few challenges, including frequent allergy or intolerance of side effects, renal or liver dysfunction, and polypharmacy or drug interactions.²³⁶

Non-pharmacological interventions for recurrent UTI include behavioural modifications such as maintaining adequate fluid intake, avoiding spermicidal use, practising post-coital voiding, and ensuring proper perineal hygiene.

General Measures for Urinary Tract Infection Prevention

- Wipe from front to back after using the bathroom.
- Wash your hands before using washcloths, tissues or toilet paper for wiping or washing.
- Double void
- Timed void
- Drink 6-8 glasses of water
- Take cranberry/ or cranberry pills

URINARY INCONTINENCE

Lower urinary tract symptoms have been shown to be common in postmenopausal women attending a menopause clinic, with 20% complaining of severe urgency and almost 50% complaining of stress incontinence. UUI is common in midlife and postmenopausal women, with hormonal changes potentially influencing lower urinary tract function. However, the relationship between estrogen deficiency and urinary incontinence remains complex and not fully understood. Evidence suggests that urinary incontinence may develop during the perimenopausal period or even prior to menopause, highlighting its multifactorial aetiology. Factors such as ageing, parity, obesity, and pelvic floor dysfunction play significant roles alongside hormonal changes.²³⁷

The prevalence of incontinence increases with age. In the United States, among women aged 80 years and older, the prevalence of incontinence is 31%, compared with women aged 40- 59 years, where the prevalence is 17.2%.²³⁸ A study across six European countries estimated that, among women over 40 years, the prevalence is 16.6%.²³⁹

Types of Incontinence

Urinary incontinence (UI) is the involuntary leakage of urine.²⁴⁰ UI affects > 50 % of postmenopausal women, and is an important social problem.²⁴¹

Types of UI are:

- Stress Urinary Incontinence (SUI)
- Urge Urinary Incontinence (UUI)
- Mixed Incontinence (MUI)
- Overflow Incontinence
- Functional Incontinence

Among almost 80 million women in the USA surveyed, the prevalence of UI is 62%, with 32% reporting symptoms monthly. Among the UI, 37.5% had stress urinary incontinence, 22.0% had urgency urinary incontinence, 31.3% had mixed symptoms, and 9.2% had unspecified incontinence. The risk factors associated were increasing age, body mass index ≥ 25 , prior vaginal birth, anxiety, depression, functional dependence, and non-Hispanic White ethnicity and race.²⁴² A meta-analysis of 6 studies, including 1,656 nursing home residents, reported that UI contributes to the overall mortality rate, with an increase in death rate by 20%.²⁴³

In the Indian population, the prevalence of UI ranges from 10% to 42%, according to the Urological Society of India.²⁴⁴ Garg et al conducted a study on opportunistic screening of UI in 601 women. They found UUI was highly prevalent among the postmenopausal women, and more than two- thirds of women affected by UI never consulted for the same, as they assumed that it is part of natural ageing.²⁴⁵

Stress Urinary Incontinence

It is the involuntary leakage of urine on effort or exertion, or on sneezing or coughing.²⁴⁶ At perimenopausal, SUI appears to peak, whereas urge and mixed incontinence predominate in older women.²⁴⁷ It is the most common form of UI, with an overall prevalence varying from 24% to 45% in women older than 30.²⁴⁸

Table 2: Differences between overactive bladder and stress urinary incontinence

Type	Stress urinary incontinence	Overactive bladder
Symptoms	Complaint of involuntary leakage on sneezing, coughing, laughing, lifting or exercising	Complaint of involuntary leakage, preceded by a strong desire to void
Causes	Insufficient urethral closure	Uncontrolled bladder contractions
Receptors	Serotonin and noradrenaline	Cholinergic muscarinic

SUI is classified pathophysiologically into intrinsic sphincter deficiency and urethral hypermobility, which often coexist, and result from loss of anatomical urethral support and impaired urethral closure due to pelvic floor muscle weakness and alterations in the urethrovesical angle. Diagnosis is based on history and physical examination, with objective assessment using the cough stress test,²⁴⁹⁻²⁵¹ the Q-tip (cotton swab)²⁵² test for urethral hypermobility, and the pad test.²⁴⁰, which is a low-cost, noninvasive method providing both qualitative and quantitative evaluation of urinary incontinence.

Urge Urinary Incontinence

UI is the involuntary loss of urine preceded by the feeling of urinary urgency. This is mainly due to detrusor overactivity.²⁴⁸ The overall prevalence of UI is approximately 9% in women aged 40 to 44, and approximately 31% in women older than 75.²⁵³ Nocturia was found to be a prominent menopausal symptom in middle-aged women with symptoms of overactive bladder (OAB) in cases of UI, and its prevalence increased with the menopausal stage.²⁵³ Postmenopausal women with urinary urgency and urge incontinence are found to have an increased incidence of falls compared to the same-aged women without UI.^{254,255}

Overactive Bladder Syndrome

Overactive bladder (OAB) is defined by the International Continence Society (ICS, 2010) as a symptom-based syndrome characterised by urinary urgency, with or without urgency urinary incontinence, usually accompanied by increased daytime frequency and nocturia, in the absence of urinary tract infection or other identifiable pathology.²⁵⁶ Epidemiological studies suggest that OAB affects approximately one in six adults, with prevalence estimates of around 16–17% and increasing symptom severity with advancing age.^{257,258} Urgency, defined by the ICS as a compelling desire to act that is difficult to defer, is the hallmark symptom of the condition. OAB may result from central nervous system disorders such as stroke, dementia, or Parkinson's disease, as well as spinal cord injury at or above the S2–S4 level. The underlying pathophysiology includes detrusor overactivity, characterised by involuntary contractions during bladder filling;^{259,260} impaired detrusor compliance, resulting in elevated intravesical pressure due to reduced bladder distensibility;^{261,262} and bladder hypersensitivity secondary to urothelial inflammation, infection, or alterations in the urinary microbiome.^{261,263}

Mixed Urinary Incontinence

It is the involuntary leakage of urine associated with urgency and physical exertion, effort, sneezing, or coughing, that is, symptoms of both urge and stress UI. Differences between OAB and SUI are depicted in Table 2. MUI affects more than 37% of women aged 65 and older.²⁶⁴ The overall prevalence of MUI is 30–40%.²⁵³

Advanced pelvic organ prolapse leads to bladder outlet obstruction and, in turn, causes detrusor muscle neuropathy during overstretching of the bladder wall.²⁶⁵ Following surgical correction of pelvic organ prolapse, MUI was corrected in > 50% of patients.²⁶⁶

Risk factors for MUI^{267–273}

- Advanced age
- Comorbidities (eg, depression, diabetes, stroke, faecal incontinence, atrophic vaginitis, cognitive impairment, history of recurrent UTIs, multiple sclerosis, hydrocephalus, and childhood enuresis)
- Ectopic ureters
- Exercise, especially high-impact (eg, running and jumping)
- Family history
- Interstitial cystitis
- Multiparity
- Neuropathy
- Nursing home residence
- Obesity
- Pelvic radiation history
- Prior pelvic surgery (eg, transurethral resection of the prostate, hysterectomy)
- Smoking

Overflow Incontinence

overdistension is impaired detrusor contractility (hypotonic bladder) and bladder outlet obstruction. Overflow incontinence can cause permanent bladder damage and renal failure. Hence, the cause needs to be addressed at the earliest. Diagnosis and treatment are discussed in the section below.²⁴⁸

Aetiology

Impaired detrusor contractility, spinal cord injuries, multiple sclerosis, and diabetes, bladder outlet obstruction, abdominal or pelvic masses, urethral strictures, and pelvic organ prolapse.

Functional Urinary Incontinence

This is defined as an involuntary leakage of urine due to environmental or physical barriers to using the toilet.²⁴⁸

Diagnosis and Investigations

Understanding the aetiology and accurately diagnosing the type of incontinence is a vital component of successful management.²⁷⁴

- A thorough history - type, severity, burden, and duration of UI.
- Medical co-morbidities - chronic obstructive pulmonary disease and asthma, heart failure, neurological or musculoskeletal conditions.
- Surgical history
- Obstetric history - number of births, vaginal or cesarian birth,
- Medication history - Medications that may worsen incontinence are benzodiazepines, diuretics, anticholinergic agents, antihistamines, antipsychotics, opiates, antispasmodics, antiparkinsonian agents, alpha-adrenergic blocking agents (such as prazosin) and calcium channel blockers.
- Physical examination: general and systemic. A physical examination should include a focused neurologic examination in which the physician evaluates sacral nerve function by testing the bulbocavernosus reflex and/or an anal wink
- Bladder diary (3IQ) - to help distinguish between stress, urge and mixed incontinence.²⁷⁵
- Urinalysis, if necessary, a urine culture
- Post-void residual volume is assessed, especially in cases of overflow UI. Ultrasound can be performed in a full bladder and after the woman voids. If the residual urine volume is >200 ml, further evaluation is needed. It suggests incomplete voiding.
- Uroflometry - rate of urine flow
- Urodynamics is reserved for complicated cases, especially if surgery is planned. If surgery is planned, there is a need to consider voiding dysfunction and coexisting types of urinary incontinence.²⁷⁶
- Cystoscopy and diagnostic renal and bladder ultrasound are not necessary in the initial workup for uncomplicated patients, and should be reserved for refractory or otherwise complicated cases.²⁴⁸

MANAGEMENT

Management of Stress Urinary Incontinence is detailed in Table 3.

A systematic review in 2023 included 715 postmenopausal patients with SUI and found that all types of pelvic floor muscle training are effective treatments for SUI. Interventions were pelvic floor muscle training (PFMT), vaginal cone (VC), biofeedback (BF), electrical muscle stimulation (EMS), radiofrequency (RF), and electroacupuncture (EA). They concluded that there was no consensus on which therapy was superior.^{258,277} Vaginal estrogen was found to improve urinary symptoms such as dysuria, frequency, urge and recurrent UTI in menopausal women. Evidence suggests greater efficacy in urgency-related incontinence, whereas its role in stress urinary incontinence remains inconsistent²²⁹

In one study of postmenopausal women with vulvovaginal atrophy and OAB, the use of oral ospemifene (60 mg/day) for 12 weeks resulted in a significant reduction in OAB symptoms.²⁷⁸

Table 3: Management options for stress incontinence²⁴⁸ (TOT: Transobturator tape; TVT: Tension-free vaginal tape; TVT-O: Tension-free vaginal tape obturator).

Conservative	Drugs	Surgery
Dietary changes	Duloxetine	Slings: minimally invasive, such as TVT, TOT, TVT-O, mini-sling, open slings
Pelvic floor muscle training	phenylpropanolamine - banned in India	Colposuspension
Vaginal cones		Urethral bulking agents
		Artificial urinary sphincter
		Urethropexy
biofeedback		

Table 4: Management options for urge incontinence²⁴⁸ (PFMT: Pelvic floor muscle training; PTNS: Percutaneous tibial nerve stimulation; TENS: Transcutaneous electrical nerve stimulation)

Lifestyle interventions	Behavioural therapy	Physical therapy/ Neuromodulation	Drug therapy	Surgery/Advanced therapy
Caffeine reduction	Bladder retraining	PFMT / TENS	Antimuscarinics (oxybutynin, tolterodine, trospium, solifenacin, darifenacin, fesoterodine)	Intravesical injection of botulinum toxin A
Fluid intake modification (timing & volume)	Timed voiding	PTNS	B-3 agonist (mirabegron)	Sacral nerve stimulation
Weight loss in obese	Urge-suppression techniques	Vaginal weight training	Combination therapy (antimuscarinic + β 3-agonist)	Augmentation cystoplasty
Moderate physical activity	Bladder diary –guided training	PFM exercises with biofeedback	Vaginal estrogen (in women with GSM)	Urinary diversion
Bowel regulation (constipation management)		PF electrical stimulation	Desmopressin (for nocturia only)	
Smoking cessation				

Another RCT studied the effect of Vitamin D on urgent urinary incontinence in postmenopausal women. A weekly dose of 50,000 IU vitamin D tablets for 8 weeks can reduce the severity of UI and the frequency of nocturia, and reduce their impact on daily life.²⁴

Systemic estrogens: Nine studies compared systemic estrogens to a placebo. The conclusion was either that there was no difference in subjective and objective symptoms of UI²⁷⁹ or, sometimes, especially estrogen with progesterone worsened urinary symptoms after menopause, as shown in the Heart and Estrogen/Progestin Replacement Study (HERS).²⁸⁰⁻²⁸²

Management of Overactive Bladder

Urge urinary incontinence (UUI) and OAB are common and can be difficult to treat because symptoms may arise from idiopathic detrusor overactivity, bladder hypersensitivity, urinary infection/inflammation, outlet obstruction, pelvic floor dysfunction, and/or neurological disease (such as multiple sclerosis, spinal pathology, cerebrovascular disease) or following pelvic surgery. Therefore, management should be aetiology-guided, symptom-severity-guided, and individualised using shared decision-making.^{23,277,283}

The options for managing urge incontinence are summarised in Table 4.

In women with OAB, the brain has lost central control over the bladder. Thus, the mainstay of treatment for OAB is bladder training (bladder drill). This is an attempt to restore central control over the bladder.

Evaluation

The initial evaluation should include a focused history (urgency, frequency, nocturia, UUI triggers), examination (including pelvic organ prolapse), urinalysis ($\pm$ culture) to exclude infection/haematuria, and post-void residual (particularly in older women, voiding symptoms, prolapse, diabetes, neurological disease, or prior incontinence surgery).^{23,277,283}

A bladder diary is strongly recommended, as it quantifies symptom burden, identifies patterns (e.g., fluid intake, nocturia), and provides a baseline for treatment response.^{23,283}

Bladder training: The training interval is set to a shorter time than this. For example, if a woman leaks after waiting 2 hours between voids, the training interval is set to 1.5 hours while awake, rather than waiting until she feels the urge to urinate. This trains the bladder to void in response to central command. The training interval is then increased by 15 minutes each week until a satisfactory time interval is reached. Usually, the training interval is not set shorter than 1 hour. The patient should discontinue training during sleep.

- Pelvic floor muscle training (PFMT) (Kegel exercises) will help reduce leakage by strengthening pelvic floor muscles. In addition, quick contractions of the pelvic floor muscles activate an inhibitory detrusor reflex that may help control urgency.
- Lifestyle and supportive measures:
- Caffeine reduction, optimisation of fluid timing, weight reduction (if overweight), constipation management, and review of medications that worsen urgency (such as diuretics and α -blockers in selected cases) are commonly recommended adjuncts.

Pharmacotherapy: Bladder contraction is mediated largely by muscarinic (M2/M3) receptors, while storage is supported by sympathetic pathways. Pharmacotherapy targets these pathways to reduce urgency, frequency, and UUI.

Antimuscarinics (anticholinergics): Antimuscarinics remain effective and widely used, but side effects (dry mouth, constipation, blurred vision) and adherence limitations are well recognised, and cognitive risk considerations are important in older women. Common options include: oxybutynin, tolterodine, trospium, solifenacin, darifenacin, and fesoterodine. Extended-release formulations generally improve tolerability compared to immediate-release preparations. Use the lowest effective dose, reassess benefit/tolerability, and consider switching agents if side effects occur. In older women or those at cognitive risk, many clinicians prefer β 3-agonists or antimuscarinics with lower central nervous system penetration, such as trospium, a quaternary amine, though choice should be individualised.^{23,277,283}

β 3-adrenergic agonists: β 3-adrenoceptor agonists improve bladder storage by promoting detrusor muscle relaxation and are now recommended alongside antimuscarinics as standard second-line pharmacotherapy for overactive bladder; key agents include mirabegron, which has robust randomised controlled trial evidence with 12-month safety and efficacy data,²⁸⁴ and vibegron, which demonstrated significant reductions in micturitions, urgency episodes, and urgency urinary incontinence in the phase 3 EMPOWUR trial with favourable tolerability.^{285,286}

Combination therapy: For patients with an inadequate response to monotherapy, combination therapy with a β 3-agonist and an antimuscarinic is an established escalation strategy in many care pathways, with consideration of potential side effects and cost.

Drugs generally not recommended. Older antispasmodics (such as flavoxate) and nonspecific anticholinergics are not

preferred in contemporary evidence-based treatment pathways because of limited efficacy data and/or unfavourable side-effect profiles compared with antimuscarinics and $\beta 3$ -agonists.^{23,277,283} If included in a local formulary, they should be described as “not preferred” rather than “first-line” agents.

Imipramine: Imipramine is not considered a first-line agent for OAB in current guideline pathways. Although it may have a role in selected patients with mixed urinary incontinence, its side-effect profile and safety concerns, particularly in older women, limit its routine use.^{23,277,283}

Minimally Invasive Therapies for Refractory

When behavioural therapy and appropriate pharmacotherapy fail or are not tolerated, guideline-supported third-line options include:

Intradetrusor onabotulinumtoxinA: Intradetrusor injections of onabotulinumtoxinA are effective for refractory OAB and urgency urinary incontinence. Patients must be counselled regarding the risks of increased post-void residual urine, the potential need for intermittent catheterisation, and UTIS.^{23,277,283} Clinical benefit typically lasts several months, and repeat injections may be required.

Neuromodulation: Percutaneous Tibial Nerve Stimulation (PTNS): A non-surgical, office-based therapy commonly used for refractory OAB and often offered before more invasive options in many treatment pathways.^{277,283}

Sacral Neuromodulation (SNM): An implantable therapy indicated for refractory OAB, urgency urinary incontinence, and selected voiding dysfunction. Escalation criteria typically include failure of conservative and medical therapy, and often prior consideration of botulinum toxin A (or when botulinum toxin is contraindicated or unacceptable).²⁷⁷

Major surgery (rare): Bladder augmentation or urinary diversion is now rarely performed for idiopathic OAB and is generally reserved for highly selected refractory cases under specialist multidisciplinary care.^{23,283}

SYNOPSIS

- Genitourinary syndrome appears 4-5 years after menopause and is seen in 40-60% of women.
- Women's health-care providers should appreciate women's perspectives and needs in vaginal health. Indian women need greater awareness of the effects of vaginal atrophy and the benefits of early treatment.
- It is essential that health-care providers routinely engage in open and sensitive discussion with postmenopausal women about their urogenital health to ensure that symptomatic atrophy is detected early and appropriately managed.
- Health-care providers should routinely assess postmenopausal women for the symptoms and signs of GSM, a common condition that exerts significant negative effects on quality of life. A vaginal pH greater than 4.5 indicates urogenital atrophy.
- Treatment should be started early to prevent irreversible atrophic changes and may need long-term treatment to maintain benefits. Regular sexual activity, including vaginal coitus, should be encouraged to maintain vaginal health.
- Vaginal estrogen therapy is most effective in the treatment of urogenital atrophy. Low-dose vaginal preparations are as effective as systemic therapy. Some women on oral estrogen therapy may require additional local therapy.
- Recurrent attacks of atrophic vaginitis require the use of the smallest effective dose over a period of time. After control of acute symptoms, the dose of local estrogen can be tapered for long-term maintenance therapy. Treatment may be continued indefinitely, although safety data from studies extend only to 1 year.
- A progesterone supplement for endometrial protection is not needed along with the use of vaginal estrogen.
- Endometrial surveillance is not necessary in low-risk asymptomatic women. Unscheduled bleeding should be investigated by an ultrasound and an endometrial biopsy.
- Limited data is available on the use of vaginal estrogen therapy in women with breast and endometrial cancer.

- Lifestyle management and nonhormonal treatments would be the first option, but in resistant cases, joint consultation with the oncologist and counselling of the woman would be done before prescribing vaginal estrogen. The preferred therapy would be low-dose, low-potency, such as estriol.
- A follow-up visit is scheduled after 1 and 3 months. If, in 3 months, she shows improvement in her signs and symptoms, the patient will be advised to try to discontinue. She is counselled that she will likely require long-term vaginal estrogen therapy to ease the vulvovaginal irritation and frequent urinary infection.
- Recurrent urinary tract infections in this age, after ruling out other causes, may benefit from the local application of estrogen therapy
- Urge incontinence associated with urogenital atrophy may benefit from local estrogen therapy.
- SERMs, such as ospemifene (Osphena), are effective for the treatment of VVA.
- Intravaginal DHEA has been found to improve VVA symptoms by acting on all three layers of the vagina. SERMs AND DHEA are not available in India
- Vaginal lubricants can be recommended for subjective symptom improvement of dyspareunia
- Vaginal moisturisers can be offered for vaginal dryness and dyspareunia
- Vaginal moisturising gels are particularly good for patients who have had breast or endometrial cancer when estrogens are contraindicated. Preparations with an acidic pH will provide some protection against infection.
- Urinary incontinence (UI) is the involuntary leakage of urine. Types of UI are SUI, UUI, MUI, overflow incontinence and functional incontinence.
- Lifestyle modification, bladder drill, and pelvic floor exercises are common management recommendations for urinary incontinence. Accurate diagnosis is vital for prescribing specific types of UI.

RESEARCH AGENDA

Barriers to Diagnosis and Treatment of Genitourinary Syndrome of Menopause Among Indian Women.

REFERENCES

1. Portman DJ, Gass MLS. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and The North American Menopause Society. *Climacteric*. 2014;17:557–63. <https://doi.org/10.3109/13697137.2014.946279>.
2. Meeta M, Digumarti L, Agarwal N, Vaze N, Shah R, Malik S. Clinical Practice Guidelines on Menopause: An Executive Summary and Recommendations: Indian Menopause Society 2019–2020. *J Mid-life Health*. 2020;11:55–95. https://doi.org/10.4103/jmh.jmh_137_20.
3. Chen GD. Pelvic floor dysfunction in aging women. *Taiwan J Obstet Gynecol*. 2007;46:374–8. [https://doi.org/10.1016/S1028-4559\(08\)60006-6](https://doi.org/10.1016/S1028-4559(08)60006-6).
4. Nappi RE, Kokot-Kierepa M. Vaginal Health: Insights, Views & Attitudes (VIVA) – results from an international survey. *Climacteric*. 2012;15:36–44. <https://doi.org/10.3109/13697137.2011.647840>.
5. Palma F, Volpe A, Villa P, Cagnacci A. Vaginal atrophy of women in postmenopause. Results from a multicentric observational study: The AGATA study. *Maturitas*. 2016;83:40–4. <https://doi.org/10.1016/j.maturitas.2015.09.001>.
6. Carlson K, Nguyen H. Genitourinary Syndrome of Menopause. [Updated 2024 Oct 5]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK559297/>
7. Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. *JAMA*. 1999;281:537–44. <https://doi.org/10.1001/jama.281.6.537>.
8. Mitchell CM, Waetjen LE. Genitourinary changes with aging. *Obstet Gynecol Clin North Am*. 2018;45:737–50. <https://doi.org/10.1016/j.ogc.2018.07.010>.
9. Nappi RE, Biglia N, Cagnacci A, Di Carlo C, Luisi S, Paoletti AM. Diagnosis and management of symptoms associated with vulvovaginal atrophy: expert opinion on behalf of the Italian VVA study group. *Gynecol Endocrinol*. 2016;32:602–6. <https://doi.org/10.1080/09513590.2016.1183627>.
10. Wysocki S, Kingsberg S, Krychman M. Management of Vaginal Atrophy: Implications from the REVIVE Survey. *Clin Med Insights Reprod Health*. 2014;8:23–30. <https://doi.org/10.4137/CMRH.S14498>.
11. Gartoulla P, Worsley R, Bell RJ, Davis SR. Moderate to severe vasomotor and sexual symptoms remain problematic for women aged 60 to 65 years. *Menopause*. 2018;25:1331–8. <https://doi.org/10.1097/GME.0000000000001237>.
12. Gandhi J, Chen A, Dagur G, Suh Y, Smith N, Cali B, Khan SA. Genitourinary syndrome of menopause: an overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. *Am J Obstet Gynecol*. 2016;215:704–11. <https://doi.org/10.1016/j.ajog.2016.07.045>.
13. Cummings SR, Browner WS, Bauer D, Stone K, Ensrud K, Jamal S, et al. Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. *N Engl J Med*. 1998;339:733–8. <https://doi.org/10.1056/NEJM199809103391104>.
14. Sarrel PM. Sexuality and menopause. *Obstet Gynecol*. 1990;75:26S–35S. <https://doi.org/10.1097/00006250-199004001-00006>.

15. Doust J, Huguenin A, Hickey M. Genitourinary Syndrome of Menopause: Does Everyone Have It? *Clin Obstet Gynecol*. 2023;67:4–12. <https://doi.org/10.1097/GRF.0000000000000834>.
16. Blakeman PJ, Hilton P, Bulmer JN. Oestrogen and progesterone receptor expression in the female lower urinary tract, with reference to oestrogen status. *BJU Int*. 2000;86:32–8. <https://doi.org/10.1046/j.1464-410x.2000.00724.x>.
17. Thomas DFM. The embryology of persistent cloaca and urogenital sinus malformations. *Asian J Androl*. 2020;22(2):124–8. https://doi.org/10.4103/aja.aja_72_19.
18. Acién P. Embryological observations on the female genital tract. *Human Reproduction*. 1992;7:437–45. <https://doi.org/10.1093/oxfordjournals.humrep.a137666>
19. Bachmann G, Pinkerton JV. Genitourinary syndrome of menopause (vulvovaginal atrophy): Clinical manifestations and diagnosis. In: Barbieri RL, editor. UpToDate [Internet]. Waltham (MA): UpToDate Inc.; 2025 [updated 2025 Mar 26]. Available from: <https://www.uptodate.com>.
20. Caillouette JC, Sharp CF Jr, Zimmerman GJ, Roy S. Vaginal pH as a marker for bacterial pathogens and menopausal status. *Am J Obstet Gynecol*. 1997;176:1270–7. [https://doi.org/10.1016/S0002-9378\(97\)70345-4](https://doi.org/10.1016/S0002-9378(97)70345-4).
21. Micks E, Reed SD, Mitchell C. The postmenopausal vaginal microbiome and genitourinary syndrome of menopause. *Clin Obstet Gynecol*. 2023;67:79–88. <https://doi.org/10.1097/GRF.0000000000000832>.
22. Jackson S, James M, Abrams P. The effect of oestradiol on vaginal collagen metabolism in postmenopausal women with genuine stress incontinence. *BJOG*. 2002;109:339–44. <https://doi.org/10.1111/j.1471-0528.2002.01052.x>.
23. Cameron AP, Chung DE, Dielubanza EJ, Enemchukwu E, Ginsberg DA, Helfand BT, et al. The AUA/SUFU Guideline on the Diagnosis and Treatment of Idiopathic Overactive Bladder. *J Urol*. 2024;212:11–20. <https://doi.org/10.1097/JU.00000000000003985>.
24. Arjmand M, Abbasi H, Behforouz A. The effect of vitamin D on urgent urinary incontinence in postmenopausal women. *Int Urogynecol J*. 2023;34:1955–60. <https://doi.org/10.1007/s00192-023-05486-5>.
25. Notelovitz M. Postmenopausal tibolone therapy: biologic principles and applied clinical practice. *MedGenMed*. 2007 Jan 3;9(1):2. PMID: 17435612; PMCID: PMC1924982.
26. Jung CE, et al. Vaginal estrogen and the urobiome in postmenopausal women with rUTIs (RCT analysis). *Female Pelvic Med Reconstr Surg*. 2022;28(1):20–26.
27. Kaufman MR, Ackerman AL, Amin KA, Coffey M, Danan E, Faubion SS, et al. The AUA/SUFU/AUGS Guideline on Genitourinary Syndrome of Menopause. *J Urol*. 2025;214:242–50. <https://doi.org/10.1097/JU.00000000000004589>.
28. Hodgins MB, Spike RC, Mackie RM, MacLean AB. An immunohistochemical study of androgen, oestrogen and progesterone receptors in the vulva and vagina. *BJOG*. 1998;105:216–22. <https://doi.org/10.1111/j.1471-0528.1998.tb10056.x>.
29. Chen GD, Oliver RH, Leung BS, Lin LY, Yeh J. Estrogen receptor α and β expression in the vaginal walls and uterosacral ligaments of premenopausal and postmenopausal women. *Fertil Steril*. 1999;71:1099–102. [https://doi.org/10.1016/S0015-0282\(99\)00113-2](https://doi.org/10.1016/S0015-0282(99)00113-2).
30. Buchanan DL, Kurita T, Taylor JA, Lubahn DB, Cunha GR, Cooke PS. Role of Stromal and Epithelial Estrogen Receptors in Vaginal Epithelial Proliferation, Stratification, and Cornification. *Endocrinology*. 1998;139:4345–52. <https://doi.org/10.1210/endo.139.10.6241>.
31. Takashina R, Nakajima T, Umezaki T, Komatsu K, Banba T, Asada T, et al. Stratification of mouse vaginal epithelium 2. Identification of factors inducing stratification. *Biol Reprod*. 2018;99:727–34. <https://doi.org/10.1093/biolre/i0y113>.
32. Carlstrom K, Karlgren E, Furuholm M. Metabolism of estrone sulfate in postmenopausal vaginal mucosa. *Acta Obstetrica et Gynecologica Scandinavica*. 1988;67(3):241–2. <https://doi.org/10.3109/00016348809004212>.
33. Maseroli E, Vignozzi L. Testosterone and Vaginal Function. *Sexual Medicine Reviews*. 2020;8:379–92. <https://doi.org/10.1016/j.sxmr.2020.03.003>.
34. Baldassarre M, Perrone AM, Giannone FA, Armillotta F, Battaglia C, Costantino A, et al. Androgen receptor expression in the human vagina under different physiological and treatment conditions. *Int J Impot Res*. 2013;25:7–11. <https://doi.org/10.1038/ijir.2012.25>.
35. Cellai I, Di Stasi V, Comeglio P, Maseroli E, Todisco T, Corno C, et al. Insight on the Intracrinology of Menopause: Androgen Production within the Human Vagina. *Endocrinology*. 2021;162. <https://doi.org/10.1210/endocr/bqaa219>.
36. Labrie F, Archer D, Bouchard C, Fortier M, Cusan L, Gomez JL, et al. Effect of intravaginal dehydroepiandrosterone (Prasterone) on libido and sexual dysfunction in postmenopausal women. *Menopause*. 2009;16:923–31. <https://doi.org/10.1097/gme.0b013e31819e85c6>.
37. Pessina MA, Hoyt RF Jr, Goldstein I, Traish AM. Differential effects of estradiol, progesterone, and testosterone on vaginal structural integrity. *Endocrinology*. 2006;147:61–9. <https://doi.org/10.1210/en.2005-0870>.
38. Nappi RE, Cucinella L, Martini E, Cassani C. The role of hormone therapy in urogenital health after menopause. *Best Practice & Research Clinical Endocrinology & Metabolism*. 2021;35:101595. <https://doi.org/10.1016/j.beem.2021.101595>.
39. Berman JR, Almeida FG, Jolin J, Raz S, Chaudhuri G, Gonzalez-Cadavid NF. Correlation of androgen receptors, aromatase, and 5- α reductase in the human vagina with menopausal status. *Fertil Steril*. 2003;79:925–31. [https://doi.org/10.1016/S0015-0282\(02\)04923-3](https://doi.org/10.1016/S0015-0282(02)04923-3).
40. Labrie F. Intracrinology and menopause: the science describing the cell-specific intracellular formation of estrogens and androgens from DHEA and their strictly local action and inactivation in peripheral tissues. *Menopause (New York, N.Y.)*. 2019;26(2):220–224. <https://doi.org/10.1097/GME.0000000000001177>.
41. Utian WH, Shoupe D, Bachmann G, Pinkerton JV, Pickar JH. Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate. *Fertil Steril*. 2001;75:1065–79. [https://doi.org/10.1016/S0015-0282\(01\)01791-5](https://doi.org/10.1016/S0015-0282(01)01791-5).
42. Henriques HN, de Carvalho AC, Soares Filho PJ, Pantaleao JA, Guzman-Silva MA. Effect of prolonged use of high dose of tibolone on the vagina of ovariectomized rats. *Int J Exp Pathol*. 2011;92(4):266–271. <https://doi.org/10.1111/j.1365-2613.2011.00774.x>.
43. Rymer J, Chapman MG, Fogelman I, Wilson POG. A study of the effect of tibolone on the vagina in postmenopausal women. *Maturitas*. 1994;18:127–33. [https://doi.org/10.1016/0378-5122\(94\)90050-7](https://doi.org/10.1016/0378-5122(94)90050-7).
44. Ting AY, Blacklock AD, Smith PG. Estrogen regulates vaginal sensory and autonomic nerve density in the rat. *Biol Reprod*. 2004;71:1397–404. <https://doi.org/10.1095/biolreprod.104.030023>.
45. Reed SD. Dyspareunia—where and why the pain? *Menopause*. 2022;29:639–41. <https://doi.org/10.1097/GME.0000000000002001>.
46. Li T, Liao Q, Zhang H, Gao X, Li X, Zhang M. Anatomic distribution of nerves and microvascular density in the human anterior vaginal wall: prospective study. *PLoS ONE*. 2014;9:e110239. <https://doi.org/10.1371/journal.pone.0110239>.

47. Li T, Ma Y, Zhang H, Yan P, Huo L, Hu Y, et al. Estrogen replacement regulates vaginal innervations in ovariectomized rats. *Biomed Res Int*. 2017;2017:7456853. <https://doi.org/10.1155/2017/7456853>.
48. Griebeling TL, Liao Z, Smith PG. Systemic and topical hormone therapies reduce vaginal innervation density in postmenopausal women. *Menopause*. 2012;19:630–5. <https://doi.org/10.1097/gme.0b013e31823b8983>.
49. Nik Hazlina NH, Norhayati MN, Shaiful Bahari I, Nik Muhammad Arif NA. Prevalence of Psychosomatic and Genitourinary Syndrome Among Menopausal Women: A Systematic Review and Meta-Analysis. *Frontiers in Medicine*. 2022;9:848202. <https://doi.org/10.3389/fmed.2022.848202>.
50. Kingsberg SA, Wysocki S, Magnus L, Krychman ML. Vulvar and vaginal atrophy in postmenopausal women: findings from the REVIVE (Real Women's Views of Treatment Options for Menopausal Vaginal Changes) survey. *J Sex Med*. 2013;10:1790–9. <https://doi.org/10.1111/jsm.12190>.
51. Santoro N, Komi J. Prevalence and impact of vaginal symptoms among postmenopausal women. *J Sex Med*. 2009;6:2133–42. <https://doi.org/10.1111/j.1743-6109.2009.01335.x>.
52. Angelou K, Grigoriadis T, Diakosavvas M, Zacharakis D, Athanasiou S. The Genitourinary Syndrome of Menopause: An Overview of the Recent Data. *Cureus*. 2020;12(4):e7586. <https://doi.org/10.7759/cureus.7586>.
53. Parish SJ, Nappi RE, Krychman ML, Kellogg-Spadt S, Simon JA, Goldstein JA, Kingsberg SA. Impact of vulvovaginal health on postmenopausal women: a review of surveys on symptoms of vulvovaginal atrophy. *Int J Womens Health*. 2013;5:437–47. <https://doi.org/10.2147/IJWH.S44579>.
54. Wyeth. REVEAL: Revealing Vaginal Effects at Mid-Life: Surveys of Postmenopausal Women and Health Care Professionals who Treat Postmenopausal Women. Madison (NJ): Wyeth; 2009. Available from: <http://www.revealsurvey.com/pdf/reveal-survey-results.pdf>
55. Nappi RE, Kokot-Kierepa M. Women's voices in the menopause: results from an international survey on vaginal atrophy. *Maturitas*. 2010;67:233–8. <https://doi.org/10.1016/j.maturitas.2010.08.001>.
56. Cumming GP, Currie HD, Moncur R, Lee AJ. Web-based survey on the effect of menopause on women's libido in a computer-literate population. *Menopause Int*. 2009;15:8–12. <https://doi.org/10.1258/mi.2009.009001>.
57. Cumming GP, Herald J, Moncur R, Currie H, Lee AJ. Women's attitudes to hormone replacement therapy, alternative therapy and sexual health: a web-based survey. *Menopause Int*. 2007;13:79–83. <https://doi.org/10.1258/175404507780796424>.
58. Levine KB, Williams RE, Hartmann KE. Vulvovaginal atrophy is strongly associated with female sexual dysfunction among sexually active postmenopausal women. *Menopause*. 2008;15:661–6. <https://doi.org/10.1097/gme.0b013e31815a5168>.
59. Mili N, Paschou SA, Armeni A, Georgopoulos N, Goulis DG, Lambrinoudaki I. Genitourinary syndrome of menopause: a systematic review on prevalence and treatment. *Menopause*. 2021;28:706–16. <https://doi.org/10.1097/GME.0000000000001752>.
60. Moral E, Delgado JL, Carmona F, Caballero B, Guillot C, González PM, et al. Genitourinary syndrome of menopause. Prevalence and quality of life in Spanish postmenopausal women. The GENISSE study. *Climacteric*. 2018;21:167–73. <https://doi.org/10.1080/13697137.2017.1421921>.
61. Bruce D, Rymer J. Symptoms of the menopause. *Best Pract Res Clin Obstet Gynaecol*. 2009;23:25–32. <https://doi.org/10.1016/j.bpobgyn.2008.10.002>.
62. MacBride MB, Rhodes DJ, Shuster LT. Vulvovaginal Atrophy. *Mayo Clin Proc*. 2010;85:87–94. <https://doi.org/10.4065/mcp.2009.0413>.
63. Nappi RE, Lachowsky M. Menopause and sexuality: prevalence of symptoms and impact on quality of life. *Maturitas*. 2009;63:138–41. <https://doi.org/10.1016/j.maturitas.2009.03.021>.
64. Singh M. Early age of natural menopause in India, a biological marker for early preventive health programs. *Climacteric*. 2012;15:581–6. <https://doi.org/10.3109/13697137.2011.643514>.
65. Ashraf AB, Meeta M, Chitra AB, Pahwa S, Shah J, Mohi M, et al. Genitourinary syndrome of menopause: a multicenter study from the Indian Midlife Registry. *Climacteric*. 2025;28:329–36. <https://doi.org/10.1080/13697137.2025.2496681>.
66. Ulhe SC, Acharya N, Vats A, Singh A. Study of Vulvovaginal Atrophy and Genitourinary Syndrome of Menopause and Its Impact on the Quality of Life of Postmenopausal Women in Central India. *Cureus*. 2024;16(2):e54802. <https://doi.org/10.7759/cureus.54802>.
67. Karamanidis D, Tamiolakis D, Koutsougeras G, Tripsanas CH, Retzos K, Karidis S, et al. Cigarette smoking and the degree of maturation of the vaginal squamous epithelium in postmenopausal women. *Clin Exp Obstet Gynecol*. 2001;28:274–6. <https://pubmed.ncbi.nlm.nih.gov/11838758/>
68. Jenczura A, Czajkowska M, Skrzypulec-Frankel A, Skrzypulec-Plinta V, Drosdzol-Cop A. Sexual function of postmenopausal women addicted to alcohol. *Int J Environ Res Public Health*. 2018;15:1639. <https://doi.org/10.3390/ijerph15081639>.
69. The 2020 genitourinary syndrome of menopause position statement of The North American Menopause Society. *Menopause*. 2020;27:976–92. <https://doi.org/10.1097/GME.0000000000001609>.
70. Lubián López DM. Management of genitourinary syndrome of menopause in breast cancer survivors: an update. *World J Clin Oncol*. 2022;13:71–100. <https://doi.org/10.5306/wjco.v13.i2.71>.
71. Palacios S, Nappi RE, Bruyniks N, Particco M, Panay N; EVES Study Investigators. The European Vulvovaginal Epidemiological Survey (EVES): prevalence, symptoms and impact of vulvovaginal atrophy of menopause. *Climacteric*. 2018 Jun;21(3):286–291. doi: 10.1080/13697137.2018.1446930.
72. Food and Drug Administration. Guidance for industry: estrogen and estrogen/progestin products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms—recommendation for clinical evaluation. Updated August 2018. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2023/216578Orig1s000SumR.pdf
73. Christmas MM, Song B, Bell RJ, Iliodromiti S, Mitchell C, Hickey M. Variation in outcome reporting and measurement tools in clinical trials of treatments for genitourinary symptoms in peri- and postmenopausal women: a systematic review. *Menopause*. 2020;27:1070–80. <https://doi.org/10.1097/GME.0000000000001570>.
74. Gass MLS, Cochrane BB, Larson JC, Manson JE, Barnabei VM, Brzyski RG, et al. Patterns and predictors of sexual activity among women in the Hormone Therapy trials of the Women's Health Initiative. *Menopause*. 2011;18:1160–71. <https://doi.org/10.1097/gme.0b013e3182227ebd>.
75. Shifren JL, Zinzavage R, Cho EL, Magnavita A, Portman DJ, Krychman ML, et al. Women's experience of vulvovaginal symptoms associated with menopause. *Menopause*. 2019;26:341–9. <https://doi.org/10.1097/GME.0000000000001275>.
76. Pérez-López FR, Vieira-Baptista P, Phillips N, Cohen-Sacher B, Fialho SCAV, Stockdale CK. Clinical manifestations and evaluation of postmenopausal vulvovaginal atrophy. *Gynecol Endocrinol*. 2021;37:740–5. <https://doi.org/10.1080/09513590.2021.1931100>.
77. Cagnacci A, Carbone MM, Palma F. Prevalence and association between objective signs and subjective symptoms of vaginal atrophy: the AGATA study. *Menopause*. 2016;23:1139–45. <https://doi.org/10.1097/GME.0000000000000675>.

78. Pastore LM, Carter RA, Hulka BS, Wells E. Self-reported urogenital symptoms in postmenopausal women: Women's Health Initiative. *Maturitas*. 2004;49:292–303. <https://doi.org/10.1016/j.maturitas.2004.06.019>.
79. Bachmann G, Bouchard C, Hoppe D, Ranganath R, Altomare C, Vieweg A, et al. Efficacy and safety of low-dose regimens of conjugated estrogens cream administered vaginally. *Menopause*. 2009;16:719–27. <https://doi.org/10.1097/gme.0b013e3181a48c4e>.
80. Waetjen LE, Crawford SL, Chang PY, Reed BD, Hess R, Avis NE, et al. Factors associated with developing vaginal dryness symptoms in women transitioning through menopause: a longitudinal study. *Menopause*. 2018;25:1094–104. <https://doi.org/10.1097/GME.0000000000001130>.
81. Bachmann GA, Nevadunsky NS. Diagnosis and treatment of atrophic vaginitis. *Am Fam Physician*. 2000;61:3090–6. <https://pubmed.ncbi.nlm.nih.gov/10839558/>
82. Castelo-Branco C, Cancelo MJ, Villero J, Nohales F, Julia MD. Management of post-menopausal vaginal atrophy and atrophic vaginitis. *Maturitas*. 2005;52:46–52. <https://doi.org/10.1016/j.maturitas.2005.06.014>.
83. Barba M, Cola A, De Vicari D, Costa C, Castelli AP, Volontè S, et al. Efficacy of a Diode Vaginal Laser in the Treatment of the Genitourinary Syndrome of Menopause. *Bioengineering*. 2023;10:1158. <https://doi.org/10.3390/bioengineering10101158>.
84. Mitchell CM, Larson JC, Reed SD, Guthrie KA. The complexity of genitourinary syndrome of menopause: number, severity, and frequency of vulvovaginal discomfort symptoms in women enrolled in a randomized trial evaluating treatment for genitourinary syndrome of menopause. *Menopause*. 2023;30:791–7. <https://doi.org/10.1097/gme.0000000000002212>.
85. Erekson EA, Li FY, Martin DK, Fried TR. Vulvovaginal symptoms prevalence in postmenopausal women and relationship to other menopausal symptoms and pelvic floor disorders. *Menopause*. 2016;23:368–75. <https://doi.org/10.1097/GME.0000000000000549>.
86. Huang AJ, Gregorich SE, Kuppermann M, Nakagawa S, Van Den Eeden SK, Brown JS, et al. Day-to-Day Impact of Vaginal Aging questionnaire. *Menopause*. 2015;22:144–54. <https://doi.org/10.1097/gme.0000000000000281>.
87. US Food and Drug Administration. Guidance for industry: estrogen and estrogen/progestin drug products to treat vasomotor symptoms and vulvar and vaginal atrophy symptoms—recommendations for clinical evaluation. Rockville (MD): US Food and Drug Administration; 2003. <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/estrogen-and-estrog-enprogestin-drug-products-treat-vasomotor-symptoms-and-vulvar-and-vaginal-atrophy>
88. Eaton AA, Baser RE, Seidel B, Stabile C, Canty JP, Goldfrank DJ, et al. Validation of Clinical Tools for Vaginal and Vulvar Symptom Assessment in Cancer Patients and Survivors. *J Sex Med*. 2016;14:144–51. <https://doi.org/10.1016/j.jsxm.2016.11.317>.
89. Dargie E, Holden RR, Pukall CF. The Vulvar Pain Assessment Questionnaire inventory. *Pain*. 2016;157:2672–86. <https://doi.org/10.1097/j.pain.0000000000000682>.
90. Wiegel M, Meston C, Rosen R. The Female Sexual Function Index (FSFI): Cross-Validation and Development of Clinical Cutoff Scores. *J Sex Marital Ther*. 2005;31:1–20. <https://doi.org/10.1080/00926230590475206>.
91. DeRogatis L, Clayton A, Lewis-D'Agostino D, Wunderlich G, Fu Y. Female Sexual Distress Scale-Revised (FSDS-R). *PsycTESTS Dataset*. 2008. <https://doi.org/10.1037/t62113-000>.
92. Murina F, Torracca M, Graziottin A, Nappi RE, Villa P, Cetin I. Validation of a clinical tool for vestibular trophism in postmenopausal women. *Climacteric*. 2023;26:149–53. <https://doi.org/10.1080/13697137.2023.2171287>.
93. Avery K, Donovan J, Peters TJ, Shaw C, Gotoh M, Abrams P. ICIQ: A brief and robust measure for evaluating the symptoms and impact of urinary incontinence. *Neurourol Urodyn*. 2004;23:322–30. <https://doi.org/10.1002/nau.20041>.
94. Good MM, Solomon ER. Pelvic Floor Disorders. *Obstetrics and Gynecology Clinics of North America*. 2019;46:527–40. <https://doi.org/10.1016/j.ogc.2019.04.010>
95. Lountzi AZ, Abhyankar P, Durand H. A scoping review of vulvodynia research: Diagnosis, treatment, and care experiences. *Womens Health (Lond)*. 2025;21:17455057251345946. <https://doi.org/10.1177/17455057251345946>.
96. Goetsch MF, Garg B, Lillemon J, Clark AL. Where does postmenopausal dyspareunia hurt? A cross-sectional report. *Menopause*. 2022;29:646–53. <https://doi.org/10.1097/GME.0000000000001956>.
97. Bachmann GA, Nodelovitz M, Kelly SJ, et al. Long-term nonhormonal treatment of vaginal dryness. *Clin Pract Sex*. 1992;8:1–12. Available at: https://www.replens.eu/fr/wp-content/uploads/sites/2/2018/02/Les-traitements-non-hormonaux-à-long-terme-de-la-sécheresse-vaginale_en.pdf
98. Meisels A. The maturation value. *Acta Cytol*. 1967;11(4):249. <https://pubmed.ncbi.nlm.nih.gov/5233434/>
99. McEndree B. Clinical application of the vaginal maturation index. *Nurse Pract*. 1999;24(9):48, 51–2, 55–6. <https://doi.org/10.1097/00006205-199909000-00004>
100. Panayi DC, Digesu GA, Tekkis P, Fernando R, Khullar V. Ultrasound measurement of vaginal wall thickness: a novel and reliable technique. *Int Urogynecol J*. 2010;21:1265–70. <https://doi.org/10.1007/s00192-010-1183-4>
101. National Institutes of Health State-of-the-Science Conference Statement: Management of Menopause-Related Symptoms. *Ann Intern Med*. 2005;142:1003–13. https://doi.org/10.7326/0003-4819-142-12_part_1-200506210-00117
102. Mensien E, Alonso I, Tortajada M, Matas I, Gomez S, Ribera L, et al. Genitourinary Syndrome of Menopause Assessment Tools. *J Mid-life Health*. 2021;12:99–102. https://doi.org/10.4103/jmh.jmh_93_21
103. Cucinella L, Martini E, Tiranini L, Battista F, Molinaro P, Casiraghi A, et al. Menopause and female sexual dysfunctions. *Minerva Obstet Gynecol*. 2022;74:234–48. <https://doi.org/10.23736/S2724-606X.22.05001-1>
104. Mahmoudnejad N, Hamidi Madani M, Roohinezhad R. The Labial Adhesion in Postmenopausal Women: A Systematic Review. *Iran J Med Sci*. 2024;49(12):752–760. <https://doi.org/10.30476/ijms.2024.101283.3395>
105. Dominguez-Bali A, Bailey N, Callihan K, Dominguez-Bali C, Nani J. (460) A Case Series on Vulvovaginal Obliteration. *J Sex Med*. 2023;20. <https://doi.org/10.1093/jsxmed/qdad060.432>
106. Mikos T, Lioupis M, Grimbizis GF. Postmenopausal complete labial fusion and pseudo-incontinence: A case series. *Case Rep Womens Health*. 2019;21:e00101. <https://doi.org/10.1016/j.crwh.2019.e00101>
107. Arpit AV, Nilam KP, Smitul AV, Anita JS. Labial Fusion in a Postmenopausal Woman Presenting with Urinary Incontinence. *J Mid-life Health*. 2024;15:217–9. https://doi.org/10.4103/jmh.jmh_107_24

108. Tanvir T, Meeta M, Singh A. Complete Labial Fusion Causing Pseudo-Urinary Incontinence: A Long-Term Sequelae of Genitourinary Syndrome. *J Mid-life Health*. 2020;11:257–9. https://doi.org/10.4103/jmh.JMH_34_20
109. Singh P, Han HC. Labial adhesions in postmenopausal women: presentation and management. *Int Urogynecol J*. 2019;30:1429–32. <https://doi.org/10.1007/s00192-018-3821-1>
110. Gungor Ugurlucan F, Yasa C, Tas IS, Aslay I, Yalcin O. Complete labial fusion causing urinary retention in a postmenopausal woman. *Am J Clin Exp Urol*. 2021;9(5):413–415. PMID: 34796258
111. Başaranoğlu S, Doğan F, Deregözü A. Acute renal failure due to complete labial fusion: A case report. *Int J Surg Case Rep*. 2016;29:162–164. <https://doi.org/10.1016/j.ijscr.2016.08.016>
112. Tsianos GI, Papatheodorou SI, Michos GM, Koliopoulos G, Stefanos T. Pyosalpinx as a sequela of labial fusion in a post-menopausal woman: a case report. *J Med Case Rep*. 2011;5:546. <https://doi.org/10.1186/1752-1947-5-546>
113. Ghosalkar E, Epstein S, Epstein A, Mauskar M, Pope R. Challenges With Diagnosis of Labial Agglutination Due to Lichen Sclerosus. *J Low Genit Tract Dis*. 2025;29:269–72. <https://doi.org/10.1097/LGT.0000000000000874>
114. Maeda T, Deguchi M, Amano T, Tsuji S, Kasahara K, Murakami T. A novel surgical treatment for labial adhesion – The combination of Z- and Y-V-plasty: A case report. *Case Rep Womens Health*. 2021;32:e00363. <https://doi.org/10.1016/j.crwh.2021.e00363>
115. Kagan R, Kellogg-Spadt S, Parish SJ. Practical Treatment Considerations in the Management of Genitourinary Syndrome of Menopause. *Drugs Aging*. 2019;36:897–908. <https://doi.org/10.1007/s40266-019-00700-w>
116. Christmas M, Huguenin A, Iyer S. Clinical Practice Guidelines for Managing Genitourinary Symptoms Associated With Menopause. *Clin Obstet Gynecol*. 2024;67(1):101–114. <https://doi.org/10.1097/GRF.0000000000000833>
117. Palacios S, Mejia A, Neyro JL. Treatment of the genitourinary syndrome of menopause. *Climacteric*. 2015;18 Suppl 1:23–9. <https://doi.org/10.3109/13697137.2015.1079100>
118. Da Silva AS, Baines G, Araklitis G, Robinson D, Cardozo L. Modern management of genitourinary syndrome of menopause. *Faculty Rev*. 2021;10:25. <https://doi.org/10.12703/r/10-25>
118. Faubion SS, Larkin LC, Stuenkel CA, Bachmann GA, Chism LA, Kagan R, et al. Management of genitourinary syndrome of menopause in women with or at high risk for breast cancer: consensus recommendations from The North American Menopause Society and The International Society for the Study of Women's Sexual Health. *Menopause*. 2018;25(6):596–608. <https://doi.org/10.1097/GME.0000000000001121>
120. Long CY, Liu CM, Hsu SC, Wu CH, Wang CL, Tsai EM. A randomized comparative study of the effects of oral and topical estrogen therapy on the vaginal vascularization and sexual function in hysterectomized postmenopausal women. *Menopause*. 2006;13(6):737–43. <https://doi.org/10.1097/01.gme.0000227401.98933.0b>
121. Alperin M, Burnett L, Lukacz E, Brubaker L. The mysteries of menopause and urogynecologic health: clinical and scientific gaps. *Menopause*. 2019;26(1):103–111. <https://doi.org/10.1097/GME.0000000000001209>
122. Weidlinger S, Schmutz C, Janka H, Gruetter C, Stute P. Sustainability of vaginal estrogens for genitourinary syndrome of menopause - a systematic review. *Climacteric*. 2021;24(6):551–559. <https://doi.org/10.1080/13697137.2021.1891218>
123. Phillips NA, Bachmann GA. The genitourinary syndrome of menopause. *Menopause*. 2021;28:579–88. <https://doi.org/10.1097/GME.0000000000001728>
124. Palacios S, Castelo-Branco C, Currie H, Mijatovic V, Nappi RE, Simon J, et al. Update on management of genitourinary syndrome of menopause: A practical guide. *Maturitas*. 2015;82(3):308–13. <https://doi.org/10.1016/j.maturitas.2015.07.020>
125. Knight C, Logan V, Fenlon D. A systematic review of laser therapy for vulvovaginal atrophy/genitourinary syndrome of menopause in breast cancer survivors. *Ecanermediscience*. 2019;13:988. <https://doi.org/10.3332/ecancer.2019.988>
126. Lethaby A, Ayeleke RO, Roberts H. Local oestrogen for vaginal atrophy in postmenopausal women. *Cochrane Database Syst Rev*. 2016;2016(8):CD001500. <https://doi.org/10.1002/14651858.CD001500.pub3>
127. Danan ER, Diem S, Sowerby C, Ullman K, Ensrud K, Landsteiner A, et al. Genitourinary Syndrome of Menopause: A Systematic Review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2024. <https://doi.org/10.23970/ahrqepccer272>
128. Aarshageetha P, Janci PRR, Tharani ND. Role of Alternate Therapies to Improve the Quality of Life in Menopausal Women: A Systematic Review. *J Mid-life Health*. 2023;14(3):153–158. https://doi.org/10.4103/jmh.jmh_222_22
129. Dubé-Zinatelli E, Cappelletti L, Ismail N. Vaginal Microbiome: Environmental, Biological, and Racial Influences on Gynecological Health Across the Lifespan. *Am J Reprod Immunol*. 2024;92(6):e70026. <https://doi.org/10.1111/aji.70026>
130. Stabile G, Topouzova GA, De Seta F. The role of microbiota in the management of genitourinary syndrome of menopause. *Climacteric*. 2023;26(4):353–360. <https://doi.org/10.1080/13697137.2023.2223923>
131. Sarmiento ACA, Kamilos MF, Costa APF, Vieira-Baptista P, Eleutério J Jr, Gonçalves AK. Use of Moisturizers and Lubricants for Vulvovaginal Atrophy. *Front Reprod Health*. 2021;3:781353. <https://doi.org/10.3389/frph.2021.781353>
132. Kennedy CE, Yeh PT, Li J, Gonsalves L, Narasimhan M. Lubricants for the promotion of sexual health and well-being: a systematic review. *Sex Reprod Health Matters*. 2022;29(3):2044198. <https://doi.org/10.1080/26410397.2022.2044198>
133. Faubion SS, Sood R, Kapoor E. Genitourinary Syndrome of Menopause: Management Strategies for the Clinician. *Mayo Clin Proc*. 2017;92:1842–9. <https://doi.org/10.1016/j.mayocp.2017.08.019>
134. Pitsouni E, Grigoriadis T, Douskos A, Kyriakidou M, Falagas ME, Athanasiou S. Efficacy of vaginal therapies alternative to vaginal estrogens on sexual function and orgasm of menopausal women: A systematic review and meta-analysis of randomized controlled trials. *Eur J Obstet Gynecol Reprod Biol*. 2018;229:45–56. <https://doi.org/10.1016/j.ejogrb.2018.08.008>
135. Mitchell CM, Reed SD, Diem S, Larson JC, Newton KM, Ensrud KE, et al. Efficacy of Vaginal Estradiol or Vaginal Moisturizer vs Placebo for Treating Postmenopausal Vulvovaginal Symptoms: A Randomized Clinical Trial. *JAMA Intern Med*. 2018;178(5):681–690. <https://doi.org/10.1001/jamainternmed.2018.0116>
136. World Health Organization, United Nations Population Fund. WHO/UNFPA specification for plain lubricants. *WHO Drug Inf*. 2019;33(4):645–654.
137. Shim S, Park KM, Chung YJ, Kim MR. Updates on Therapeutic Alternatives for Genitourinary Syndrome of Menopause: Hormonal and Non-Hormonal Managements. *J Menopausal Med*. 2021;27(1):1–7. <https://doi.org/10.6118/jmm.20034>

138. Buzzaccarini G, Marin L, Noventa M, Vitagliano A, Riva A, Dessole F, et al. Hyaluronic acid in vulvar and vaginal administration: evidence from a literature systematic review. *Climacteric*. 2021;24(6):560-571. <https://doi.org/10.1080/13697137.2021.1898580>
139. De Seta F, Caruso S, Di Lorenzo G, Romano F, Mirandola M, Nappi RE. Efficacy and safety of a new vaginal gel for the treatment of symptoms associated with vulvovaginal atrophy in postmenopausal women: A double-blind randomized placebo-controlled study. *Maturitas*. 2021;147:34-40. <https://doi.org/10.1016/j.maturitas.2021.03.002>
140. Artym J, Zimecki M. Colostrum and Lactoferrin Protect against Side Effects of Therapy with Antibiotics, Anti-inflammatory Drugs and Steroids, and Psychophysical Stress: A Comprehensive Review. *Biomedicines*. 2023;11(4):1015. <https://doi.org/10.3390/biomedicines11041015>
141. Vailati S, Melloni E, Riscassi E, Behr Roussel D, Sardina M. Evaluation of the effects of a new intravaginal gel, containing purified bovine colostrum, on vaginal blood flow and vaginal atrophy in ovariectomized rat. *Sex Med*. 2013;1(2):35-43. <https://doi.org/10.1002/sm2.8>
142. Farahat RA, Salamah HM, Mahmoud A, Hamouda E, Hashemy M, Hamouda H, et al. The efficacy of oxytocin gel in postmenopausal women with vaginal atrophy: an updated systematic review and meta-analysis. *BMC Womens Health*. 2023;23(1):494. <https://doi.org/10.1186/s12905-023-02645-0>
143. Albertazzi P, Pansini F, Bottazzi M, Bonaccorsi G, De Aloysio D, Morton MS. Dietary soy supplementation and phytoestrogen levels. *Obstet Gynecol*. 1999;94(2):229-31. [https://doi.org/10.1016/s0029-7844\(99\)00275-6](https://doi.org/10.1016/s0029-7844(99)00275-6)
144. Lima SM, Bernardo BF, Yamada SS, Reis BF, da Silva GM, Galvao MA. Effects of Glycine max (L.) Merr. soy isoflavone vaginal gel on epithelium morphology and estrogen receptor expression in postmenopausal women: a 12-week, randomized, double-blind, placebo-controlled trial. *Maturitas*. 2014;78(3):205-11. <https://doi.org/10.1016/j.maturitas.2014.04.007>
145. Unfer V, Casini ML, Costabile L, Mignosa M, Gerli S, Di Renzo GC. Endometrial effects of long-term treatment with phytoestrogens: a randomized, double-blind, placebo-controlled study. *Fertil Steril*. 2004;82(1):145-8. <https://doi.org/10.1016/j.fertnstert.2003.11.041>
146. Parnan Emamverdikhani A, Golmakani N, Tabassi SA, Hassanzadeh M, Sharifi N, Shakeri MT. A survey of the therapeutic effects of Vitamin E suppositories on vaginal atrophy in postmenopausal women. *Iran J Nurs Midwifery Res*. 2016;21(5):475-481. <https://doi.org/10.4103/1735-9066.193393>
147. Porterfield L, Wur N, Delgado ZS, Syed F, Song A, Weller SC. Vaginal Vitamin E for Treatment of Genitourinary Syndrome of Menopause: A Systematic Review of Randomized Controlled Trials. *J Menopausal Med*. 2022;28(1):9-16. <https://doi.org/10.6118/jmm.21028>
148. Riazi H, Ghazanfarpour M, Taebi M, Abdollahian S. Effect of Vitamin D on the Vaginal Health of Menopausal Women: A Systematic Review. *J Menopausal Med*. 2019;25(3):109-116. <https://doi.org/10.6118/jmm.19194>
149. Li D, Zhang T, Yang H, Yang W, Zhang C, Gao G. Effect of Vitamin D on the Proliferation and Barrier of Atrophic Vaginal Epithelial Cells. *Molecules*. 2023;28(18):6605. <https://doi.org/10.3390/molecules28186605>
150. Yildirim B, Kaleli B, Dincan E, Topuz O. The effects of postmenopausal Vitamin D treatment on vaginal atrophy. *Maturitas*. 2004;49(4):334-7. <https://doi.org/10.1016/j.maturitas.2004.02.008>
151. Kamronrithisorn T, Manonai J, Vallibhakara SA, Sophonsritsuk A, Vallibhakara O. Effect of Vitamin D Supplement on Vulvovaginal Atrophy of the Menopause. *Nutrients*. 2020;12(9):2876. <https://doi.org/10.3390/nu12092876>
152. Robinson D, Flint R, Veit-Rubin N, Araklitis G, Cardozo L. Is there enough evidence to justify the use of laser and other thermal therapies in female lower urinary tract dysfunction? Report from the ICI-RS 2019. *Neurourol Urodyn*. 2020;39 Suppl 3:S140-S147. <https://doi.org/10.1002/nau.24298>
153. Mortensen OE, Christensen SE, Lokkegaard E. The evidence behind the use of LASER for genitourinary syndrome of menopause, vulvovaginal atrophy, urinary incontinence and lichen sclerosis: A state-of-the-art review. *Acta Obstet Gynecol Scand*. 2022;101(6):657-692. <https://doi.org/10.1111/aogs.14353>
154. Gambacciani M, Palacios S. Laser therapy for the restoration of vaginal function. *Maturitas*. 2017;99:10-15. <https://doi.org/10.1016/j.maturitas.2017.01.012>
155. Blaganje M, Šćepanović D, Žgur L, Verdenik I, Pajk F, Lukanović A. Non-ablative Er:YAG laser therapy effect on stress urinary incontinence related to quality of life and sexual function: A randomized controlled trial. *Eur J Obstet Gynecol Reprod Biol*. 2018;224:153-158. <https://doi.org/10.1016/j.ejogrb.2018.03.038>
156. Zhang C, Chen Y, Liu S, Chen J, Shen H, Luo D. Effect of vaginal energy-based treatment on female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials. *World J Urol*. 2023;41(2):405-411. <https://doi.org/10.1007/s00345-022-04247-1>
157. Athanasiou S, Pitsouni E, Douskos A, Salvatore S, Loutradis D, Grigoriadis T. Intravaginal energy-based devices and sexual health of female cancer survivors: a systematic review and meta-analysis. *Lasers Med Sci*. 2020;35(1):1-11. <https://doi.org/10.1007/s10103-019-02855-9>
158. Paraiso MFR, Ferrando CA, Sokol ER, Rardin CR, Matthews CA, Karram MM, et al. A randomized clinical trial comparing vaginal laser therapy to vaginal estrogen therapy in women with genitourinary syndrome of menopause: The VeLVET Trial. *Menopause*. 2020;27(1):50-56. <https://doi.org/10.1097/GME.0000000000001416>
159. Lőczi LL, Vleskő G, Éliás M, Turan C, Kajtár P, Tóth R, et al. Effect of Vaginal Laser and Topical Therapies on Vulvovaginal Atrophy Symptoms in Breast Cancer Patients: A Systematic Review and Meta-Analysis. *J Clin Med*. 2024;13(20):6131. <https://doi.org/10.3390/jcm13206131>
160. Salvatore S, Ruffolo AF, Phillips C, Athanasiou S, Cardozo L, Serati M, et al. Vaginal laser therapy for GSM/VVA: where we stand now - a review by the EUGA Working Group on Laser. *Climacteric*. 2023;26(4):336-352. <https://doi.org/10.1080/13697137.2023.2225766>
161. Food and Drug Administration. Statement from FDA Commissioner Scott Gottlieb, M.D., on efforts to safeguard women's health from deceptive health claims and significant risks related to devices marketed for use in medical procedures for "vaginal rejuvenation". FDA website. 2018 Jul 30. <https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-efforts-safeguard-womens-health-deceptive-health-claims>
162. Gordon C, Gonzales S, Krychman ML. Rethinking the techno vagina: a case series of patient complications following vaginal laser treatment for atrophy. *Menopause*. 2019;26(4):423-427. <https://doi.org/10.1097/gme.0000000000001293>
163. Moccia F, Pentangelo P, Ceccaroni A, Raffone A, Losco L, Alfano C. Injection Treatments for Vulvovaginal Atrophy of Menopause: A Systematic Review. *Aesthetic Plast Surg*. 2023;47(6):2788-2799. <https://doi.org/10.1007/s00266-023-03550-5>
164. Mercier J, Dumoulin C, Carrier-Noreau G. Pelvic floor muscle rehabilitation for genitourinary syndrome of menopause: why, how and when? *Climacteric*. 2023;26(4):302-308. <https://doi.org/10.1080/13697137.2023.2194527>
165. Krause M, Wheeler TL 2nd, Snyder TE, Richter HE. Local Effects of Vaginally Administered Estrogen Therapy: A Review. *J Pelvic Med Surg*. 2009;15(3):105-114. <https://doi.org/10.1097/SPV.0b013e3181ab4804>

166. Ali A, Iftikhar A, Tabassum M, Imran R, Shaid MU, Hashmi MR, et al. Efficacy and Safety of Intravaginal Estrogen in the Treatment of Atrophic Vaginitis: A Systematic Review and Meta-Analysis. *J Menopausal Med.* 2024;30(2):88-103. <https://doi.org/10.6118/jmm.23037>
167. Goldstein I. Recognizing and treating urogenital atrophy in postmenopausal women. *J Womens Health (Larchmt).* 2010;19(3):425-432. <https://doi.org/10.1089/jwh.2009.1384>
168. Naumova I, Castelo-Branco C. Current treatment options for postmenopausal vaginal atrophy. *Int J Womens Health.* 2018;10:387-395. <https://doi.org/10.2147/IJWH.S158913>
169. Willhite LA, O'Connell MB. Urogenital atrophy: prevention and treatment. *Pharmacotherapy.* 2001;21(4):464-480. <https://doi.org/10.1592/phco.21.5.464.34486>
170. Santen RJ. Vaginal administration of estradiol: effects of dose, preparation and timing on plasma estradiol levels. *Climacteric.* 2015;18(2):121-134. <https://doi.org/10.3109/13697137.2014.947254>
171. Notelovitz M, Funk S, Nanavati N, Mazzeo M. Estradiol absorption from vaginal tablets in postmenopausal women. *Obstet Gynecol.* 2002;99(4):556-562. <https://doi.org/10.1097/00006250-200204000-00008>
172. Derzko CM, Rich S, Panay N. Does age at the start of treatment for vaginal atrophy predict response to vaginal estrogen therapy? Post hoc analysis of data from a randomized clinical trial involving 205 women treated with 10 µg estradiol vaginal tablets. *Menopause.* 2020;28(2):113-118. <https://doi.org/10.1097/gme.0000000000001666>
173. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric.* 2005;8 Suppl 1:3-63. <https://doi.org/10.1080/13697130500148875>
174. Santen RJ, Mirkin S, Bernick B, Constantine GD. Systemic estradiol levels with low-dose vaginal estrogens. *Menopause.* 2020;27(3):361-370. <https://doi.org/10.1097/GME.0000000000001463>
175. Krause M, Wheeler TL 2nd, Richter HE, Snyder TE. Systemic effects of vaginally administered estrogen therapy: a review. *Female Pelvic Med Reconstr Surg.* 2010;16(3):188-95. <https://doi.org/10.1097/SPV.0b013e3181d7e86e>
176. Kolokythas A, Betschart C, Wunder D, Janka H, Stute P. Impact of vaginal estradiol on serum hormone levels: a systematic review. *Climacteric.* 2024;27(2):137-153. <https://doi.org/10.1080/13697137.2023.2287624>
177. Griesser H, Skonietzki S, Fischer T, Fielder K, Suesskind M. Low dose estriol pessaries for the treatment of vaginal atrophy: A double-blind placebo-controlled trial investigating the efficacy of pessaries containing 0.2 mg and 0.03 mg estriol. *Maturitas.* 2012;71(4):360-368. <https://doi.org/10.1016/j.maturitas.2011.12.022>
178. Biehl C, Plotsker O, Mirkin S. A systematic review of the efficacy and safety of vaginal estrogen products for the treatment of genitourinary syndrome of menopause. *Menopause.* 2019;26(4):431-453. <https://doi.org/10.1097/GME.0000000000001221>
179. Electronic Medicines Compendium. Vagifem 10 micrograms vaginal tablets. <https://www.medicines.org.uk/emc/product/5719/smpc>
180. Jaisamrarn U, Triratanachai S, Chaikittisilpa S, Grob P, Prasauskas V, Taechakraichana N. Ultra-low-dose estriol and lactobacilli in the local treatment of postmenopausal vaginal atrophy. *Climacteric.* 2013;16(3):347-355. <https://doi.org/10.3109/13697137.2013.769097>
181. Donders G, Neven P, Moegle M, Lintermans A, Bellen G, Prasauskas V, et al. Ultra-low-dose estriol and Lactobacillus acidophilus vaginal tablets (Gyn flor®) for vaginal atrophy in postmenopausal breast cancer patients on aromatase inhibitors: pharmacokinetic, safety, and efficacy phase I clinical study. *Breast Cancer Res Treat.* 2014;145(2):371-379. <https://doi.org/10.1007/s10549-014-2930-x>
182. Mueck AO, Ruan X, Prasauskas V, Grob P, Ortmann O. Treatment of vaginal atrophy with estriol and lactobacilli combination: a clinical review. *Climacteric.* 2018;21(2):140-147. <https://doi.org/10.1080/13697137.2017.1421923>
183. Villa P, Tagliaferri V, Amar ID, Cipolla C, Ingravalle F, Scambia G, et al. Local ultra-low-dose estriol gel treatment of vulvo-vaginal atrophy: efficacy and safety of long-term treatment. *Gynecol Endocrinol.* 2020;36(6):535-539. <https://doi.org/10.1080/09513590.2019.1702016>
184. Vooijs GP, Geurts TB. Review of the endometrial safety during intravaginal treatment with estriol. *Eur J Obstet Gynecol Reprod Biol.* 1995;62(1):101-106. [https://doi.org/10.1016/0301-2115\(95\)02170-c](https://doi.org/10.1016/0301-2115(95)02170-c)
185. Punnonen R, Lukola A. High-affinity binding of estrone, estradiol and estriol in human cervical myometrium and cervical and vaginal epithelium. *J Endocrinol Invest.* 1982;5(4):203-207. <https://doi.org/10.1007/bf03348324>
186. Gaspard U, Taziaux M, Jost M, Coelingh Bennink HJT, Utian WH, Lobo RA, et al. A multicenter, randomized, placebo-controlled study to select the minimum effective dose of estriol in postmenopausal participants (E4Relief): part 2-vaginal cytology, genitourinary syndrome of menopause, and health-related quality of life. *Menopause.* 2023;30(5):480-489. <https://doi.org/10.1097/GME.0000000000002167>
187. Pitkin J. BMS - Consensus statement. *Post Reprod Health.* 2018;24(3):133-138. <https://doi.org/10.1177/2053369118795349>
188. Hurst BS, Jones AI, Elliot M, Marshburn PB, Matthews ML. Absorption of vaginal estrogen cream during sexual intercourse: a prospective, randomized, controlled trial. *J Reprod Med.* 2008;53(1):29-32. PMID: 18251358
189. Palacios S. Sequential treatment in vulvovaginal atrophy. *Climacteric.* 2023;26:292-5. <https://doi.org/10.1080/13697137.2023.2197588>
190. Crandall CJ, Hovey KM, Andrews CA, Chlebowski RT, Stefanick ML, Lane DS, et al. Breast cancer, endometrial cancer, and cardiovascular events in participants who used vaginal estrogen in the Women's Health Initiative Observational Study. *Menopause.* 2018;25(1):11-20. <https://doi.org/10.1097/gme.0000000000000956>
191. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ.* 2019;364:k4810. <https://doi.org/10.1136/bmj.k4810>
192. Crandall CJ, Diamant A, Santoro N. Safety of vaginal estrogens: a systematic review. *Menopause.* 2020;27(3):339-360. <https://doi.org/10.1097/GME.0000000000001468>
193. Mikkola TS, Tuomikoski P, Lyytinen H, Korhonen P, Hoti F, Vattulainen P, et al. Vaginal estradiol use and the risk for cardiovascular mortality. *Hum Reprod.* 2016;31(4):804-809. <https://doi.org/10.1093/humrep/dew014>
194. Constantine GD, Graham S, Lapane K, Ohleth K, Bernick B, Liu J, et al. Endometrial safety of low-dose vaginal estrogens in menopausal women: a systematic evidence review. *Menopause.* 2019;26(7):800-807. <https://doi.org/10.1097/GME.0000000000001315>
195. Haddadan KG, Eckert-Lind C, Meaidi A, Johansen ND, Hojbjerg Lassen MC, Skarup KG, et al. Recurrent Ischemic Stroke and Vaginal Estradiol in Women With Prior Ischemic Stroke: A Nationwide Nested Case-Control Study. *Stroke.* 2025;56(10):2888-2894. <https://doi.org/10.1161/strokeaha.125.050986>

196. Rueda C, Osorio AM, Avellaneda AC, Pinzón CE, Restrepo OI. The efficacy and safety of estriol to treat vulvovaginal atrophy in postmenopausal women: a systematic literature review. *Climacteric*. 2017;20(4):321-330. <https://doi.org/10.1080/13697137.2017.1329291>
197. Bhupathiraju SN, Grodstein F, Stampfer MJ, Willett WC, Crandall CJ, Shifren JL, et al. Vaginal estrogen use and chronic disease risk in the Nurses' Health Study. *Menopause*. 2019;26(6):603-610. <https://doi.org/10.1097/gme.0000000000001284>
198. Overview | Menopause: identification and management | Guidance | NICE [Internet]. NICE; 2015 [cited 2026 Feb 12]. Available from: <https://www.nice.org.uk/guidance/ng23>
199. Collaborative Group on Hormonal Factors in Breast Cancer. Type and timing of menopausal hormone therapy and breast cancer risk: individual participant meta-analysis of the worldwide epidemiological evidence. *The Lancet*. 2019;394:1159-68. [https://doi.org/10.1016/s0140-6736\(19\)31709-x](https://doi.org/10.1016/s0140-6736(19)31709-x)
200. Tzingounis VA, Aksu MF, Greenblatt RB. Estriol in the Management of the Menopause. *JAMA*. 1978 Apr 21;239(16):1638-41. <https://doi.org/10.1001/jama.1978.03280430054016>
201. Kloosterboer HJ. Tibolone: a steroid with a tissue-specific mode of action. *The Journal of Steroid Biochemistry and Molecular Biology*. 2001;76:231-8. [https://doi.org/10.1016/s0960-0760\(01\)00044-9](https://doi.org/10.1016/s0960-0760(01)00044-9)
202. Simon JA, Altomare C, Cort S, Jiang W, Pinkerton JV. Overall Safety of Ospemifene in Postmenopausal Women from Placebo-Controlled Phase 2 and 3 Trials. *Journal of Women's Health*. 2018;27:14-23. <https://doi.org/10.1089/jwh.2017.6385>
203. Joint Formulary Committee. *British National Formulary 79*. London: Pharmaceutical Press; 2020.
204. Alvisi S, Baldassarre M, Martelli V, Gava G, Seracchioli R, Meriggiola MC. Effects of ospemifene on vaginal epithelium of post-menopausal women. *Gynecological Endocrinology*. 2017;33:946-50. <https://doi.org/10.1080/09513590.2017.1332589>
205. Goldstein SW, Winter AG, Goldstein I. Improvements to the Vulva, Vestibule, Urethral Meatus, and Vagina in Women Treated With Ospemifene for Moderate to Severe Dyspareunia: A Prospective Vulvoscopic Pilot Study. *Sexual Medicine*. 2018;6:154-61. <https://doi.org/10.1016/j.esxm.2018.03.002>
206. Nordstrom BL, Cai B, De Gregorio F, Ban L, Fraeman KH, Yoshida Y, et al. Risk of venous thromboembolism among women receiving ospemifene: a comparative observational study. *Therapeutic Advances in Drug Safety*. 2022;13. <https://doi.org/10.1177/20420986221135931>
207. Cai B, Simon J, Villa P, Biglia N, Panay N, Djumaeva S, et al. No increase in incidence or risk of recurrence of breast cancer in ospemifene-treated patients with vulvovaginal atrophy (VVA). *Maturitas*. 2020;142:38-44. <https://doi.org/10.1016/j.maturitas.2020.06.021>
208. Sánchez-Borrego R, de Diego Pérez de Zabalza MV, Alfageme Gullón MJ, Alija Castrillo ML, Sánchez Prieto M, Palacios S, et al. Satisfaction and medication adherence in women with vulvovaginal atrophy: the Creta. *Climacteric*. 2023;26:437-44. <https://doi.org/10.1080/13697137.2023.2190508>
209. Bell RJ, Rizvi F, Islam RM, Davis SR. A systematic review of intravaginal testosterone for the treatment of vulvovaginal atrophy. *Menopause*. 2018;25:704-9. <https://doi.org/10.1097/gme.0000000000001052>
210. Labrie F. Intracrinology: The New Science of Sex Steroid Physiology in Women. In: *Pre-Menopause, Menopause and Beyond*. Cham: Springer International Publishing; 2018. p. 3-15. https://doi.org/10.1007/978-3-319-63540-8_1
211. Labrie F, Archer DF, Koltun W, Vachon A, Young D, Frenette L, et al. Efficacy of intravaginal dehydroepiandrosterone (DHEA) on moderate to severe dyspareunia and vaginal dryness, symptoms of vulvovaginal atrophy, and of the genitourinary syndrome of menopause. *Menopause*. 2016;23:243-56. <https://doi.org/10.1097/gme.0000000000000571>
212. Laupland KB, Ross T, Pitout JDD, Church DL, Gregson DB. Community-onset Urinary Tract Infections: A Population-based Assessment. *Infection*. 2007;35:150-3. <https://doi.org/10.1007/s15010-007-6180-2>
213. Aydin A, Ahmed K, Zaman I, Khan MS, Dasgupta P. Recurrent Urinary Tract Infections in Women. *Obstetrical & Gynecological Survey*. 2015;70:621-2. <https://doi.org/10.1097/ogx.0000000000000246>
214. Doumouchtsis SK, de Tayrac R, Lee J, Daly O, Melendez-Munoz J, Lindo FM, et al. An International Continence Society (ICS)/ International Urogynecological Association (IUGA) joint report on the terminology for the assessment and management of obstetric pelvic floor disorders. *Continence*. 2022;4:100502. <https://doi.org/10.1016/j.cont.2022.100502>
215. Hooton TM. Recurrent urinary tract infection in women. *International Journal of Antimicrobial Agents*. 2001;17:259-68. [https://doi.org/10.1016/s0924-8579\(00\)00350-2](https://doi.org/10.1016/s0924-8579(00)00350-2)
216. Swatesutipun V. Can recurrent UTIs in women be cured? Review article. *Continence Reports*. 2023;5:100021. <https://doi.org/10.1016/j.contre.2023.100021>
217. Nicolle LE, Bradley S, Colgan R, Rice JC, Schaeffer A, Hooton TM. Infectious Diseases Society of America Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults. *Clinical Infectious Diseases*. 2005;40:643-54. <https://doi.org/10.1086/427507>
218. Bono, Michael J, et al. "Uncomplicated Urinary Tract Infections." National Library of Medicine, StatPearls Publishing, 2025, www.ncbi.nlm.nih.gov/books/NBK470195/.
219. Sabih, Ayan, and Stephen W Leslie. "Complicated Urinary Tract Infections." National Library of Medicine, StatPearls Publishing, 2024, www.ncbi.nlm.nih.gov/books/NBK436013/.
220. Raz R. Urinary Tract Infection in Postmenopausal Women. *Korean Journal of Urology*. 2011;52:801-8. <https://doi.org/10.4111/kju.2011.52.12.801>
221. Marino JM. Genitourinary Syndrome of Menopause. *J Midwifery Womens Health*. 2021 Nov;66(6):729-739. <https://doi.org/10.1111/jmwh.13277>
222. Siddiqui H, Nederbragt AJ, Lagesen K, Jeansson SL, Jakobsen KS. Assessing diversity of the female urine microbiota by high throughput sequencing of 16S rDNA amplicons. *BMC Microbiology*. 2011;11:244. <https://doi.org/10.1186/1471-2180-11-244>
223. Whiteside SA, Razvi H, Dave S, Reid G, Burton JP. The microbiome of the urinary tract—a role beyond infection. *Nature Reviews Urology*. 2015;12:81-90. <https://doi.org/10.1038/nrurol.2014.361>
224. Thomas-White K, Brady M, Wolfe AJ, Mueller ER. The bladder is not sterile: History and current discoveries on the urinary microbiome. *Curr Bladder Dysfunct Rep*. 2016 Mar;11(1):18-24. <https://doi.org/10.1007/s11884-016-0345-8>
225. Srisukho S, Pantasri T, Piyamongkol W, Phongnarisorn C, Morakote N. The experience of genitourinary syndrome of menopause (GSM) among Thai postmenopausal women: the non-reporting issue. *International Urogynecology Journal*. 2019;30:1843-7. <https://doi.org/10.1007/s00192-019-03991-0>
226. Shardell M, Gravitt PE, Burke AE, Ravel J, Brotman RM. Association of Vaginal Microbiota With Signs and Symptoms of the Genitourinary Syndrome of Menopause Across Reproductive Stages. *The Journals of Gerontology: Series A*. 2021;76:1542-50. <https://doi.org/10.1093/gerona/glab120>

227. Bent S, Nallamothu BK, Simel DL, Fihn SD, Saint S. Does This Woman Have an Acute Uncomplicated Urinary Tract Infection? *JAMA*. 2002;287:2701. <https://doi.org/10.1001/jama.287.20.2701>
228. Aggarwal N, Leslie SW. Recurrent Urinary Tract Infections. [Updated 2025 Jan 20]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK557479/>
229. Christmas MM, Iyer S, Daisy C, Maristany S, Letko J, Hickey M. Menopause hormone therapy and urinary symptoms: a systematic review. *Menopause*. 2023;30:672–85. <https://doi.org/10.1097/gme.0000000000002187>
230. Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database of Systematic Reviews*. 2008;(2):CD005131. <https://doi.org/10.1002/14651858.cd005131.pub2>
231. Dueñas-García OF, Sullivan G, Hall CD, Flynn MK, O'Dell K. Pharmacological Agents to Decrease New Episodes of Recurrent Lower Urinary Tract Infections in Postmenopausal Women. A Systematic Review. *Female Pelvic Medicine & Reconstructive Surgery*. 2016;22:63–9. <https://doi.org/10.1097/spv.0000000000000244>
232. Williams G, Stothart CI, Hahn D, Stephens JH, Craig JC, Hodson EM. Cranberries for preventing urinary tract infections. *Cochrane Database of Systematic Reviews*. 2023;2023. <https://doi.org/10.1002/14651858.cd001321.pub7>
233. Lenger SM, Chu CM, Ghetti C, Durkin MJ, Jennings Z, Wan F, et al. d-Mannose for Recurrent Urinary Tract Infection Prevention in Postmenopausal Women Using Vaginal Estrogen: A Randomized Controlled Trial. *Urogynecology*. 2022. <https://doi.org/10.1097/spv.0000000000001270>
234. Pugliese D, Acampora A, Porreca A, Schips L, Cindolo L. Effectiveness of a novel oral combination of D-Mannose, pomegranate extract, prebiotics and probiotics in the treatment of acute cystitis in women. *Archivio Italiano Di Urologia e Andrologia*. 2020;92:34–8. <https://doi.org/10.4081/aiua.2020.1.34>
235. Ahmed H, Davies F, Francis N, Farewell D, Butler C, Paranjothy S. Long-term antibiotics for prevention of recurrent urinary tract infection in older adults: systematic review and meta-analysis of randomised trials. *BMJ Open*. 2017;7:e015233. <https://doi.org/10.1136/bmjopen-2016-015233>
236. Query H, Carroll A, Klausner AP, Burkett LS. A Review for Clinical Practice in the Treatment and Prevention of Recurrent Urinary Tract Infections in Women over Age 65. *Journal of Women's Health*. 2024;33:1735–42. <https://doi.org/10.1089/jwh.2023.0987>
237. Russo E, Caretto M, Giannini A, Bitzer J, Cano A, Ceausu I, et al. Management of urinary incontinence in postmenopausal women: An EMAS clinical guide. *Maturitas*. 2021;143:223–30. <https://doi.org/10.1016/j.maturitas.2020.09.005>
238. Bresee C, Dubina ED, Khan AA, Sevilla C, Grant D, Eilber KS, Anger JT. Prevalence and correlates of urinary incontinence among older community-dwelling women. *Female Pelvic Medicine and Reconstructive Surgery*. 2014;20:328–33. <https://doi.org/10.1097/spv.0000000000000093>
239. Milsom I, Abrams P, Cardozo L, Roberts RG, Th off J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU International*. 2001;87:760–6. <https://doi.org/10.1046/j.1464-410x.2001.02228.x>
240. Tran L, Puckett Y. Urinary Incontinence [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2026 Feb 12]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK559095/>
241. Barnaś E, Barańska E, Gawlik B, Zych B. Factors most significantly affecting quality of life in women with urinary incontinence. *Hygeia Public Health*. 2015;50(4):643–8.
242. Patel UJ, Godecker AL, Giles DL, Brown HW. Updated Prevalence of Urinary Incontinence in Women: 2015–2018 National Population-Based Survey Data. *Female Pelvic Medicine and Reconstructive Surgery*. 2022;28:181–7. <https://doi.org/10.1097/spv.0000000000001135>
243. Huang P, Luo K, Wang C, Guo D, Wang S, Jiang Y, Huang W, Zhang W, Ding M, Wang J. Urinary Incontinence Is Associated With Increased All-Cause Mortality in Older Nursing Home Residents: A Meta-Analysis. *Journal of Nursing Scholarship*. 2021;53:561–7. <https://doi.org/10.1111/jnu.12666>
244. Sinha S, Agarwal M, Vasudeva P, Khattar N, Madduri VS, Yande S, et al. The Urological Society of India guidelines for the evaluation and management of nonneurogenic urinary incontinence in adults (executive summary). *Indian Journal of Urology*. 2019;35:185. https://doi.org/10.4103/iju.iju_125_19
245. Garg P, Goyal LD, Goyal S, Verma M. Utility of opportunistic screening to assess the impact of urinary incontinence on quality of life and barriers to seeking treatment among women attending a tertiary healthcare centre in North India. *BMC Urology*. 2024;24. <https://doi.org/10.1186/s12894-024-01434-7>
246. Malinauskas AP, Bressan EFM, de Melo AMZRP, Brasil CA, Lordêlo P, Torelli L. Efficacy of pelvic floor physiotherapy intervention for stress urinary incontinence in postmenopausal women: systematic review. *Archives of Gynecology and Obstetrics*. 2022;308:13–24. <https://doi.org/10.1007/s00404-022-06693-z>
247. Sultana A, Najeeba AGF, Rahman K, Saeedi R, Khanam M. Mixed Urinary Incontinence (MUI) in Women: From Evidence to Clinical Practice. *Journal of Health Science Research*. 2021:39–50. <https://doi.org/10.7324/jhsr/2020/25044>
248. Khandelwal C, Kistler C. Diagnosis of urinary incontinence. *Am Fam Physician*. 2013 Apr 15;87(8):543–50. PMID: 23668444.
249. Castillo PA, Espallat-Rijo LM, Davila GW. Outcome measures and definition of cure in female stress urinary incontinence surgery: a survey of recent publications. *International Urogynecology Journal*. 2010;21:343–8. <https://doi.org/10.1007/s00192-009-1032-5>
250. Zimmern P, Kobashi K, Lemack G. Outcome measure for stress urinary incontinence treatment (OMIT): Results of two society of urodynamics and female urology (SUFU) surveys. *Neurourology and Urodynamics*. 2010;29:715–8. <https://doi.org/10.1002/nau.20840>
251. Pereira LC do R, Silva JP da, Lima CRO de P, Ferreira CWS. Prevalence, knowledge, and factors associated with urinary incontinence in female students of a physical therapy undergraduate course.
252. Fisioterapia e Pesquisa. 2022;29:230–8. <https://doi.org/10.1590/1809-2950/19022929032022enKrhutJ>, Zachoval R, Smith PP, Rosier PFWM, Valansky L, Martan A, et al. Pad weight testing in the evaluation of urinary incontinence. *Neurourology and Urodynamics*. 2013;33:507–10. <https://doi.org/10.1002/nau.22436>
253. Park J, Chang Y, Kim JH, Choi HR, Kwon R, Lim G, et al. Menopausal stages and overactive bladder symptoms in middle-aged women: A cross-sectional study. *BJOG: An International Journal of Obstetrics & Gynaecology*. 2024;131:1805–14. <https://doi.org/10.1111/1471-0528.17912>
254. Gibson W, Hunter KF, Camicioli R, Booth J, Skelton DA, Dumoulin C, et al. The association between lower urinary tract symptoms and falls: Forming a theoretical model for a research agenda. *Neurourology and Urodynamics*. 2017;37:501–9. <https://doi.org/10.1002/nau.23295>
255. Schluter PJ, Askew DA, Jamieson HA, Arnold EP. Urinary and fecal incontinence are independently associated with falls risk among older women and men with complex needs: A national population study. *Neurourology and Urodynamics*. 2020;39:945–53. <https://doi.org/10.1002/nau.24266>
256. Haylen BT, de Ridder D, Freeman RM, Swift SE, Berghmans B, Lee J, et al. An international urogynecological association (IUGA)/international continence society (ICS) joint report on the terminology for female pelvic floor dysfunction. *Neurourology and Urodynamics*. 2009;29:4–20. <https://doi.org/10.1002/nau.20798>

257. Irwin DE, Kopp ZS, Agatep B, Milsom I, Abrams P. Worldwide prevalence estimates of lower urinary tract symptoms, overactive bladder, urinary incontinence and bladder outlet obstruction. *BJU International*. 2011;108:1132–8. <https://doi.org/10.1111/j.1464-410x.2010.09993.x>
258. Milsom I, Abrams P, Cardozo L, Roberts RG, Thuroff J, Wein AJ. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. *BJU Int*. 2001 Jun;87(9):760–6. doi: 10.1046/j.1464-410x.2001.02228.x. Erratum in: *BJU Int* 2001 Nov;88(7):807. PMID: 11412210.
259. Thomas-White KJ, Hilt EE, Fok C, Pearce MM, Mueller ER, Kliethermes S, et al. Incontinence medication response is associated with the female urinary microbiota. *International Urogynecology Journal*. 2015;27:723–33. <https://doi.org/10.1007/s00192-015-2847-x>
260. Al Taweel W, Seyam R. Neurogenic bladder in spinal cord injury patients. *Research and Reports in Urology*. 2015;85. <https://doi.org/10.2147/rru.s29644>
261. Nandy S, Ranganathan S. Urge Incontinence [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 [updated 2022 Sep 19; cited 2026 Feb 12]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK563172/>
262. Aoki Y, Brown HW, Brubaker L, Cornu JN, Daly JO, Cartwright R. Urinary incontinence in women. *Nature Reviews Disease Primers*. 2017;3. <https://doi.org/10.1038/nrdp.2017.42>
263. Reid G, Burton JP. Urinary incontinence: Making sense of the urinary microbiota in clinical urology. *Nature Reviews Urology*. 2016;13:567–8. <https://doi.org/10.1038/nrurol.2016.149>
264. Harris S, Leslie SW, Riggs J. Mixed Urinary Incontinence [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [updated 2024 Jun 8; cited 2026 Feb 12]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK534234/>
265. Azadzoi KM, Pontari M, Vlachiotis J, Siroky MB. Canine bladder blood flow and oxygenation: changes induced by filling, contraction and outlet obstruction. *Journal of Urology*. 1996;155:1459–65. <https://doi.org/10.1097/00005392-199604000-00075>
266. Lo TS, Uy-Patrimonio MC, Kao CC, Chua S, Huang TX, Wu MP. Urodynamics mixed type urinary incontinence with advanced pelvic organ prolapse, management and outcomes. *Scientific Reports*. 2020;10. <https://doi.org/10.1038/s41598-020-58896-7>
267. Abrar S, Mohsin R, Samad A. Female Urinary Incontinence: Frequency, Risk Factors, and Impact on the Quality of Life of Pregnant Pakistani Women. *Pakistan Journal of Medical Sciences*. 2023;39. <https://doi.org/10.12669/pjms.39.3.6944>
268. Lukacz ES, Lawrence JM, Contreras R, Nager CW, Lubner KM. Parity, mode of delivery, and pelvic floor disorders. *Obstetrics & Gynecology*. 2006;107:1253–60. <https://doi.org/10.1097/01.aog.0000218096.54169.34>
269. Subak LL, Richter HE, Hunskaar S. Obesity and urinary incontinence: epidemiology and clinical research update. *Journal of Urology*. 2009;182:S2–7. <https://doi.org/10.1097/ju.0b013e3181bf9cef>
270. Hannestad YS, Lie RT, Rortveit G, Hunskaar S. Familial risk of urinary incontinence in women: population based cross sectional study. *BMJ*. 2004;329:889–91. <https://doi.org/10.1136/bmj.38254.620699.ae>
271. Elia G, Bergman J, Dye TD. Familial incidence of urinary incontinence. *American Journal of Obstetrics and Gynecology*. 2002;187:53–5. <https://doi.org/10.1067/mob.2002.124839>
272. Subak LL, Wing R, West DS, Franklin F, Vittinghoff E, Creasman JM, et al. Weight loss to treat urinary incontinence in overweight and obese women. *New England Journal of Medicine*. 2009;360:481–90. <https://doi.org/10.1056/nejmoa0806375>
273. Rortveit G, Hannestad YS, Daltveit AK, Hunskaar S. Age- and type-dependent effects of parity on urinary incontinence: the Norwegian EPINCONT study. *Obstetrics & Gynecology*. 2001;98:1004–10. <https://doi.org/10.1097/00006250-200112000-00013>
274. Ghoniem G, Stanford E, Kenton K, Achari C, Goldberg R, Mascarenhas T, et al. Evaluation and outcome measures in the treatment of female urinary stress incontinence: International Urogynecological Association (IUGA) guidelines for research and clinical practice. *International Urogynecology Journal*. 2007;19:5–33. <https://doi.org/10.1007/s00192-007-0495-5>
275. Moons KG. Questionnaire to distinguish between stress and urge urinary incontinence. *Annals of Internal Medicine*. 2006;145:934. <https://doi.org/10.7326/0003-4819-145-12-200612190-00016>
276. Lugo T, Leslie SW, Mikes BA, et al. Stress Urinary Incontinence [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [updated 2024 Aug 31; cited 2026 Feb 12]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK539769/>
277. National Institute for Health and Care Excellence. Urinary incontinence and pelvic organ prolapse in women: management (NICE guideline NG123). London: NICE; 2019. Updated 2023. <https://doi.org/10.1111/bju.14763>
278. Russo E, Misasi G, Montt-Guevara MM, Giannini A, Simoncini T. Effects of ospemifene on overactive bladder in postmenopausal women with vulvovaginal atrophy. *Climacteric*. 2023;26:284–8. <https://doi.org/10.1080/13697137.2023.2185002>
279. Cardozo L, Rekers H, Tapp A, Barnick C, Versi E, Stephens D, et al. Oestriol in the treatment of postmenopausal urgency: a multicentre study. *Maturitas*. 1993;18:47–53. [https://doi.org/10.1016/0378-5122\(93\)90028-g](https://doi.org/10.1016/0378-5122(93)90028-g)
280. Grady D, Brown JS, Vittinghoff E, Applegate W, Varner E, Snyder T. Postmenopausal Hormones and Incontinence. *Obstetrics & Gynecology*. 2001;97:116–20. <https://doi.org/10.1097/00006250-200101000-00023>
281. Fantl JA, Bump RC, Robinson D, McClish D, Wyman J. Efficacy of estrogen supplementation in the treatment of urinary incontinence. *Obstetrics & Gynecology*. 1996;88:745–9. [https://doi.org/10.1016/0029-7844\(96\)00281-5](https://doi.org/10.1016/0029-7844(96)00281-5)
282. Steinauer JE, Waetjen LE, Vittinghoff E, Subak LL, Hulley SB, Grady D, et al. Postmenopausal Hormone Therapy. *Obstetrics & Gynecology*. 2005;106:940–5. <https://doi.org/10.1097/01.aog.0000180394.08406.15>
283. EAU Guidelines on Non-neurogenic Female LUTS - INTRODUCTION - Uroweb [Internet]. Available from: <https://uroweb.org/guidelines/non-neurogenic-female-luts>. Accessed on 10/01/2026
284. Chapple CR, Kaplan SA, Mitcheson D, Klecka J, Cummings J, Drogendijk T, et al. Randomized Double-blind, Active-controlled Phase 3 Study to Assess 12-Month Safety and Efficacy of Mirabegron, a β 3-Adrenoceptor Agonist, in Overactive Bladder. *European Urology*. 2013;63:296–305. <https://doi.org/10.1016/j.eururo.2012.10.048>
285. Staskin D, Frankel J, Varano S, Shortino D, Jankowich R, Mudd PN Jr. Once-Daily Vibegron 75 mg for Overactive Bladder: Long-Term Safety and Efficacy from a Double-Blind Extension Study of the International Phase 3 Trial (EMPOWUR). *Journal of Urology*. 2021;205:1421–9. <https://doi.org/10.1097/ju.0000000000001574>
286. Newman DK, Thomas E, Greene H, Haag-Molkenteller C, Varano S. Efficacy and Safety of Vibegron for the Treatment of Overactive Bladder in Women: A Subgroup Analysis From the Double-Blind, Randomized, Controlled EMPOWUR Trial. *Urogynecology*. 2022;29:48–57 <https://doi.org/10.1097/spv.0000000000001258>

QUALITY OF LIFE

Keywords: Quality of life, menopause and perimenopause, menopause hormone therapy, patient-reported outcomes

11

INTRODUCTION

The World Health Organisation (WHO) defines quality of life (QoL) as an individual's perception of their position in life, within the context of their culture and value systems, in which they dwell and in relation to their expectation, purposes, standards, and concerns and in relation to their goals, expectations, purposes, standards, and concerns. QoL is multidimensional, encompassing physical, psychological, social, and environmental domains.¹ QoL as it relates to menopausal women usually refers to health-related quality of life (HRQoL), taking into account a woman's symptoms, but often does not include physical, emotional, or social functioning or limitations. However, menopause is not a disease, and QoL is related to more than health. During perimenopause and beyond, symptoms are often compounded by the effects of ageing.² Across menopause transition (MT) and beyond, women also experience important physical, emotional, and social transitions. For some, irregular cycles and heavy bleeding are particularly distressing and contribute meaningfully to impaired QoL.³ Many women accept MT as a natural life stage;⁴ however, large studies demonstrate that bothersome symptoms are associated with poorer HRQoL and increased healthcare-seeking.² Demographic ageing is accelerating globally. In India, the proportion of older adults is projected to rise from 10.5% (2022) to 20.8% by 2050, with significant implications for health systems, the economy, and social infrastructure.⁵ A 2-year cross-sectional study was conducted among 302 elderly people aged >60 years residing in elder care facilities in Chennai. The QoL was assessed using the World Health Organisation Quality of Life-Brief (WHOQOL-BREF) scale. The physical and psychological domains of QoL were notably low among residents experiencing health problems, social isolation, and a lack of personalised care. Those with high QoL scores had received consistent social support and retained autonomy. The authors concluded that strengthening support systems, formal programmes of organised social activities, and adequate personnel in these facilities will enhance the QoL and provide a more supportive and fulfilling environment for these individuals.⁶ As longevity increases, preserving QoL across the midlife transition becomes a public health priority.

QUALITY OF LIFE SCALES

The World Health Organisation Quality of Life-Brief (WHOQOL-BREF) is a self-reported questionnaire that assesses QoL across four domains: physical health, psychological health, social relationships, and the environment, along with two global items on overall QoL and general health. It contains 26 items scored on a 1–5 Likert scale reflecting the preceding two weeks. The WHOQOL-BREF is available in multiple Indian languages and captures broader QoL beyond symptom severity, including contextual and environmental determinants.¹

36-Item Short Form Survey

World Health Organisation Quality of Life-Brief The 36-Item Short Form Survey (SF-36) is a widely used, validated measure of HRQoL, comprising 36 items across eight domains (physical functioning, role limitations due to physical health, bodily pain, general health, vitality, social functioning, role limitations due to emotional problems, and mental health).

It also provides summary scores for the physical and mental components and is sensitive to clinical differences and changes, such as pain and role limitations.⁷ A validated Hindi version has been used to assess QoL in North Indian populations.⁸ Convergent validity between SF-36 and WHOQOL-BREF has been demonstrated in older adults; in general, SF-36 captures health status well, while WHOQOL-BREF better reflects broader well-being and contextual factors.⁹

Scales to Assess Menopause Quality of Life

Menopause Rating Scale: The Menopause Rating Scale (MRS) is a menopause-specific symptom scale comprising 11 symptoms across three domains: somato-vegetative, psychological, and urogenital. It is commonly used to quantify symptom burden and monitor response to interventions.¹⁰

Menopause-Specific Quality of Life: The Menopause-Specific Quality of Life (MENQOL) is a tool developed in 1996 for perimenopausal and postmenopausal women. It includes 29 items across four domains: vasomotor (3), psychosocial (7), physical (16), and sexual (3), assessing symptom presence and the degree of bother over the previous month.¹¹ MENQOL is particularly useful when treatment decisions are driven by symptom-related impairment in daily functioning.

Utian Quality of Life Scale: The Utian Quality of Life (UQoL) Scale quantifies a broader sense of well-being rather than solely symptom severity. It comprises 23 items across four domains: occupational, health, emotional, and sexual, with a total score range of 23–161 (higher scores indicate better QoL).¹²

Cervantes Scale: It covers Menopause and health, Psychological, Sexuality, and couple relationship specific for menopause, comprising 31 items.¹³

MenoScale: The MenoScale is a newer digital tool designed to capture the number and impact of menopausal symptoms in a single composite score (0–100) based on ratings of 20 symptoms over the past week. Higher scores reflect greater symptom burden and a greater impact on QoL.¹⁴ Early validation suggests higher average scores during perimenopause than postmenopause and signals the potential to track symptom-QoL trajectories in real-world settings.¹³

Work Productivity Scales: Menopause can affect workplace functioning through absenteeism, presenteeism, and impaired non-work activity. The Work Productivity and Activity Impairment questionnaire (WPAI) is a validated instrument that assesses work time missed, impairment while working, overall work impairment, and activity impairment over the prior 7 days; outcomes are expressed as impairment percentages (higher = worse).^{15–17} The tool has been applied to quantify the impact of vasomotor symptoms (VMS) severity on sleep and work outcomes.¹⁶ The Work Ability Index (WAI) complements WPAI by assessing broader occupational capacity and can be useful where job-function adaptation is being considered.¹⁸

DETERMINANTS OF QUALITY OF LIFE IN MENOPAUSE

Sociocultural Factors

Attitudes toward menopause, self-perceived efficacy, family decision-making, and sociocultural context emerge as critical determinants of QoL during the menopausal transition and beyond.¹⁹ Evidence consistently demonstrates that menopause-related QoL is not determined solely by biological status, but by a complex interplay of symptoms, psychosocial factors, education, employment, marital relationships, and cultural perceptions.²⁰ In a Spanish study, lower HRQoL was associated with younger age, obesity, postmenopausal status, early menopause, lower education level, not having a partner, not being employed, lack of sexual activity, smoking, no or occasional alcohol consumption, diagnosis of depression, having undergone hysterectomy and oophorectomy, and having experienced bone fractures. Current smoking, symptom burden, and negative attitudes are consistently associated with poorer QoL scores.^{21–24} Prospective evidence from the Study of Women's Health Across the Nation (SWAN) suggests that menopausal status per se is not the dominant determinant of QoL; rather, perceived stress, marital status, and attitudes toward ageing exert stronger influences.^{25–27} Practice-based and cross-sectional studies using validated instruments have likewise demonstrated that socioeconomic and cultural factors often outweigh menopause itself in determining QoL outcomes.²⁵ Current smoking, symptom burden, and negative attitudes are consistently associated with poorer QoL scores.²⁸ Education, socioeconomic status, marital satisfaction, and employment consistently emerge as protective factors for better QoL in menopausal women across global and regional studies.^{16,24–31} Conversely, lower education levels may contribute to under-recognition and under-reporting of menopausal symptoms.^{10,20–25,29–32} Systematic reviews further confirm the roles of body mass index, age, marital and economic dimensions, duration of menopause, parity, and race in shaping menopausal QoL.²⁴ Cultural variability in symptom reporting and coping strategies is substantial, underscoring the importance of culturally sensitive care models.³²

NON-COMMUNICABLE DISEASES

Metabolic and cardiovascular diseases, osteoporosis, fractures, cancer and urinary incontinence can have a severe impact on quality of life. A study involving 12,148 patients from seven leading cancer hospitals in India showed, unsurprisingly, that QoL decreased with advancing cancer stage among both inpatients and outpatients. The outpatients on hormone therapy showed significantly better quality of life in comparison to patients on chemotherapy. However, palliative care and surgery were found to be associated with significantly poorer QoL

compared to chemotherapy.³³ Dziedzic M et al. assessed QOL in women with osteoporotic vertebral fractures. Women who sustained a fracture when falling from a standing position had a significantly lower overall quality of life concerning pain and physical functioning, compared to those in whom the fracture was caused by minor trauma while performing daily life activities.³⁴ A study in Gujarat examined QOL among patients with heart failure. The study demonstrated that patients with heart failure had impaired QOL; among them, most experienced dyspnoea (80%), fatigue (75%), and 74% had reduced appetite. The authors concluded that low physical activity and moderate QOL can be improved by early rehabilitation.³⁵ A meta-analysis of 24,983 participants found that urinary incontinence was significantly associated with poor QoL.³⁶ A systematic scoping review of longitudinal evidence indicate that cardiovascular disease, psychiatric disorders, diabetes, and reduced bone mineral density were positively associated with menopausal symptoms. Breast cancer was associated with an asymptomatic menopause. Psychological menopausal symptoms and cognitive decline improved after menopause, except among women from low socioeconomic backgrounds.³⁷

Dietary Intake

Dietary intake has been associated with the severity of menopausal symptoms; however, evidence for this association is inconsistent and inconclusive, and comes from only a small number of studies.³⁸

Workplace and Quality of Life

Age, educational level, type of work, working environment (such as crowding, confined spaces, noise, workstation design), permanent place of residency, mental factors (such as stress level, workload, work pattern), comorbidities, menopausal symptoms, time since menopause and physical activity have repeatedly been shown to affect QoL in the workplace in menopausal women. Low-threshold access to medical and psychological support, as well as individualised adaptation of the workplace environment, are among the recommendations for employers derived from these findings.³⁹

Menopausal Symptoms and Quality of Life

Menopausal symptoms are broadly categorised into somato-vegetative, psychological, and urogenital/sexual domains, as operationalised by the MRS.¹⁰ Presence and severity of symptoms correlate strongly with reduced QoL, with worsening outcomes as symptom burden increases.³² Fifty to 80% of women complain about menopausal symptoms such as hot flushes, night sweats, sleep disturbances, tiredness, and depression. These are the main factors that reduce HRQoL, which is detectable soon after menopause.⁴⁰ The SWAN measured health-related quality of life of approximately 3,000 women and found that several of the symptoms associated with menopause, such as hot flushes, night sweats, vaginal dryness, and leaking urine, were also associated with lower QOL.²⁵ Higher self-reported frequency of VMS, and a greater number of menopausal symptoms, have all been found to be significantly associated with lower quality of life.²¹ Women who experience menopausal symptoms show poor HRQoL compared to those with no symptoms of menopause.⁴¹ Compared with women without menopausal symptoms, women with menopausal symptoms were observed to have approximately 2-point decrements in the mental and physical component summaries of the 8-Item Short Form Survey (SF-8), which may be considered clinically meaningful.⁴² Haji et al commented that in the perimenopausal phase, vasomotor, physical and psychosocial domains had the highest scores, whereas in the postmenopause stages, the sexual domain was most affected. Low physical activity was observed in 45.4% of participants.⁴³ Longitudinal data indicate that overall well-being declines during the early menopausal transition, particularly within the first two years following the final menstrual period, but may improve spontaneously thereafter.⁴⁴

Vasomotor Symptoms and Quality of Life

The impact of VMS on individuals' quality of life (QOL) can be significant. Women with moderate-to-severe VMS may experience sleep problems, fatigue, anxiety, and depression, which may impact their ability to work and carry out day-to-day activities.⁴⁵⁻⁴⁷ Overall, globally, there is an acceptance of menopause as a natural process of ageing. Women reported a wide range of psychological and physical symptoms of VMS, most frequently feeling tired and worn out, which was consistently the highest reported symptom across all regions. The most bothersome VMS symptom reported in the United States (US) and Europe was weight gain, and in Japan, dissatisfaction with personal life. Difficulty sleeping was also considered highly bothersome in all regions.⁴⁸ Results from the SWAN study have also shown strong associations between VMS and perceived sleep disturbance.⁴⁹ Across the regions, VMS had a greater impact on daily activities than on working activities. There is an increase in work days lost in women with untreated

VMS. More severe VMS were associated with greater impairments in daytime activities and work productivity. VMS had a detrimental effect on sleep, and the resulting sleep deficit in turn affected their daytime productivity. VMS-related sleep and productivity impacts could affect a large number of midlife women. These findings point to unmet needs to address for women at work.¹⁵

Genitourinary Syndrome of Menopause and Quality of Life

Symptoms of genitourinary syndrome of menopause (GSM) are caused by estrogen deficiency and include vulvovaginal dryness, itching, burning, irritation, and dyspareunia, of which vulvovaginal dryness and dyspareunia are the most bothersome.⁵⁰⁻⁵¹ It is well established that vulvovaginal atrophy (VVA) can have a major impact on quality of life and sexual function in women, as well as personal relationships.⁵¹⁻⁵³ Discomfort and pain make sexual life impossible at times and affect both the woman and her partner.

GSM includes both VVA and urinary symptoms like frequency, urge incontinence and recurrent urinary tract infection (UTI). The quality-of-life domain most affected by bothersome vulvovaginal symptoms or VVA is sexual function, impacting 40% of women.⁵⁴ Mohamed et al. correlated menopause-related symptoms with women's quality of life. They reported that the prevalence of severe symptoms across various domains, the sexual domain had the highest scores affecting the QOL.⁵⁵

Physical Domain

A study by Nisar et al. showed that physical domain scores were significantly higher in the postmenopausal group, and that menopausal symptoms negatively affected the QoL of these women.⁵⁶

Psychological Domain

Depression and anxiety have the largest effects on mental HRQoL, and joint stiffness and heart palpitations are two symptoms with the largest effects on physical HRQoL.^{45, 57} The most affected domain is psychological, with a mean score was 68.53%. In other domains, such as social and environmental, the quality of life was 72.1% and 72.66%, respectively. The higher the score, the better the QOL.⁵⁸ In agreement with the above finding, several other studies from the literature reported that physical and psychological symptoms were highly significant in Asian women.⁵⁹⁻⁶¹

RURAL POPULATION AND QUALITY OF LIFE

Menopause symptoms have a poor QOL both in urban and rural women. However, the physical domain of menopausal symptoms affected rural women. Psychological symptoms, as well as the lack of health care and its accessibility, are important. In a study by Poomalar, menopause related symptoms had a negative impact on the QoL of perimenopausal and postmenopausal women, and the scores of the physical domain were significantly higher in the late postmenopausal group in rural women.⁶² Prevalence of menopausal symptoms was found to be 87.7% in a rural cohort. The majority of women had anxiety (80%), followed by physical and mental exhaustion (71.5%), sleep problems (61.2%), irritability (60.7%), joint and muscular discomfort (56%) and heart problems (54%). The QOL was impaired in 70.2% of study subjects. The psychological symptoms were attributed 70.8% to the poor QOL. A holistic approach, including lifestyle and behavioural modification, is required.⁶³ The median MRS overall score is 14 (moderate severity), which is too high to be considered a major problem faced by rural women. A poor quality of life was observed in 69.3% of rural women. Another study by Sudhaa et al. suggests that the quality of life among rural women is poorer than that of urban women.^{3,64} Currently, the majority (92%) address their menopausal symptoms at home and through self-care. Indian women usually do not seek medical attention because they believe that menopausal symptoms are a natural physiological byproduct of ageing. Family commitment and the cultural taboo against discussing sexual and reproductive issues because of social stigma are the primary causes of these attitudes.⁶⁵

URBAN POPULATION AND QUALITY OF LIFE

In an urban Hyderabad cohort of women aged >40 years, the MENQOL physical domain contributed the highest symptom burden, followed by vasomotor and psychosocial domains, while sexual symptoms were least reported; younger postmenopausal age (<50 years), lack of formal education, higher socioeconomic status, homemaker status, and shorter duration since menopause were associated with higher vasomotor scores and poorer QOL, highlighting the role of modifiable factors.⁶⁶ Similarly, a Delhi-based study reported a very high prevalence (89%) and botheration score of physical symptoms, significantly associated with age and menopausal status.⁶⁷ Data from Guntur showed that advancing age (>50 years), lower education, lower socioeconomic status, longer duration since menopause, poor

symptom awareness, and comorbidities were independently associated with poorer overall QOL across physical and psychological domains.⁶⁸ Urban-rural comparisons from Jammu revealed significantly worse overall MENQOL scores among rural women, with greater impairment in psychological, social, and environmental domains compared with urban counterparts.⁶⁴ Regional South Asian data echo these findings: over half of menopausal women in Nepal reported poor QOL, with education, treatment of health problems, and physical activity acting as key determinants.⁶⁹ In Pakistan, older age (>60 years) was associated with greater symptom burden across all MENQOL domains, with illiteracy linked to worse physical symptoms and higher education paradoxically associated with greater sexual concerns.⁷⁰ Data from Malaysia indicate that while over half of women perceived menopausal symptoms to affect QOL, severe impairment was uncommon, and treatment-seeking behaviour remained low and unrelated to sociodemographic factors, underscoring gaps in awareness and healthcare utilisation across Asian settings.⁷¹

MANAGEMENT AND QUALITY OF LIFE

Education and Empowerment

Menopause health education demonstrated an improvement in both QoL and symptom control in menopausal women; trusted educational programmes would facilitate this change both emotionally and physically. Meta-analysis of the primary outcomes, QOL and symptom control, showed significant improvement after the educational programme.⁷²

Lifestyle Interventions

An interventional study was conducted in Tamil Nadu, in which 130 participants underwent yoga training and were advised to practice yoga daily for 18 weeks, while 130 participants served as the control group. There was a statistically significant difference ($P=0.001$) between the study and control groups in the physical, psychological, social, and environmental domains of quality of life at 6, 12, and 18 weeks of yoga therapy. QoL for menopausal women improved significantly after 18 weeks of yoga practice. The authors observed that women who regularly practice yoga can enjoy menopause and experience the freedom, liberation, and energy it brings. They concluded that yoga is an effective complementary health approach for improving QoL in menopausal women.⁷³ Nguyen TM et al. conducted a meta-analysis of the effect of exercise on quality of life in women with menopausal symptoms and found evidence of positive effects on physical and psychological QOL scores. However, there was no evidence for the effects of exercise on general, social, and menopause-specific QOL scores.⁷⁴ The most common interventions for women with menopausal and urinary symptoms were yoga and pelvic floor muscle training (PFMT), respectively. In our meta-analyses, while yoga significantly improved physical QOL, its effects on general, psychological, sexual, and vasomotor symptoms QOL scores, as well as the effect of PFMT on general QoL, were not significant. Our findings suggest that well-designed studies are needed to confirm the effect of exercise on QOL in women with menopausal symptoms.

Diet and Physical Activity

Participating in physical exercise, using products containing phytestrogens and isoflavones, and participating in educational and counselling sessions play an effective role in improving the QoL in menopausal women.⁷⁵ Exercise might improve vasomotor symptom severity.⁷⁶ Future rigorous RCTs that address the limitations of the current review are warranted to explore optimal exercise prescription principles for targeting the severity of vasomotor symptoms.

Hormone Therapy

Postmenopausal hormone therapy is commonly used by women for disease prevention, but its effects on quality of life have not been well documented in Asian women. A prospective, randomised, double-blind, multinational clinical trial involving 1028 healthy postmenopausal women from 9 ethnic groups across 11 Asian countries/regions was conducted. Following 2 weeks of baseline observation, the women received one of three conjugated estrogens (CE)/medroxyprogesterone acetate (MPA) doses (in mg) daily for 24 weeks: 0.625/2.5, 0.45/1.5, or 0.3/1.5. At baseline and at the end of weeks 4, 12, and 24 following the start of therapy, the study participants were asked to record, using a menopause-specific QoL (MENQOL) questionnaire, 29 menopausal symptoms experienced during the preceding month. The MENQOL scores in the overall population declined significantly within 4 weeks of the intervention, indicating an improvement in QoL. The beneficial effects were similar in the three dose groups.⁷⁷ A meta-analysis on menopause hormone therapy (MHT) for menopausal syndrome found that there was a significant positive impact of MHT on alleviating menopausal symptoms and maintaining quality of life for women undergoing menopause.⁷⁸ In postmenopausal women with climacteric symptoms, lower than standard doses of MHT have been

shown to be adequate in significantly improving individual domains (attractiveness, menstrual symptoms, sleep problems, sexual behaviour, anxiety/fears, vasomotor symptoms, memory/concentration, somatic symptoms and depressed mood) and generally overall measures of quality of life with both generic- and disease-specific tools.⁷⁹⁻⁸⁰

Managing Vasomotor Symptoms

Hormonal and nonhormonal treatments for VMS had partial improvements in sleep. A one-point reduction in VMS severity led to a clinically significant improvement in sleep and QOL.⁸¹⁻⁸² An umbrella review was done to comprehensively summarise evidence on the benefits and harms of MHT across diverse health outcomes. All health outcomes from previous systematic reviews were included: menopausal symptoms, surrogate endpoints, biomarkers, various morbidity outcomes, and mortality. MHT was beneficial for VMS, and all fracture risk, sexual function, diabetes, cardiovascular mortality and colorectal cancer, but harmful for stroke and venous thromboembolism. The major limitations include the inability to address the varying effects of MHT by type, dose, formulation, duration of use, route of administration, and age at initiation, and to account for the quality of the individual studies included in the systematic reviews. MHT has a complex balance of benefits and harms on multiple health outcomes. Some effects differ qualitatively between ET and estrogen-progesterone therapy (EPT). The quality of available evidence is only moderate to poor.⁷⁹ The Women's Health Initiative (WHI) evidence does not support routine supplementation with calcium plus vitamin D for menopausal women to prevent fractures, or a low-fat diet with increased fruits, vegetables, and grains to prevent breast or colorectal cancer. A potential role of a low-fat dietary pattern in reducing breast cancer mortality, a secondary outcome, warrants further study.⁸⁰ Korean studies have also shown significant improvements in Women's Health Questionnaire (WHQ) scores and overall quality of life, including better management of physical and depressive symptoms, improved sleep, and enhanced self-perceived attractiveness. SF-36 assessments indicated higher QoL scores among HT users compared to non-users.⁸³⁻⁸⁴

Menopause Hormone Therapy and Quality of Life

While MHT remains a common treatment for menopausal symptoms, its association with poorer psychosocial QoL and memory issues suggests a need for personalised approaches.⁸⁵ Engaging in physical activity and yoga appears to offer greater mental health benefits, whereas mindfulness alone is associated with worse mental health. A total of 125,000 participants in the United Kingdom (UK) Biobank were studied to assess associations between menopause, hormone therapy (HT) use, and outcomes related to mental health, cognition, and brain morphology. Specifically, they focused on grey matter volumes in the medial temporal lobe (MTL) and anterior cingulate cortex (ACC). Menopause was associated with increased levels of anxiety, depression, and sleep difficulties. Women using HT reported greater mental health challenges than post-menopausal women not using HT. Post-hoc analyses revealed that women prescribed HT had higher levels of pre-existing mental health symptoms. The authors concluded that menopause is linked to adverse mental health outcomes and reductions in grey matter volume in key brain regions. The use of HT does not appear to mitigate these effects and may be associated with more pronounced mental health challenges, potentially due to underlying baseline differences. These results have important implications for understanding the neurobiological effects of HT and highlighting the unmet need for addressing mental health problems during menopause.⁸⁶ Surgical menopause and estrogen replacement: As a subgroup analysis of the WHI trial, women in the age group of 50-79 with hysterectomy with or without bilateral salpingo-oophorectomy (BSO) were studied. A randomised trial allocation to treatment with conjugated estrogens alone in women with or without BSO for 7 years showed a similar pattern of benefits and risks. However, age at randomisation affected the outcome. Younger women with BSO given conjugated equine estrogens (CEE) had a statistically significant 32% decrease in all-cause mortality over 18 years of follow-up. In women over 70 years, CEE led to adverse effects, and those less than 60 had a benefit over the long term.⁸⁷ Vasomotor symptoms, palpitations and features of GSM were higher, and body aches, tiredness, insomnia, depression and memory loss were less in surgical menopause than in natural menopause. Ovaries should be conserved during hysterectomies whenever possible.⁸⁸

Patient-Reported Outcomes for Menopause Management Intervention Study

Patient-reported outcomes (PROMs) are central to contemporary menopause research, as symptom burden, treatment benefit, and tolerability are best captured from the patient's perspective. While VMS remain the most common and distressing manifestation of the menopausal transition, their evaluation in clinical studies has historically been heterogeneous and episodic. To address this, a menopause-specific core outcome set has been proposed, focusing on six key patient-centred outcomes: frequency and severity of VMS, distress or interference

caused by symptoms, impact on sleep, satisfaction with treatment, and treatment-related adverse effects. This framework aligns closely with the Patient-Reported Outcomes for Menopause Management Intervention Study (PROMMIS)-Menopause domains of VMS, sleep disturbance, mood and well-being, sexual health, and overall quality of life, and enables standardised assessment of both hormonal and non-hormonal interventions.⁸⁹ The relevance of such PROM-based evaluation is underscored by recent real-world and phase 3b data, including the DAYLIGHT study of fezolinetant, which demonstrated meaningful improvements in patient-reported symptom burden and quality-of-life outcomes among women with moderate-to-severe VMS who were unsuitable for hormone therapy, highlighting the importance of PROMs in capturing clinically meaningful benefit beyond symptom counts alone.⁹⁰

SYNOPSIS

- Symptoms and diseases associated with ageing affect quality of life, as do the treatment modalities used.
- QoL is an important consideration when evaluating and managing a woman at or beyond menopause.
- Education and empowerment by reinforcing a healthy lifestyle, incorporating enjoyable and relaxing activities, will add immensely to the QOL of women at menopause transition.
- The addition of menopausal health services in primary health centres would ensure better support to older women in rural India.
- Structured research on patient-related outcomes of disease and treatment should be conducted to improve management and QOL.

RESEARCH AGENDA

Effect of MHT on QoL in Indian women

REFERENCES

1. The WHOQOL Group. The World Health Organization Quality of Life assessment (WHOQOL): position paper from the World Health Organization. *Soc Sci Med*. 1995 Nov;41(10):1403-9. [https://doi.org/10.1016/0277-9536\(95\)00112-k](https://doi.org/10.1016/0277-9536(95)00112-k)
2. Williams RE, Kalilani L, DiBenedetti DB, Zhou X, Fehnel SE, Clark RV. Healthcare seeking and treatment for menopausal symptoms in the United States. *Maturitas*. 2007 Dec 20;58(4):348-58. <https://doi.org/10.1016/j.maturitas.2007.09.006>
3. Roshini RA, Meriton Stanley A, Samya V. A study on the prevalence of menopausal symptoms and its impact on quality of life among women aged 41 to 60 years in a rural area. *J Family Med Prim Care*. 2025 Sep;14(9):3912-3919. https://doi.org/10.4103/jfmpc.jfmpc_2101_24
4. Hvas L. Positive aspects of menopause: a qualitative study. *Maturitas*. 2001 Jul 25;39(1):11-7. [https://doi.org/10.1016/s0378-5122\(01\)00184-0](https://doi.org/10.1016/s0378-5122(01)00184-0)
5. UNFPA India. India Ageing Report 2023. New Delhi: UNFPA India; 2023. Caring for our elders: Institutional responses. Sep 26. [Accessed 2026 Feb 6]. Available from: <https://india.unfpa.org/en/publications/caring-our-elders-institutional-responsesindiaageing-report-2023>
6. Kalamegam S, Damodaran A, Shah PB. Quality of Life in Geriatric Populations within Long-term Care Facilities: Prospective Observational Study Addressing Contemporary Challenges and Enduring Barriers in Geriatric Support Systems. *J Mid-life Health*. 2025 Jan-Mar;16(1):83-90. https://doi.org/10.4103/jmh.jmh_209_24
7. Ware JE Jr. SF-36 health survey update. *Spine (Phila Pa 1976)*. 2000 Dec 15;25(24):3130- <https://doi.org/10.1097/00007632-200012150-00008>
8. Kumari R, Singh C, Kumar M, Singh AK, Kaushik A, Sachan B, et al. Validation of the Hindi version of the MOS SF-36 health survey for evaluating quality of life among the elderly population in North India. *J Family Med Prim Care*. 2025 Mar;14(3):880-887. https://doi.org/10.4103/jfmpc.jfmpc_1157_24
9. Castro PC, Driusso P, Oishi J. Convergent validity between SF-36 and WHOQOL-BREF in older adults. *Rev Saude Publica*. 2014 Feb;48(1):63-7. <https://doi.org/10.1590/s0034-8910.2014048004783>
10. Heinemann K, Ruebig A, Potthoff P, Schneider HP, Strelow F, Heinemann LA, et al. The Menopause Rating Scale (MRS) scale: a methodological review. *Health Qual Life Outcomes*. 2004 Sep 1;2(1):45. <https://doi.org/10.1186/1477-7525-2-45>
11. Hilditch JR, Lewis J, Peter A, van Maris B, Ross A, Franssen E, et al. A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas*. 1996 Sep;24(3):161-75. [https://doi.org/10.1016/0378-5122\(96\)01038-9](https://doi.org/10.1016/0378-5122(96)01038-9)
12. Utian WH, Janata JW, Kingsberg SA, Schluchter M, Hamilton JC. The Utian Quality of Life (UQOL) Scale: development and validation of an instrument to quantify quality of life through and beyond menopause. *Menopause*. 2002 Nov-Dec;9(6):402-10. <https://doi.org/10.1097/00042192-200211000-00005>
13. Coronado PJ, Borrego RS, Palacios S, Ruiz MA, Rejas J. Structural validity of a 16-item abridged version of the Cervantes Health-Related Quality of Life scale for menopause: the Cervantes Short-Form Scale. *Menopause*. 2015 Mar;22(3):325-36. <https://doi.org/10.1097/GME.0000000000000321>
14. Kim C, Marples L, Platts A, Bermingham KM, Amati F, Hamoda H, et al. MenoScale: A novel digital tool to measure menopause symptoms and subjective quality of life – validation, preliminary insights on the menopausal experience and association with diet quality. *Post Reprod Health*. 2025 May;31(2):73-86. <https://doi.org/10.1177/20533691251335807>
15. DePree B, Shiozawa A, King D, Schild A, Zhou M, Yang H, et al. Association of menopausal vasomotor symptom severity with sleep and work impairments: a US survey. *Menopause*. 2023 Sep 1;30(9):887-897. <https://doi.org/10.1097/GME.0000000000002237>

16. Reilly MC, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics*. 1993 Nov;4(5):353-65. <https://doi.org/10.2165/00019053-199304050-00006>
17. Work Productivity and Activity Impairment Questionnaire: Specific Health Problem V2.0 (WPAI:SHP). [Accessed 2026 Feb 6]. Available at: http://www.reillyassociates.net/WPAI_SHP.html
18. Tuomi K, Ilmarinen J, Eskelinen L, Jarvinen E, Toikkanen J, Klockars M. Work Ability Index. PsycTESTS Dataset 1991. <https://doi.org/10.1037/t58607-000>
19. Coronado PJ, Fasero M, Mendoza N, González SP, Sánchez-Méndez S, Presa J, et al. Quality of life at perianal postmenopause: analysis of the results from app "MiMenopausia". *Maturitas*. 2025 Jun;197:108267. <https://doi.org/10.1016/j.maturitas.2025.108267>
20. Yemde A, Kawthalkar A, Bhalerao A. Determinants impacting the quality of life in postmenopausal women: an in-depth narrative review. *International Journal of Reproduction, Contraception, Obstetrics and Gynecology*. 2024;13(9):2570-6. <https://doi.org/10.18203/2320-1770.ijrcog20242281>
21. Karaçam Z, Şeker SE. Factors associated with menopausal symptoms and their relationship with the quality of life among Turkish women. *Maturitas*. 2007 Oct 20;58(1):75-82. <https://doi.org/10.1016/j.maturitas.2007.06.004>
22. Barati M, Akbari-Heidari H, Samadi-Yaghin E, Jenabi E, Jormand H, Kamyari N. The factors associated with the quality of life among postmenopausal women. *BMC Womens Health*. 2021 May 22;21(1):208. <https://doi.org/10.1186/s12905-021-01361-x>
23. Sharifirad G, Norozi E, Mostafavi F, Hasanzadeh A, Moodi M. Factors affecting quality of life in postmenopausal women, Isfahan, 2011. *J Educ Health Promot*. 2013 Oct 24;2:58. <https://doi.org/10.4103/2277-9531.120857>
24. Mukherjee S, Som N, Roy S. Menopause-specific quality of life and attitude towards menopause among a group of postmenopausal women living in the city of Kolkata, India. *Post Reprod Health*. 2025 Mar;31(1):23-31. <https://doi.org/10.1177/20533691251320433>
25. Avis NE, Colvin A, Bromberger JT, Hess R, Matthews KA, Ory M, et al. Change in health-related quality of life over the menopausal transition in a multiethnic cohort of middle-aged women: Study of Women's Health Across the Nation. *Menopause*. 2009 Sep- Oct;16(5):860-9. <https://doi.org/10.1097/gme.0b013e3181a3cdaf>
26. Avis NE, Assmann SF, Kravitz HM, Ganz PA, Ory M. Quality of life in diverse groups of midlife women: assessing the influence of menopause, health status and psychosocial and demographic factors. *Qual Life Res*. 2004 Jun;13(5):933-46. <https://doi.org/10.1023/B:QURE.0000025582.91310.9f>
27. Avis NE, Ory M, Matthews KA, Schocken M, Bromberger J, Colvin A. Health-related quality of life in a multiethnic sample of middle-aged women: Study of Women's Health Across the Nation (SWAN). *Med Care*. 2003 Nov;41(11):1262-76. <https://doi.org/10.1097/01.MLR.0000093479.39115.AF>
28. Nazarpour S, Simbar M, Ramezani Tehrani F, Alavi Majd H. Factors associated with quality of life of postmenopausal women living in Iran. *BMC Womens Health*. 2020 May 14;20(1):104. <https://doi.org/10.1186/s12905-020-00960-4>
29. Jenabi E, Shobeiri F, Hazavehei SMM, Roshanaei G. Assessment of Questionnaire Measuring Quality of Life in Menopausal Women: A Systematic Review. *Oman Med J*. 2015 May;30(3):151-6. <https://doi.org/10.5001/omj.2015.34>
30. Abedzadeh Kalarhousi M, Taebi M, Sadat Z, Saberi F. Assessment of quality of life in menopausal periods: a population study in Kashan, Iran. *Iran Red Crescent Med J*. 2011 Nov;13(11):811-7. <https://pubmed.ncbi.nlm.nih.gov/22737420/>
31. Singh P, Vyas S, Vallabh V, Nautiyal R, Srivastava A, Semwal J. A Study to Assess the Prevalence and Factors Affecting Menopausal Symptoms among Middle-Aged Females in the Garhwal Region of Uttarakhand. *J Mid-life Health*. 2023 Oct-Dec;14(4):237-245. https://doi.org/10.4103/jmh.jmh_198_22
32. Lalo R, et al. Menopausal Symptoms and Women's Quality of Life Outcomes: Literature Review. *EC Gynaecology*. 2017;6.5:167-172.
33. Dixit J, Gupta N, Katakia A, Roy P, Mehra N, Kumar L, et al. Health-related quality of life and its determinants among cancer patients: evidence from 12,148 patients of Indian database. *Health Qual Life Outcomes*. 2024 Mar 13;22(1):26. <https://doi.org/10.1186/s12955-024-02227-0>
34. Dziedzic M, Janiszewska M, Goździewska M, Kowalska W, Roliński J. Assessment of the Quality of Life of Women after Osteoporotic Vertebral Fracture with Consideration of Socio-Demographic Characteristics and Selected Factors Concerning the State of Health. *Int J Environ Res Public Health*. 2022 Sep 27;19(19):12237. <https://doi.org/10.3390/ijerph191912237>
35. Shah P, Mehta M, Oza F, Makwana P. Prevalence of Quality of Life and Physical Activity in Patients with Different Stages of Heart Failure – An Observational Cross-Sectional Study. *J Indian Coll Cardiol*. 2023;13:154-9. https://doi.org/10.4103/jicc.jicc_35_23
36. Pizzol D, Demurtas J, Celotto S, Maggi S, Smith L, Angiolelli G, et al. Urinary incontinence and quality of life: a systematic review and meta-analysis. *Aging Clin Exp Res*. 2021 Jan;33(1):25-35. <https://doi.org/10.1007/s40520-020-01712-y>
37. Andrews R, Lacey A, Bache K, Kidd EJ. The role of menopausal symptoms on future health and longevity: A systematic scoping review of longitudinal evidence. *Maturitas*. 2024 Dec;190:108130. <https://doi.org/10.1016/j.maturitas.2024.108130>
38. Noll PRES, Campos CAS, Leone C, Zangirolami-Raimundo J, Noll M, Baracat EC, et al. Dietary intake and menopausal symptoms in postmenopausal women: a systematic review. *Climacteric*. 2021 Apr;24(2):128-138. <https://doi.org/10.1080/13697137.2020.1828854>
39. Theis S, Baumgartner SJ, Janka H, Kolokythas A, Skala C, Stute P. Quality of life in menopausal women in the workplace – a systematic review. *Climacteric*. 2023;26(2):80-7. <https://doi.org/10.1080/13697137.2022.2158729>
40. Nelson HD. Menopause. *Lancet*. 2008 Mar 1;371(9614):760-70. [https://doi.org/10.1016/s0140-6736\(08\)60346-3](https://doi.org/10.1016/s0140-6736(08)60346-3)
41. Whiteley J, DiBonaventura M daCosta, Wagner J-S, Alvir J, Shah S. The Impact of Menopausal Symptoms on Quality of Life, Productivity, and Economic Outcomes. *J Womens Health (Larchmt)*. 2013 Nov;22(11):983-90. <https://doi.org/10.1089/jwh.2012.3719>
42. Hays RD, Morales LS. The RAND-36 measure of health-related quality of life. *Ann Med*. 2001 Jul;33(5):350-7. <https://doi.org/10.3109/07853890109002089>
43. El Hajj A, Wardy N, Haidar S, Bourgi D, Haddad ME, Chammas DE, et al. Menopausal symptoms, physical activity level and quality of life of women living in the Mediterranean region. *PLoS One*. 2020 Mar 25;15(3):e0230515. <https://doi.org/10.1371/journal.pone.0230515>
44. Dennerstein L, Dudley E, Burger H. Well-being and the menopausal transition. *J Psychosom Obstet Gynaecol*. 1997 Jun;18(2):95-101. <https://doi.org/10.3109/01674829709085575>
45. Williams RE, Levine KB, Kalilani L, Lewis J, Clark RV. Menopause-specific questionnaire assessment in US population-based study shows negative impact on health-related quality of life. *Maturitas*. 2009 Feb 20;62(2):153-9. <https://doi.org/10.1016/j.maturitas.2008.12.006>
46. Worsley R, Bell RJ, Gartoulla P, Robinson PJ, Davis SR. Moderate-Severe Vasomotor Symptoms Are Associated with Moderate-Severe Depressive Symptoms. *J Womens Health (Larchmt)*. 2017 Jul;26(7):712-718. <https://doi.org/10.1089/jwh.2016.6142>

47. Burleson MH, Todd M, Trevathan WR. Daily vasomotor symptoms, sleep problems, and mood: using daily data to evaluate the domino hypothesis in middle-aged women. *Menopause*. 2010 Jan-Feb;17(1):87-95. <https://doi.org/10.1097/gme.0b013e3181b20b2d>
48. Nappi RE, Kroll R, Siddiqui E, Stoykova B, Rea C, Gemmen E, et al. Global cross-sectional survey of women with vasomotor symptoms associated with menopause: prevalence and quality of life burden. *Menopause*. 2021 May 24;28(8):875-882. <https://doi.org/10.1097/GME.0000000000001793>
49. Kravitz HM, Zhao X, Bromberger JT, Gold EB, Hall MH, Matthews KA, et al. Sleep disturbance during the menopausal transition in a multi-ethnic community sample of women. *Sleep*. 2008 Jul;31(7):979-90. <https://doi.org/10.5665/sleep/31.7.979>
50. Portman DJ, Gass ML. Genitourinary syndrome of menopause: new terminology for vulvovaginal atrophy from the International Society for the Study of Women's Sexual Health and the North American Menopause Society. *Maturitas*. 2014 Nov;79(3):349-54. <https://doi.org/10.1016/j.maturitas.2014.07.013>
51. Palacios S, Nappi RE, Bruyniks N, Particco M, Panay N. The European Vulvovaginal Epidemiological Survey (EVES): prevalence, symptoms and impact of vulvovaginal atrophy of menopause. *Climacteric*. 2018 Jun;21(3):286-291. <https://doi.org/10.1080/13697137.2018.1446930>
52. Nappi RE, Mattsson L-Å, Lachowsky M, Maamari R, Giral di A. The CLOSER survey: impact of postmenopausal vaginal discomfort on relationships between women and their partners in Northern and Southern Europe. *Maturitas*. 2013 Aug;75(4):373-9. <https://doi.org/10.1016/j.maturitas.2013.05.003>
53. Panay N, Palacios S, Bruyniks N, Particco M, Nappi RE. Symptom severity and quality of life in the management of vulvovaginal atrophy in postmenopausal women. *Maturitas*. 2019 Jun;124:55-61. <https://doi.org/10.1016/j.maturitas.2019.03.013>
54. Diem SJ, Danan ER. GSM and Quality of Life Measures. *Clin Obstet Gynecol*. 2024 Mar 1;67(1):58-67. <https://doi.org/10.1097/GRE.0000000000000836>
55. Mohamed H, Lamadah S, Zamil L. Quality of life among menopausal women. *Int J Reprod Contracept Obstet Gynecol*. 2014;3(3):552-61. <https://doi.org/10.5455/2320-1770.ijrcog20140906>
56. Nisar N, Sohoo NA. Frequency of menopausal symptoms and their impact on the quality of life of women: a hospital based survey. *J Pak Med Assoc*. 2009 Nov;59(11):752-6. <https://pubmed.ncbi.nlm.nih.gov/20361673/>
57. Daly E, Gray A, Barlow D, McPherson K, Roche M, Vessey M. Measuring the impact of menopausal symptoms on quality of life. *BMJ*. 1993 Oct 2;307(6908):836-40. <https://doi.org/10.1136/bmj.307.6908.836>
58. Wayal R, Kashyap MM. Study of Quality of Life among Postmenopausal Women using WHOQOL-BREF. *Int J Curr Adv Res*. 2025;14(07):329-333. <https://doi.org/10.24327/ijcar.2025.0333.0070>
59. Karmakar N, Majumdar S, Dasgupta A, Das S. Quality of life among menopausal women: A community-based study in a rural area of West Bengal. *J Mid-life Health*. 2017 Jan- Mar;8(1):21. https://doi.org/10.4103/jmh.jmh_78_16
60. Madhukumar S, Gaikwad V, Sudeepa D. A community based study on perceptions about menopausal symptoms and quality of life of post-menopausal women in Bangalore rural. *Int J Health Sci Res*. 2012;2:49-56.
61. Rao A, Nayak G, Kamath A, Kumar P. A study of quality of life among perimenopausal women in selected coastal areas of Karnataka, India. *J Mid-life Health*. 2012 Jul- Dec;3(2):71-75. <https://doi.org/10.4103/0976-7800.104456>
62. Poomalar G K , Arounassalame B. The quality of life during and after menopause among rural women. *J Clin Diagn Res*. 2013 Jan;7(1):135-9. <https://doi.org/10.7860/JCDR/2012/4910.2688>
63. Kalhan M, Singhania K, Choudhary P, Verma S, Kaushal P, Singh T. Prevalence of menopausal symptoms and its effect on quality of life among rural middle aged women (40–60 years) of Haryana, India. *Int J App Basic Med Res*. 2020 Jul-Sep;10(3):183-188. https://doi.org/10.4103/ijabmr.ijabmr_428_19
64. Sharma S, Mahajan N. Menopausal symptoms and its effect on quality of life in urban versus rural women: A cross-sectional study. *J Mid-life Health*. 2015 Jan-Mar;6(1):16-20. <https://doi.org/10.4103/0976-7800.153606>
65. Bhutani S, Bhutani J, Bhutani P. Social issues in post menopausal women. *J Mid-life Health*. 2013 Jan;4(1):68-69. <https://doi.org/10.4103/0976-7800.109649>
66. Yerra AK, Bala S, Yalamanchili RK, Bandaru RK, Mavoori A. Menopause-related quality of life among urban women of Hyderabad, India. *J Mid-life Health*. 2021 Apr-Jun;12(2):161-167. https://doi.org/10.4103/jmh.jmh_272_20
67. Madan U, Chhabra P, Gupta G, Madan J. Menopausal symptoms and quality of life in women above 40 years in an urban resettlement colony of East Delhi. *Int J Med Sci Public Health*. 2019;8(6):1. <https://doi.org/10.5455/ijmsph.2019.0203012052019>
68. Muhseenah, Nallapu SSR. Evaluating the quality of life among menopausal women in the urban field practice area of a medical college in Guntur. *J Mid-life Health*. 2025 Jan-Mar;16(1):76-82. https://doi.org/10.4103/jmh.jmh_156_24
69. Baral S, Kaphle HP. Health-related quality of life among menopausal women: A cross-sectional study from Pokhara, Nepal. *PLoS One*. 2023 Jan 26;18(1):e0280632. <https://doi.org/10.1371/journal.pone.0280632>
70. among Postmenopausal Women in Pakistan. *Arch Pharm Pract*. 2021;12(3):29-33. <https://doi.org/10.51847/mapshk83eb>
71. Abdullah B, Moize B, Ismail BA, Zamri M, Nasir M. Prevalence of menopausal symptoms, its effect to quality of life among Malaysian women and their treatment seeking behaviour. *Med J Malaysia*. 2017 Apr;72(2):94-99. <https://pubmed.ncbi.nlm.nih.gov/28473671/>
72. JKeye C, Varley J, Patton D. The impact of menopause education on quality of life among menopausal women: a systematic review with meta-analysis. *Climacteric*. 2023 Oct;26(5):419-427. <https://doi.org/10.1080/13697137.2023.2226318>
73. ayabharathi B, Judie A. Complementary health approach to quality of life in menopausal women: a community-based interventional study. *Clin Interv Aging*. 2014 Nov 7;9:1913-21. <https://doi.org/10.2147/CIA.S70064>
74. Nguyen TM, Do TTT, Tran TN, Kim JH. Exercise and Quality of Life in Women with Menopausal Symptoms: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Int J Environ Res Public Health*. 2020 Sep 26;17(19):7049. <https://doi.org/10.3390/ijerph17197049>
75. Kariman N, Taebe M, Abdolhian S, Ozgoli G, Ebadi A. Strategies to improve menopausal quality of life: A systematic review. *J Educ Health Promot*. 2018 Jul 6;7:93. https://doi.org/10.4103/jehp.jehp_137_17
76. Liu T, Chen S, Mielke GI, McCarthy AL, Bailey TG. Effects of exercise on vasomotor symptoms in menopausal women: a systematic review and meta-analysis. *Climacteric*. 2022 Dec;25(6):552-561. <https://doi.org/10.1080/13697137.2022.2097865>
77. Limpaphayom KK, Darmasetiawan MS, Hussain RI, Burriss SW, Holinka CF, Ausmanas MK. Differential prevalence of quality-of-life categories (domains) in Asian women and changes after therapy with three doses of conjugated estrogens/medroxyprogesterone acetate: the Pan-Asia Menopause (PAM) study. *Climacteric*. 2006 Jun;9(3):204-214. <https://doi.org/10.1080/13697130600722520>

78. Tang Y, Ma R, Zhang L, Sun X, Wang Y. Effectiveness and safety of hormone replacement therapy in the treatment of menopausal syndrome: a meta-analysis. *Am J Transl Res*. 2025 Jan 15;17(1):1-15. <https://doi.org/10.62347/uglt3830>
79. Zhang GQ, Chen JL, Luo Y, Mathur MB, Anagnostis P, Nurmatov U, et al. Menopausal hormone therapy and women's health: An umbrella review. *PLoS Med*. 2021 Aug 2;18(8):e1003731. <https://doi.org/10.1371/journal.pmed.1003731> hormone therapy and women's health: An umbrella review. *PLoS Med*. 2021 Aug 2;18(8):e1003731.
80. Manson JE, Crandall CJ, Rossouw JE, Chlebowski RT, Anderson GL, Stefanick ML, et al. The Women's Health Initiative Randomized Trials and Clinical Practice. *JAMA*. 2024 May 28;331(20):1748-1760. <https://doi.org/10.1001/jama.2024.6542>
81. Mirkin S, Graham S, Revicki DA, Bender RH, Bernick B, Constantine GD. Relationship between vasomotor symptom improvements and quality of life and sleep outcomes in menopausal women treated with oral, combined 17 β -estradiol/progesterone. *Menopause*. 2019 Jan 9;26(6):637-642. <https://doi.org/10.1097/GME.0000000000001294>
82. Cintron D, Lipford M, Larrea-Mantilla L, Spencer-Bonilla G, Lloyd R, Gionfriddo MR, et al. Efficacy of menopausal hormone therapy on sleep quality: systematic review and meta-analysis. *Endocrine*. 2017 Mar;55(3):702-711. <https://doi.org/10.1007/s12020-016-1072-9>
83. Lim H-J, Cho H-J, Lee MS. Pilot Study of Hormone Replacement Therapy and Menopausal Symptoms, Depression, and Quality of Life in Korean Climacteric Women. *Psychol Rep*. 2006;98:374-378. <https://doi.org/10.2466/pr0.98.2.374-378>
84. Kim YS, Jung EY, Lee BY. The Necessity of Thyroid Function Test of Perimenopausal Women with Menopausal Symptoms. *J Korean Soc Menopause*. 2012;18:174. <https://doi.org/10.6118/jksm.2012.18.3.174>
85. Kuck MJ, Hogervorst E. Menopausal hormone therapy and exercise on psychosocial well-being and stress in menopausal women. *Front Reprod Health*. 2025;7:1582406. <https://doi.org/10.3389/frph.2025.1582406>
86. Zuhlsdorff K, Langley C, Bethlehem R, Warriar V, Romero Garcia R, Sahakian BJ. Emotional and cognitive effects of menopause and hormone replacement therapy. *Psychol Med*. 2026 Jan 27;56:e24. <https://doi.org/10.1017/S0033291725102845>
87. Manson JE, Aragaki AK, Bassuk SS, Chlebowski RT, Anderson GL, Rossouw JE, et al. Menopausal Estrogen-Alone Therapy and Health Outcomes in Women With and Without Bilateral Oophorectomy. *Ann Intern Med*. 2019 Sep 17;171(6):406-414. <https://doi.org/10.7326/m19-0274>
88. Mahjabeen N, Nasreen SZA. Clinical profile of 550 cases of surgical and natural menopause. *BIRDEM Med J*. 2020;10(3):168-171. <https://doi.org/10.3329/birdem.v10i3.48705>
89. Lensen S, Archer D, Bell RJ, Carpenter JS, Christmas M, Davis SR, et al. A core outcome set for vasomotor symptoms associated with menopause: the COMMA (Core Outcomes in Menopause) global initiative. *Menopause*. 2021 Apr 26;28(8):852-858. <https://doi.org/10.1097/GME.0000000000001787>
90. Shapiro CM, Wu X, Wang X, Miyazaki K, Morga A, Nappi RE, et al. 5092 Effect of Fezolinetant treatment on Patient-Reported Outcomes: Data from Phase 3b study (DAYLIGHT) for Moderate-To-Severe Vasomotor Symptoms Associated with Menopause in Women Considered Unsuitable for Hormone Therapy. *J Endocr Soc*. 2024;8(Suppl 1):bva6163.1587. <https://doi.org/10.1210/jendso/bvae163.1587>

Section 2

CARDIOVASCULAR SYSTEM

12. Cardiovascular Disease

13. Effects of Hormone Therapy on Cardiovascular Disease

CARDIOVASCULAR DISEASE

12

Keywords: Cardiovascular disease, menopause, risk factors, cardiovascular health

INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death globally. They accounted for 32% of all deaths (17.9 million deaths) in 2019.¹ Every 80 seconds, one woman dies due to heart disease. This mortality is more than that due to all cancers put together.² The risk of CVD increases with age in both men and women. However, in women, the risk rises around midlife, particularly during the menopause transition (MT). The disease presents a decade later in women than in men.³ Menopause is defined retrospectively as a persistent cessation of menses, defined as amenorrhoea of twelve months due to declining ovarian function with no other pathology explaining it. Menopause is preceded by the Menopause Transition (MT). It lasts 4-6 years and is characterised by irregular cycles and hormonal changes.⁴

As menopause sets in, estrogen levels decline. Various metabolic changes occur in women at MT and during menopause. There is a redistribution of body fat, with increased visceral adiposity, impaired glucose tolerance, diabetes mellitus (DM), hypertension, dyslipidaemia, and elevated inflammatory markers, all of which also occur at this time. There are adverse changes in vascular health.⁵ These changes can increase the risk of cardiovascular disease. This is an opportune time to screen a woman for CVD risk, counsel her, and start appropriate preventive measures. Many women and even healthcare providers are not aware of this increased risk of CVD in women. Ischaemic heart disease (IHD) is not considered to be an important cause of mortality in women. The presentation in women differs from that in men and can be atypical, making diagnosis difficult. Women are denied health care at various levels. This leads to a delay in diagnosis and management. The Lancet Women and CVD Commission said that addressing the knowledge gaps in the diagnosis, treatment and prevention of CVD in women is important to reduce the global burden of CVD by 2030.⁶

CVDs comprise mainly the following groups:⁷

- Coronary artery disease (CAD) is clinically manifested by myocardial infarction (MI), angina pectoris, heart failure (HF), and coronary death.
- Cerebrovascular disease is clinically manifested by stroke and transient ischaemic attack.
- Peripheral artery disease is clinically manifested by intermittent claudication.
- Aortic atherosclerosis and thoracic or abdominal aortic aneurysm.

With rising life expectancy in women, there is a global increase in population ageing. It is important to study CVD risk factors and the disease and to implement preventive measures to support a healthy older population in the future. A gynaecologist may generally see a woman for menopausal problems. It is essential for a gynaecologist to know the high-risk factors for CVD, screening for disease and institute preventive care or if found high-risk, refer to a physician/cardiologist.

EPIDEMIOLOGY

In 2019, an estimated 275.2 million (95% UI 261.4–289.8 million) women worldwide were living with CVD. Rising prevalence was observed in China, Indonesia, and India. Premenopausal women have a lower CVD risk than age-matched men due to estrogenic protection; however, after 55 years of age, all-cause mortality is higher in women, highlighting the loss of cardiovascular protection after menopause.^{6,8} Recent national mortality data indicate that CVDs account for nearly 31% of all deaths in India, exceeding the contribution of communicable diseases and malignancies, and remain predominant in the 30+ age group.⁹ Meta-analysis of Indian studies estimates a pooled CVD prevalence of about 11% among adults, with slightly higher rates in females than males.¹⁰ Ischaemic heart disease and stroke are the predominant cardiovascular outcomes in India, together accounting for the majority of CVD deaths and disability.¹¹

Cardiovascular risk factors are widespread and increasing across urban and rural populations. Hypertension prevalence is high and contributes substantially to mortality and disability; dyslipidaemia, diabetes, obesity, physical inactivity, and tobacco use comprise major modifiable risks.¹² Emerging evidence also highlights low public awareness and knowledge of modifiable cardiovascular risk factors in the Indian population, underscoring gaps in prevention strategies.¹³ Environmental and lifestyle determinants, including air pollution and sedentary habits, further amplify CVD risk and contribute to premature cardiovascular events, particularly in urban settings.¹⁴ In Western countries, the average age of menopause is 52 years, whereas for Indian women, the age of menopause is 46–47 years. Menopause between 40 and 45 is termed as early menopause. If it occurs before the age of 40, the term premature ovarian insufficiency (POI) is used. Both conditions are estrogen-deficient.⁴ Age-standardised CVD mortality rates in women have declined in the last 30 years, but this has been observed mainly in countries with a higher sociodemographic index as per the Global Burden of Disease study. In lower-sociodemographic-index countries, the rates have stabilised, but mortality has shifted more towards women than towards men.¹⁵

Figure 1 illustrates the prevalence of non-communicable diseases (NCDs) among women aged 35–80 years, based on a pan-India, hospital-based survey conducted by the Indian Menopause Society (IMS) in 2009, involving 1,805 women.

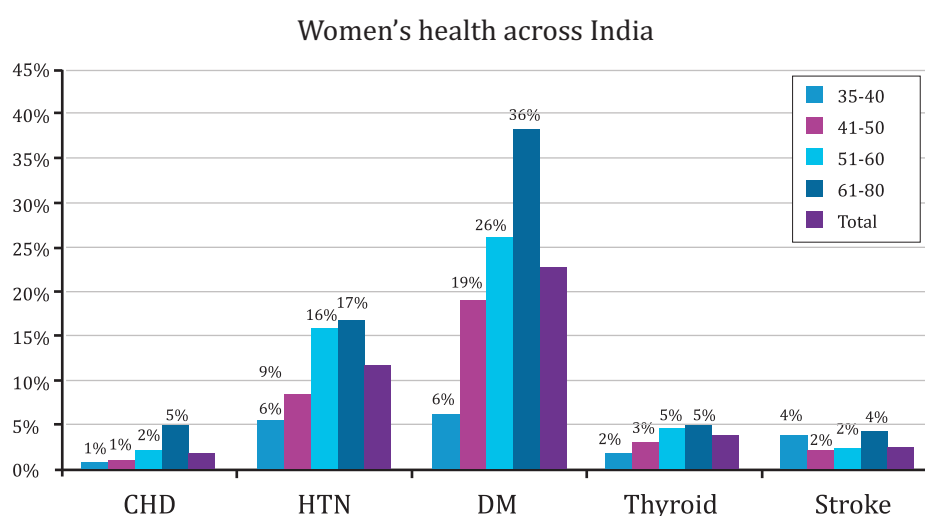


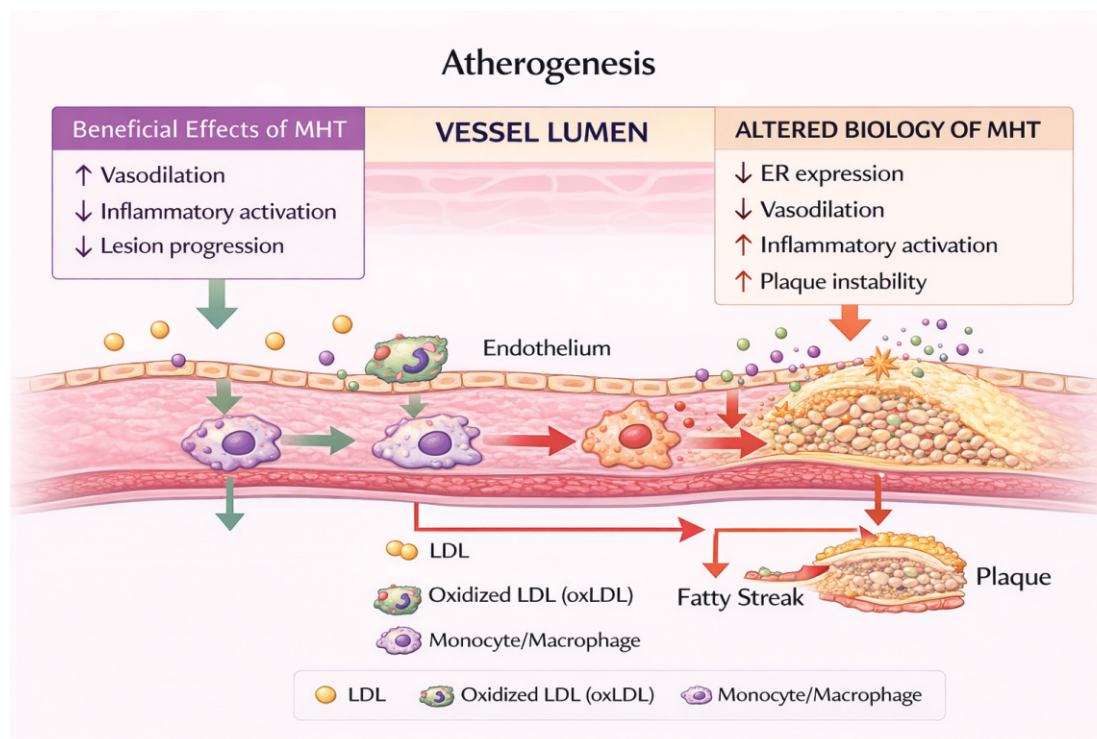
Figure 1. Prevalence of non-communicable diseases (NCDs) among women aged 35–80 years, based on a pan-India hospital-based survey conducted by the Indian Menopause Society (IMS) in 2009 (n = 1,805).

PATHOLOGY

Cardiovascular disease has a long latency period during which atheroma formation and endothelial dysfunction precede clinical cardiovascular events by many years. However, subjective and objective markers are available to diagnose the population at risk. Atherosclerosis is a chronic inflammatory condition of the arterial wall. It involves the formation of plaques in the arterial walls, which can narrow the arteries and restrict blood flow, leading to arterial occlusion. It represents increased oxidative stress, as evidenced by lipid and protein oxidation in the vascular wall. Low-density lipoprotein (LDL) oxidation leads to atherogenesis. A mature atherosclerotic plaque has an acellular necrotic core composed of cholesterol and dead macrophage foam cells. These become calcified later. During an acute event like myocardial infarction, stroke or deep venous thrombosis, the plaque ruptures or gets eroded and a thrombus forms on it.

PATHOPHYSIOLOGY SPECIFIC TO WOMEN

The pathophysiology of atherosclerosis differs between women and men. Refer to Figure 2 Women have a higher predisposition to thrombus formation, as they also have a higher risk of blood coagulability. It is seen that, in most women, endothelial dysfunction, small vessel size and diffuse atherosclerosis are major causes of ischaemia without evidence of blockade in the coronary arteries. Further, atherosclerotic plaque in women is less fibrotic and contains more lipid filled foam cells, suggesting greater potential for reversibility but also greater vulnerability to plaque rupture and thrombosis.



CARDIOVASCULAR DISEASE IS A MULTIFACTORIAL DISEASE

Cardiovascular disease is a multifactorial condition with origins extending from the intrauterine period through adulthood. Early-life influences, as described by the Developmental Origins of Health and Disease (DOHaD) hypothesis, interact with genetic, sex-specific, sociocultural, environmental, lifestyle, and psychological factors to shape lifelong cardiovascular risk.¹⁶

WOMEN AND CARDIOVASCULAR DISEASE: GENDER BIAS

Female-specific factors which increase the risk of CVD are present throughout her life. This may be seen as adolescent obesity, polycystic ovary syndrome (PCOS), preeclampsia, gestational diabetes mellitus (GDM), use of oral contraceptives, menopause.¹⁷

CHANGES AT MENOPAUSE TRANSITION: PATHOPHYSIOLOGY

It is important to define MT. It is a period of hormonal fluctuations, with decreased estrogen levels and increased follicle-stimulating hormone (FSH). Depending on the level of menstrual cycle variability, women may be classified as being in the early MT, characterised by a persistent difference of at least 7 days between consecutive menstrual cycle lengths. Late MT is characterised by at least 60 days of amenorrhoea, with at least one episode. The perimenopause includes early and late MT and continues for a year after the final menstrual period.¹⁸ Important hormonal, metabolic and psychological changes occur at this time in a female.

CHANGES IN FAT DISTRIBUTION

There is a redistribution of fat with increased visceral and abdominal subcutaneous fat. This change is seen more in those with early menopause and surgically induced menopause, signifying a correlation with falling estrogen levels.¹⁹ Falling estrogen levels reduce sex hormone binding globulin (SHBG), increasing bioavailable testosterone and promoting visceral fat accumulation. Rising insulin resistance further lowers SHBG, while increasing FSH during the menopausal transition may directly stimulate lipid synthesis in visceral adipose tissue, together contributing to central obesity.²⁰

CHANGES IN LIPID METABOLISM

The Study of Women's Health Across the Nation (SWAN) provides some of the strongest longitudinal evidence on lipid changes across reproductive ageing. Alterations in lipid metabolism begin early in the menopause transition, with consistent increases in total cholesterol, LDL cholesterol (LDL-C), triglycerides, and apolipoprotein B, changes that are

temporally related to menopause rather than to chronological ageing, body mass index, or lifestyle factors.²¹ Although HDL-cholesterol (HDL-C) levels may remain stable or even increase during the menopausal transition, emerging evidence indicates that higher HDL-C levels in midlife women are not uniformly protective. In SWAN, an increasingly lower risk of CVD compared with men of similar age, a protection largely attributed to endogenous estrogen exposure.³¹ Large population-based cohorts, including the Framingham Heart Study and the Nurses' Health Study, demonstrate that this advantage diminishes across the menopausal transition, with a clear acceleration of long-term cardiometabolic and vascular risk after menopause.³¹⁻³³ The incidence of CVD rises sharply after menopause, and after adjustment for chronological age, postmenopausal women have approximately a two-fold higher risk of CVD compared with premenopausal women.³¹ The impact is particularly pronounced in women with premature menopause. Natural menopause occurring before 40 years of age is associated with a two- to three-fold increase in myocardial infarction risk, while bilateral oophorectomy at a young age (especially before 35 years) is linked to a markedly higher risk of coronary events and premature cardiovascular mortality.³⁴⁻³⁷ These observations support the concept of menopause as an independent, sex-specific, non-modifiable cardiovascular risk factor, distinct from traditional risk factors shared by both sexes.

Mechanistic and imaging data reinforce this epidemiologic evidence. In a substudy of the Study of Women's Health Across the Nation (SWAN) using serial carotid ultrasonography, late perimenopause was characterised by significant increases in carotid intima-media thickness, plaque burden, and vascular remodelling compared with premenopause, independent of ageing alone.³⁸ Parallel imaging studies have shown greater accumulation of epicardial and perivascular adipose tissue in late perimenopausal and postmenopausal women compared with pre- or early perimenopause, even after adjustment for age and other confounders.³⁹

Although women tend to develop clinical CVD approximately 10–20 years later than men, this temporal advantage is attenuated or lost in the presence of premature menopause or cardiometabolic risk factors such as diabetes, dyslipidaemia, smoking, or hypertension.⁴⁰ Manson and colleagues have shown that women presenting with coronary disease are more likely than men to have multiple concomitant risk factors, while a much smaller proportion of women are free of traditional risk factors at presentation.⁴¹ Age-specific prevalence data further illustrate this shift. CVD affects approximately one in seven women between 45 and 64 years and nearly one in three women over 65 years.² Sex differences in mortality narrow with advancing age: the female-to-male mortality ratio is highest in younger adults and progressively declines in older age groups.⁴²

Reflecting this epidemiology, the Adult Treatment Panel (ATP) III guidelines defined age ≥ 55 years as a cardiovascular risk factor for women, compared with ≥ 45 years for men, an age disparity thought to reflect estrogen-mediated vascular protection.⁴³ Following menopause, the risk of coronary heart disease and fatal myocardial infarction approximately doubles, independent of chronological ageing.^{34,44} In parallel, the risk of ischaemic stroke, particularly atherosclerotic and carotid-related stroke, rises substantially in postmenopausal women. Epidemiologic studies indicate that stroke accounts for a higher proportion of cardiovascular mortality in women than in men.^{45,46} Sex differences in lipid biology also modify risk. Across adult life, men have HDL-cholesterol levels approximately 8–12 mg/dL lower than women, while LDL-cholesterol, triglycerides, and blood pressure rise earlier in men.⁴⁷

In women, however, low HDL-cholesterol and elevated triglycerides are stronger predictors of coronary risk than LDL-cholesterol alone, and traditional risk algorithms may underestimate coronary heart disease (CHD) risk in women.⁴⁸⁻⁵⁰ Inflammatory biomarkers, particularly C-reactive protein (CRP), show a strong linear association with cardiovascular events and may improve long-term risk prediction, especially for ischaemic stroke when added to traditional risk factors.⁵¹ Finally, psychosocial factors contribute importantly to sex-specific outcomes. Depression, which is more prevalent in women, has been consistently associated with poorer prognosis and higher complication rates following myocardial infarction.⁵²

CARDIOVASCULAR DISEASE RISK FACTORS

Early detection of CVD risk factors is important for managing them and reducing premature mortality. This is especially important for our country, where menopause occurs earlier than its Western counterparts.

CVD risk factors: Cardiovascular disease risk factors may be classified as non-modifiable and modifiable. Traditional modifiable risk factors include diabetes, hypertension, and dyslipidaemia. In addition, women have sex-specific risk factors such as polycystic ovary syndrome, pre-eclampsia, menopause, and use of oral contraceptives. Emerging contributors to cardiovascular risk include adverse social determinants of health, particularly poverty, air pollution, and exposure to abuse.⁶ Refer to Table 1

Table 1: Cardiovascular Disease Risk Factors

Traditional	Women Specific	Under-recognised
Hypertension	Premature menopause	Psychosocial risk factors
Diabetes	Hypertensive disorders of pregnancy	Abuse and intimate partner violence
Obesity	Gestational Diabetes	Socio-economic deprivation
Dyslipidaemia	PCOS	Poor health literacy
Smoking and tobacco use	Preterm delivery	Environment risk factors
Unhealthy diet	Systemic inflammatory & autoimmune diseases	
Sedentary lifestyle	Radiation & chemotherapy for breast cancer	
Family history of premature CVD (men < 55 years, women < 65 years)		

GENDER SPECIFIC

Age: Women have a lower risk than men when premenopausal due to the protective effect of estrogens. However, this advantage is lost with age, and after 60 years, women develop a higher incidence of stroke and coronary artery disease. This occurs a decade earlier in men. However, the symptoms and clinical presentation of Ischaemic heart disease in women are nonspecific, and the severity of both IHD and stroke is greater in women.⁵³

Premature ovarian insufficiency (POI) and early menopause: Both are estrogen-deficient states and are associated with increased prevalence of hypertension, vascular endothelial dysfunction, dyslipidaemia, and insulin resistance.⁵⁴⁻⁵⁵ Women undergoing surgical menopause before 40 years had a higher risk of CVD than those having a natural menopause. Even if a hysterectomy is performed at a younger age (before 35 years) without oophorectomy, it increases long-term CVD risk. A 4.6-fold increased risk of congestive heart failure and a 2.5-fold increased risk of coronary artery disease on 20 years of follow-up were seen as compared to those who did not have a hysterectomy.⁵⁶

POLYCYSTIC OVARY SYNDROME

This is the most common endocrine disorder in the reproductive age group. It is seen in 10-15% of reproductive age group. It is characterised by hyperandrogenaemia and insulin resistance with anovulation. Excess androgens causes weight gain, hirsutism, male pattern alopecia, insulin resistance, acne. The androgenic phenotype has a more severe PCOS.⁵⁷ Insulin resistance is a key factor in PCOS and is associated with hypertension, dyslipidaemia, and metabolic syndrome. Inflammatory markers are increased in PCOS and elevate the risk of CVD. However, insulin resistance may also occur without obesity.⁵⁸ Women with PCOS have increased visceral fat, impaired glucose tolerance and may have diabetes. Hypertension, elevated LDL cholesterol, and an increase in homocysteine levels and CRP are also seen. These are all risk factors for developing CVD later on and should be treated appropriately. In postmenopause the clinical features of PCOS may not be present however insulin resistance and hyperandrogenaemia persist. An umbrella review showed that women with PCOS had a 1.3-fold greater risk of developing composite CVD (ischaemic heart disease, cerebrovascular accident, heart failure, and peripheral arterial disease) than women without.⁵⁹

GESTATIONAL DIABETES MELLITUS

GDM is seen in the second and third trimesters of pregnancy without prior evidence of impaired glucose tolerance or diabetes. Though it resolves after birth it is associated with a higher risk of developing diabetes mellitus, hypertension, chronic renal disease and cardiovascular disease later in life.⁶⁰ GDM increases CVD risk by itself within a decade postpartum irrespective of development of Type 2 Diabetes mellitus (T2DM) later on. The risk includes coronary events, heart failure, and stroke, persisting even after adjusting for BMI, smoking, and comorbidities.⁶¹ GDM involves endothelial dysfunction which links the placenta and adipose tissue and is mediated by pro-inflammatory factors, oxidative radicals and endocrine signals. It may be a common pathway for both hypertensive disorders of pregnancy and GDM and increase long-term CVD risk.⁶²

HYPERTENSIVE DISORDERS OF PREGNANCY

Hypertensive disorders of pregnancy (HDP) include gestational hypertension, preeclampsia, and chronic hypertension and superimposed preeclampsia seen in 8-10% of pregnancies. They are associated with significant morbidity and mortality. The risk of cardiovascular disease is twofold in those with HDP as compared to normotensive pregnancies. There is a genetic susceptibility predisposing to HDP (for example, near FLT1 for angiogenesis) which also elevates CVD risk factors like systolic/diastolic BP and earlier onset of hypertension (OR 1.20-1.24 for CVD events). The vascular susceptibility of both HDP and CVD is probably the same, presenting at different stages.⁶³ A history of pre-eclampsia has the most severe long-term cardiovascular outcomes, including hypertension, coronary artery disease, heart failure, non-fatal stroke, venous thromboembolism, and type 2 diabetes.⁶⁴ HDP induce endothelial dysfunction, early atherosclerosis and decreased nitrous oxide availability with increase in systemic inflammation. This leads to plaque formation. After 6- 12 month postpartum screening should be done for CVD risks and then annually till 50 years of age. Monitoring of Blood pressure and lipid profile should be done.⁶⁵

OTHER PREGNANCY CONDITIONS

A woman with history of early miscarriages, small for gestation age babies, still births also has a higher risk of CVD later on. In these also endothelial dysfunction and thrombosis, and autoimmune conditions are seen.⁶⁶

HORMONAL CONTRACEPTIVES

These should be used with caution especially in women who are smokers, obese, have hypercoagulable states. The risk is increased with higher dose of estrogens.⁶⁷

BREAST CANCER TREATMENT

Anthracyclines and Trastuzumab used for treatment have a higher CVD risk. Anthracyclines are cardiotoxic and gradually decrease left ventricular ejection fraction. Follow up and assessment is necessary. Integration of preventive oncology into the breast cancer follow- up is essential.⁶⁸

FAMILY HISTORY

Family history of premature atherosclerotic cardiovascular disease(ASCVD) defined as occurrence of an ASCVD event in a male first-degree relative <55 years of age and in a female first-degree relative <65 years of age or before menopause identifies individuals at an elevated ASCVD risk. This may reflect various known and unknown genetic, environmental and epigenetic risk factors that may be prevalent in a family. In addition, the occurrence of early ASCVD among family members implies heightened risk of early ASCVD in descendants. Early screening for ASCVD risk factors and implementation of risk factor modification should be done.⁶⁹

HYPERTENSION

This is the most important risk factor for CVD. Less than 25% of hypertensive women have their blood pressure controlled. It may be due to a lack of awareness, limited access to health care and medications, economic reasons and poor compliance. With age hypertension increases both in men and women. Systolic blood pressure is lower in women than in men at a younger age, but it rises more rapidly in women with age. The responsiveness to antihypertensives is also less in women.⁷⁰ Hypertension is the most important modifiable risk factor for CVD. Screening and assessment for HT should be done and appropriate pharmacological and nonpharmacological treatment should be started early.¹⁷ Women with hypertension have a higher relative risk of developing heart failure as compared to men and especially a heart failure with preserved ejection fraction.⁷¹ They also have a higher lifetime risk of stroke as compared to men.⁷²

DIABETES

Cardiovascular diseases are much more prevalent in women with either Type 1 Diabetes mellitus (T1DM) or T2DM. Women with DM have a higher risk (25-50%) of myocardial infarction, heart failure and stroke as compared to men.⁷³ The UK Biobank study was a prospective population- based study. This included 471998 persons with 56% women and demonstrated a 50% excess risk of cardiovascular events in women as compared to men.⁷⁴ The risk is less if glycaemic control is good and associated renal disease is not there.⁷⁵

Lipoproteins are validated biomarkers for CVD. The major lipid category includes the triglycerides(synthesised by the liver and used as the source of energy and storage in the adipose tissue) and the cholesterol(precursors of steroid

hormones, maintain structure and function of cell membrane), phospholipids (maintain structure and function of cell membrane) and free fatty acids (source of energy). All plasma lipoproteins contain cholesterol, triglycerides, phospholipids and the specific proteins. These plasma lipoproteins are based on the differing and increasing particle density (which is based on the percentage contribution from the lipid and protein components) are classified as chylomicrons, very low-density lipoprotein (VLDL), LDL and HDLs contain the bulk of the triglycerides, LDLs are the most cholesterol rich and HDL contain 50% protein and serve as a reservoir for the key lipoproteins and act as scavengers of cholesterol. Apolipoproteins are the circulating lipoproteins that transport the lipids to and from the liver and to other tissues. Apolipoprotein A1 is the protein constituent of HDL. Apolipoprotein B is the chief protein constituent of the atherogenic LDL and VLDL. Of clinical significance is the fact that apolipoprotein A is not affected by triglyceride levels, unlike LDL, HDL, and total cholesterol levels, which are inaccurate if triglycerides are greater than 400 mg/dL. An increase in triglycerides by greater than 500 mg/dL is due to an increase in chylomicrons and VLDL and may be due to a genetic or a secondary cause like the use of steroids, oral estrogens, alcohol abuse, renal disorders, uncontrolled diabetes and severe hypothyroidism. It is important to remember that triglyceride levels of greater than 500 mg/dL can precipitate pancreatitis.

LIPOPROTEIN(A)

It is genetically predetermined and cannot be decreased by lifestyle modifications or by use of 3-hydroxy-3-methylglutaryl coenzyme A (HMG- CoA) reductase inhibitors (statin drugs). Currently, niacin and estrogen are the only substances known to reduce Lp(a), suggesting that a subset of women with elevated Lp(a) levels may benefit from HT for CHD prevention.

DYSLIPIDAEMIA

Deranged lipid profiles are strong risk factors for IHD in women. There may be a familial increase in cholesterol levels, or they may be due to environmental factors such as a sedentary lifestyle, diet, and comorbid conditions. Lipoprotein a (Lpa) levels increase during MT. This increase in LDL levels may be due to the menopause transition rather than ageing alone. Total cholesterol(TC) values are also higher in women than in men. The Indian dyslipidemic profile is characterised by elevated triglyceride levels and low HDL-C. Levels of Lpa are higher in Asian Indians than in non-Hispanic White individuals. It is an independent risk factor for CVD. An analysis from INTERHEART reflected an association between high Lpa and increased risk among Chinese and South Asians adults. The sex specific data were not mentioned.⁴⁶

HIGH-SENSITIVITY C-REACTIVE PROTEIN

Robust evidence demonstrates that elevated C-reactive protein (CRP) is associated with an increased risk of arterial CVD, including myocardial infarction and ischaemic stroke, while its association with venous thromboembolism is inconsistent and not well established.^{76,77} CRP is synthesised predominantly by hepatocytes, with hepatic production primarily regulated by interleukin-6 (IL-6) and, to a lesser extent, interleukin-1 β .⁷⁸ Although CRP expression has been demonstrated within atherosclerotic plaques, the liver remains the principal source of circulating CRP.⁷⁶ Women using oral estrogen therapy exhibit higher circulating CRP concentrations compared with non-users, whereas transdermal estrogen has minimal or no effect on CRP levels.⁷⁹ Plasma IL-6 concentrations have been shown to be lower among women using menopausal hormone therapy, suggesting that the CRP-raising effect of oral estrogen therapy is largely mediated by first-pass hepatic stimulation rather than cytokine-driven systemic inflammation.⁷⁸ The clinical relevance of estrogen-associated increases in CRP remains uncertain, as these changes have not been consistently linked to higher cardiovascular event rates.³ CRP is an acute-phase reactant and rises substantially during infectious and inflammatory conditions. Measurement of high-sensitivity CRP (hs-CRP) enables detection of low-grade inflammation and is widely used for cardiovascular risk stratification in asymptomatic individuals^{1,2} and in combination with LDL-C and Lp(a), it will effectively predict CVD events.⁴

HOMOCYSTEINE

Homocysteine is a sulphur-containing amino acid formed during the metabolism of methionine, with major sources being dietary animal protein. Hyperhomocysteinaemia is recognised as an independent risk factor for CVD and is known to increase with advancing age, menopause, smoking, and deficiencies of vitamin B6, vitamin B12, and folate.⁸⁰ Data from the Women's Health Study, which included 28,263 apparently healthy postmenopausal women, demonstrated a strong, graded association between elevated plasma homocysteine levels and incident cardiovascular

events, independent of traditional risk factors.³ These findings are supported by multiple retrospective and prospective cohort studies linking elevated homocysteine to coronary artery disease, stroke, and cardiovascular mortality.⁸¹

However, while homocysteine is a consistent risk marker, its role as a therapeutic target for secondary prevention of CVD remains unproven, as vitamin supplementation trials have not consistently reduced cardiovascular events.⁸¹ Indian studies have reported a very high prevalence of hyperhomocysteinaemia, affecting approximately 77–84% of adults, in contrast to 5–7% in Caucasian populations.⁸² This marked disparity is largely attributed to nutritional vitamin B12 deficiency, vegetarian dietary patterns, and genetic factors. In the Indian context, homocysteine is particularly important as a population-level risk marker, with potential relevance for primary prevention strategies, especially through nutritional interventions and early risk stratification.⁸³

CHRONIC KIDNEY DISEASE

Cardiometabolic risk factors have been lately associated with chronic renal disease. Chronic renal disease has been included into scores for calculating risk assessment for CVD. The association has been termed as cardiovascular kidney metabolic syndrome. Prevalence is less in women but mortality is more than men.⁸⁴

AUTOIMMUNE DISEASES

Autoimmune diseases are seen more commonly in females. They are associated with increased atherosclerosis and ischaemic heart disease. Systemic lupus erythematosus and T1DM have a higher risk of CVD.⁸⁵

ANAEMIA

Evidence from the Women's Ischaemia Syndrome Evaluation (WISE) study demonstrated that lower haemoglobin levels were independently associated with a higher risk of adverse cardiovascular outcomes in women presenting with ischaemic-type symptoms, irrespective of the presence or severity of obstructive coronary artery disease.⁴⁹

Anaemia may contribute to myocardial ischaemia through reduced oxygen-carrying capacity, increased cardiac workload, and endothelial dysfunction, and should be regarded as a modifiable cardiovascular risk marker.

This association is particularly relevant in the Indian context, given the high prevalence of anaemia among women of reproductive age. According to the National Family Health Survey (NFHS-4, 2015–16), 50.8% of urban women and 53.1% of rural women aged 15–49 years are anaemic.⁸⁶

Given its widespread prevalence and correctable nature, anaemia represents an important and often under-recognised target for cardiovascular risk reduction, particularly in midlife and menopausal women. Anaemia should be actively screened and appropriately corrected across the reproductive menopausal transition as part of comprehensive cardiovascular risk assessment, particularly in populations with a high background prevalence.

LIFESTYLE RISK FACTORS

OBESITY

Obesity is a high risk for CVD. It is associated with T2DM and more so in women. As shown by the Nurses Health Study obesity has a relative risk of Diabetes of 40% in excess if BMI exceeded $\geq 35 \text{ kg/m}^2$ than those with a BMI $< 23 \text{ kg/m}^2$.⁸⁷ Visceral adiposity is linked with an increase in inflammatory markers like IL-6 which cause insulin resistance and increased CVD risk.⁸⁸

DIET AND SEDENTARY LIFESTYLE

Unhealthy diet with increased fats and sweetened beverages is a risk factor for CVD. A healthy balanced plant based diet is recommended.^{6,89} Women are less physically active than men. A sedentary lifestyle is a known cause of increased CVD.⁹⁰ Initiatives to increase physical activity of girls and sports should be encouraged at childhood levels.

SMOKING, TOBACCO AND BETEL NUT CHEWING

Globally younger women are smoking and using electronic cigarettes, vape pens. This increases the risk of CVD associated with smoking and is 25% higher than in men.⁹¹ Conversely, the INTERHEART study found that the risk of myocardial infarction associated with smoking was similar for both women and men. Added research is needed to

evaluate interaction between outcomes of smoking in different sexes for CVD.⁹² Tobacco is chewed, used smokeless and chewing betel quid or areca nut consumption is prevalent in Asia. It has been shown to increase IHD risk.⁹³

UNDER-RECOGNISED RISK FACTORS IN WOMEN

Psychosocial Risk Factors

Depression and anxiety are associated with increased risk of cardiovascular disease morbidity and mortality. Depression is an independent and long-term risk factor for both obstructive and non-obstructive coronary artery disease in women.^{94,95}

Abuse and Intimate Partner Violence

Physical and psychological abuse of women and, in particular, intimate partner violence, affects 15–71% of women in their lifetime. Analysts suggest that intimate partner violence is associated with an increased incidence of cardiovascular disease.⁹⁶

ENVIRONMENTAL RISK FACTORS, SOCIOECONOMIC STATUS

Air pollution, including domestic air pollution from cooking, affects women and is recognised as a risk factor for cardiovascular disease. This may present as increased risk of coronary artery disease, heart failure, cardiac arrhythmias or cardiac arrest, and cerebrovascular disease or thromboembolism.⁹⁷ A large meta-analysis found that low income, low levels of education, and living in disadvantaged areas are strongly associated with cardiovascular risk in women.⁹⁸

CORONARY ARTERY CALCIUM SCORE

The presence of calcium in the coronary arteries invariably confirms the presence of coronary atherosclerosis. There are some exceptions, like calcification, which may be seen in chronic kidney disease and hyperparathyroidism without atherosclerosis. However, its absence does not rule out atherosclerosis.

ROLE OF GYNAECOLOGIST/MENOPAUSE SPECIALIST

AWARENESS OF HEALTH CARE PROVIDER FOR CARDIOVASCULAR DISEASE

RISK IN WOMEN

The Gynaecologists and health care workers need to be made aware of CVD risk in women, about the risk factors, screening, risk assessment scores and management.

Pregnancy may be the first clinical encounter of a woman with a health care provider. The opportunity should not be lost to counsel her about ideal weight, a healthy balanced diet, the advantages of screening for hypertension, diabetes and cancer. If there are comorbidities like GDM, preeclampsia, obesity or other pregnancy risk factors like abortion, prematurity, small for gestational age baby postpartum counselling is a must to be followed by appropriate follow ups, and investigations for timely prevention of cardiovascular disease.

Gynaecologist treating any woman for a menopausal complaint should include risk assessment for CVD and screening in their protocol.

HISTORY

When woman meets a gynaecologist for any problem detailed history should be taken. This should include presenting complaints, history of PCOS, infertility, hypertension, diabetes, autoimmune disorders, pregnancy complications, premature menopause, addictions like tobacco alcohol, diet and physical activity should be asked. Family history of medical diseases, CVD, cancers should be recorded.

EXAMINATION

A detailed general physical examination should be carried out. Blood pressure, BMI, waist circumference, signs of dyslipidaemia like xanthomas or corneal arcus should be noted. Systemic and gynaecological examination as indicated should be done.

INVESTIGATIONS

Haemogram, fasting blood sugar levels, HbA1c, Thyroid functions, Lipid profile, urine routine examination should be done and others like imaging should be done as indicated.

CARDIOVASCULAR RISK ASSESSMENT SCORES

Cardiovascular risk factors have been identified as mentioned over the years. Multiple risk factors together in a person determine the probability of having CVD later on. Over the years various risk prediction models or scores have come up to determine the risk for a person to have a fatal or a non fatal cardiovascular event over a specific period.

Indian population has early onset ASCVD due to which the screening has to start early and so are the preventive measures. The conventional clinical ASCVD risk assessment tools do not work for Indians. Life time risk becomes more important in place of 10 year risk.⁶⁹ The pooled cohort equations (PCE) are commonly used tools for prediction of ASCVD risk but underestimate risk in South Asians and this population has not been included in the cohort. However QRISK 3 score is better for risk assessment in Indians as Asians in United Kingdom were included. The QRISK3 score, used in the NHS, incorporates additional factors such as mental illness, autoimmune diseases, and CKD. Many CVD risk prediction models are used including Framingham risk score, American College of Cardiology and American Heart Association (ACC/AHA guidelines, Systematic COronary Risk Evaluation (SCORE), and SCORE2.⁹⁹

FRAMINGHAM RISK SCORE

It was developed for calculating Cardiovascular risk score using data from Framingham heart study population. It is used for the 10 year risk assessment for CVD in asymptomatic men and women without CVD or Diabetes. It is widely used. Major risk factors for CVD used in the score are age, sex, cigarette smoking, hypertension (blood pressure 140/90 mm Hg or on antihypertensive medication), low HDL cholesterol <50mg/dl.

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE RISK CALCULATOR

It calculates 10 year risk for atherosclerotic disease and helps to decide for statin therapy. It is to be calculated for those patients who never had atherosclerotic disease in the past. Risk is divided as follows:

Risk Category	10-Year ASCVD Risk
Low risk	< 5%
Borderline risk	5–7.4%
Intermediate risk	7.5–19.9%
High risk	> 20%

Ten year risk is calculated for patients between age 40-79 years and lifetime risk is for age 20- 59 years.¹⁰⁰

SCORE: SYSTEMATIC CORONARY RISK EVALUATION SCORE

SCORE: Systematic coronary risk evaluation score was recommended by European Society of Cardiology. It assesses 10 year risk for mortality from CVD in healthy individuals. It includes age, total cholesterol, or ratio of total cholesterol and high density lipoprotein, systolic Blood pressure and smoking status.¹⁰¹

SCORE2

SCORE2 was given to predict the 10 year risk of first onset of CVD and SCORE 2-OP for older individuals including diabetes mellitus

PREVENT: PREDICTING RISK OF CARDIOVASCULAR DISEASE EVENTS

The Pooled cohort equation risk assessment for ASCVD over estimated risk of statin use. The American heart association published PREVENT equations to replace previous ASCVD risk calculator. This removed race from the risk. Kidney disease was addressed by using kidney biomarkers and social deprivation index was used. The prediction is for

total cardiovascular disease including ASCVD and heart failure. Heart failure was not previously included. Less than 7% of the cohort were Asians or Hispanic. So it cannot be used as a generalisation for Asian population.

The Pooled cohort equation risk assessment for ASCVD over estimated risk of statin use. The American heart association published PREVENT equations to replace previous ASCVD risk calculator. This removed race from the risk. Kidney disease was addressed by using kidney biomarkers and social deprivation index was used. The prediction is for total cardiovascular disease including ASCVD and heart failure. Heart failure was not previously included. Less than 7% of the cohort were Asians or Hispanic. So it cannot be used as a generalisation for Asian population.

PREVENT Predicts 10- and 30-year risk of CVD and CVD subtypes in patients aged 30-79 without known CVD. There are two PREVENT equations: (1) PREVENT Base and (2) PREVENT Full (PREVENT Base plus urine albumin/creatinine ratio, glycated haemoglobin, and SDI).¹⁰²

QRISK SCORE

This is used widely in United Kingdom and estimated 10 year risk of CVD. The latest updated is QRISK3. It includes apart from age, systolic blood pressure, BMI, TC/HDL ratio, smoking, family history of premature CAD, diabetes, antihypertensives, added risk factors like deprivation, ethnic origin, rheumatoid arthritis, chronic kidney disease, migraine, steroid use, systemic lupus erythematosus, mental illness, HIV/AIDS among others. Separate risk scores are there for men and women. Certain women specific factors have been added. The base population also included south Asian cohort. It can be used for Indian population.¹⁰³

All above tools have been beneficial for CVD risk prediction but have been made and tested in Europe and America. The risk and population characteristics differ across countries and regions so they are not useful for South Asia including India.

WORLD HEALTH ORGANIZATION/INTERNATIONAL SOCIETY OF HYPERTENSION CARDIOVASCULAR RISK PREDICTION CHARTS

These are available for India (South Asia) and are simple to use. The World Health Organization/International Society of Hypertension (WHO/ISH) risk prediction charts predict the 10-year risk for fatal or nonfatal cardiovascular events based on the age, gender, systolic blood pressure (SBP), smoking status, diabetic status, and blood cholesterol levels.

WHO updated the CVD risk charts in 2019. Risk-prediction charts provided for different ethnic-geographic regions. South Asian region was also included. However individual country wise chart was not there. It has a laboratory and non-laboratory form which is available. It is externally validated in numerous studies. Risk distribution assessed in datasets representing 79 countries.

GLOBORISK CHART

Globorisk chart is a new CVD risk calculator that is country-specific developed by Harvard School of public health. Globorisk has been validated and calibrated using data from 182 countries and its external validity has been examined in different regions.^{104,105} It predicts the risk of fatal or nonfatal cardiovascular event for patients at country level. Globorisk CVD risk prediction equations have a laboratory-based and non-laboratory-based version. Laboratory-based models estimate CVD risk using age, sex, SBP, smoking, diabetes, and cholesterol. Non-laboratory-based estimated CVD risk using age, sex, smoking, SBP, and BMI.¹⁰⁶ The Globorisk and Reynolds risk scores are designed for CVD-naïve women. Globorisk-India estimates the 10-year probability of a first fatal or nonfatal myocardial infarction (MI) or stroke, not procedure-based events.

GLOBORISK-INDIA (PRIMARY RECOMMENDATION)

Globorisk-India (laboratory or non laboratory version) as the First-line tool for women aged 35 years. After estimating baseline risk, reclassify upward if any female-specific risk enhancer is present. Manage according to the revised risk category. Advantages of Globorisk-India (2023): Include its calibration specifically for the Indian population, availability of both laboratory-based and nonlaboratory versions suitable for urban and rural settings, ease of use via mobile or paper-based tools, and its ability to provide more accurate, context-appropriate risk estimates than Western models. It is also cost-effective, scalable, and well-suited for integration into national women's

health and NCD screening programmes.¹⁰⁷

How to calculate Globorisk-India tool

- Access: Use the web calculator at www.globorisk.org or the validated desk/pocket chart
- Collect core data: Age, sex (female), systolic blood pressure (mmHg), BMI or total cholesterol, diabetes (yes/no), and smoking (yes/no)
- Select version: Nonlaboratory for PHC/outreach use. Laboratory-based for hospitals or specialist clinics.

Interpret Risk

- <10% = Low → Lifestyle optimisation
- 10%–20% = Moderate → Intensified lifestyle ± pharmacotherapy.
- 20% = High → Comprehensive medical management (blood pressure [BP], lipids, glycaemia).

Integrate female-specific modifiers into clinical judgement: Premature or EM (<45 years) history of gestational diabetes, preeclampsia, or PCOS, autoimmune disease, hypothyroidism, or chronic inflammatory disorders.

Upgrade risk category: If any one modifier → move up one tier (Low → Moderate; Moderate → High). If two or more modifiers or modifier + diabetes/dyslipidaemia → move up two tiers.

Document: Globorisk-India = %; upgraded due to-modifier.

REYNOLDS RISK SCORE (SECONDARY RECOMMENDATION)

It has a version which specially assesses CVD risks in women. This risk score uses information on age, systolic blood pressure, high-sensitivity C-reactive protein, TC, HDL, glycated haemoglobin (HbA1c) in women with diabetes, smoking, and family history of premature myocardial infarction to predict 10-year CVD risk. Reserved for women 45–80 years of age with no prior CVD but ambiguous results on standard scores. It incorporates hs-CRP to account for inflammation as a risk factor. Also includes familial (parental MI) factor for greater precision in borderline-risk cases.¹⁰⁸ However, the derivation cohort consisted predominantly of white, middle- to upper-socioeconomic status women, which may limit its generalisability. The Reynolds risk score is available online.^{109,110} Reassess every 3–5 years or when major risk factors change.

ADDITION OF CORONARY ARTERY CALCIUM SCORES

If after using the risk calculating charts there is a lack of decision for initiation of preventive therapy coronary artery calcium (CAC) scores may be assessed by non contrast CT to enhance the risk assessment. CAC is effective in predicting CVD risk among women who may have been labelled as low risk inspite of some high risk features.^{111,112} A CAC score of more than 100 or higher is considered high risk and should seriously start preventive care.¹¹³ Women with extensive CAC in multiple vessels have a higher mortality due to CVD than men. Patient knowledge about the score helps them to adhere to the treatment and life style changes counselled.

THERAPEUTIC LIFESTYLE MANAGEMENT

Lifestyle modifications are important to prevent CVD over a larger frame of time. Modifiable risk factors for CVD can be influenced through these. Adopting a healthy diet, regular physical activity, quitting smoking, managing stress and achieving a healthy weight target these risk factors and reduce them.^{114,115} Lifestyle modifications offer a comprehensive approach to CVD prevention. Unlike pharmaceutical interventions that target specific pathways or risk factors, lifestyle modifications impact multiple risk factors simultaneously. Lifestyle modifications provide long-term benefits for cardiovascular health. By adopting healthy habits early in life and maintaining them over time, individuals can significantly reduce their risk of developing CVDs in the future.¹¹⁶

DIET

It is important to have a heart healthy diet to prevent CVD. High LDL is a major risk factor for atherosclerosis. Intake of saturated and trans fats should be decreased to maintain optimal cholesterol levels and prevent plaque formation. Diet

should be rich in fruits, vegetables, whole grains and low fat dairy products. Dietary approaches to stop hypertension (DASH) diet effectively helps to lower blood pressure. It guides to use foods low in sodium and high in potassium, magnesium and calcium. It improves lipids also.¹¹⁷ Chronic inflammation is a risk factor for developing CVD. Anti inflammatory diet comprising of fatty fish rich in omega-3 fatty acids, nuts, seeds, whole grains, fruits help in promoting cardiovascular health.¹¹⁸

MEDITERRANEAN DIET

This is characterised by plant based foods including fruits, grains, vegetables and nuts. Olive oil is the primary source of fat. Fish and poultry is encouraged. It improves lipid profiles by improving high density lipoproteins levels. It also improves endothelial function and insulin sensitivity.^{119,120} Antioxidants, such as vitamins C and E, beta-carotene, and polyphenols, have been associated with cardiovascular benefits. They help reduce oxidative stress and inflammation, which are involved in the development of CVDs.

PHYSICAL ACTIVITY AND CARDIOVASCULAR HEALTH

Aerobic exercise involves cardiovascular exercise. The activities increase heart rate. This would include running, cycling, climbing. Resistance training is strength or weight training and uses resistance equipment or weights. This improves muscular strength and has cardiovascular benefits. Combined training includes both aerobic and resistance training in a single programme. Improves cardiovascular health and overall fitness. This reduces blood pressure, improves lipid profiles and improves insulin sensitivity.¹²¹ The target for adult exercise should be 30 minutes of moderate intensity workout or aerobic exercise per day or 150 minutes per week. 75 minutes of vigorous intensity aerobic exercise per week may be done. Moderate intensity exercise are brisk walk, cycling at a moderate pace, dancing. Vigorous exercises are running, cycling at high speed, aerobic dancing. Duration can be increased to 300 minutes for moderate and 150 minutes for vigorous exercise per week. Resistance training should have strength training at least two days a week. All major muscle should be targeted. Variety of exercises using body weight, resistance bands can be done. The resistance used can be increased over time.¹²²

TACKLING OBESITY, MAINTAINING A HEALTHY WEIGHT

To optimise weight and BMI in range of 18.5-23 kg/m² and a waist circumference till 80 cm a healthy diet is very important. Nutrient dense foods less in calories should be used. Lean proteins, fibre rich foods and healthy fats with regular exercise would go a long way to prevent obesity. Weight loss goals should target a loss of 10% of body weight over 6 months or a loss of 1-2 pounds per week. A reduction of 500-1000 calories per day may be achieved. BMI should be measured yearly. Surgery and pharmacotherapy should be individualised.¹²³

SMOKING CESSATION AND CARDIOVASCULAR HEALTH

Smoking is a well-established risk factor for CVDs. It acts through causing endothelial dysfunction, inflammation, oxidative stress, lipid abnormalities, platelet activation, thrombosis, increased blood pressure, coronary spasm, and impaired cardiac function. Apart from primary smoker second-hand smoke exposure (inhalation of smoke from others) is a risk. Quitting smoking significantly reduces the risk of developing CVDs and improves overall health.^{124,125}

STRESS MANAGEMENT AND CARDIOVASCULAR HEALTH

Chronic stress increases CVD risk by causing chronic inflammation, activation of sympathetic symptoms leading to stress and anxiety. Dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis occurs with changes in blood clotting and platelet function, and unhealthy coping behaviours. Disrupted sleep, anxiety, depression occurs and social isolation may also happen. Yoga, meditation, relaxation techniques, regular exercise and cognitive behaviour therapy are important. Mindfulness based stress reduction (MBSR) should be practised.¹²⁶ Lifestyle interventions improve blood pressure (SBP and DBP) and blood lipid (triglycerides, HDLc and LDLc) profiles in adult South Asians. These findings suggest that diet and/or physical activity interventions be actively promoted among the South Asian population in order to lower their cardiovascular risk.¹¹⁵

Table 2: Optimal Targets for Cardiovascular Disease Risks

Parameter	Target
Lipid Targets	
Total cholesterol	< 160 mg/dL
LDL cholesterol	< 100 mg/dL
HDL cholesterol	> 50 mg/dL
Triglycerides	< 150 mg/dL
Physical Targets	
Waist circumference	< 80 cm (31 inches) for wome
Body Mass Index (BMI)	< 23 kg/m ²
Blood Pressure	
Standard target	< 130/85 mmHg
High-risk target (diabetes, heart failure, end-organ damage)	< 130/85 mmHg
Glycaemic & Lifestyle Targets	
HbA1c (in diabetic women)	< 7.0%
Sleep duration	7–8 hours per day

Antihypertensives: Thiazide diuretics (such as chlorthalidone and indapamide) are the preferred first-line antihypertensive agents unless contraindicated. Angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, and calcium- channel blockers may be added or substituted as required to achieve optimal BP control.¹²⁷

HYPERTENSION

Blood pressure should be measured for all individuals visiting a clinic or for those at high risk every 6 months. Health care providers should be aware of recommendations for the general population.

Measurement should be in a seated position and arms supported at heart level with feet on the floor. It should be measured after 5 minutes of rest. Cuff size should be appropriate. Those with elevated blood pressure should have it reconfirmed by taking multiple readings, even on separate days.¹²⁸

Hypertension is defined as a systolic blood pressure of ≥ 130 mmHg or a diastolic blood pressure ≥ 80 mmHg based on an average of two or more readings obtained on two or more occasions. Initiation of pharmacological BP-lowering therapy is again recommended for all individuals with stage 2 hypertension (BP $\geq 140/90$ mmHg).¹²⁹ However, in those with CVD risk and blood pressure of $\geq 180/110$ mmHg, a single reading is enough to diagnose. On treatment, the blood pressure goal should be $< 130/80$ mmHg; a systolic blood pressure goal of < 120 mmHg should be achieved in individuals with high cardiovascular or kidney risk.¹³⁰ The 2025 ACC/AHA guideline recommends initiating BP-lowering therapy for individuals with stage 1 hypertension (BP 130–139/80–89 mmHg) and clinical CVD, chronic kidney disease, diabetes mellitus, or a PREVENT 10-year total CVD risk of $\geq 7.5\%$.

Lifestyle management, reduced salt intake, less than 1.5 -2 g of sodium, equivalent to $\frac{3}{4}$ to 1 level teaspoon, regular antihypertensive therapy, treating obesity, decreased consumption of nonsteroidal anti-inflammatory drugs, and saturated fat intake not more than 7% will all go a long way toward controlling hypertension.¹²⁷

DIABETES MELLITUS

T2DM, defined as a haemoglobin A1c (HbA1c) >6.5%, is a metabolic disorder characterised by insulin resistance leading to hyperglycaemia. Unlike type 1 diabetes mellitus (an autoimmune condition largely unrelated to lifestyle factors), the development and progression of T2DM are heavily influenced by dietary patterns, physical activity, and body weight. The target should to maintain levels of HbA1c less than 7% in women with diabetes.

T2DM, defined as a haemoglobin A1c (HbA1c) >6.5%, is a metabolic disorder characterised by insulin resistance leading to hyperglycaemia. Unlike type 1 diabetes mellitus (an autoimmune condition largely unrelated to lifestyle factors), the development and progression of T2DM are heavily influenced by dietary patterns, physical activity, and body weight. The target should to maintain levels of HbA1c less than 7% in women with diabetes.

For adults with type 2 diabetes mellitus, lifestyle changes, such as improving dietary habits and achieving exercise recommendations, are crucial. If medication is indicated, metformin is first-line therapy, followed by consideration of a sodium-glucose cotransporter 2 inhibitor or a glucagon-like peptide-1 receptor agonist.¹³¹

Psychosocial factors such as depression, anxiety, and acute or chronic emotional stress are often observed to be more prevalent among women compared to men. Given the association between these factors and CVD risk, providers are recommended to identify and assist in managing them as part of CVD prevention.

PREVENTIVE DRUG REGIMEN

Beyond lifestyle optimisation, the interventions with the most consistent evidence for reducing first cardiovascular events are risk-based control of major modifiable factors, particularly blood pressure reduction and LDL cholesterol lowering with statins. Statins reduce CVD events in women for primary prevention with a benefit proportional to baseline risk. Therefore, statin therapy should be offered using a risk-based approach rather than sex based exclusion.^{132,133}

LIPID OPTIMISATION

For Indian midlife women, optimal lipid targets should aim for low-density lipoprotein cholesterol (LDL-C) <130 mg/dL in low-risk and <100 mg/dL (preferably <70 mg/dL) in higher-risk groups. Triglycerides <150 mg/dL and high-density lipoprotein cholesterol (HDL-C) >50 mg/dL are desirable. Early initiation of statin therapy is recommended when LDL-C exceeds these thresholds, particularly in the presence of South Asian ethnicity or other female-specific risk enhancers (such as premature menopause and gestational diabetes).¹³⁴

Current evidence supports the use of statin therapy in women with:¹³⁵

- Established clinical atherosclerotic cardiovascular disease (ASCVD);
- Primary hypercholesterolaemia, with low-density lipoprotein cholesterol of 190 mg/dL (4.9 mmol/L) or higher;
- Diabetes mellitus, regardless of ASCVD risk category (ages 40-75 y);
- For primary prevention of ASCVD in women at high risk (10-y risk, $\geq 20\%$) or intermediate risk (10-y risk, $\geq 7.5-20\%$) with the presence of guideline-derived risk enhancers (age 40-75 y), such as premature menopause or a history of preeclampsia

ASPRIN

Aspirin should be used infrequently in the routine primary prevention of ASCVD because of a lack of net benefit. Primary prevention in women without risk factors is not recommended at any age. Indian guidelines emphasise that, given the high burden of CVD, low-dose aspirin may be considered only in high-risk women ($\geq 10\%$ CVD risk), aged 40-60 years ($\geq$ two risk factors: diabetes, hypertension, CKD, family history, high LDL/Lp(a), CAC >100) with low bleeding risk, after shared decision-making and risk assessment.¹³⁶ Aspirin should not be given for primary prevention at ≥ 60 years.^{137,138} Aspirin therapy confers a conclusive nett benefit on the risk of subsequent MI, stroke, or vascular death among subjects at high risk of vascular complications.¹³⁹

THE ROLE OF MENOPAUSAL HORMONE THERAPY

MHT can alleviate many cardiovascular disease risk factors to varying degree, like visceral adiposity, lipid derangements and glucose impairment. Low- dose transdermal and oral MHT is safe in the context of CVD risk in

menopausal women if used within 10 years of menopause. The type of estrogen, its dose and route along with the different formulations of progestogen can lower concentrations of TC, LDL-C Lp(a) and increase concentration of HDL-C. There are no recommendations for the use of menopausal hormonal therapy for the intent of CVD primary prevention at this time. Long-standing evidence suggests either no benefit or increased risk for women when hormonal therapy is used.

However, researchers have and continue to investigate the potential for a “timing hypothesis” where hormonal therapy may be of benefit (related to CV risk) among women closer to the time of menopausal onset. Providers are recommended to review each woman’s risk factor profile and provide a tailored and shared decision-making discussion when menopausal hormonal therapy is considered, even among younger perimenopausal women. Lipoprotein(a) is a risk-enhancing factor. Estrogen therapy can lower Lp(a) but outcome evidence does not support prescribing systemic HT for CVD prevention.¹⁴⁰ Niacin also lowers Lp(a) but major trials failed to show cardiovascular benefit and demonstrated adverse effects. Therefore, niacin is not recommended for solely lowering Lp(a).¹⁴¹ PCSK9 inhibitors modestly lower Lp(a) and reduce events in high risk populations while dedicated Lp(a) targeting therapies are under investigation with outcomes pending.¹⁴²

ISCHAEMIC HEART DISEASE

Most of the knowledge about IHD is based on findings in men. The women’s data is under-represented. There are differences in clinical presentation between men and women. Women have atypical symptoms. Much of the foundational knowledge on ischaemic heart disease (IHD) is derived from studies conducted predominantly in men, resulting in under-representation of women in cardiovascular research. Consequently, important sex-based differences in pathophysiology, clinical presentation, and outcomes have historically been under-recognised.

A TYPICAL CLINICAL PRESENTATION

Women frequently present without classic exertional retrosternal chest pain. Instead, symptoms may include unusual fatigue, breathlessness, palpitations, epigastric discomfort, nausea, dizziness, or pain in the jaw, neck, back, or arms, rather than the typical chest heaviness seen in men. Silent or unrecognised myocardial infarction is also more common in women, particularly among older women and those with diabetes.^{100,101} Ischaemic heart disease in women is frequently under-recognised, under-diagnosed, and under-treated due to atypical presentation and non-obstructive coronary pathology. A sex-specific, mechanism-based approach is essential to improve diagnosis, treatment, and outcomes across the life course.

ISCHAEMIA WITH NON-OBSTRUCTIVE CORONARY ARTERIES

Ischaemia with non-obstructive coronary arteries (INOCA) is more common in women than men, with especially high prevalence among women aged 45–65 years.¹⁴³ All those with stable ischaemic heart disease were included. They had moderate or severe ischaemia on stress testing.¹⁴⁴ Out of these, those with nonobstructive coronary artery disease on coronary CT angiogram 34.4% of 1022 women were there compared to 11.3% men.

It is not necessary that INOCA would be diagnosed if coronary stenosis is not detected. These women should not be presumed to be without CAD. They still might be at increased risk of cardiac events and will need treatment. It may be coronary microvascular dysfunction or epicardial vessel spasm causing angina.^{145,146} In patients with nonobstructive coronary artery disease, high-risk preventive treatment with aspirin and statins should be started. If coronary microvascular dysfunction is diagnosed by coronary intravascular ultrasound, still treatment should be given because of high chances of atherosclerotic plaque formation.¹⁴⁷ Positive stress test, objective ischaemia (ST depression, reversible perfusion defect, or stress-induced wall motion change) despite nonobstructive coronaries (<50%) on angiography or CT suggests INOCA.^{143,148}

Obstructive coronary artery disease plaque rupture is the most common cause of myocardial infarction. An analysis of 27 clinical trials and registries showed a prevalence of 6-15% of MI without obstruction. The term myocardial infarction in absence of obstructive coronary artery disease (MINOCA) has been given. It may be caused by coronary artery dissection, coronary emboli or mimicked by myocarditis or pulmonary embolism.^{149,150} In women presenting with MINOCA, understanding the mechanisms of the underlying disease is essential in providing therapeutic options. Consideration of non-atherosclerotic causes of myocardial infarction is key to improving health outcomes of women globally.

ST SEGMENT ELEVATION MYOCARDIAL INFARCTION

ST-segment elevation myocardial infarction (STEMI) in women is usually caused by a ruptured plaque and thrombus formation. This is the most acute presentation of coronary artery disease and needs a primary coronary intervention within 120 minutes of first medical contact and a skilled team. Women present late, with atypical symptoms, delayed health care and intervention even after reaching the hospital and are less treated with protocol-based therapy. It is important to address these barriers at different levels, at home, at health care facilities, and by the woman herself.¹⁵¹

CHRONIC HEART FAILURE

Even though the overall incidence of heart failure is similar for women and men, pronounced sex differences are seen in specific heart failure phenotypes (heart failure with preserved ejection fraction vs heart failure with reduced ejection fraction; ischaemic vs non-ischaemic cardiomyopathy; takotsubo syndrome; and peripartum cardiomyopathy). Women are strikingly over-represented among patients with heart failure with preserved ejection fraction, especially in the oldest age categories.^{152,153}

Incidence of heart failure is similar in men and women, but sex differences are seen. In women, heart failure with preserved ejection fraction, as compared to that with decreased ejection fraction, and peripartum cardiomyopathy are common. In older women, heart failure with preserved ejection fraction is seen more commonly than in men. It is important to keep these points in mind when evaluating older women for heart failure.^{152,153}

STROKE

Stroke is the second leading cause of death worldwide. Stroke is defined as an acute-onset focal neurological deficit of vascular aetiology, persisting for more than 24 hours. It is of two types: ischaemic and haemorrhagic. Women suffer more strokes than men, mainly because of longer life expectancy, with a lifetime risk of 1 in 5 as compared to 1 in 6 in men. Prevalence increases only after age 85 in women. Women present 5 years later than men.¹⁵⁴

The Risk Assessment

The Framingham stroke risk profile (FSRP) was used initially and it has been updated to the new revised Framingham stroke risk profile (rFRSP) in 2018. This is because of a change in the risk factors, and better prediction is possible with the new profile.¹⁵⁵

Risk Factors

Increasing age, hypertension, diabetes, elevated fasting blood glucose smoking, tobacco use and obesity are the most important risk factors.⁴⁶

Menopause and Hypertension

Hypertension is the most important modifiable risk factor for stroke, with a strong and continuous relationship between systolic blood pressure and stroke risk, showing an exponential increase as systolic pressure rises. While systolic blood pressure is higher in men than women before 40 years of age, this pattern reverses after 60 years. Longitudinal studies indicate a rise in blood pressure beginning within the first year after menopause, becoming statistically significant within five years. Effective blood pressure control in postmenopausal women, as in men, remains the most effective strategy for primary stroke prevention, reducing stroke risk by approximately 40%.

Menopause: An Atherogenic State

During the MT changes in fat distribution, increased visceral fat, increased inflammatory markers and elevated lipid levels increase the incidence of coronary heart disease and stroke postmenopause.^{4,46,156}

Premature and Early Menopause, Vasomotor Symptoms

Women with premature or early menopause are associated with higher risk of CVD. Those with vasomotor symptoms are also predisposed to cardiovascular disease. Premature ovarian insufficiency increases the risk of stroke by 32%. Early menopause has a hazard ratio of 1.09. Primary prevention of CVD and screening for and managing risk factors are warranted for those with a history of premature and early menopause.

Vasomotor Symptoms

Those with vasomotor symptoms also have a higher cardiometabolic risk. Estrogen-based therapies are the most

effective treatments for moderate to severe vasomotor symptoms however oral estrogens increase the risk of stroke as seen in multiple RCTs and meta-analyses. Thus, risk factor assessment and evaluation of the individual benefits and risks of HT must be carefully considered before prescribing them. It is also important to note that topical estrogen treatments are not associated with stroke risk. The newer risk factors for stroke are, atrial fibrillation, inflammation, elevated lipids, chronic stress seen in younger women and depression.

Adverse Pregnancy Outcome

Women with adverse pregnancy outcome like hypertensive diseases of pregnancy, recurrent abortion, foetal growth restriction, placental abruption are at a higher risk of developing early onset cardiovascular disease later on. They should be counselled and made aware of the risk and optimised.¹⁵⁷

Endometriosis

Endometriosis has been associated with cardiovascular risk factors, including increased risk of hypertension and hypercholesterolaemia.¹⁵⁸

Hormonal Contraceptives

The overall rate of stroke in women using hormonal contraception is lower than the rate of stroke in women from pregnancy (30 in 100 000 pregnancies).¹⁵⁹ Harman et al. from Denmark did a prospective nationwide cohort study evaluation real world data titled Stroke and Myocardial infarction with contemporary hormonal contraception use. Current use of contemporary hormonal contraception, including combined oral contraceptive pills, vaginal ring, patch, progestin-only pills, and subcutaneous implant, was associated with an increased risk of ischaemic stroke and for some also myocardial infarction compared with no use. This increased arterial thrombotic risk was not seen by levonorgestrel releasing intrauterine device. This translated to low absolute excess risks. The highest statistically significant number per 100000 person years were 34 additional ischaemic strokes and 14 additional myocardial infarctions, with the use of combined pills containing third or fourth generation progestins. The increased risk with progestin-only pill, implant, and injection was accompanied by uncertainty due to limited data.¹⁶⁰

Clinical Presentation

Stroke occurs when blood circulation in the brain is disturbed, leading to focal or at times global loss of cerebral function. Mostly in 80% of cases, it is due to an arterial occlusion, rarely may occur as a result of haemorrhage from a cerebral vessel into the surrounding brain tissue. If the resulting neurological deficit resolves fully within 24 hours, the event is termed a “transient ischaemic attack” (TIA).

Symptoms

Patients with stroke typically experience symptoms characterised by sudden onset of a neurological deficit. The more common presentations include loss of motor power or sensation involving the face, arm and leg on ability to speak, comprehend speech, read or write due to involvement of the areas of brain responsible for the processing of language. Disturbances of blood flow through the brainstem and cerebellum may cause vertigo, ataxia, dysarthria, dysphagia and palsies of lower cranial nerves. Large strokes in this area cause extensive neurological deficits, including reduction in level of consciousness and quadriplegia. The spectrum of stroke is wide and varied, and the initial diagnosis may prove challenging. Modern management of cerebrovascular disease uses a variety of imaging modalities that enable clinicians to identify the nature and aetiology of the patient’s symptoms, and thus elicit optimal treatment.

Investigation

The diagnosis of stroke usually begins with clinical examination of a focal neurological deficit. Brain imaging is necessary so that cerebral haemorrhage can be reliably excluded. Conventional X-ray computed tomography (CT) will reliably detect intracerebral haemorrhage within 2 weeks of stroke.

However, if more than 2 weeks have elapsed, involutional change within the intracerebral haematoma makes haemorrhage hard to distinguish from infarct using CT scanning, and magnetic resonance imaging (MRI) may be required.

Prevention

Life’s Essential 8, is an educational tool to help everyone know how to stay healthy and prevent all forms of cardiovascular disease (CVD).¹⁵⁷ The 8 strategies are as follows: eat better, be more active, quit tobacco, get healthy

sleep, manage weight, control cholesterol, manage blood sugar, and manage blood pressure (BP). The prevention gap between various pathways to manage risk factors should be reduced. This phenomenon exists for behavioural risk factors like (low physical activity, poor diet quality, inadequate sleep duration), risk factors that respond to pharmacotherapy such as (high BP, dyslipidaemia, diabetes, and atrial fibrillation AF), and the most complex risk factors that are typically managed with combination behaviour change and pharmacology (such as cigarette smoking and high body weight).¹⁶¹

VENOUS THROMBOEMBOLISM

Venous thromboembolic disease (VTE) includes venous thrombosis and pulmonary embolism (PE). The incidence of VTE increases with age, with an annual incidence of 1.25/1000 women in the 40–59 age group, 2.36 in the 60–74 age group, and 7.87 after age 75 in 2013.¹⁶² Venous thromboembolism is seen more in women during pregnancy, puerperium, use of combined contraceptives and menopause hormone therapy. Men have a higher incidence with increasing age.¹⁶³

VENOUS THROMBOEMBOLISM: PHYSIOLOGICAL CHANGES IN COAGULATION

After Menopause

The menopause induces minor changes in the level of coagulation factors. These changes involve an increase in the level of clotting factors including levels of fibrinogen, factor VII and factor VIII, but also minor increases in the level of the coagulation inhibitors AT, PC56 and tissue factor pathway inhibitor (TFPI) suggesting an overall balanced physiological change of coagulation during and after menopause. Hence, incidence of VTE is not much increased in postmenopausal women.

RISK OF VENOUS THROMBOEMBOLISM IN POSTMENOPAUSAL WOMEN

- 1 per 10,000 patient-years—rare event
- 2–3 non-fatal VTE per year for every 10,000 women given HT—rare event
- Deaths from VTE: 1 per 1,000,000 patient-years—very rare event.

RISK FACTORS FOR VENOUS THROMBOEMBOLISM

Age, obesity, malignancy, immobilisation, history/ family history of VTE in the 1st degree relative before the age of 50, oral estrogen, specific selective estrogen receptor modulators (SERMs) are risk factors for VTE.

Obesity

Increased risk is associated with elevated coagulation factor levels, venous stasis, and physical inactivity.¹⁶⁴ Factor V Leiden (3–4x risk), prothrombin mutations, protein C/S deficiencies, or acquired thrombophilias greatly elevate the risk of VTE. Where hospitalisation is associated with reduced mobility for ≥3 days, or with surgery requiring general anaesthesia for more than 30 minutes, this is considered a major provoking factor for VTE.¹⁶⁵

Screening for Thrombophilia

Women with a personal history or a family history of venous thrombosis can be screened for risk factors to assist decision on the route of delivery for MHT. However routine thrombophilia screening for low-risk women before starting MHT is not considered necessary.

Clinical Presentation

The clinical presentation is nonspecific and varied. Deep venous thrombosis presents with unilateral pain in the leg, swelling and redness. Pulmonary embolism may be seen as breathlessness, cough, chest pain and dizziness. Examination may reveal hypotension, tachycardia, hypoxia and even cardiac arrest.

Assessment

History, family history, detailed examination should be done. Risk assessment, X-ray chest, ECG and D-dimer should be done. CT pulmonary angiography is the predominantly used imaging modality for the diagnosis of PE.

MANAGEMENT

The main aim of treatment to prevent progress of thrombosis and subsequent embolisation.¹⁶⁶ Anticoagulation is the main stay. Direct oral anticoagulants are the standard of care for VTE treatment and low molecular weight heparin and vitamin K antagonists are used for selected patients.

Thromboprophylaxis

There is no indication for stopping hormone replacement therapy preoperatively, and it is not necessary to stop oral contraceptives preoperatively in patients who are at low risk for venous thromboembolism. For major surgery with prolonged immobilisation (>30 min), COCs should ideally be discontinued 4–6 weeks before surgery to reduce the risk of VTE. If continued, appropriate perioperative VTE prophylaxis should be provided. In general, patients already on low-dose aspirin for primary or secondary cardiovascular prevention should discontinue it 5–7 days before surgery and restart it once haemostasis is confirmed. Patients should be encouraged to ambulate as soon as possible (within the first 24 h) after surgery in order to decrease the risk of venous thromboembolism. Intermittent compression stockings, when available, are preferred to graduated compression stockings. Either low-molecular-weight heparin or low-dose unfractionated heparin is recommended as the first choice for pharmacological thromboprophylaxis in most cases; dose adjustment of pharmacologic thromboprophylaxis is recommended for patients with a BMI >40 kg/m².¹⁶⁷

Hormones and Venous Thromboembolism

Women who acquire temporary risk factors for clotting including fracture of lower limbs, certain surgical procedures or any prolonged immobilisation may be advised to cease oral MHT in the short term. The use of compression stockings +/- short-term anticoagulation may be recommended.¹⁶⁸ In clinical practice, previous VTE and thrombophilias indicate a woman at higher risk and a transdermal estrogen preparation is preferred. Taking oral combined MHT will increase the “baseline” risk of thrombosis approximately twofold but a woman’s overall, or “absolute risk” risk will still be small, at about 2 in 1000 per year for women aged 50–59 years. Tibolone has been associated with an increased risk of stroke but the pooled data from four studies did not find that tibolone was associated with the risk of VTE.¹⁶⁹ In the recent study by Vinogradova et al., the combination of oral 17-β-estradiol and dydrogesterone was associated with the lowest risk of VTE (OR: 1.18 [0.98–1.42]) among HRT regimens containing oral estrogen therapy.¹⁷⁰

Risk of Recurrence of Venous Thromboembolism

The risk of recurrence of VTE in a woman with previous VTE depends on the setting in which that VTE has occurred. VTEs occurring after surgery have a very low risk of recurrence. Those with non-surgical trigger factors, such as immobilisation, fracture, plaster cast, COCP, have an 8% risk of recurrence at 2 years, compared with 20% in patients with unprovoked VTE.

VARICOSE VEINS

They are a form of chronic venous insufficiency. Healthy veins become dilated and tortuous. There is a valvular dysfunction and venous pressure which aggravate the condition. It has been postulated that the extracellular matrix around the veins and smooth muscle cells undergoes changes, and the veins dilate. Female sex hormones may play a predominant role in varicose physiopathology, especially considering the influence of gender and pregnancy on varicose vein development.¹⁷¹ The venous system is especially affected by changes in ageing, and the effects are unequal between the genders. Per the Framingham study, the annual occurrence of varicose veins is 2.6% in women and 1.9% in men.¹⁷² The number of estrogen and progesterone receptors in varicose veins was significantly higher in women when studied with semiquantitative methods.¹⁷³ Mashiah et al. found that both receptors were expressed in the adventitial vasa vasorum cells. These authors described a nonuniform distribution of these cells, with more estrogen and progesterone receptors (for both genders) in the varicose samples than in the controls.

The overexpression of estrogen and progesterone receptors and the redistribution of androgen receptors in the varicose vein wall support the hypothesis that hormones are involved in varicose vein pathophysiology. The hormonal decline at menopause may reduce the tensile strength of the vessel wall. Obesity and lack of exercise can also lead to blood stasis and dilatation of these veins, leading to varicose veins.

Management: Life style changes like weight reduction, exercise helps. Compression stockings and sclerotherapy are

the conservative options. Vein stripping is a surgical procedure. Laser therapy or endovenous ablation to remove or seal off problematic veins can be done. A vascular specialist or a provider trained in menopausal care can recommend the most appropriate intervention

ADVANCES

Machine learning (ML) integrates data and produces risk assessment scores that may more precisely estimate an individual patient's CVD risk. However, it cannot replace the clinician's expertise in diagnosis and clinical decisions. So ML should be part of clinical training to help doctors better understand and communicate.¹⁷⁴

PRIMORDIAL CARDIOVASCULAR DISEASE PREVENTION: ACT BEFORE THE RISK EMERGES

2026 trends in primordial CVD prevention focus on stopping risk factors before they emerge, emphasising early-life interventions and societal-level changes. This approach targets children and young adults to reshape long-term cardiovascular health

CARDIOVASCULAR HEALTH: LIFE'S ESSENTIAL⁸

A cardiovascular health initiative was proposed, based on 7 health behaviours. If they were optimised, they provided the longest CVD-free survival, greater longevity, and a higher quality of life. They included dietary quality, physical activity, body mass index, fasting blood glucose levels, total cholesterol, exposure to cigarette smoking, and blood pressure levels. Each metric was classified as poor, intermediate, or ideal on the basis of accepted clinical thresholds. The ideal is to have all metrics at ideal levels. Now sleep has been added as the 8th behaviour, now called Life's essential 8. Each metric is assigned a score of 0-100, with higher scores indicating more ideal behaviour. This generates a new composite cardiovascular health score, which is the unweighted average of all components. The patient can also calculate their score and follow it to upgrade and improve themselves.¹⁷⁵

Team-based care uses multidisciplinary health professionals to improve the quality and maintenance of ASCVD prevention. It is a multifaceted approach that supports clinical decision-making (ie, treatment algorithms), collaboration among different clinicians, and patient and family member participation to facilitate the treatment goals of patients. Decisions about primary prevention should be collaborative between a clinician and a patient. Shared decision-making is important. Socioeconomic inequalities are strong determinants of CVD risk internationally. Therefore, the clinician should tailor advice to a patient's socioeconomic and educational status, as well as cultural, work, and home environments.¹⁷⁶

SYNOPSIS

- Cardiovascular diseases are an important cause of mortality in women.
- Physicians, gynaecologists, and health workers should be aware of CVD risks, their calculation, and provide counselling on preventive therapies.
- Prevention should start from pregnancy, and preconception optimisation should be prioritised.
- Risk scores for CVD assessment, such as Globorisk charts, should be used by all and prevention measures implemented accordingly.
- Modifiable risk factors, including hypertension, diabetes, obesity, and dyslipidaemia, must be addressed.
- Lifestyle counselling is the key to maintaining good cardiovascular health.
- Blood pressure should be maintained below 120/80 mmHg. Pharmacotherapy should be initiated at 140/90 mmHg to avoid end-organ damage.
- HbA1c should be targeted to less than 7% in women with diabetes.
- Low-density lipoprotein (LDL) should be less than 100 mg/dL, with HDL greater than 50 mg/dL.
- Aspirin should only be prescribed in high-risk conditions.

- Other critical factors such as stress, depression, socioeconomic conditions, and environmental pollution must be addressed.
- MHT is not indicated for the primary or secondary prevention of cardiovascular diseases.
- “Life’s Essential 8” should be followed to support cardiovascular health.
- Women present differently with coronary artery disease; non-obstructive angina and MI may occur.
- Healthcare, diagnosis, and interventions should be provided to women with the same rigour as they are to men.
- Delays in diagnosis and treatment at various levels should be addressed.
- It is essential to incorporate Artificial Intelligence (AI) and Machine Learning (ML) into the clinical curriculum to improve outcomes, without replacing clinical expertise.

RESEARCH AGENDA

Adverse pregnancy outcome and association with cardiovascular disease at menopause.

REFERENCES

1. Di Cesare M, Perel P, Taylor S, Kabudula C, Bixby H, Gaziano TA, et al. The Heart of the World. *Global Heart* 2024;19(1):11. <https://doi.org/10.5334/gh.1288>
2. Tsao CW, Aday AW, Almarazooq ZI, Anderson CA, Arora P, et al. Heart Disease and Stroke Statistics-2023 Update: A Report From the American Heart Association. *Circulation*. 2023 Feb 21;147(8):e93-e621. <https://doi.org/10.1161/CIR.0000000000001123>
3. Kannel WB, Hjortland MC, McNamara PM, Gordon T. Menopause and risk of cardiovascular disease: the Framingham study. *Ann Intern Med*. 1976 Oct;85(4):447-52. <https://doi.org/10.7326/0003-4819-85-4-447>
4. El Khoudary SR, Aggarwal B, Beckie TM, Hodis HN, Johnson AE, Langer RD, et al. Menopause Transition and Cardiovascular Disease Risk: Implications for Timing of Early Prevention: A Scientific Statement From the American Heart Association. *Circulation*. 2020 Dec 22;142(25):e506-e532. <https://doi.org/10.1161/CIR.0000000000000912>
5. El Khoudary SR. Gaps, limitations and new insights on endogenous estrogen and follicle stimulating hormone as related to risk of cardiovascular disease in women traversing the menopause: A narrative review. *Maturitas*. 2017 Oct;104:44-53. <https://doi.org/10.1016/j.maturitas.2017.08.003>
6. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, et al. The Lancet women and cardiovascular disease Commission: reducing the global burden by 2030. *Lancet*. 2021 Jun 19;397(10292):2385-2438. [https://doi.org/10.1016/S0140-6736\(21\)00684-X](https://doi.org/10.1016/S0140-6736(21)00684-X)
7. Podfigurna A, Męczekalski B. Cardiovascular health in patients with premature ovarian insufficiency. Management of long-term consequences. *Prz Menopauzalny*. 2018;17(3):109-111. <https://doi.org/10.5114/pm.2018.78551>
8. Goossens GH, Jocken JWE, Blaak EE. Sexual dimorphism in cardiometabolic health: the role of adipose tissue, muscle and liver. *Nat Rev Endocrinol*. 2021 Jan;17(1):47-66. <https://doi.org/10.1038/s41574-020-00431-8>
9. Office of the Registrar General & Census Commissioner, India. Sample Registration System (SRS)-Cause of Death in India 2021-2023. New Delhi: Office of the Registrar General & Census Commissioner, India; 2025 Sep 3 [cited 2026 Feb 9]. Available from: <https://censusindia.gov.in/nada/index.php/catalog/46176>
10. Shannawaz M, Rath I, Shah N, Saeed S, Chandra A, Singh H. Prevalence of CVD Among Indian Adult Population: Systematic Review and Meta-Analysis. *Int J Environ Res Public Health*. 2025 Apr 1;22(4):539. <https://doi.org/10.3390/ijerph22040539>
11. India State-Level Disease Burden Initiative CVD Collaborators. The changing patterns of cardiovascular diseases and their risk factors in the states of India: the Global Burden of Disease Study 1990-2016. *Lancet Glob Health*. 2018 Dec;6(12):e1339-e1351. [https://doi.org/10.1016/S2214-109X\(18\)30407-8](https://doi.org/10.1016/S2214-109X(18)30407-8)
12. Kodali NK, Bhat LD, Phillip NE, Koya SF. Prevalence and associated factors of cardiovascular diseases among men and women aged 45 years and above: Analysis of the longitudinal ageing study in India, 2017-2019. *Indian Heart J*. 2023 Jan-Feb;75(1):31-35. <https://doi.org/10.1016/j.ihj.2022.12.003>
13. Kaur K, Abu-Qamar MZ, Rashidi A, McKay N, Saunders R. Knowledge and perceptions of modifiable ischaemic heart disease risk among Indians: Scoping review. *Collegian*. 2025;32(4):266-280. <https://doi.org/10.1016/j.colegn.2025.06.005>
14. Patel P, Krishnan NN, Shrivastava A, Dikid T, Bhan SC. Piloting surveillance of environmental risks and cardiovascular events in Delhi and Shimla, India, 2021. *Discover Public Health*. 2025;22:1299. <https://doi.org/10.1186/s12982-025-01299-7>
15. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *J Am Coll Cardiol*. 2017 Jul 4;70(1):1-25. <https://doi.org/10.1016/j.jacc.2017.04.052>
16. Barker DJP. The Developmental Origins of Adult Disease. *J Am Coll Nutr*. 2004 Dec;23(sup6):588S-595S. <https://doi.org/10.1080/07315724.2004.10719428>
17. Shahid I, Avenatti E, Titus A, Al-Kindi S, Nasir K. Primary Prevention of Cardiovascular Disease in Women. *Methodist DeBaakey Cardiovasc J*. 2024 Mar 14;20(2):94-106. <https://doi.org/10.14797/mdcvj.1313>
18. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. *Climacteric*. 2012;15:105-14. <https://doi.org/10.3109/13697137.2011.650656>
19. Sutton-Tyrrell K, Zhao X, Santoro N, Lasley B, Sowers M, Johnston J, et al. Reproductive Hormones and Obesity: 9 Years of Observation From the Study of Women’s Health Across the Nation. *Am J Epidemiol*. 2010 Jun 1;171(11):1203-13. <https://doi.org/10.1093/aje/kwq049>

20. Liu X, Chan HC, Ding G, Cai J, Song Y, Wang T, et al. FSH regulates fat accumulation and redistribution in aging through the Gai/Ca2+/CREB pathway. *Aging Cell*. 2015 Jun;14(3):409-20. <https://doi.org/10.1111/ace.12331>
21. Anagnostis P, Bitzer J, Cano A, Ceausu I, Chedraui P, Durmusoglu F, et al. Menopause symptom management in women with dyslipidemias: An EMAS clinical guide. *Maturitas*. 2020 May;135:82-88. <https://doi.org/10.1016/j.maturitas.2020.03.007>
22. El Khoudary SR, Wang L, Brooks MM, Thurston RC, Derby CA, Matthews KA. Increase HDL-C level over the menopausal transition is associated with greater atherosclerotic progression. *J Clin Lipidol*. 2016 Jul-Aug;10(4):962-969. <https://doi.org/10.1016/j.jacl.2016.04.008>
23. El Khoudary SR, Hutchins PM, Matthews KA, Brooks MM, Orchard TJ, Ronsein GE, et al. Cholesterol Efflux Capacity and Subclasses of HDL Particles in Healthy Women Transitioning Through Menopause. *J Clin Endocrinol Metab*. 2016 Oct;101(10):3419-3428. <https://doi.org/10.1210/jc.2016-2144>
24. Yan X-N, Jin J-L, Hong L-F, Guo Y-L, Wu N-Q, Zhu C-G, et al. Lipoprotein(a) Is Associated with the Presence and Severity of New-Onset Coronary Artery Disease in Postmenopausal Women. *J Womens Health (Larchmt)*. 2020 Apr;29(4):503-510. <https://doi.org/10.1089/jwh.2019.7773>
25. Serviente C, Tuomainen TP, Virtanen J, Witkowski S, Niskanen L, Bertone-Johnson E. Follicle-stimulating hormone is associated with lipids in postmenopausal women. *Menopause*. 2019 May;26(5):540-545. <https://doi.org/10.1097/GME.0000000000001273>
26. Anagnostis P, Stevenson JC, Crook D, Johnston DG, Godsland IF. Effects of menopause, gender and age on lipids and high-density lipoprotein cholesterol subfractions. *Maturitas*. 2015 May;81(1):62-8. doi: 10.1016/j.maturitas.2015.02.262. Epub 2015 Mar 6. PMID: 25804951.
27. Chedraui P, Escobar GS, Pérez-López FR, Palla G, Montt-Guevara M, Cecchi E, et al. Angiogenesis, inflammation and endothelial function in postmenopausal women screened for the metabolic syndrome. *Maturitas*. 2014 Mar;77(3):370-374. <https://doi.org/10.1016/j.maturitas.2014.01.014>
28. Davis SR, Lambrinoudaki I, Lumsden M, Mishra GD, Pal L, Rees M, Santoro N, Simoncini T. Menopause. *Nat Rev Dis Primers*. 2015 Apr 23;1:15004. <https://doi.org/10.1038/nrdp.2015.4>
29. Matthews KA, Crawford SL, Chae CU, Everson-Rose SA, Sowers MF, Sternfeld B, et al. Are Changes in Cardiovascular Disease Risk Factors in Midlife Women Due to Chronological Aging or to the Menopausal Transition? *J Am Coll Cardiol*. 2009 Dec 15;54(25):2366-2373. <https://doi.org/10.1016/j.jacc.2009.10.009>
30. Chedraui P, Pérez-López FR. Metabolic syndrome during female midlife: what are the risks? *Climacteric*. 2019 Apr;22(2):127-132. <https://doi.org/10.1080/13697137.2018.1561666>
31. Lerner DJ, Kannel WB. Patterns of coronary heart disease morbidity and mortality in the sexes: a 26-year follow-up of the Framingham population. *Am Heart J*. 1986 Feb;111(2):383-90. [https://doi.org/10.1016/0002-8703\(86\)90155-9](https://doi.org/10.1016/0002-8703(86)90155-9)
32. Stampfer MJ, Hu FB, Manson JE, Rimm EB, Willett WC. Primary Prevention of Coronary Heart Disease in Women through Diet and lifestyle. *N Engl J Med*. 2000 Jul 6;343(1):16-22. <https://doi.org/10.1056/NEJM200007063430103>
33. Stampfer MJ, Colditz GA, Willett WC. Menopause and Heart Disease. *Ann N Y Acad Sci*. 1990;592:193-203. <https://doi.org/10.1111/j.1749-6632.1990.tb30329.x>
34. Atsma F, Bartelink ML, Grobbee DE, van der Schouw YT. Postmenopausal status and early menopause as independent risk factors for cardiovascular disease: a meta-analysis. *Menopause*. 2006 Mar-Apr;13(2):265-79. <https://doi.org/10.1097/01.gme.0000218683.97338.ea>
35. Rocca WA, Grossardt BR, Shuster LT. Oophorectomy, menopause, estrogen treatment, and cognitive aging: Clinical evidence for a window of opportunity. *Brain Res*. 2011 Mar 25;1379:188-198. <https://doi.org/10.1016/j.brainres.2010.10.031>
36. Parker WH, Broder MS, Chang E, Feskanich D, Farquhar C, Liu Z, et al. Ovarian Conservation at the Time of Hysterectomy and Long-Term Health Outcomes in the Nurses' Health Study. *Obstet Gynecol*. 2009 May;113(5):1027-1037. <https://doi.org/10.1097/AOG.0b013e3181a11c64>
37. Zhu D, Chung HF, Dobson AJ, Pandeya N, Giles GG, Bruinsma F, et al. Age at natural menopause and risk of incident cardiovascular disease: a pooled analysis of individual patient data. *Lancet Public Health*. 2019 Oct;4(10):e553-e564. [https://doi.org/10.1016/S2468-2667\(19\)30155-0](https://doi.org/10.1016/S2468-2667(19)30155-0)
38. Thurston RC, Sutton-Tyrrell K, Everson-Rose SA, Hess R, Powell LH, Matthews KA. Hot flashes and carotid intima media thickness among midlife women. *Menopause*. 2011 Apr;18(4):352-358. <https://doi.org/10.1097/GME.0b013e3181fa27fd>
39. El Khoudary SR, Shields KJ, Janssen I, Budoff MJ, Everson-Rose SA, Powell LH, et al. Postmenopausal Women With Greater Paracardial Fat Have More Coronary Artery Calcification Than Premenopausal Women: The Study of Women's Health Across the Nation (SWAN) Cardiovascular Fat Ancillary Study. *J Am Heart Assoc*. 2017 Jan 29;6(2):e004545. <https://doi.org/10.1161/JAHA.116.004545>
40. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender differences in cardiovascular disease prevention: what a difference a decade makes. *Circulation*. 2011 Nov 8;124(19):2145-2154. <https://doi.org/10.1161/CIRCULATIONAHA.110.968792>
41. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, et al. A Prospective Study of Obesity and Risk of Coronary Heart Disease in Women. *N Engl J Med*. 1990 Mar 29;322(13):882-889. <https://doi.org/10.1056/NEJM199003293221303>
42. Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. *BMJ Glob Health*. 2017 Mar 1;2(2):e000298. <https://doi.org/10.1136/bmjgh-2017-000298>
43. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report. *Circulation*. 2002 Dec 17;106(25):3143-3421. <https://doi.org/10.1161/circ.106.25.3143>
44. Colditz GA, Willett WC, Stampfer MJ, Rosner B, Speizer FE, Hennekens CH. Menopause and the Risk of Coronary Heart Disease in Women. *N Engl J Med*. 1987 Apr 30;316(18):1105-1110. <https://doi.org/10.1056/NEJM198704303161801>
45. Lisabeth LD, Beiser AS, Brown DL, Murabito JM, Kelly-Hayes M, Wolf PA. Age at Natural Menopause and Risk of Ischemic Stroke. *Stroke*. 2009 Apr;40(4):1044-1049. <https://doi.org/10.1161/STROKEAHA.108.542993>
46. Bushnell C, McCullough LD, Awad IA, Chireau MV, Fedder WN, Furie KL, et al. Guidelines for the Prevention of Stroke in Women. *Stroke*. 2014 May;45(5):1545-1588. <https://doi.org/10.1161/01.str.0000442009.06663.48>
47. Stevenson JC, Crook D, Godsland IF. Influence of age and menopause on serum lipids and lipoproteins in healthy women. *Atherosclerosis*. 1993 Jan 4;98(1):83-90. [https://doi.org/10.1016/0021-9150\(93\)90225-j](https://doi.org/10.1016/0021-9150(93)90225-j)
48. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population-based prospective studies. *J Cardiovasc Risk*. 1996 Apr;3(2):213-219. <https://doi.org/10.1097/00043798-199604-000-00014>

49. Shaw LJ, Bugiardini R, Merz CNB. Women and Ischemic Heart Disease. *J Am Coll Cardiol*. 2009 Oct 20;54(17):1561-1575. <https://doi.org/10.1016/j.jacc.2009.04.098>
50. El Khoudary SR, Chen X, Nasr A, Billheimer J, Brooks MM, McConnell D, et al. HDL (High-Density Lipoprotein) Subclasses, Lipid Content, and Function Trajectories Across the Menopause Transition. *Arterioscler Thromb Vasc Biol*. 2021 Feb;41(2):951-961. <https://doi.org/10.1161/atvbaha.120.315355>
51. Ridker PM, Hennekens CH, Buring JE, Rifai N. C-Reactive Protein and Other Markers of Inflammation in the Prediction of Cardiovascular Disease in Women. *N Engl J Med*. 2000 Mar 23;342(12):836-843. <https://doi.org/10.1056/nejm200003233421202>
52. Lichtman JH, Froelicher ES, Blumenthal JA, Carney RM, Doering LV, Frasure-Smith N, et al. Depression as a Risk Factor for Poor Prognosis Among Patients With Acute Coronary Syndrome: Systematic Review and Recommendations. *Circulation*. 2014 Mar 25;129(12):1350-1369. <https://doi.org/10.1161/cir.0000000000000019>
53. Bushnell C, Howard VJ, Lisabeth L, Caso V, Gall S, Kleindorfer D, et al. Sex differences in the evaluation and treatment of acute ischaemic stroke. *Lancet Neurol*. 2018 Aug;17(8):641-650. [https://doi.org/10.1016/s1474-4422\(18\)30201-1](https://doi.org/10.1016/s1474-4422(18)30201-1)
54. Hamoda H, Sharma A. Premature ovarian insufficiency, early menopause, and induced menopause. *Best Pract Res Clin Endocrinol Metab*. 2024 Jan;38(1):101823. <https://doi.org/10.1016/j.beem.2023.101823>
55. Anagnostis P, Christou K, Artzouchaltzi A-M, Gkekakos NK, Kosmidou N, Siolos P, et al. Early menopause and premature ovarian insufficiency are associated with increased risk of type 2 diabetes: a systematic review and meta-analysis. *Eur J Endocrinol*. 2019 Jan 1;180(1):41-50. <https://doi.org/10.1530/eje-18-0602>
56. Laughlin-Tommaso SK, Khan Z, Weaver AL, Smith CY, Rocca WA, Stewart EA. Cardiovascular and metabolic morbidity after hysterectomy with ovarian conservation: a cohort study. *Menopause*. 2018 May;25(5):483-492. <https://doi.org/10.1097/GME.0000000000001043>
57. Barber TM, Franks S. Obesity and polycystic ovary syndrome. *Clin Endocrinol (Oxf)*. 2021 Oct;95(4):531-541. <https://doi.org/10.1111/cen.14421>
58. Diamanti-Kandarakis E, Dunaif A. Insulin Resistance and the Polycystic Ovary Syndrome Revisited: An Update on Mechanisms and Implications. *Endocr Rev*. 2012 Dec;33(6):981-1030. <https://doi.org/10.1210/er.2011-1034>
59. Okoth K, Chandan JS, Marshall T, Thangaratinam S, Thomas GN, Nirantharakumar K, et al. Association between the reproductive health of young women and cardiovascular disease in later life: umbrella review. *BMJ*. 2020 Oct 7;371:m3502. <https://doi.org/10.1136/bmj.m3502>
60. Retnakaran R, Shah BR. Role of Type 2 Diabetes in Determining Retinal, Renal, and Cardiovascular Outcomes in Women With Previous Gestational Diabetes Mellitus. *Diabetes Care*. 2017 Jan;40(1):101-108. <https://doi.org/10.2337/dc16-1400>
61. Xie W, Wang Y, Xiao S, Qiu L, Yu Y, Zhang Z. Association of gestational diabetes mellitus with overall and type specific cardiovascular and cerebrovascular diseases: systematic review and meta-analysis. *BMJ*. 2022 Sep 21;378:e070244. <https://doi.org/10.1136/bmj-2022-070244>
62. McElwain CJ, Tuboly E, McCarthy FP, McCarthy CM. Mechanisms of Endothelial Dysfunction in Pre-eclampsia and Gestational Diabetes Mellitus: Windows Into Future Cardiometabolic Health? *Front Endocrinol (Lausanne)*. 2020 Sep 25;11:655. <https://doi.org/10.3389/fendo.2020.00655>
63. Tschiderer L, van der Schouw YT, Burgess S, Bloemenkamp KWM, Seekircher L, Willeit P, et al. Hypertensive disorders of pregnancy and cardiovascular disease risk: a Mendelian randomisation study. *Heart*. 2024 May 22;110(12):710-717. <https://doi.org/10.1136/heartjnl-2023-323490>
64. Ying W, Catov JM, Ouyang P. Hypertensive Disorders of Pregnancy and Future Maternal Cardiovascular Risk. *J Am Heart Assoc*. 2018 Sep 4;7(17):e009382. <https://doi.org/10.1161/JAHA.118.009382>
65. Benschop L, Duvekot JJ, Roeters van Lennep JE. Future risk of cardiovascular disease risk factors and events in women after a hypertensive disorder of pregnancy. *Heart*. 2019 Sep;105(16):1273-1278. <https://doi.org/10.1136/heartjnl-2018-313453>
66. Peters SAE, Yang L, Guo Y, Chen Y, Bian Z, Du H, et al. Pregnancy, pregnancy loss, and the risk of cardiovascular disease in Chinese women: findings from the China Kadoorie Biobank. *BMC Med*. 2017 Aug 16;15(1):148. <https://doi.org/10.1186/s12916-017-0912-7>
67. Roach REJ, Helmerhorst FM, Lijfering WM, Stijnen T, Algra A, Dekkers OM. Combined oral contraceptives: the risk of myocardial infarction and ischemic stroke. *Cochrane Database Syst Rev*. 2015 Aug 27;2015(8):CD011054. <https://doi.org/10.1002/14651858.CD011054.pub2>
68. Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, et al. Risk Factors for Doxorubicin-Induced Congestive Heart Failure. *Ann Intern Med*. 1979 Nov;91(5):710-717. <https://doi.org/10.7326/0003-4819-91-5-710>
69. Puri R, Bansal M, Mehta V, Duell PB, Wong ND, Iyengar SS, et al. Lipid Association of India 2023 update on cardiovascular risk assessment and lipid management in Indian patients: Consensus statement IV. *J Clin Lipidol*. 2024 May-Jun;18(3):e351-e373. <https://doi.org/10.1016/j.jacl.2024.01.006>
70. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, et al. Sex Differences in Blood Pressure Trajectories Over the Life Course. *JAMA Cardiol*. 2020 Mar 1;5(3):19-26. <https://doi.org/10.1001/jamacardio.2019.5306>
71. Lala A, Tayal U, Hamo CE, Youmans Q, Al-Khatib SM, Bozkurt B, et al. Sex Differences in Heart Failure. *J Card Fail*. 2022 Mar;28(3):477-498. <https://doi.org/10.1016/j.cardfail.2021.10.006>
72. Rexrode KM, Madsen TE, Yu AYY, Carcel C, Lichtman JH, Miller EC. The Impact of Sex and Gender on Stroke. *Circ Res*. 2022 Feb 18;130(4):512-528. <https://doi.org/10.1161/CIRCRESAHA.121.319915>
73. Regensteiner JG, Reusch JEB. Sex Differences in Cardiovascular Consequences of Hypertension, Obesity, and Diabetes: JACC Focus Seminar 4/7. *J Am Coll Cardiol*. 2022 Apr 19;79(15):1492-1505. <https://doi.org/10.1016/j.jacc.2022.02.010>
74. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. *BMJ*. 2018 Nov 7;363:k4247. <https://doi.org/10.1136/bmj.k4247>
75. Huxley RR, Peters SAE, Mishra GD, Woodward M. Risk of all-cause mortality and vascular events in women versus men with type 1 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol*. 2015 Mar;3(3):198-206. [https://doi.org/10.1016/S2213-8587\(14\)70248-7](https://doi.org/10.1016/S2213-8587(14)70248-7)
76. Ridker PM. C-reactive protein and the prediction of cardiovascular events among those at intermediate risk: moving an inflammatory hypothesis toward consensus. *J Am Coll Cardiol*. 2007 May 29;49(21):2129-2138. <https://doi.org/10.1016/j.jacc.2007.02.052>
77. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO, Criqui M, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: A statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003 Jan 28;107(3):499-511. <https://doi.org/10.1161/01.cir.0000052939.59093.45>
78. Pradhan AD, Manson JE, Rossouw JE, Siscovick DS, Mouton CP, Rifai N, et al. Inflammatory biomarkers, hormone replacement therapy, and incident coronary heart disease: prospective analysis from the Women's Health Initiative observational study. *JAMA*. 2002 Aug 28;288(8):980-987. <https://doi.org/10.1001/jama.288.8.980>

79. Vongpatanasin W, Tuncel M, Wang Z, Arbique D, Mehrad B, Jialal I. Differential effects of oral versus transdermal estrogen replacement therapy on C-reactive protein in postmenopausal women. *J Am Coll Cardiol*. 2003 Apr 16;41(8):1358-1363. [https://doi.org/10.1016/s0735-1097\(03\)00156-6](https://doi.org/10.1016/s0735-1097(03)00156-6)
80. Humphrey LL, Fu R, Rogers K, Freeman M, Helfand M. Homocysteine level and coronary heart disease incidence: a systematic review and meta-analysis. *Mayo Clin Proc*. 2008 Nov;83(11):1203-1212. <https://doi.org/10.4065/83.11.1203>
81. Wald DS, Law M, Morris JK. Homocysteine and cardiovascular disease: evidence on causality from a meta-analysis. *BMJ*. 2002 Nov 23;325(7374):1202. <https://doi.org/10.1136/bmj.325.7374.1202>
82. Yajnik CS, Deshpande SS, Lubree HG, Naik SS, Bhat DS, Uradey BS, et al. Vitamin B12 deficiency and hyperhomocysteinemia in rural and urban Indians. *J Assoc Physicians India*. 2006 Oct;54(775-82). PMID: 17214273
83. Refsum H, Yajnik CS, Gadkari M, Schneede J, Vollset SE, Örnning L, et al. Hyperhomocysteinemia and elevated methylmalonic acid indicate a high prevalence of cobalamin deficiency in Asian Indians. *Am J Clin Nutr*. 2001 Aug;74(2):233-241. <https://doi.org/10.1093/ajcn/74.2.233>
84. Ji H, Sabanayagam C, Matsushita K, Cheng C-Y, Rim TH, Sheng B, et al. Sex Differences in Cardiovascular-Kidney-Metabolic Syndrome: 30-Year US Trends and Mortality Risks—Brief Report. *Arterioscler Thromb Vasc Biol*. 2025 Jan;45(1):157-161. <https://doi.org/10.1161/atvbaha.124.321629>
85. Conrad N, Verbeke G, Molenberghs G, Goetschalckx L, Callender T, Cambridge G, et al. Autoimmune diseases and cardiovascular risk: a population-based study on 19 autoimmune diseases and 12 cardiovascular diseases in 22 million individuals in the UK. *Lancet*. 2022 Sep 3;400(10354):733-743. [https://doi.org/10.1016/S0140-6736\(22\)01349-6](https://doi.org/10.1016/S0140-6736(22)01349-6)
86. International Institute for Population Sciences (IIPS) and ICF. National Family Health Survey (NFHS-5), 2019-21: India. Mumbai: IIPS; 2021.
87. Hu FB, Manson JE, Stampfer MJ, Colditz G, Liu S, Solomon CG, et al. Diet, Lifestyle, and the Risk of Type 2 Diabetes Mellitus in Women. *N Engl J Med*. 2001 Sep 13;345(11):790-797. <https://doi.org/10.1056/NEJMoa010492>
88. Li H, Konja D, Wang L, Wang Y. Sex Differences in Adiposity and Cardiovascular Diseases. *Int J Mol Sci*. 2022 Aug 19;23(16):9338. <https://doi.org/10.3390/ijms23169338>
89. Foreman KJ, Marquez N, Dolgert A, Fukutaki K, Fullman N, McGaughey M, et al. Forecasting life expectancy, years of life lost, and all-cause and cause-specific mortality for 250 causes of death: reference and alternative scenarios for 2016-40 for 195 countries and territories. *Lancet*. 2018 Nov 10;392(10159):2052-2090. [https://doi.org/10.1016/S0140-6736\(18\)31694-5](https://doi.org/10.1016/S0140-6736(18)31694-5)
90. Belletiere J, LaMonte MJ, Evenson KR, Rillamas-Sun E, Kerr J, Lee IM, et al. Sedentary Behavior and Cardiovascular Disease in Older Women: The Objective Physical Activity and Cardiovascular Health (OPACH) study. *Circulation*. 2019 Feb 19;139(8):1036-1046. <https://doi.org/10.1161/CIRCULATIONAHA.118.035312>
91. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. *Lancet*. 2011 Oct 8;378(9799):1297-1305. [https://doi.org/10.1016/S0140-6736\(11\)60781-2](https://doi.org/10.1016/S0140-6736(11)60781-2)
92. Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusufali AH, et al. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. *Eur Heart J*. 2008 Apr;29(7):932-940. <https://doi.org/10.1093/eurheartj/ehn018>
93. Guh J-Y, Chen H-C, Tsai J-F, Chuang L-Y. Betel-quid use is associated with heart disease in women. *Am J Clin Nutr*. 2007 May;85(5):1229-1235. <https://doi.org/10.1093/ajcn/85.5.1229>
94. O'Neil A, Fisher AJ, Kibbey KJ, Jacka FN, Kotowicz MA, Williams LJ, et al. Depression is a risk factor for incident coronary heart disease in women: An 18-year longitudinal study. *J Affect Disord*. 2016 May 15;196:117-124. <https://doi.org/10.1016/j.jad.2016.02.029>
95. Wheeler A, Schrader G, Tucker G, Adams R, Tavella R, Beltrame JF. Prevalence of depression in patients with chest pain and non-obstructive coronary artery disease. *Am J Cardiol*. 2013 Sep 1;112(5):656-659. <https://doi.org/10.1016/j.amjcard.2013.04.042>
96. Scott-Storey KA. Abuse as a gendered risk factor for cardiovascular disease: a conceptual model. *J Cardiovasc Nurs*. 2013 Nov-Dec;28(6):E1-8. <https://doi.org/10.1097/JCN.0b013e318279e372>
97. Newby DE, Mannucci PM, Tell GS, Baccarelli AA, Brook RD, Donaldson K, et al. Expert position paper on air pollution and cardiovascular disease. *Eur Heart J*. 2015 Jan 7;36(2):83-93b. <https://doi.org/10.1093/eurheartj/ehu458>
98. Backholer K, Peters SAE, Bots SH, Peeters A, Huxley RR, Woodward M. Sex differences in the relationship between socioeconomic status and cardiovascular disease: a systematic review and meta-analysis. *J Epidemiol Community Health*. 2017 Jun;71(6):550-557. <https://doi.org/10.1136/jech-2016-207890>
99. SCORE2 working group and ESC Cardiovascular risk collaboration. SCORE2 risk prediction algorithms: new models to estimate 10-year risk of cardiovascular disease in Europe. *Eur Heart J*. 2021 Jul 1;42(25):2439-2454. <https://doi.org/10.1093/eurheartj/ehab309>
100. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2014 Jun 24;129(25 Suppl 2):S49-73. <https://doi.org/10.1161/01.cir.0000437741.48606.98>
101. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Eur Heart J*. 2016 Aug 1;37(29):2315-2381. <https://doi.org/10.1093/eurheartj/ehw106>
102. Khan SS, Matsushita K, Sang Y, Ballew SH, Grams ME, Surapaneni A, et al. Development and Validation of the American Heart Association's PREVENT Equations. *Circulation*. 2024 Feb 6;149(6):430-449. <https://doi.org/10.1161/CIRCULATIONAHA.123.067626>
103. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ*. 2017 May 23;357:j2099. <https://doi.org/10.1136/bmj.j2099>
104. Hajifathalian K, Ueda P, Lu Y, Woodward M, Ahmadvand A, Aguilar-Salinas CA, et al. A novel risk score to predict cardiovascular disease risk in national populations (Globorisk): a pooled analysis of prospective cohorts and health examination surveys. *Lancet Diabetes Endocrinol*. 2015 May;3(5):339-355. [https://doi.org/10.1016/S2213-8587\(15\)00081-9](https://doi.org/10.1016/S2213-8587(15)00081-9)
105. Ueda P, Woodward M, Lu Y, Hajifathalian K, Al-Wotayan R, Aguilar-Salinas CA, et al. Laboratory-based and office-based risk scores and charts to predict 10-year risk of cardiovascular disease in 182 countries: a pooled analysis of prospective cohorts and health surveys. *Lancet Diabetes Endocrinol*. 2017 Mar;5(3):196-213. [https://doi.org/10.1016/S2213-8587\(17\)30015-3](https://doi.org/10.1016/S2213-8587(17)30015-3)
106. Kaptoge S, Seshasai SRK, Sun L, Walker M, Bolton T, Pennells L, et al. World Health Organization cardiovascular disease risk charts: revised models to estimate risk in 21 global regions. *Lancet Glob Health*. 2019 Oct;7(10):e1332-e1345. [https://doi.org/10.1016/S2214-109X\(19\)30318-3](https://doi.org/10.1016/S2214-109X(19)30318-3)

107. Kar SS, Kannusamy S, Rehman T, Murali S, Laxminarayanan S, Balachander J. Cardiovascular Risk Profiling Using the Globorisk Calculator among Noncommunicable Disease Patients Attending Primary Health Centers of a Tertiary Care Teaching Hospital in South India: A Cross-Sectional Analytical Study. *Indian J Community Med*. 2024 Mar-Apr;49(2):290-295. https://doi.org/10.4103/ijcm.ijcm_300_22
108. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds risk score. *JAMA*. 2007 Feb 14;297(6):611-619. <https://doi.org/10.1001/jama.297.6.611>
109. MDCalc. Reynolds Risk Score for Cardiovascular Risk in Women. Available from: <https://www.mdcalc.com/calc/3932/reynolds-risk-score-cardiovascular-risk-women>. Accessed February 9, 2026.
110. Medscape. Reynolds CAD Risk Score. Available from: <https://reference.medscape.com/calculator/192/reynolds-cad-risk>. Accessed February 9, 2026.
111. Budoff MJ, Young R, Burke G, Jeffrey Carr J, Detrano RC, Folsom AR, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of atherosclerosis (MESA). *Eur Heart J*. 2018 Jul 1;39(25):2401-2408. <https://doi.org/10.1093/eurheartj/ehy217>
112. Michos ED, Blaha MJ, Blumenthal RS. Use of the Coronary Artery Calcium Score in Discussion of Initiation of Statin Therapy in Primary Prevention. *Mayo Clin Proc*. 2017 Dec;92(12):1831-1841. <https://doi.org/10.1016/j.mayocp.2017.10.001>
113. Rosenblatt S, Blaha MJ, Blankstein R, Nasir K, Lin F, Yeboah-Kordieh Y, et al. Racial and Ethnic Differences in Long-Term Cardiovascular Mortality Among Women and Men From the CAC Consortium. *JACC Cardiovasc Imaging*. 2025 Jun;18(6):664-675. <https://doi.org/10.1016/j.jcmg.2025.01.013>
114. Slater K, Colyvas A, Taylor R, Collins CE, Hutchesson M. Primary and secondary cardiovascular disease prevention interventions targeting lifestyle risk factors in women: A systematic review and meta-analysis. *Front Cardiovasc Med*. 2022 Oct 24;9:1010528. <https://doi.org/10.3389/fcvm.2022.1010528>
115. Limbachia J, Ajmeri M, Keating BJ, de Souza RJ, Anand SS. Effects of lifestyle interventions on cardiovascular risk factors in South Asians: a systematic review and meta-analysis. *BMJ Open*. 2022 Jun 13;12(6):e059666. <https://doi.org/10.1136/bmjopen-2021-059666>
116. Ghodeswar GK, Dube A, Khobragade D. Impact of Lifestyle Modifications on Cardiovascular Health: A Narrative Review. *Cureus*. 2023 Jul 28;15(7):e42616. <https://doi.org/10.7759/cureus.42616>
117. Daley SF, Vadakekut ES. The DASH Diet: A Guide to Managing Hypertension Through Nutrition. 2024 Jan 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024.
118. Stromsnes K, Correias AG, Lehmann J, Gambini J, Olaso-Gonzalez G. Anti-Inflammatory Properties of Diet: Role in Healthy Aging. *Biomedicines*. 2021 Jul 30;9(8):922. <https://doi.org/10.3390/biomedicines9080922>
119. Schwingshackl L, Morze J, Hoffmann G. Mediterranean diet and health status: Active ingredients and pharmacological mechanisms. *Br J Pharmacol*. 2020 Mar;177(6):1241-1257. <https://doi.org/10.1111/bph.14778>
120. Tyson CC, Nwankwo C, Lin PH, Svetkey LP. The Dietary Approaches to Stop Hypertension (DASH) eating pattern in special populations. *Curr Hypertens Rep*. 2012 Oct;14(5):388-396. <https://doi.org/10.1007/s11906-012-0296-1>
121. Liang M, Pan Y, Zhong T, Zeng Y, Cheng ASK. Effects of aerobic, resistance, and combined exercise on metabolic syndrome parameters and cardiovascular risk factors: a systematic review and network meta-analysis. *Rev Cardiovasc Med*. 2021 Dec 22;22(4):1523-1533. <https://doi.org/10.31083/j.rcm2204156>
122. Piercy KL, Troiano RP, Ballard RM, Carlson SA, Fulton JE, Galuska DA, et al. The Physical Activity Guidelines for Americans. *JAMA*. 2018 Nov 20;320(19):2020-2028. <https://doi.org/10.1001/jama.2018.14854>
123. De Bacquer D, Jennings CS, Mirrakhimov E, Lovic D, Bruthans J, De Smedt D, et al. Potential for optimizing management of obesity in the secondary prevention of coronary heart disease. *Eur Heart J Qual Care Clin Outcomes*. 2022 Aug 17;8(5):568-576. <https://doi.org/10.1093/ehjqcco/qcab043>
124. Pahwa V, Pimple SA, Bhattacharjee A, Kuberkar D, Mishra GA, Chaturvedi P. Behavioural interventions for tobacco cessation in India: A systematic review and meta-analysis. *J Family Med Prim Care*. 2023 Nov;12(11):2542-2551. https://doi.org/10.4103/jfmpc.jfmpc_1017_23
125. Gallucci G, Tartarone A, Lerosé R, Lalinga AV, Capobianco AM. Cardiovascular risk of smoking and benefits of smoking cessation. *J Thorac Dis*. 2020 Jul;12(7):3866-3876. <https://doi.org/10.21037/jtd.2020.02.47>
126. Rainforth MV, Schneider RH, Nidich SI, Gaylord-King C, Salerno JW, Anderson JW. Stress reduction programs in patients with elevated blood pressure: a systematic review and meta-analysis. *Curr Hypertens Rep*. 2007 Dec;9(6):520-528. <https://doi.org/10.1007/s11906-007-0094-3>
127. Maheshwari A, Gupta R, Verma N, Narasingan SN, Singh RB, Saboo B, et al. Position statement on hypertension by Indian Society of Hypertension, 2023. *J Hum Hypertens*. 2024 Sep;38(9):736-744. <https://doi.org/10.1038/s41371-024-00960-z>
128. Ishigami J, Charleston J, Miller ER, Matsushita K, Appel LJ, Brady TM. Effects of cuff size on the accuracy of blood pressure readings: the Cuff (SZ) randomized crossover trial. *JAMA Intern Med*. 2023 Oct 1;183(10):1061-1068. <https://doi.org/10.1001/jamainternmed.2023.3264>
129. Jones DW, Ferdinand KC, Taler SJ, Johnson HM, Shimbo D, Abdalla M, et al. 2025 AHA/ACC/AANP/AAPA/ABC/ACCP/ACPM/AGS/AMA/ASPC/NMA/PCNA/SGIM Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2025;152:e114–e218. <https://doi.org/10.1161/CIR.0000000000001356>
130. American Diabetes Association Professional Practice Committee. 10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes-2026. *Diabetes Care*. 2026 Jan 1;49(Supplement_1):S216-S245. <https://doi.org/10.2337/dc26-S010>. PMID: 41358899; PMCID: PMC12690187
131. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn RT, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2019 Sep 10;140(11):e596-e646. <https://doi.org/10.1161/CIR.0000000000000678>
132. Mora S, Glynn RJ, Hsia J, MacFadyen JG, Genest J, Ridker PM. Statins for the primary prevention of cardiovascular events in women with elevated high-sensitivity C-reactive protein or dyslipidemia: results from JUPITER and meta-analysis. *Circulation*. 2010 Mar 9;121(9):1069-1077. <https://doi.org/10.1161/CIRCULATIONAHA.109.906479>
133. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. *J Am Coll Cardiol*. 2012 Feb 7;59(6):572-582. <https://doi.org/10.1016/j.jacc.2011.09.067>
134. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2019 Jun 25;73(24):e285-e350. <https://doi.org/10.1016/j.jacc.2018.11.003>
135. Shufelt CL. Statin therapy in midlife women. *Menopause*. 2021 Oct 1;28(10):1067-1069. <https://doi.org/10.1097/GME.0000000000001802>

136. Cho L, Davis M, Elgendy I, Epps K, Lindley KJ, Mehta PK, et al. Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2020 May 26;75(20):2602-2618. <https://doi.org/10.1016/j.jacc.2020.03.060>
137. US Preventive Services Task Force, Davidson KW, Barry MJ, Mangione CM, Cabana M, Chelmow D, et al. Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement. *JAMA*. 2022 Apr 26;327(16):1577-1584. <https://doi.org/10.1001/jama.2022.4983>
238. Patrono C. Low-dose aspirin for the prevention of atherosclerotic cardiovascular disease. *Eur Heart J*. 2024 Jul 1;45(25):2362-2376. <https://doi.org/10.1093/eurheartj/ehae324>
139. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ*. 2002 Jan 12;324(7329):71-86. <https://doi.org/10.1136/bmj.324.7329.71>
140. Shlipak MG, Simon JA, Vittinghoff E, Lin F, Ensrud KE, Barrett-Connor E, et al. Estrogen and Progestin, Lipoprotein(a), and the Risk of Recurrent Coronary Heart Disease Events After Menopause. *JAMA*. 2000 Apr 12;283(14):1845-1852. <https://doi.org/10.1001/jama.283.14.1845>
141. HPS2-Thrive Collaborative Group, Landray MJ, Haynes R, Hopewell JC, Parish S, Aung T, et al. Effects of extended-release niacin with laropiprant in high-risk patients. *N Engl J Med*. 2014 Jul 17;371(3):203-212. <https://doi.org/10.1056/NEJMoa1300955>
142. O'Donoghue ML, Fazio S, Giugliano RP, Stroes ESG, Kanevsky E, Gouni-Berthold I, et al. Lipoprotein(a), PCSK9 Inhibition, and Cardiovascular Risk. *Circulation*. 2019 Mar 19;139(12):1483-1492. <https://doi.org/10.1161/CIRCULATIONAHA.118.037184>
143. Bairey Merz CN, Pepine CJ, Walsh MN, Fleg JL, Camici PG, Chilian WM, et al. Ischemia and No Obstructive Coronary Artery Disease (INOCA). *Circulation*. 2017 Mar 14;135(11):1075-1092. <https://doi.org/10.1161/circulationaha.116.024534>
144. Reynolds HR, Shaw LJ, Min JK, Page CB, Berman DS, Chaitman BR, et al. Association of sex with severity of coronary artery disease, ischemia, and symptom burden in patients with moderate or severe ischemia: secondary analysis of the ISCHEMIA randomized clinical trial. *JAMA Cardiol*. 2020 Jul 1;5(7):773-786. <https://doi.org/10.1001/jamacardio.2020.0822>
145. Padro T, Manfrini O, Bugiardi R, Canty J, Cenko E, De Luca G, et al. ESC Working Group on Coronary Pathophysiology and Microcirculation position paper on 'coronary microvascular dysfunction in cardiovascular disease'. *Cardiovasc Res*. 2020 May 1;116(4):741-755. <https://doi.org/10.1093/cvr/cvaa003>
146. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM, et al. An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation endorsed by Coronary Vasomotor Disorders International Study Group. *Eur Heart J*. 2020 Oct 1;41(37):3504-3520. <https://doi.org/10.1093/eurheartj/ehaa503>
147. Taqueti VR, Di Carli MF. Coronary Microvascular Disease Pathogenic Mechanisms and Therapeutic Options: JACC State-of-the-Art Review. *J Am Coll Cardiol*. 2018 Nov 27;72(21):2625-2641. <https://doi.org/10.1016/j.jacc.2018.09.042>
148. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, et al. Emergence of Nonobstructive Coronary Artery Disease: A Woman's Problem and Need for Change in definition on Angiography. *J Am Coll Cardiol*. 2015 Nov 3;66(17):1918-1933. <https://doi.org/10.1016/j.jacc.2015.08.876>
149. Pasupathy S, Air T, Dreyer RP, Tavella R, Beltrame JF. Systematic Review of Patients Presenting With Suspected Myocardial Infarction and Nonobstructive Coronary Arteries. *Circulation*. 2015 Mar 10;131(9):861-870. <https://doi.org/10.1161/circulationaha.114.011201>
150. Reynolds HR, Maehara A, Kwong RY, Saw J, Smilowitz NR, Hochman JS, et al. Coronary Optical Coherence Tomography and Cardiac Magnetic Resonance Imaging to Determine Underlying Causes of Myocardial Infarction With Nonobstructive Coronary Arteries in Women. *Circulation*. 2021 Feb 23;143(7):624-640. <https://doi.org/10.1161/CIRCULATIONAHA.120.052008>
151. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018 Jan 7;39(2):119-177. <https://doi.org/10.1093/eurheartj/ehx393>
152. Lam CSP, Arnott C, Beale AL, Chandramouli C, Hilfiker-Kleiner D, Kaye DM, et al. Sex differences in heart failure. *Eur Heart J*. 2019 Dec 7;40(47):3859-3868c. <https://doi.org/10.1093/eurheartj/ehz835>
153. Ceia F, Fonseca C, Mota T, Morais H, Matias F, de Sousa A, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. *Eur J Heart Fail*. 2002 Aug;4(4):531-539. [https://doi.org/10.1016/s1388-9842\(02\)00034-x](https://doi.org/10.1016/s1388-9842(02)00034-x)
154. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Neurol*. 2021 Oct;20(10):795-820. [https://doi.org/10.1016/S1474-4422\(21\)00252-0](https://doi.org/10.1016/S1474-4422(21)00252-0)
155. Dufouil C, Beiser A, McLure LA, Wolf PA, Tzourio C, Howard VJ, et al. Revised Framingham Stroke Risk Profile to Reflect Temporal Trends. *Circulation*. 2017 Mar 21;135(12):1145-1159. <https://doi.org/10.1161/CIRCULATIONAHA.115.021275>
156. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender differences in stroke incidence and poststroke disability in the Framingham Heart Study. *Stroke*. 2009 Apr;40(4):1032-1037. <https://doi.org/10.1161/STROKEAHA.108.542894>
157. Bushnell C, Kernan WN, Sharrief AZ, Chaturvedi S, Cole JW, de Havenon A, et al. 2024 Guideline for the Primary Prevention of Stroke: A Guideline From the American Heart Association/American Stroke Association. *Stroke*. 2024 Dec;55(12):e344-e424. <https://doi.org/10.1161/STR.0000000000000475>
158. Mu F, Rich-Edwards J, Rimm EB, Spiegelman D, Forman JP, Missmer SA. Association Between Endometriosis and Hypercholesterolemia or Hypertension. *Hypertension*. 2017 Jul;70(1):59-65. <https://doi.org/10.1161/HYPERTENSIONAHA.117.09056>
159. Miller EC, Leffert L. Stroke in Pregnancy: A Focused Update. *Anesth Analg*. 2020 Apr;130(4):1085-1096. <https://doi.org/10.1213/ANE.00000000000004203>
160. Yonis H, Løkkegaard E, Kragholm K, Granger CB, Møller AL, Mørch LS, et al. Stroke and myocardial infarction with contemporary hormonal contraception: real-world, nationwide, prospective cohort study. *BMJ*. 2025 Feb 12;388:e082801. <https://doi.org/10.1136/bmj-2024-082801>
161. Krist AH, Shenson D, Woolf SH, Bradley C, Liaw WR, Rothenich SF, et al. Clinical and community delivery systems for preventive care: an integration framework. *Am J Prev Med*. 2013 Oct;45(4):508-516. <https://doi.org/10.1016/j.amepre.2013.06.008>
162. Delluc A, Tromeur C, Le Ven F, Gouillou M, Paleiron N, Bressollette L, et al. Current incidence of venous thromboembolism and comparison with 1998: a community-based study in Western France. *Thromb Haemost*. 2016 Nov;116(11):967-974. <https://doi.org/10.1160/th16-03-0205>
163. Scheres LJJ, van Hylckama Vlieg A, Cannegieter SC. Sex-specific aspects of venous thromboembolism: What is new and what is next? *Res Pract Thromb Haemost*. 2022 May 30;6(4):e12722. <https://doi.org/10.1002/rth2.12722>
164. Bowles LK, Cooper JA, Howarth DJ, Miller GJ, MacCallum PK. Associations of haemostatic variables with body mass index: a community-based study. *Blood Coagul Fibrinolysis*. 2003 Sep;14(6):569-573. <https://doi.org/10.1097/00001721-200309000-00009>

165. Bergendal A, Bremme K, Hedenmalm K, Lärfors G, Odeberg J, Persson I, et al. Risk factors for venous thromboembolism in pre-and postmenopausal women. *Thromb Res.* 2012 Oct;130(4):596-601. <https://doi.org/10.1016/j.thromres.2012.05.024>
166. Cox C, Roberts LN. Basics of diagnosis and treatment of venous thromboembolism. *J Thromb Haemost.* 2025 Apr;23(4):1185-1202. <https://doi.org/10.1016/j.jtha.2025.01.009>
167. Tafler K, Kuriya A, Gervais N, Leyland N. Guideline No. 417: Prevention of Venous Thromboembolic Disease in Gynaecological Surgery. *J Obstet Gynaecol Can.* 2022 Jan;44(1):82-96.e1. <https://doi.org/10.1016/j.jogc.2021.04.003>
168. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* 2012 Feb;141(2 Suppl):e195S-e226S. . <https://doi.org/10.1378/chest.11-2296>
169. Committee Opinion No. 556: Postmenopausal estrogen therapy: route of administration and risk of venous thromboembolism. *Obstet Gynecol.* 2013 Apr;121(4):887-890. <https://doi.org/10.1097/01.AOG.0000428645.90795.d9>
170. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of combined oral contraceptives and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *BMJ.* 2015 May 26;350:h2135. <https://doi.org/10.1136/bmj.h2135>
171. Ortega MA, Asúnsolo Á, Álvarez-Rocha MJ, Romero B, De León-Luis J, Álvarez-Mon M, et al. Remodelling of collagen fibres in the placentas of women with venous insufficiency during pregnancy. *Histol Histopathol.* 2018 Jun;33(6):567-576. <https://doi.org/10.14670/HH-11-948>
172. Cesarone MR, Belcaro G, Nicolaidis AN, Geroulakos G, Griffin M, Incandela L, et al. 'Real' epidemiology of varicose veins and chronic venous diseases: the San Valentino Vascular Screening Project. *Angiology.* 2002 Mar-Apr;53(2):119-130. <https://doi.org/10.1177/000331970205300201>
173. Mashiah A, Berman V, Thole HH, Rose SS, Pasik S, Schwarz H, et al. Estrogen and progesterone receptors in normal and varicose saphenous veins. *Cardiovasc Surg.* 1999 Apr;7(3):327-331. [https://doi.org/10.1016/s0967-2109\(98\)00132-x](https://doi.org/10.1016/s0967-2109(98)00132-x)
174. Russak AJ, Chaudhry F, De Freitas JK, Baron G, Chaudhry FF, Bienstock S, et al. Machine Learning in Cardiology-Ensuring Clinical Impact Lives Up to the Hype. *J Cardiovasc Pharmacol Ther.* 2020 Sep;25(5):379-390. <https://doi.org/10.1177/1074248420928651>
175. Lloyd-Jones DM, Allen NB, Anderson CAM, Black T, Brewer LC, Foraker RE, et al. Life's Essential 8: Updating and Enhancing the American Heart Association's Construct of Cardiovascular Health: A Presidential Advisory From the American Heart Association. *Circulation.* 2022 Aug 2;146(5):e18-e43. <https://doi.org/10.1161/CIR.0000000000001078>
176. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, et al. Socioeconomic Status and Cardiovascular Outcomes: Challenges and Interventions. *Circulation.* 2018 May 15;137(20):2166-2178. <https://doi.org/10.1161/CIRCULATIONAHA.117.029652>

EFFECTS OF HORMONE THERAPY ON CARDIOVASCULAR DISEASE

13

Keywords: Hormones, cardiovascular disease, stroke, thromboembolism, Indian context

INTRODUCTION

Cardiovascular Disease (CVD) is one of the leading causes of death, contributing to 30% of all causes of death. Women develop CVD several years later than men, with a notable increase in midlife attributed to a decline in estrogen.¹ Compared with premenopausal women, CVD occurs more frequently in postmenopausal women and in adult men.²

The effects of exogenous hormones on the cardiovascular system (CVS) of women with menopause transition (MT) and beyond are of great interest and surrounded by controversies. Animal experiments in cynomolgus monkeys and observational studies indicate a cardioprotective effect of estrogens, supported by surrogate markers and hard endpoints³⁻⁸, whereas other studies have shown an increased risk of CVD.^{1,9-14} This hypothesis led to the Heart and Estrogen/Progestosterone Replacement Study (HERS) in 1998, the first secondary prevention trial published. Use of hormone therapy (HT) as primary prevention was the primary objective of the largest randomised controlled trial (RCT), the Women's Health Initiative (WHI). The conflicting results from HERS and WHI challenged the hypothesis that estrogens have a cardioprotective effect. The analysis and reanalysis of the data of observational, epidemiological, and RCTs on the effects of menopausal hormone therapy (MHT) on the CVS over the past few decades has led to the concept of the "timing hypothesis" and the importance of the type, route and dosage of HT and the genetic makeup of the woman.²

BIOLOGICAL EFFECTS OF HORMONE THERAPY

There are several mechanisms by which HT benefits the CVS.

- HT affects lipids and lipoproteins, which are involved in the development of atherosclerotic disease. These effects vary depending on the type of estrogen or progesterone used and the route of administration.²
- Oral estrogens reduce low-density lipoprotein (LDL) cholesterol and appear more effective than transdermal oestradiol.¹⁵ Oral estrogens are also more effective than transdermal estradiol in increasing high-density lipoprotein (HDL) cholesterol. This increase in HDL may be negated by the addition of a progestogen with androgenic properties.¹⁶
- Transdermal estradiol reduces triglycerides, whereas oral estrogens increase them.¹⁷ The addition of androgenic progesterone prevents any rise or has a neutral effect on triglycerides.^{17,18}
- Estrogens also affect glucose and insulin metabolism. Estrogens increase pancreatic insulin secretion, insulin sensitivity, and insulin elimination.¹⁹ Androgenic progestogens may oppose these effects, but non-androgenic progestogens do not.¹⁹
- Estrogens affect body fat distribution by helping to prevent the postmenopausal increase in central 307 abdominal visceral fat.²⁰
- Estrogen affects coagulation and fibrinolysis, increasing both pro-coagulant and fibrinolytic activity, but at high doses may result in an overall increase in thrombogenesis.²¹
- Estrogens have direct effects on arteries through various genomic and non-genomic mechanisms.²²
- At appropriate physiological doses, estradiol likely improves vascular remodelling, but at inappropriately high doses it may have adverse effects, including plaque progression or instability.²³

THE EFFECTS OF HT ON SURROGATE MARKERS OF CARDIAC DISEASE

Cardiac Function: Estrogen is found to increase cardiac contractility^{24,25} and stroke volume and decrease left ventricular mass.²⁶ The ejection time, however, returns to near baseline within one year.²⁵ MHT use may significantly decrease left ventricular (LV) systolic and diastolic volumes, which have been linked with favourable cardiovascular outcomes.²⁷

Lipid And Lipoprotein Metabolism: Oral estrogen increases HDL-C and Triglycerides (TG), decreasing total cholesterol, Lipoprotein LP(a) and LDL-C.

Homocysteine Metabolism: Estrogens decrease homocysteine levels. This effect is not influenced by the cyclic addition of the progesterone-like drug dydrogesterone and micronised progesterone.

Effect of HT on Carbohydrate Metabolism and Obesity: According to the PEPI trial, fasting glucose levels and post-challenge insulin levels decrease slightly with HT.²⁸

Hemodynamics: Estrogens decrease peripheral vascular resistance and pulsatility index (PI) in healthy postmenopausal women.

Endothelium-Dependent Vasodilatation: Estradiol has been proposed to reduce cardiovascular events by promoting endothelium-dependent vasodilatation and decreasing plasma endothelin-1 levels.²⁵

Endothelium-Independent Vasodilatation: Estrogen decreases calcium influx in vascular smooth muscle cells. Calcium antagonism by estrogen has been experimentally demonstrated by increasing the inhibitory effect of nifedipine and other calcium channel blockers on endothelium-denuded vessels and by observing its relaxing effect on endothelin-1-contracted coronary arteries.²⁵

Hemostatic Factors: Estrogen replacement decreases fibrinogen levels and increases factor VII levels.²⁹ Increased factor VII in oral ET users was associated with higher total triglycerides, suggesting a possible relationship between lipoprotein and hemostatic factors.

THE EFFECTS OF MHT ON CARDIOVASCULAR HEALTH

If the cardiovascular changes after menopause are a consequence of the loss of ovarian function, one might expect them to reverse with the replacement of most ovarian hormones to their former physiological levels. This explanation has served as the rationale for MHT use, which began in time for cardioprotection, based on experimental and epidemiological data, as well as observational case studies and their meta-analyses.³⁻⁸

Review of the literature, however, reveals contradictory results, possibly because these studies were conducted in an older age group of women, in which the pro-atherosclerotic phase may already have set in.⁹⁻¹⁴ The net effect of the hormonal formulation on cardiovascular health would depend on the nature of the hormones used, the androgenicity of the progestogen, the route of administration, the type, dose, regimen, and timing, duration, and schedule of use of either or both estrogens and progestogens, as well as vascular ERs, number variants, distribution and sensitivity, hormonal environment such as the levels of testosterone, gonadotropins and sex hormone binding globulin, pre-existing cardiovascular health and other disorders. The results must be interpreted for each individual formulation separately and not generalised across all formulations.² Refer to Figure 1 for the vascular benefits of MHT.

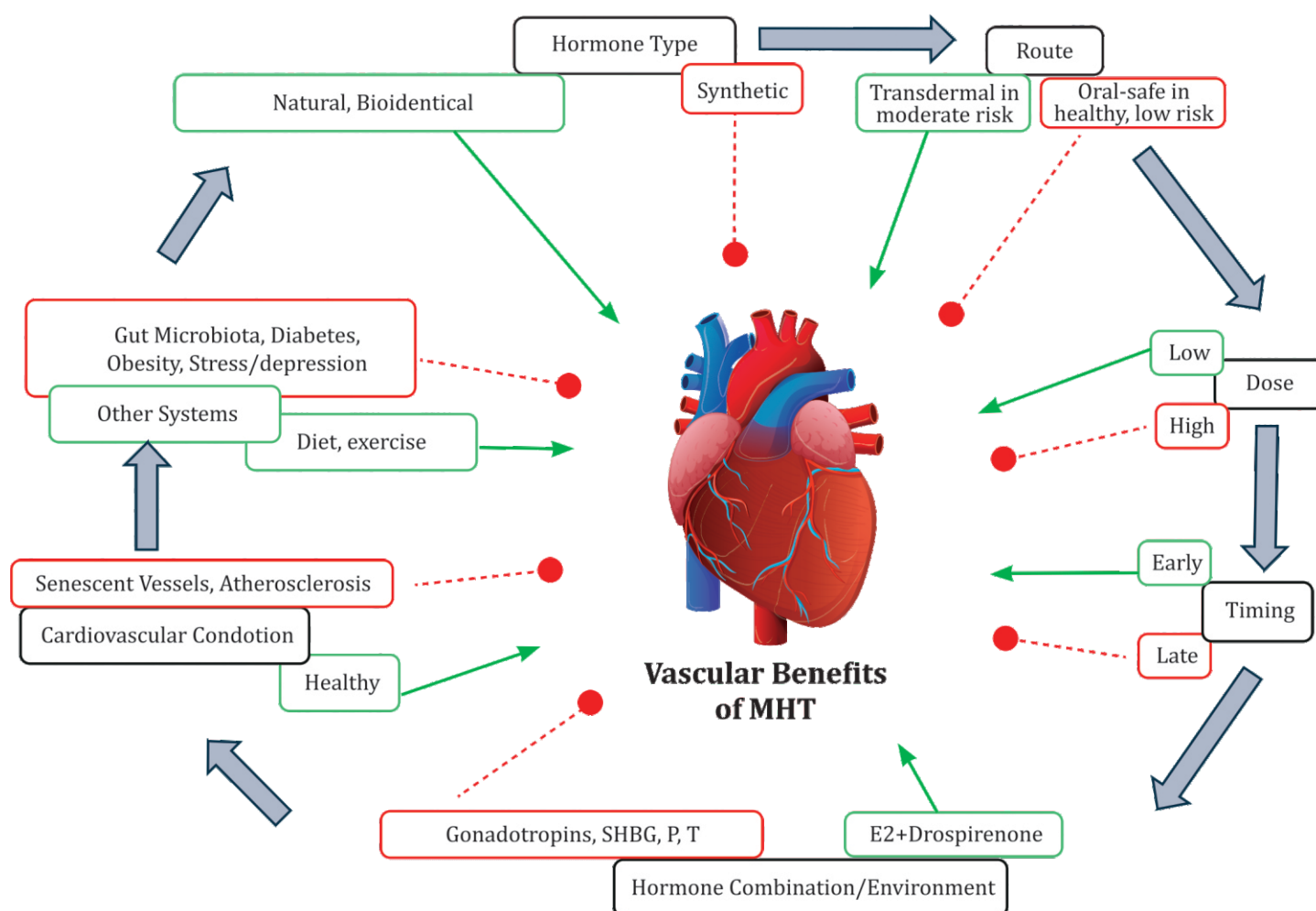


Fig 1. Vascular Benefits of MHT.2

SHBG-Sex Hormone Binding Globulin; P- Progesterins; T-Testosterone; Red-indicates harm; Green-indicates benefits

MHT AND CVD

Data do not currently support recommendations for use of estrogen therapy (ET)/ estrogen-progestin therapy (EPT) regimens in primary or secondary prevention of CVD in women of any age.²

Primary Prevention: CVS Refer to Chapter 37

WHI confirmed that there is no primary cardio-protection for those who take continuous combined conjugated equine estrogens (CEE) 0.625 mg and 2.5 mg medroxyprogesterone acetate (MPA).¹² However, MHT has the potential to improve cardiovascular risk profile through its beneficial effects on vascular function, cholesterol levels, glucose metabolism, and blood pressure (BP). Subgroup analysis of women less than 60 yrs indicated that ET may be cardioprotective if started around the time of menopause, referred to as the 'window of opportunity' concept.^{2,30} It also reduces the risk of diabetes and improves the lipid profile and metabolic health.

Less than 60 years old, recently menopausal and without evidence of CVD, the initiation of MHT does not cause any harm and may reduce morbidity and mortality from coronary heart disease. MHT beyond the age of 60 years should be decided as a part of the overall risk-benefit analysis. MHT in elderly women or in those who are more than 10 years postmenopause is not recommended.^{2,31} In conclusion, for women with low risk of CVD, MHT is not contraindicated; for those at moderate risk, opt for transdermal therapy and avoid it in those at high risk of CVD.

Secondary Prevention: Refer to Chapter 377

The clinical outcome trial, the HERS II, conducted in postmenopausal women with existing CVD, showed an increased risk of cardiovascular events in the first years, followed by a trend toward fewer events in subsequent years. An increase in thrombo-embolic events was also observed in this trial.¹¹ This may be explained by pro-inflammatory markers (CRP), thrombotic effects, and increased triglyceride and small, dense LDL particle production (more susceptible to oxidation by HT).

Regarding considering this therapy as a long-term preventive measure, it should be noted that there are no primary or secondary cardioprotective benefits, and there are no additional cardiac risks in the long term either. This combination should not be recommended to women seeking to initiate or continue HT for cardioprotection, particularly if they belong to the 'at greater risk for developing Coronary Heart Disease (CHD)' group.²

MHT AND STROKE

- Contemporary combined oral MHT containing oral estradiol-progestogen therapy carries a lower risk of stroke than do products used in the previous trials- CEE and MPA.¹
- MHT is associated with increased risk of all strokes as well as ischemic stroke and subarachnoid haemorrhage, particularly in the first year after the initiation of therapy.⁹
- Another study found increased risk of stroke with oral MHT and no risk of stroke with transdermal application and vaginal estrogen.¹⁰
- Use of oral CEE alone increases the risk of stroke.¹⁴
- In the largest RCT, WHI oral ET and EPT showed an increased risk of ischemic stroke in relatively healthy postmenopausal women. The absolute risk is 1.5 cases per 10,000 women /year at age 50-54, 2.2 at age 59, and 2.8 at ages 60-64. The risk increases with age, yet it remains in the rare category defined by the World Health Organisation. The increase in stroke in younger women is possibly due to their genetic and environmental susceptibility. Based on these trials, postmenopausal women should not be prescribed MHT for primary or secondary prevention of stroke.¹²
- CEE compared with estradiol has been associated with an increased risk of stroke.³²
- Risk of stroke appears to vary by dose and route of administration. Overall, transdermal therapy was associated with a lower risk of stroke and venous thromboembolism (VTE) compared to oral MHT,^{33,34} or almost no risk, but high-dose transdermal therapy alone (doses >50 µcg) was associated with increased risk.
- Unlike CHD, the timing hypothesis does not appear to apply to the risk of stroke, most likely because the risk of stroke is probably due to thrombotic rather than atherosclerotic mechanisms. Therefore, although the literature is suggestive of an increased risk of stroke with oral HRT, there is a dose-dependent relationship, and the event rate is low, especially in younger women.

COAGULATION

VTE Safety

- VTE is one of the adverse events during the use of oral contraceptives combined with progestogens. The relative risks in two RCTs were: HERS, RR 2.9; and WHI (E alone), RR 1.3.^{11,12} A similar increase was found with tamoxifen, the RR was 1.63, and with raloxifene, the RR was 1.44.^{35,36}
- There is an increased risk of VTE with the use of oral combined MHT³⁷, a lower risk with the use of oral estrogen only and no risk with tibolone or transdermal products.³⁷
- The risk increases with estrogen dose, age and body mass index and is greater during the first year of therapy.
- Data from the Estrogen Administration and Progestogens (ESTHER) study suggest that transdermal estrogens, by avoiding the hepatic first-pass effect, may be preferable for those at increased risk of VTE.³⁸ Norpregnane derivatives may be thrombogenic, whereas micronised progesterone and pregnane derivatives like dydrogesterone have no effect on thrombosis.³⁸ Overall, transdermal therapy is associated with a lower risk of VTE^{33,34} and/or no risk.¹

- Addition of progestins in combination therapy may increase estrogenicity and thus risk of thrombosis.³⁹
- Micronised progesterone and dydrogesterone, when combined with MHT, have a neutral effect on VTE, MI, and stroke.⁴⁰

MHT AND HYPERTENSION

MHT does not pose much threat to postmenopausal women with underlying controlled hypertension. In a small percentage, very rarely, there is an idiosyncratic increase in the hypertension for which the patient has to be monitored for the first three months. The transdermal/non-oral form of estrogen is usually recommended in such patients. Tibolone and raloxifene have almost no effect on BP. Similarly, micronised progesterone and dydrogesterone also have no effect on hypertension. Drospirenone reduces BP.

Although some studies show no clinically meaningful effect of oral E2 on BP in women with pre-existing hypertension, WHI showed that CEE either alone or in combination with medroxy progesterone acetate increased BP by 1-1.5 mm Hg.^{41,42} Transdermal estradiol and micronised progesterone, lower diastolic BP, Improve cardiac autonomic barorflex sensitivity and prevent age-related decrease in brachial artery flow-mediated dilation (FMD) (endothelium dependent) and increase in stress reactivity score.⁴³

SELECTIVE ESTROGEN RECEPTOR MODULATOR

Selective estrogen receptor modulators (SERMs) are compounds that exhibit both agonist and antagonist effects at estrogen receptors. Its role in the prevention and treatment of osteoporosis is established. The Raloxifene Use for the Heart (RUTH) was a randomised, placebo-controlled trial investigating the use of raloxifene in 10,101 women. Overall, there was no effect of raloxifene on coronary events, but there was a significantly increased risk of VTE and stroke. Further analysis of the RUTH data has revealed the importance of age in cardiovascular outcomes, showing a reduction in coronary events among women younger than 60 years who initiated raloxifene treatment (HR: 0.59, 95% CI: 0.41–0.83).³⁵

In small human studies, phytoestrogens, such as isoflavones, have shown beneficial effects on lipid levels. RCTs are required before any firm conclusion can be drawn. Phytoestrogens reduce mean systolic and diastolic BP compared with placebo. Other studies using soya derivatives showed no or slight benefits on BP.⁴⁴⁻⁴⁶ Soy is flavones improve CVD risk markers in women during the early menopause.⁴⁷ The beneficial effects of tibolone on lipid profile and coagulation factors have been documented in human trials, but larger RCTs evaluating its effect on cardiovascular or cerebrovascular events are not yet available. So, the verdict on its cardiovascular safety has not yet been confirmed.⁴⁸ However, a study has shown an increased risk of Ischemic Heart Disease (IHD), cerebral infarction and MI with tibolone.¹

Exercise, MHT and Cardiac Health

Combined aerobic physical training with oral MHT might improve systolic BP. Exercise alone appeared superior for improving diastolic BP and overall physical fitness in postmenopausal women. However, longer clinical trials are needed to establish the same.⁴⁹

BENEFITS IN SELECTED CLINICAL SUBGROUPS

- Whether initiating MHT soon after menopause can delay the onset of atherosclerosis or whether decreasing the dosage of estrogen or altering the progesterone component can overcome the pattern of early risk needs to be firmly established. Certain gene polymorphisms, statins, or targeting women with elevated Lp (a) may modify the risk profile. Avoiding oral MHT in women with baseline-raised levels of high-risk CRP may be justified.
- Low-dose E2/drospirenone treatment did not adversely affect carbohydrate metabolism and had a neutral effect on insulin sensitivity. The treatment induced favourable changes in the lipid profile and led to a significant improvement in vascular reactivity.⁵⁰
- Transdermal estradiol has minimal risk of VTE and of stroke. Micronised progesterone and dydrogesterone have also been shown not to increase the risk of VTE.
- Micronised progesterone and dydrogesterone have a neutral effect on the vasculature and a neutral or beneficial effect on BP. Transdermal estradiol and micronised progesterone could represent the optimal MHT, particularly in

women at risk of adverse events.⁵¹ Moreover, it seems that CVD protection mediated by replacement therapy is maximum when treatment is initiated in the absence of signs of atherosclerosis (typically in the premenopausal period), whereas it vanishes as atherosclerosis progresses (postmenopausal period).^{52,53}

- Oral estrogen alone and combined with progestogen are associated with a similar increased risk, which may be dose dependent. Conversely, a low dose of transdermal estrogens with or without a progestogen does not seem to be associated with such an increased risk of stroke, whereas tibolone, a synthetic steroid, may be associated with increased risk of IHD, cerebral infarction and MI.¹
- There is enough evidence demonstrating that oral MHT is associated with increased risk of stroke, particularly the ischemic subtype.⁵⁴

CARDIOVASCULAR RISK FACTORS AND ROLE OF MHT IN THE INDIAN CONTEXT

CVDs are the leading cause of morbidity in India. CVD affects Indians at least a decade earlier and in their most productive midlife years. Key risk factors include hypertension, dyslipidemia, obesity, diabetes mellitus, a sedentary lifestyle, tobacco use, urbanisation, and dietary changes contributing to rising rates, particularly in rural areas.⁵⁵ CVD is more common in postmenopausal women of the age group 40-55 years as compared to those who have not yet achieved menopause in a population of western Indian women, and this risk is significantly associated with central obesity, an abnormal lipid profile and the postmenopausal state in itself.⁵⁶

Certain cardiometabolic risk factors are disproportionately prevalent among Indian women and contribute to premature CVD. Atherogenic dyslipidaemia, characterised by elevated triglycerides, low HDL-cholesterol, and increased small dense LDL particles, is common in South Asian populations, including Indian women.⁵⁷⁻⁵⁹ Insulin resistance syndrome, encompassing hypertension, type 2 diabetes mellitus, central obesity, elevated lipoprotein(a) [Lp(a)], and atherogenic dyslipidaemia, is highly prevalent and manifests at younger ages in Indian women.^{57,60,61} Low HDL-cholesterol and smaller overall HDL particle size have been consistently identified as a strong and independent predictor of coronary artery disease (CAD) in Indian and South Asian women, even at relatively low LDL-cholesterol levels.^{58,61,62} Elevated Lp(a) and homocysteine levels occur more frequently in Indian women and are strongly associated with premature and accelerated CAD, partly explaining excess cardiovascular risk despite modest traditional risk factor burden.^{59,63,64} High prevalence of most of the conventional cardiovascular risk factors has been found, such as diabetes, hypertension, dyslipidemia, obesity, and other risk factors, in postmenopausal women from rural areas.⁶⁵

Data on MHT and CVD in India are scarce. Further research is needed to determine the optimal timing, route, and formulation of MHT to deliver clear benefits in the Indian context. However, we should consider the specific cardiovascular risk factors prevalent in our population before prescribing MHT. MHT prescription should be a shared decision between the health care provider and the patient. It should be rational, individualised, and tailored for a particular patient. Women should undergo thorough screening and assessment in accordance with standard protocols before starting MHT.⁶⁶ They should also be well counselled, educated, and guided to ensure proper follow-up and check-up for therapy monitoring.

INDIAN CLINICAL PRACTICE GUIDELINES BY THE INDIAN MENOPAUSE SOCIETY

- Systemic therapy is not to be used for primary or secondary prevention of CHD. At any age, avoid MHT in women at high risk of CVD or in established CVD.
- ET may be cardioprotective if started around the time of menopause, “window of opportunity” in a healthy woman. It reduces the risk of diabetes and has positive effects on the lipid profile and metabolic syndrome.
- Less than 60 years old, recently menopausal and without evidence of CVD, at mild to moderate risk of CVD, the initiation of MHT does not cause any harm and may reduce morbidity and mortality from CHD. For moderate-risk women, if indicated, transdermal MHT is preferable.
- MHT beyond the age of 60 years should be decided as a part of the overall risk–benefit analysis.
- Transdermal ET and the natural progesterones may not cause VTE. Population screening for thrombophilia is not indicated before MHT use.
- Standard dose oral MHT increased stroke risk by about one-third in generally healthy postmenopausal women. The

risk increases with estrogen dose, age, and BMI, and is higher in the first years of therapy. Low-dose ET, transdermal route, may not increase the risk of stroke.

TRENDS IN MHT USE AND CARDIOVASCULAR RISK

Following the publication of WHI¹², HERS¹¹, and other key studies in 2002-2003, a decline in MHT prescribing was observed. But soon, the discrepancy among these studies was attributed to differences in population, other selection criteria, and methodological biases. Thereafter, in the trend of MHT prescriptions stabilised from 2010 to 2016, and use rose again after 2017. However, the outcomes of trials on MHT and CVD remain inconclusive, variable, and contradictory. What is needed is to do more studies and re-evaluate the risk of CVD with contemporary hormone therapy in women around the age of menopause. The comprehensive knowledge gained to date should help us develop targeted therapies that optimise benefits while minimising risk and improving cardiovascular outcomes across diverse populations. Rigorous research into these dynamic interactions is crucial to refining MHT practices and tailoring interventions

SYNOPSIS

- MHT can have beneficial effects on CHD if started in younger women closer to menopause. Low-dose MHT may be initiated in older postmenopausal women if otherwise indicated for non-cardiac benefits.
- A clear trend towards increased use of transdermal therapy or oral bioidentical estrogen combined with levonorgestrel intrauterine system has been observed.
- The benefits of MHT in preventing atherosclerosis may occur only when therapy is started in the early postmenopausal years, known as the “window of opportunity” before advanced atherosclerosis develops.
- Initiation and continuation of MHT should be based on established non-coronary benefits and risks, as well as patient preference.
- Lifestyle changes and a healthy diet are recommended for preventing CHD.
- Mind modulation by Yoga and pranayama is a good suggestion for the prevention of CHD along with diet and exercise, avoidance of excessive alcohol, stress and smoking.

RESEARCH AGENDA

Effect of oral & transdermal MHT on Lp(a), lipid profile, insulin resistance, obesity, & metabolic syndrome

REFERENCES

1. Johansson T, Karlsson T, Blüed D, Schmitz D, Ek WE, Skalkidou A, et al. Contemporary menopausal hormone therapy and risk of cardiovascular disease: Swedish nationwide register based emulated target trial. *The BMJ* [Internet]. 2024 Nov 27 [cited 2026 Feb 13];387:e078784. doi: 10.1136/bmj-2023-078784. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11600536/>
2. Xia W, Khalil RA. Hormone Replacement Therapy and Cardiovascular Health in Postmenopausal Women. *Int J Mol Sci* [Internet]. 2025 May 24 [cited 2026 Feb 13];26(11):5078. doi: 10.3390/ijms26115078. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC12154064/>
3. Fredette NC, Meyer MR, Prossnitz ER. Role of GPER in estrogen-dependent nitric oxide formation and vasodilation. *J Steroid Biochem Mol Biol* [Internet]. 2018 Feb [cited 2026 Feb 13];176:65–72. doi: 10.1016/j.jsbmb.2017.05.006. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC5694388/>
4. Pedram A, Razandi M, Narayanan R, Levin ER. Estrogen receptor beta signals to inhibition of cardiac fibrosis. *Mol Cell Endocrinol* [Internet]. 2016 [cited 2026 Feb 13];434:57–68. Available from: <https://www.sciencedirect.com/science/article/pii/S0303720716302209>
5. Iwakura A, Shastri S, Luedemann C, Hamada H, Kawamoto A, Kishore R, et al. Estradiol Enhances Recovery After Myocardial Infarction by Augmenting Incorporation of Bone Marrow-Derived Endothelial Progenitor Cells Into Sites of Ischemia-Induced Neovascularization via Endothelial Nitric Oxide Synthase-Mediated Activation of Matrix Metalloproteinase-9. *Circulation* [Internet]. 2006 Mar 28 [cited 2026 Feb 13];113(12):1605–14. doi: 10.1161/CIRCULATIONAHA.105.553925. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.105.553925>
6. Grodstein F, Stampfer MJ, Manson JE, Colditz GA, Willett WC, Rosner B, et al. Postmenopausal Estrogen and Progestin Use and the Risk of Cardiovascular Disease. *N Engl J Med* [Internet]. 1996 Aug 15 [cited 2026 Feb 13];335(7):453–61. doi: 10.1056/NEJM199608153350701. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJM199608153350701>
7. Grodstein F, Manson JE, Colditz GA, Willett WC, Speizer FE, Stampfer MJ. A Prospective, Observational Study of Postmenopausal Hormone Therapy and Primary Prevention of Cardiovascular Disease. *Ann Intern Med* [Internet]. 2000 Dec 19 [cited 2026 Feb 13];133(12):933–41. doi: 10.7326/0003-4819-133-12-200012190-00008. Available from: <https://www.acpjournals.org/doi/10.7326/0003-4819-133-12-200012190-00008>
8. Varas-Lorenzo C, García-Rodríguez LA, Perez-Gutthann S, Duque-Oliart A. Hormone Replacement Therapy and Incidence of Acute Myocardial Infarction: A Population-Based Nested Case-Control Study. *Circulation* [Internet]. 2000 June 6 [cited 2026 Feb 13];101(22):2572–8. doi: 10.1161/01.CIR.101.22.2572. Available from: <https://www.ahajournals.org/doi/10.1161/01.CIR.101.22.2572>

9. Johansson T, Fowler P, Ek WE, Skalkidou A, Karlsson T, Johansson Å. Oral Contraceptives, Hormone Replacement Therapy, and Stroke Risk. *Stroke* [Internet]. 2022 Oct [cited 2026 Feb 13];53(10):3107–15. doi: 10.1161/STROKEAHA.121.038659. Available from: <https://www.ahajournals.org/doi/10.1161/STROKEAHA.121.038659>
10. Løkkegaard E, Nielsen LH, Keiding N. Risk of Stroke With Various Types of Menopausal Hormone Therapies: A National Cohort Study. *Stroke* [Internet]. 2017 Aug [cited 2026 Feb 13];48(8):2266–9. doi: 10.1161/STROKEAHA.117.017132. Available from: <https://www.ahajournals.org/doi/10.1161/STROKEAHA.117.017132>
11. Hulley S, Grady D, Bush T, Furberg C, Herrington D, Riggs B, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. *Jama* [Internet]. 1998 [cited 2026 Feb 13];280(7):605–13. Available from: <https://jamanetwork.com/journals/jama/article-abstract/187879>
12. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *Jama* [Internet]. 2002 [cited 2026 Feb 11];288(3):321–33. Available from: <https://escholarship.org/uc/item/3mr6f93p>
13. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus Progestin and the Risk of Coronary Heart Disease. *N Engl J Med* [Internet]. 2003 Aug 7 [cited 2026 Feb 13];349(6):523–34. doi: 10.1056/NEJMoa030808. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMoa030808>
14. Anderson GL, Limacher M, Assaf AR, Bassford T, Beresford SA, Black H, et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *Jama* [Internet]. 2004 [cited 2026 Feb 13];291(14):1701–12. Available from: <https://europepmc.org/article/med/15082697>
15. Godsland IF. Effects of postmenopausal hormone replacement therapy on lipid, lipoprotein, and apolipoprotein (a) concentrations: analysis of studies published from 1974–2000. *Fertil Steril* [Internet]. 2001 [cited 2026 Feb 13];75(5):898–915. Available from: <https://www.sciencedirect.com/science/article/pii/S0015028201016995>
16. Stevenson JC, Crook D, Godsland IF, Collins P, Whitehead MI. Hormone Replacement Therapy and the Cardiovascular System: Nonlipid Effects. *Drugs* [Internet]. 1994 [cited 2026 Feb 13];47(Supplement 2):35–41. doi: 10.2165/00003495-199400472-00007. Available from: <http://link.springer.com/10.2165/00003495-199400472-00007>
17. Crook D, Cust MP, Gangar KF, Worthington M, Hillard TC, Stevenson JC, et al. Comparison of transdermal and oral estrogen-progestin replacement therapy: effects on serum lipids and lipoproteins. *Am J Obstet Gynecol* [Internet]. 1992 [cited 2026 Feb 13];166(3):950–5. Available from: <https://www.sciencedirect.com/science/article/pii/S000293789291370P>
18. Jiang Y, Tian W. The effects of progesterones on blood lipids in hormone replacement therapy. *Lipids Health Dis* [Internet]. 2017 Dec [cited 2026 Feb 13];16(1):219. doi: 10.1186/s12944-017-0612-5. Available from: <https://lipidworld.biomedcentral.com/articles/10.1186/s12944-017-0612-5>
19. Spencer CP, Godsland IF, Cooper AJ, Ross D, Whitehead MI, Stevenson JC. Effects of oral and transdermal 17 β -estradiol with cyclical oral norethindrone acetate on insulin sensitivity, secretion, and elimination in postmenopausal women. *Metabolism* [Internet]. 2000 [cited 2026 Feb 13];49(6):742–7. Available from: <https://www.sciencedirect.com/science/article/pii/S0026049500800591>
20. Gambacciani M, Ciaponi M, Cappagli B, Piaggese L, De Simone L, Orlandi R, et al. Body weight, body fat distribution, and hormonal replacement therapy in early postmenopausal women. *J Clin Endocrinol Metab* [Internet]. 1997 [cited 2026 Feb 13];82(2):414–7. Available from: <https://academic.oup.com/jcem/article-abstract/82/2/414/2823229>
21. Winkler UH. Menopause, hormone replacement therapy and cardiovascular disease: a review of haemostaseological findings. *Fibrinolysis* [Internet]. 1992 [cited 2026 Feb 13];6:5–10. Available from: <https://www.sciencedirect.com/science/article/pii/S0268949992900042>
22. Stevenson JC. Cardiovascular effects of oestrogens. *J Steroid Biochem Mol Biol* [Internet]. 2000 Nov 30 [cited 2026 Feb 13];74(5):387–93. doi: 10.1016/S0960-0760(00)00117-5. Available from: <https://www.sciencedirect.com/science/article/pii/S0960076000001175>
23. Wingrove CS, Garr E, Godsland IF, Stevenson JC. 17 β -Oestradiol enhances release of matrix metalloproteinase-2 from human vascular smooth muscle cells. *Biochim Biophys Acta BBA-Mol Basis Dis* [Internet]. 1998 [cited 2026 Feb 13];1406(2):169–74. Available from: <https://www.sciencedirect.com/science/article/pii/S0925443997000975>
24. Özdemir K, Çelik Ç, Altunkeser BB, Içli A, Albeni H, Düzenli A, et al. Effect of postmenopausal hormone replacement therapy on cardiovascular performance. *Maturitas* [Internet]. 2004 [cited 2026 Feb 13];47(2):107–13. Available from: <https://www.sciencedirect.com/science/article/pii/S0378512203002482>
25. Mijatovic V, Pines A. Menopause-induced changes in cardiovascular functions and HRT. *Eur Menopause J*. 1995;2:4–9.
26. Pines A. Menopause-induced changes in left ventricular wall thickness. *Am J Cardiol* [Internet]. 1993 [cited 2026 Feb 13];72:240–1. Available from: <https://cir.nii.ac.jp/crid/1572261551266868224>
27. Sanghvi MM, Aung N, Cooper JA, Paiva JM, Lee AM, Zemrak F, et al. The impact of menopausal hormone therapy (MHT) on cardiac structure and function: insights from the UK Biobank imaging enhancement study. *PloS One* [Internet]. 2018 [cited 2026 Feb 13];13(3):e0194015. Available from: <https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0194015>
28. Miller VT, LaRosa J, Barnabei V, Kessler C, Levin G, Smith-Roth A, et al. Effects of Estrogen or Estrogen/ Progestin Regimens on Heart Disease Risk Factors in Postmenopausal Women: The Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA* [Internet]. 1995 Jan 18 [cited 2026 Feb 13];273(3):199–208. doi: 10.1001/jama.1995.03520270033028. Available from: <https://doi.org/10.1001/jama.1995.03520270033028>
29. Nabulsi AA, Folsom AR, White A, Patsch W, Heiss G, Wu KK, et al. Association of Hormone-Replacement Therapy with Various Cardiovascular Risk Factors in Postmenopausal Women. *N Engl J Med* [Internet]. 1993 Apr 15 [cited 2026 Feb 13];328(15):1069–75. doi: 10.1056/NEJM199304153281501. Available from: <https://www.nejm.org/doi/full/10.1056/NEJM199304153281501>
30. Hodis HN, Mack WJ. Menopausal Hormone Replacement Therapy and Reduction of All-Cause Mortality and Cardiovascular Disease: It's About Time and Timing. *Cancer J Sudbury Mass* [Internet]. 2022 [cited 2026 Feb 13];28(3):208–23. doi: 10.1097/PP0.0000000000000591. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC9178928/>
31. Swedish Society of Obstetrics and Gynecology. SFOG Council for Menopausal Hormone Therapy (MHT) 2025 [Internet]. 2025. Available from: <https://www.sfog.se/dokument/sfog-rad-for-menopausal-hormonbehandling-2019-antagna-210121/>
32. Chang WC, Wang JH, Ding DC. Conjugated equine estrogen used in postmenopausal women associated with a higher risk of stroke than estradiol. *Sci Rep* [Internet]. 2021 [cited 2026 Feb 13];11(1):10801. Available from: <https://www.nature.com/articles/s41598-021-90357-6>

33. Scarabin PY. Progestogens and venous thromboembolism in menopausal women: an updated oral versus transdermal estrogen meta-analysis. *Climacteric* [Internet]. 2018 July 4 [cited 2026 Feb 13];21(4):341–5. doi: 10.1080/13697137.2018.1446931. Available from: <https://www.tandfonline.com/doi/full/10.1080/13697137.2018.1446931>
34. Laliberté F, Dea K, Duh MS, Kahler KH, Rolli M, Lefebvre P. Does the route of administration for estrogen hormone therapy impact the risk of venous thromboembolism? Estradiol transdermal system versus oral estrogen-only hormone therapy. *Menopause* [Internet]. 2011 [cited 2026 Feb 13];18(10):1052–9. Available from: https://journals.lww.com/menopausejournal/fulltext/2011/10000/does_the_route_of_administration_for_estrogen.6.aspx
35. Barrett-Connor E, Mosca L, Collins P, Geiger MJ, Grady D, Kornitzer M, et al. Effects of Raloxifene on Cardiovascular Events and Breast Cancer in Postmenopausal Women. *N Engl J Med*. 2006 July 13;355(2):125–37. doi: 10.1056/NEJMoa062462.
36. Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hozowski K, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *Jama* [Internet]. 2002 [cited 2026 Feb 13];287(7):847–57. Available from: <https://jamanetwork.com/journals/jama/article-abstract/194654>
37. Vinogradova Y, Coupland C, Hippisley-Cox J. Use of hormone replacement therapy and risk of venous thromboembolism: nested case-control studies using the QResearch and CPRD databases. *bmj* [Internet]. 2019 [cited 2026 Feb 13];364. Available from: <https://www.bmj.com/content/364/bmj.k4810.abstract>
38. Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, et al. Hormone Therapy and Venous Thromboembolism Among Postmenopausal Women: Impact of the Route of Estrogen Administration and Progestogens: The ESTHER Study. *Circulation* [Internet]. 2007 Feb 20 [cited 2026 Feb 13];115(7):840–5. doi: 10.1161/CIRCULATIONAHA.106.642280. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.106.642280>
39. García-Sáenz M, Ibarra-Salce R, Pozos-Varela FJ, Mena-Ureta TS, Flores-Villagómez S, Santana-Mata M, et al. Understanding progestins: From basics to clinical applicability. *J Clin Med* [Internet]. 2023 [cited 2026 Feb 13];12(10):3388. Available from: <https://www.mdpi.com/2077-0383/12/10/3388>
40. Kaemmler LM, Stadler A, Janka H, Von Wolff M, Stute P. The impact of micronized progesterone on cardiovascular events – a systematic review. *Climacteric* [Internet]. 2022 July 4 [cited 2026 Feb 13];25(4):327–36. doi:10.1080/13697137.2021.2022644. Available from: <https://www.tandfonline.com/doi/full/10.1080/13697137.2021.2022644>
41. Mehta J, Manson JE. Menopausal hormone therapy and hypertension: minimizing risk. *Menopause* [Internet]. 2021 [cited 2026 Feb 13];28(11):1201–2. Available from: https://journals.lww.com/menopausejournal/fulltext/2021/11000/menopausal_hormone_therapy_and_hypertension_1.aspx
42. Shimbo D, Wang L, Lamonte MJ, Allison M, Wellenius GA, Bavry AA, et al. The effect of hormone therapy on mean blood pressure and visit-to-visit blood pressure variability in postmenopausal women: results from the Women's Health Initiative randomized controlled trials. *J Hypertens* [Internet]. 2014 [cited 2026 Feb 13];32(10):2071–81. Available from: https://journals.lww.com/jhypertension/FullText/2014/10000/The_effect_of_hormone_therapy_on_mean_blood.23.aspx
43. Gordon JL, Rubinow DR, Watkins L, Hinderliter AL, Caughey MC, Girdler SS. The effect of perimenopausal transdermal estradiol and micronized progesterone on markers of risk for arterial disease. *J Clin Endocrinol Metab* [Internet]. 2020 [cited 2026 Feb 13];105(5):e2050–60. Available from: <https://academic.oup.com/jcem/article-abstract/105/5/e2050/5678085>
44. Liu ZM, Ho SC, Chen YM, Woo J. Effect of soy protein and isoflavones on blood pressure and endothelial cytokines: a 6-month randomized controlled trial among postmenopausal women. *J Hypertens* [Internet]. 2013 [cited 2026 Feb 13];31(2):384–92. Available from: https://journals.lww.com/jhypertension/fulltext/2013/02000/Effect_of_soy_protein_and_isoflavones_on_blood.23.aspx
45. Husain D, Khanna K, Puri S, Haghighizadeh M. Supplementation of Soy Isoflavones Improved Sex Hormones, Blood Pressure, and Postmenopausal Symptoms. *J Am Coll Nutr* [Internet]. 2015 Jan 2 [cited 2026 Feb 13];34(1):42–8. doi: 10.1080/07315724.2013.875434. Available from: <https://www.tandfonline.com/doi/full/10.1080/07315724.2013.875434>
46. Liu ZM, Ho SC, Chen YM, Tomlinson B, Ho S, To K, et al. Effect of whole soy and purified daidzein on ambulatory blood pressure and endothelial function—A 6-month double-blind, randomized controlled trial among Chinese postmenopausal women with prehypertension. *Eur J Clin Nutr* [Internet]. 2015 [cited 2026 Feb 13];69(10):1161–8. Available from: <https://www.nature.com/articles/ejcn201524>
47. Sathyapalan T, Aye M, Rigby AS, Thatcher NJ, Dargham SR, Kilpatrick ES, et al. Soy isoflavones improve cardiovascular disease risk markers in women during the early menopause. *Nutr Metab Cardiovasc Dis* [Internet]. 2018 [cited 2026 Feb 13];28(7):691–7. Available from: <https://www.sciencedirect.com/science/article/pii/S093947531830098X>
48. Yuk J, Kim GS, Byun YS, Yang S, Kim M, Yoon S, et al. Effect of menopausal hormonal therapy on cardiovascular risks in Korean postmenopausal women: A nationwide cohort study. *BJOG Int J Obstet Gynaecol* [Internet]. 2024 Aug [cited 2026 Feb 13];131(9):1306–17. doi: 10.1111/1471-0528.17803. Available from: <https://obgyn.onlinelibrary.wiley.com/doi/10.1111/1471-0528.17803>
49. Sánchez-Delgado JC, Jácome-Hortúa AM, Uribe-Sarmiento OM, Philbois SV, Pereira AC, Rodrigues KP, et al. Combined effect of physical exercise and hormone replacement therapy on cardiovascular and metabolic health in postmenopausal women: A systematic review and meta-analysis. *Braz J Med Biol Res* [Internet]. 2023 [cited 2026 Feb 13];56:e12241. Available from: <https://www.scielo.br/j/bjmb/a/TZDxg75Hm6RnJj36N3f8NRk/?lang=en>
50. Mueck AO. Postmenopausal hormone replacement therapy and cardiovascular disease: the value of transdermal estradiol and micronized progesterone. *Climacteric* [Internet]. 2012 Apr [cited 2026 Feb 13];15(sup1):11–7. doi: 10.3109/13697137.2012.669624. Available from: <http://www.tandfonline.com/doi/full/10.3109/13697137.2012.669624>
51. Villa P, Suriano R, Ricciardi L, Tagliaferri V, De Cicco S, De Franciscis P, et al. Low-dose estrogen and drospirenone combination: effects on glycoinsulinemic metabolism and other cardiovascular risk factors in healthy postmenopausal women. *Fertil Steril* [Internet]. 2011 [cited 2026 Feb 14];95(1):158–63. Available from: <https://www.sciencedirect.com/science/article/pii/S0015028210010514>
52. Rosano G, Vitale C, Spoletini I, Fini M. Cardiovascular health in the menopausal woman: impact of the timing of hormone replacement therapy. *Climacteric* [Internet]. 2012 Aug [cited 2026 Feb 14];15(4):299–305. doi: 10.3109/13697137.2012.658899. Available from: <http://www.tandfonline.com/doi/full/10.3109/13697137.2012.658899>
53. Leuzzi C, Marzullo R, Modena MG. Is menopause a risk factor for ischemic heart disease? *G Ital Cardiol* [Internet]. 2012 [cited 2026 Feb 14];13(6):401–6. Available from: <https://iris.unimore.it/handle/11380/792689>
54. Renoux C, Suissa S. Hormone Therapy Administration in Postmenopausal Women and Risk of Stroke. *Womens Health* [Internet]. 2011 May [cited 2026 Feb 14];7(3):355–61. doi: 10.2217/WHE.11.28. Available from: <https://journals.sagepub.com/doi/10.2217/WHE.11.28>
55. Prabhakaran D, Jeemon P, Roy A. Cardiovascular Diseases in India: Current Epidemiology and Future Directions. *Circulation* [Internet]. 2016 Apr 19 [cited 2026 Feb 14];133(16):1605–20. doi: 10.1161/CIRCULATIONAHA.114.008729. Available from: <https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.114.008729>

56. Dosi R, Bhatt N, Shah P, Patell R. Cardiovascular Disease and Menopause. *J Clin Diagn Res JCDR* [Internet]. 2014 Feb [cited 2026 Feb 14];8(2):62–4. doi: 10.7860/JCDR/2014/6457.4009. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3972600/>
57. Misra A, Vikram NK. Insulin resistance syndrome (metabolic syndrome) and obesity in Asian Indians: evidence and implications. *Nutrition* [Internet]. 2004 [cited 2026 Feb 14];20(5):482–91. Available from: <https://www.sciencedirect.com/science/article/pii/S0899900704000346>
58. Enas EA, Yusuf S, Mehta JL. Prevalence of coronary artery disease in Asian Indians. *Am J Cardiol* [Internet]. 1992 [cited 2026 Feb 14];70(9):945–9. Available from: <https://cir.nii.ac.jp/crid/1363951794942129024>
59. Enas EA, Senthilkumar A. 3. Coronary Artery Disease in Asian Indians: An Update and Review..... 21. 2001 [cited 2026 Feb 14]; Available from: <https://jaypeebrothers.s3.ap-south-1.amazonaws.com/TOC-new/9788180614507.pdf>
60. Gupta R, Guptha S, Sharma KK, Gupta A, Deedwania P. Regional variations in cardiovascular risk factors in India: India heart watch. *World J Cardiol* [Internet]. 2012 [cited 2026 Feb 14];4(4):112. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3342579/>
61. Joshi SR, Saboo B, Vadivale M, Dani SI, Mithal A, Kaul U, et al. Prevalence of Diagnosed and Undiagnosed Diabetes and Hypertension in India—Results from the Screening India's Twin Epidemic (SITE) Study. *Diabetes Technol Ther* [Internet]. 2012 Jan [cited 2026 Feb 14];14(1):8–15. doi: 10.1089/dia.2011.0243. Available from: <https://journals.sagepub.com/doi/full/10.1089/dia.2011.0243>
62. Bhalodkar NC, Blum S, Rana T, Kitchappa R, Bhalodkar AN, Enas EA. Comparison of high-density and low-density lipoprotein cholesterol subclasses and sizes in asian indian women with caucasian women from the framingham offspring study. *Clin Cardiol* [Internet]. 2005 May [cited 2026 Feb 14];28(5):247–51. doi: 10.1002/clc.4960280510. Available from: <https://onlinelibrary.wiley.com/doi/10.1002/clc.4960280510>
63. Enas EA, Chacko V, Senthilkumar A, Puthumana N, Mohan V. Elevated Lipoprotein(a)—A Genetic Risk Factor for Premature Vascular Disease in People With and Without Standard Risk Factors: A Review. *Dis Mon* [Internet]. 2006 Jan 1 [cited 2026 Feb 14];52(1):5–50. doi: 10.1016/j.disamonth.2006.01.002. Available from: <https://www.sciencedirect.com/science/article/pii/S0011502906000137>
64. Refsum H, Ueland PM, Nygård O, Vollset SE. Homocysteine and Cardiovascular Disease. *Annu Rev Med* [Internet]. 1998 Feb [cited 2026 Feb 14];49(1):31–62. doi: 10.1146/annurev.med.49.1.31. Available from: <https://www.annualreviews.org/doi/10.1146/annurev.med.49.1.31>
65. Tandon VR, Mahajan A, Sharma S, Sharma A. Prevalence of cardiovascular risk factors in postmenopausal women: A rural study. *J -Life Health* [Internet]. 2010 [cited 2026 Feb 14];1(1):26–9. Available from: https://journals.lww.com/jomh/_layouts/15/oaks.journals/downloadpdf.aspx?an=01525309-201001010-00008
66. Aggarwal N, Meeta M, Chawla N. Menopause management: A manual for primary care practitioners and nurse practitioners. *J -Life Health* [Internet]. 2022 [cited 2026 Feb 14];13(Suppl 1):S2–51. Available from: https://journals.lww.com/jomh/citation/2022/13001/Menopause_management_A_manual_for_primary_care.2.aspx
67. Meeta M, Digumarti L, Agarwal N, Vaze N, Shah R, Malik S. Clinical practice guidelines on menopause: An executive summary and recommendations: Indian Menopause Society 2019–2020. *J -Life Health* [Internet]. 2020 [cited 2026 Feb 14];11(2):55–95. Available from: https://journals.lww.com/jomh/fulltext/2020/11020/Clinical_Practice_Guidelines_on_Menopause__An.3.aspx

Section 3

NERVOUS SYSTEM

14. Neurobiology and Neuropsychiatric Symptoms

15. Neurological Disorders

16. Sleep Disorders

NEUROBIOLOGY AND NEUROPSYCHIATRIC SYMPTOMS

14

Keywords: Neuropeptides, neurotransmitters, Kisspeptin–Neurokinin B–Dynorphin, autonomic nervous system

INTRODUCTION

Menopause comprises a complex neural and hormonal transition process, represented on a clinical spectrum that extends far beyond reproductive senescence, with fundamental alterations in both endocrine and neurological systems that significantly impact women's health.¹ While traditionally conceptualised as ovarian failure, contemporary understanding recognises menopause as a sophisticated interplay between declining ovarian hormones and extensive nervous system adaptations that orchestrate the diverse symptomatology observed in clinical practice.¹ For gynaecologists managing menopausal patients, understanding these intricate mechanisms is essential for providing comprehensive care, as the majority of menopausal symptoms are neurological in nature, affecting thermoregulation, cognition, sleep, mood, and sensory processing. The menopausal transition (MT) typically commences in the mid-40s. This 4–8-year period is characterised by profound hormonal instability.² During this time, women experience dramatic fluctuations in progesterone, androgens and estradiol. Profound alterations in gonadotropin levels and various neuropeptides also occur.³ These hormonal changes set in motion a cascade of neurological adaptations that manifest as diverse symptom profiles. Recent research has revealed that perimenopause is a state of flux, with symptoms emerging in multiple estrogen-regulated systems, including thermoregulation, sleep, circadian rhythms, sensory perception and cognitive processing.¹

CENTRAL NERVOUS SYSTEM NEUROPEPTIDES AND NEUROTRANSMITTER RECEPTOR DYNAMICS

In response to diminishing ovarian function, the hypothalamus undergoes complex neuroadaptive changes that extend beyond simple feedback mechanisms. Gonadotropin-releasing hormone (GnRH) neurons in the Arcuate nucleus undergo significant modifications, with increased GnRH pulse frequency and amplitude. Autopsy studies demonstrate increased GnRH expression in the medial basal hypothalamus after menopause. This process is mediated by enhanced stimulatory neuropeptides (neurokinin B and kisspeptin) and decreased inhibitory dynorphin.⁴ Recent research has revealed significant changes in estrogen receptor (ER) expression and activity during the MT. Contrary to earlier assumptions of receptor downregulation, positron emission tomography studies using 18Fluoro-estradiol demonstrate that ER density progressively increases during perimenopause.⁵ This upregulation represents a compensatory response to declining estrogen availability, with brain cells expressing additional receptors to maximise hormone capture. Studies show reduced ER α and ER β expression in specific brain regions with ageing, including significant reductions in the hippocampus and cerebral cortex, which correlate with cognitive and mood symptoms.⁵

NEUROLOGICAL MANIFESTATIONS: UNDERSTANDING THE CLINICAL PHENOTYPE

Vasomotor Symptoms: Neural Mechanisms And Pathophysiology

Hot flushes represent the most characteristic neurological manifestation of menopause, affecting 50–80% of women during the transition.⁶ These episodes fundamentally represent alterations in central thermoregulation, involving a narrowed thermoneutral zone and enhanced heat-dissipation responses mediated by specific neural circuits. Recent breakthrough research has identified the precise neural pathways underlying hot flushes, centring on the kisspeptin–neurokinin B–dynorphin (KNDy) neurons in the arcuate nucleus.⁷ KNDy neurons undergo hypertrophy as circulating estrogen levels decline during the MT and are considered a central mechanistic link between ovarian hormone withdrawal and VMS.⁸ These neurons co-express ER α , kisspeptin, and neurokinin B, with menopause associated with a marked increase in neurokinin B gene expression that correlates with neuronal hypertrophy.⁹ Experimental and translational studies demonstrate that estrogen withdrawal activates KNDy neurons, promoting neurokinin B release in the preoptic area.¹⁰ Neurokinin B subsequently stimulates Nk3 receptor-expressing glutamatergic neurons in the median preoptic nucleus, triggering downstream thermoregulatory responses, including cutaneous vasodilation and

sweating characteristic of hot flushes.⁷ Advanced neuroimaging studies reveal specific brain activation patterns during hot flushes, with significant insular cortex involvement correlating with subjective heat experience and brainstem activation preceding physiological symptom onset, confirming central initiation of these episodes.¹¹ During menopause, alterations in glutamatergic and gamma-aminobutyric acid (GABAergic) neurons in the hypothalamic preoptic area result in thermoregulatory dysfunction, with decreased numbers of glutamatergic neurons responsible for heat signals and increased GABAergic neurons mediating cold signals.¹²

Cognitive Dysfunction: Neurobiological Underpinnings

Cognitive complaints affect 44-62% of women during the MT, with verbal memory and processing speed being particularly affected.¹³ These changes reflect genuine alterations in brain structure and function rather than subjective perceptions, as demonstrated by comprehensive neuroimaging and neuropsychological assessments.¹⁴ Recent research indicates that perimenopause may be associated with deficits in processing speed, attention, and working memory, in addition to the well-documented verbal memory changes.¹³ Longitudinal neuroimaging studies demonstrate substantial differences in brain structure, connectivity, and energy metabolism across stages of the MT.¹⁵ The most pronounced effects occur in regions that subserve higher-order cognitive processes, including decreased grey matter volume in cortical and subcortical structures such as the hippocampus, amygdala, and thalamus. Importantly, grey matter volume generally stabilises postmenopause and selectively recovers in the precuneus, an associative cortical area involved in episodic memory and information integration.¹⁵ Brain metabolism studies reveal a critical role for estrogen in maintaining cerebral glucose utilisation. Women receiving estrogen replacement therapy (ERT) demonstrate preserved glucose metabolism in estrogen-dependent brain regions, including the hippocampus, entorhinal cortex, and posterior cingulate, whereas untreated women show metabolic decline in these areas, with compensatory increases in other regions.¹ This metabolic disruption may contribute to the hypometabolic state associated with neurological dysfunction during perimenopause.

Sleep Architecture And Circadian Disruption

Sleep disturbances increase dramatically during the MT, affecting 40-60% of perimenopausal women compared to 20-40% of premenopausal women. These alterations extend beyond vasomotor symptom-related awakenings, involving fundamental changes in sleep architecture and circadian rhythm regulation.¹⁶ Postmenopausal women demonstrate weakened circadian signals promoting sleep and wakefulness, with reduced amplitude of circadian variation in melatonin and core body temperature rhythms.¹⁷ Sleep architecture modifications include increased Stage N1 and N2 sleep, decreased Stage N3 sleep, and increased arousal frequency.¹⁷ Estrogen and progesterone directly influence sleep through effects on the suprachiasmatic nucleus and circadian timing systems, with declining hormone levels disrupting melatonin production and altering circadian phase relationships.¹⁶ The relationship between reproductive hormones and circadian rhythms is bidirectional, with sleep disruption potentially exacerbating hormonal imbalances and menopausal symptoms.¹⁷

NEUROTRANSMITTER SYSTEMS: MOLECULAR MECHANISMS OF ADAPTATION SEROTONERGIC PATHWAYS AND MOOD REGULATION

Estrogen profoundly modulates serotonin neurotransmission through multiple mechanisms, including regulating tryptophan hydroxylase (the rate-limiting enzyme in serotonin synthesis) and altering serotonin receptor sensitivity. During perimenopause, declining estrogen levels are associated with increased monoamine oxidase A activity, leading to enhanced serotonin degradation and contributing to mood disturbances.¹⁸ The relationship between hormonal fluctuations and mood symptoms involves not only absolute hormone levels but also the rate and pattern of hormonal change, with greater estrogen variability during perimenopause predicting a higher risk for mood symptoms.¹⁴ Recent research has elucidated the impact of estradiol on the serotonin, glutamate, and dopamine systems, revealing complex interactions that influence mood, cognition, and behaviour.¹⁹ Estrogen's effects on serotonergic neurotransmission contribute significantly to the increased risk of depression during the menopausal transition, with this risk being significantly reduced in perimenopausal women receiving estrogen therapy.²⁰

GAMMA-AMINOBUTYRIC ACID-GLUTAMATE BALANCE AND THERMOREGULATION

The balance between excitatory glutamate and inhibitory GABA neurotransmission is significantly altered during menopause, with profound implications for thermoregulatory function. Research demonstrates that during menopause, the number of glutamatergic neurons in the preoptic area decreases, while the number of GABAergic

neurons increases, resulting in dysfunction of the thermoregulatory centre.¹² These changes directly contribute to hot flush pathophysiology by altering heat dissipation and control of heat production.

Mechanistically, estrogen regulates the transcription and expression of glutamate decarboxylases (GADs) and thermosensitive transient receptor potential proteins (TRPs) through estrogen receptors, thereby affecting both the number and function of glutamatergic and GABAergic neurons. During menopause, GAD1 expression increases while GAD2 expression decreases, and thermosensitive TRPM2 expression in glutamatergic neurons declines, while TRPM8 expression in GABAergic neurons increases.¹² Estrogen therapy can correct these abnormalities, providing mechanistic support for hormonal treatment of vasomotor symptoms.

ESTROGEN RECEPTOR SYSTEMS: NEUROPROTECTIVE MECHANISMS

Receptor Distribution and Cellular Actions: ER α and ER β are widely distributed throughout the central nervous system, with particularly high concentrations in regions governing reproduction, thermoregulation, cognition, and mood.²⁰ These receptors mediate both genomic and non-genomic effects, coordinating neuroprotective signalling cascades and modulating cerebral blood flow, energy metabolism, and oxidative processes.²¹ The ageing process affects receptor expression, with studies showing decreased levels of both receptor types in skin and brain tissue of postmenopausal women. In the hippocampus, decreased estradiol levels during postmenopause are associated with a subsequent decrease in ER α activation, leading to a long-term reduction in ER α expression and downstream signalling. Animal studies reveal age-related decreases in ER β in the cerebral cortex and in ER α in the periventricular preoptic nucleus.²² These receptor changes may contribute to the loss of neuroprotective capacity observed during the menopausal transition.

MITOCHONDRIAL FUNCTION AND BIOENERGETICS

Estrogen serves as an essential regulator of brain metabolism, contributing to glucose utilisation, glucose transport, ATP production, and mitochondrial respiration. The decline of 15-25% in brain metabolic function observed after ovarian hormone loss represents a fundamental disruption of cerebral bioenergetics. During reproductive senescence in mice, the drop in estrogen and progesterone concentrations correlates with increased expression of genes involved in fatty acid oxidation and ketogenic pathways, coupled with myelin degeneration and increased brain ketone body utilisation. Recent research confirms that estrogen, particularly estradiol and estrone, improves bioenergetics and antioxidant defences in neuronal cultures by increasing mitochondrial membrane potential, ATP levels, basal respiration, and manganese superoxide dismutase activity.²³ Estrogen treatment effectively reduces bioenergetic impairments observed in cellular models of Alzheimer's disease, highlighting its potential as a therapeutic intervention for mitochondrial dysfunction in aging.²³

NEUROINFLAMMATION AND MICROGLIAL ACTIVATION

Estrogen's Anti-Inflammatory Effects: Recent research has revealed that menopause triggers microglia-associated neuroinflammation, particularly relevant to neurodegenerative diseases such as Parkinson's disease. Microglial cells, the brain's immune cells, can polarise into proinflammatory M1 or anti-inflammatory M2 phenotypes, with estrogen promoting the protective M2 phenotype.²⁴ Age- and inflammation-associated microglial activation is attenuated by ovarian estrogen through inhibition of specific ion channels, particularly Kir2.1.²⁵ The loss of estrogenic anti-inflammatory protection during menopause increases vulnerability to neuroinflammation-mediated neurodegeneration, with the progression being more pronounced in menopausal women due to low circulating estrogen levels.²⁴ Estrogen's neuroprotective effects include modulation of microglial activation, reduction of proinflammatory cytokine production, and promotion of anti-inflammatory responses.²⁶

AUTONOMIC NERVOUS SYSTEM DYSFUNCTION

Central Autonomic Regulation: Hypothalamic-Limbic Control: Menopause is characterised by a decline and fluctuation in estradiol that disrupts central autonomic regulation within the hypothalamus and limbic system, regions densely populated with ER α and ER β .²⁷ Estrogen modulates neurotransmitters critical for autonomic balance, including serotonin, norepinephrine, and GABA; its withdrawal shifts autonomic tone toward sympathetic predominance.²⁸ This dysregulation contributes to impaired homeostatic integration between thermoregulation, mood, sleep, and cardiovascular control, explaining the close association between vasomotor symptoms, anxiety, and sleep disturbance during the menopausal transition.

Sympathetic Nervous System: Estrogen deficiency during menopause is associated with increased sympathetic nervous system activity, reflected by elevated plasma norepinephrine levels, increased sympathetic nervous system activity, reflected by elevated plasma norepinephrine levels, increased muscle sympathetic nerve activity, and reduced baroreflex sensitivity. Heightened sympathetic tone underlies common menopausal symptoms such as palpitations, anxiety, tremulousness, and blood pressure lability.²⁹ The loss of estrogen's inhibitory effect on central noradrenergic neurons and peripheral adrenergic receptors promotes vasoconstriction and cardiovascular hyperreactivity, contributing to increased cardiovascular risk after menopause.³⁰

Parasympathetic (Vagal) Function: Menopause is associated with reduced parasympathetic (vagal) activity, as evidenced by decreased heart rate variability (HRV), particularly in high-frequency components linked to vagal tone. Estrogen normally enhances vagal modulation through nitric oxide-dependant pathways and central cholinergic mechanisms; its decline results in diminished cardioprotective parasympathetic influence.³¹ Reduced vagal tone contributes to increased resting heart rate, impaired stress resilience, sleep disruption, and heightened vulnerability to anxiety and depressive symptoms in midlife women.³²

Thermoregulatory Autonomic System: VMS are a hallmark of menopausal autonomic dysfunction and arise from estrogen-mediated narrowing of the hypothalamic thermoneutral zone. Small fluctuations in core body temperature trigger exaggerated autonomic responses, including cutaneous vasodilation, sweating, and transient sympathetic surges. These hot flushes are accompanied by acute increases in heart rate and sympathetic activation, followed by parasympathetic withdrawal, highlighting a dynamic instability of autonomic control rather than simple peripheral vasodilation.^{8,33}

CARDIOVASCULAR AUTONOMIC CONTROL

Estrogen withdrawal adversely affects cardiovascular autonomic regulation by impairing endothelial nitric oxide synthesis, reducing arterial compliance, and altering baroreceptor sensitivity. These changes result in increased sympathetic dominance, reduced heart rate variability, and diminished blood pressure buffering capacity. Collectively, these autonomic alterations contribute to the sharp rise in hypertension, arrhythmias, and cardiovascular disease observed after menopause, independent of chronological ageing.^{34, 35}

GASTROINTESTINAL AUTONOMIC FUNCTION

Estrogen and progesterone influence enteric nervous system activity and gastrointestinal motility through autonomic and serotonergic pathways.³⁶ Menopausal hormonal changes may lead to autonomic imbalance within the gut, contributing to symptoms such as bloating, constipation, altered visceral sensitivity, and functional gastrointestinal disorders.³⁷ Reduced estrogen levels may also affect gut-brain axis signalling, linking gastrointestinal symptoms with mood and sleep disturbances common in menopause.^{37,38}

UROGENITAL AND PELVIC AUTONOMIC FUNCTION

Autonomic innervation of the lower urinary tract and genital tissues is highly estrogen sensitive. Estrogen deficiency leads to impaired parasympathetic-mediated vasodilation and reduced sympathetic coordination of urethral tone, contributing to urinary urgency, frequency, incontinence, and sexual dysfunction. These effects are mediated through estrogen-dependent regulation of nitric oxide synthase and autonomic neurotransmitter release in pelvic tissues.^{39,40}

CLINICAL IMPLICATIONS AND THERAPEUTIC CONSIDERATIONS

HORMONE THERAPY: MECHANISMS AND TIMING

Hormone therapy (HT) addresses menopausal symptoms by restoring estrogen signalling pathways disrupted during the transition. For vasomotor symptoms, ET modulates hypothalamic neurokinin B signalling pathways, restoring normal thermoregulatory function and reducing hot flush frequency by up to 85%.⁴¹ The therapy's effects on cognitive symptoms remain complex, with evidence suggesting potential benefit in younger postmenopausal women but possible harm in older women with established cardiovascular disease.²⁰ The "critical window" or "timing hypothesis" suggests that HT benefits are maximised when initiated within 10 years of menopause onset, before the establishment of pathological processes.⁴² This concept is supported by neuroimaging studies showing that women who began estrogen replacement therapy during perimenopause maintained preserved glucose metabolism in estrogen-dependent brain regions compared to untreated women.¹

EMERGING THERAPEUTIC TARGETS

The identification of KNDy neurons and neurokinin B pathways as central mediators of vasomotor symptoms has led to the development of neurokinin B receptor antagonists as novel treatments.⁶ These agents target specific neural pathways responsible for hot flushes without systemic hormonal effects, offering alternatives for women who cannot or choose not to use hormone therapy.⁶ Understanding of tissue-specific estrogen receptor function has prompted the development of selective estrogen receptor modulators (SERMs) that provide beneficial effects in specific tissues while minimising adverse effects in others. Additionally, targeting ER β specifically may avoid systemic ER α -activation side effects while preserving neuroprotective benefits, as ER β -selective ligands are currently in clinical trials for menopausal symptoms.²⁰

FUTURE DIRECTIONS AND CLINICAL APPLICATIONS

Personalised Medicine Approaches: Current research is expanding the understanding of individual variation in menopausal experiences, including genetic factors that affect estrogen metabolism, receptor sensitivity, and neurotransmitter function.⁵ Personalised approaches to menopause management may emerge from better characterisation of individual differences, including genetic polymorphisms that affect treatment response and symptom severity. The development of biomarkers to predict symptom severity and treatment response is an important research priority. Estrogen receptor imaging and other neuroimaging techniques may provide insights into brain changes during menopause and guide therapeutic decisions.⁵ Understanding the relationship between receptor density patterns and symptom profiles could enable more targeted interventions.

CLINICAL MANAGEMENT STRATEGIES

Comprehensive evaluation of menopausal women requires recognition that symptoms arise from complex neurohormonal interactions rather than simple hormone deficiency. The variability and intensity of symptoms reflect individual differences in receptor sensitivity, neurotransmitter function, and adaptive responses to hormonal change.¹ Assessment should encompass VMS, sleep quality, cognitive function, mood symptoms, and autonomic function measures. Treatment decisions must consider the multisystem nature of menopausal changes and the interconnected relationships among symptoms. Improving sleep quality may enhance cognitive function, while addressing VMS may benefit both sleep and mood.¹⁴ The neurological basis of menopausal symptoms supports a rationale for various treatment approaches, including hormone therapy, non-hormonal medications affecting neurotransmitter systems, and lifestyle interventions targeting circadian rhythm regulation.⁴³

SYNOPSIS

- Menopause represents a profound neurohormonal transition that extends far beyond reproductive system changes, involving complex interactions between declining ovarian hormones and extensive nervous system adaptations.
- The diverse symptomatology observed in clinical practice reflects disruption of multiple estrogen-regulated neural systems, including thermoregulation, cognition, sleep, mood regulation, and autonomic function. Understanding these mechanisms provides the foundation for evidence-based patient care and rational therapeutic decision-making.
- For gynaecologists, recognising menopause as fundamentally a neurological transition enhances patient care through validation of symptom experiences, appropriate therapeutic interventions, and comprehensive management strategies.
- As research continues elucidating complex mechanisms underlying menopausal symptoms, clinical practice increasingly benefits from mechanistic understanding, moving toward personalised approaches based on individual neurohormonal profiles and symptom patterns.
- The future of menopause care lies in integrated approaches that address both hormonal and neurological aspects of this transition, utilising emerging therapeutic targets and personalised medicine strategies to optimise outcomes and quality of life for women navigating this critical life stage.

RESEARCH AGENDA

Decoding Estrogen KNDy Autonomic Network Plasticity During the Menopausal Transition.

REFERENCES

1. Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. *Nature Reviews Endocrinology* 2015;11:393–405. <https://doi.org/10.1038/nrendo.2015.82>.
2. Santoro N, Randolph JF. Reproductive Hormones and the Menopause Transition. *Obstetrics and Gynecology Clinics of North America* 2011;38:455–66. <https://doi.org/10.1016/j.ogc.2011.05.004>.
3. Delamater L, Santoro N. Management of the Perimenopause. *Clinical Obstetrics & Gynecology* 2018;61:419–32. <https://doi.org/10.1097/grf.0000000000000389>.
4. Hall JE. Endocrinology of the Menopause. *Endocrinology and Metabolism Clinics of North America* 2015;44:485–96. <https://doi.org/10.1016/j.ecl.2015.05.010>.
5. GMosconi L, Nerattini M, Matthews DC, Jett S, Andy C, Williams S, et al. In vivo brain estrogen receptor density by neuroendocrine aging and relationships with cognition and symptomatology. *Scientific Reports* 2024;14. <https://doi.org/10.1038/s41598-024-62820-7>.
6. ombert-Labedens M, Vesterdorf K, Fuller A, Maloney SK, Baker FC. Effects of menopause on temperature regulation. *Temperature* 2025;12:92–132. <https://doi.org/10.1080/23328940.2025.2484499>.
7. Padilla SL, Johnson CW, Barker FD, Patterson MA, Palmiter RD. A Neural Circuit Underlying the Generation of Hot Flashes. *Cell Reports* 2018;24:271–7. <https://doi.org/10.1016/j.celrep.2018.06.037>.
8. Rance NE, Dacks PA, Mittelman-Smith MA, Romanovsky AA, Krajewski-Hall SJ. Modulation of body temperature and LH secretion by hypothalamic KNDy (kisspeptin, neurokinin B and dynorphin) neurons: A novel hypothesis on the mechanism of hot flashes. *Frontiers in Neuroendocrinology* 2013;34:211–27. <https://doi.org/10.1016/j.yfrne.2013.07.003>.
9. Rometo AM, Krajewski SJ, Lou Voytko M, Rance NE. Hypertrophy and Increased Kisspeptin Gene Expression in the Hypothalamic Infundibular Nucleus of Postmenopausal Women and Ovariectomized Monkeys. *The Journal of Clinical Endocrinology & Metabolism* 2007;92:2744–50. <https://doi.org/10.1210/jc.2007-0553>.
10. Mittelman-Smith MA, Williams H, Krajewski-Hall SJ, McMullen NT, Rance NE. Role for kisspeptin/neurokinin B/dynorphin (KNDy) neurons in cutaneous vasodilatation and the estrogen modulation of body temperature. *Proceedings of the National Academy of Sciences* 2012;109:19846–51. <https://doi.org/10.1073/pnas.1211517109>.
11. Deecher DC, Dorries K. Understanding the pathophysiology of vasomotor symptoms (hot flashes and night sweats) that occur in perimenopause, menopause, and postmenopause life stages. *Archives of Women's Mental Health* 2007;10:247–57. <https://doi.org/10.1007/s00737-007-0209-5>.
12. Sun Y, Wang H, Wang W, Lu J, Zhang J, Luo X, et al. Glutamatergic and GABAergic neurons in the preoptic area of the hypothalamus play key roles in menopausal hot flashes. *Frontiers in Aging Neuroscience* 2022;14. <https://doi.org/10.3389/fnagi.2022.993955>.
13. Metcalf CA, Duffy KA, Page CE, Novick AM. Cognitive Problems in Perimenopause: A Review of Recent Evidence. *Current Psychiatry Reports* 2023;25:501–11. <https://doi.org/10.1007/s11920-023-01447-3>.
14. Gava G, Orsili I, Alvisi S, Mancini I, Seracchioli R, Meriggiola MC. Cognition, Mood and Sleep in Menopausal Transition: The Role of Menopause Hormone Therapy. *Medicina* 2019;55:668. <https://doi.org/10.3390/medicina55100668>.
15. Mosconi L, Berti V, Dyke J, Schelbaum E, Jett S, Loughlin L, et al. Menopause impacts human brain structure, connectivity, energy metabolism, and amyloid-beta deposition. *Scientific Reports* 2021;11. <https://doi.org/10.1038/s41598-021-90084-y>.
16. Brown AMC, Gervais NJ. Role of Ovarian Hormones in the Modulation of Sleep in Females Across the
17. Pérez-Medina-Carballo R, Kosmadopoulos A, Boudreau P, Robert M, Walker CD, Boivin DB. The circadian variation of sleep and alertness of postmenopausal women. *Sleep* 2023;46. <https://doi.org/10.1093/sleep/zsac272>.
18. Barth C, Villringer A, Sacher J. Sex hormones affect neurotransmitters and shape the adult female brain during hormonal transition periods. *Frontiers in Neuroscience* 2015;9. <https://doi.org/10.3389/fnins.2015.00037>.
19. Bendis PC, Zimmerman S, Onisiforou A, Zanos P, Georgiou P. The impact of estradiol on serotonin, glutamate, and dopamine systems. *Frontiers in Neuroscience* 2024;18. <https://doi.org/10.3389/fnins.2024.1348551>.
20. Maioli S, Leander K, Nilsson P, Nalvarte I. Estrogen receptors and the aging brain. *Essays in Biochemistry* 2021;65:913–25. <https://doi.org/10.1042/EBC20200162>.
21. Zarate S, Stevnsner T, Gredilla R. Role of Estrogen and Other Sex Hormones in Brain Aging. *Neuroprotection and DNA Repair. Frontiers in Aging Neuroscience* 2017;9. <https://doi.org/10.3389/fnagi.2017.00430>.
22. Yang JL, Hodara E, Sriprasert I, Shoupe D, Stanczyk FZ. Estrogen deficiency in the menopause and the role of hormone therapy: integrating the findings of basic science research with clinical trials. *Menopause* 2024;31:926–39. <https://doi.org/10.1097/GME.0000000000002407>.
23. Lejri I, Grimm A, Eckert A. Mitochondria, Estrogen and Female Brain Aging. *Frontiers in Aging Neuroscience* 2018;10. <https://doi.org/10.3389/fnagi.2018.00124>.
24. Usman S, Mondal AC. Menopause triggers microglia-associated neuroinflammation in Parkinson's disease. *Brain Research* 2025;1859:149649. <https://doi.org/10.1016/j.brainres.2025.149649>.
25. Wu S-Y, Chen Y-W, Tsai S-F, Wu S-N, Shih Y-H, Jiang-Shieh Y-F, et al. Estrogen ameliorates microglial activation by inhibiting the Kir2.1 inward-rectifier K⁺ channel. *Scientific Reports* 2016;6. <https://doi.org/10.1038/srep22864>.
26. Villa A, Vegeto E, Poletti A, Maggi A. Estrogens, Neuroinflammation, and Neurodegeneration. *Endocrine Reviews* 2016;37:372–402. <https://doi.org/10.1210/er.2016-1007>.
27. Rance NE. Menopause and the human hypothalamus: Evidence for the role of kisspeptin/neurokinin B neurons in the regulation of estrogen negative feedback. *Peptides* 2009;30:111–22. <https://doi.org/10.1016/j.peptides.2008.05.016>.

28. Schwarz KG, Vicencio SC, Inestrosa NC, Villaseca P, Del Rio R. Autonomic nervous system dysfunction throughout menopausal transition: A potential mechanism underpinning cardiovascular and cognitive alterations during female ageing. *The Journal of Physiology* 2024;602:263–80. <https://doi.org/10.1113/JP285126>.
29. Seals DR, Esler MD. Human ageing and the sympathoadrenal system. *The Journal of Physiology* 2000;528:407–17. <https://doi.org/10.1111/j.1469-7793.2000.00407.x>.
30. Thurston RC, Christie IC, Matthews KA. Hot flashes and cardiac vagal control. *Menopause* 2010;17:456–61. <https://doi.org/10.1097/gme.0b013e3181c7dea7>.
31. Huikuri HV, Pikkujamsa SM, Airaksinen KEJ, Ikaheimo MJ, Rantala AO, Kauma H, et al. Sex-Related Differences in Autonomic Modulation of Heart Rate in Middle-aged Subjects. *Circulation* 1996;94:122–5. <https://doi.org/10.1161/01.cir.94.2.122>.
32. Thurston RC, Matthews KA, Chang Y, Santoro N, Barinas-Mitchell E, von Kanel R, et al. Changes in heart rate variability during vasomotor symptoms among midlife women. *Menopause* 2016;23:499–505. <https://doi.org/10.1097/gme.0000000000000586>.
33. Freedman RR. Menopausal hot flashes: Mechanisms, endocrinology, treatment. *The Journal of Steroid Biochemistry and Molecular Biology* 2014;142:115–20. <https://doi.org/10.1016/j.jsbmb.2013.08.010>.
34. Joyner MJ, Barnes JN, Hart EC, Wallin BG, Charkoudian N. Neural Control of the Circulation: How Sex and Age Differences Interact in Humans. *Comprehensive Physiology* 2015;5:193–215. <https://doi.org/10.1002/cphy.c140005>.
35. Mendelsohn ME, Karas RH. Molecular and Cellular Basis of Cardiovascular Gender Differences. *Science* 2005;308:1583–7. <https://doi.org/10.1126/science.1112062>.
36. Jiang Y, Greenwood-Van Meerveld B, Johnson AC, Travagli RA. Role of estrogen and stress on the brain-gut axis. *American Journal of Physiology-Gastrointestinal and Liver Physiology* 2019;317:G203–9. <https://doi.org/10.1152/ajpgi.00144.2019>.
37. Mulak A, Taché Y. Sex difference in irritable bowel syndrome: do gonadal hormones play a role? *Gastroenterol Pol.* 2010;17(2):89–97.
38. Nacar G, Hazar S, Hatun B. Investigating the relationship between menopausal symptoms and gastrointestinal symptoms. *Menopause* 2025. <https://doi.org/10.1097/gme.0000000000002685>.
39. Al-Hijji J, Batra S. Downregulation by estrogen of nitric oxide synthase activity in the female rabbit lower urinary tract. *Urology* 1999;53:637–41. [https://doi.org/10.1016/s0090-4295\(98\)00526-3](https://doi.org/10.1016/s0090-4295(98)00526-3).
40. Gamé X, Rischmann P, Arnal J-F, Malavaud B. Rôle des estrogènes sur la physiologie et la physiopathologie du bas appareil urinaire. *Progres En Urologie* 2013;23:502–10. <https://doi.org/10.1016/j.purol.2013.03.012>.
41. Modi M, Dhillon WS. Neurokinin B and Neurokinin-3 Receptor Signaling: Promising Developments in the Management of Menopausal Hot Flashes. *Seminars in Reproductive Medicine* 2019;37:125–30. <https://doi.org/10.1055/s-0039-3400241>.
42. Sharma A, Davies R, Kapoor A, Islam H, Webber L, Jayasena CN. The effect of hormone replacement therapy on cognition and mood. *Clinical Endocrinology* 2023;98:285–95. <https://doi.org/10.1111/cen.14856>.
43. Souza HC, Tezini GC. Autonomic Cardiovascular Damage during Post-menopause: the Role of Physical Training. *Aging and Disease* 2013;4:320–8. <https://doi.org/10.14336/AD.2013.0400320>.

NEUROLOGICAL DISORDERS

15

Keywords: Mood changes, headache, dementia, Alzheimer's disease, menopause, hormone therapy.

INTRODUCTION

The MT constitutes a neurobiological shift that fundamentally alters multiple brain systems, leading to complex neurological symptomatology that extends far beyond reproductive senescence.¹ Recent research has established that while menopause is clinically defined by reproductive changes, the symptoms are largely neurological in nature, reflecting disruption of multiple estrogen-regulated systems, including thermoregulation, sleep, circadian rhythms, cognitive processing, and pain modulation.² For gynaecologists managing menopausal women, understanding these neurological manifestations is essential, as they represent genuine neurobiological changes requiring evidence-based clinical interventions. The range of neurological manifestations, ranging from migraine headaches and cognitive dysfunction to sleep disorders and mood changes, indicates disruption of multiple neural systems, while their simultaneous emergence during the same transition suggests involvement of common controlling factors.¹ Among potential controlling factors, estrogen fulfils multiple requirements as a master regulator that functions through a network of estrogen receptors to coordinate signalling and transcriptional pathways regulating brain energy metabolism.¹ Temperature dysregulation affects up to 80% of perimenopausal women, cognitive dysfunction affects 62-78% depending on age group, and headache disorders affect 10% to 29% during perimenopause with distinct patterns of improvement or worsening across transition stages.^{3,4} These symptoms often persist into post menopause and can significantly impact functional capacity, occupational performance, and quality of life measures.

NEUROPSYCHIATRIC SYMPTOMS

Gender and Neuropsychiatric Symptoms

Neuropsychiatric symptoms, particularly depression and anxiety, are consistently reported to be more prevalent in women than in men. This gender disparity is multifactorial and reflects the interplay of genetic susceptibility, psychosocial vulnerability, heightened exposure to chronic stress, and the burden of somatic comorbidities.⁵ In addition, there is compelling evidence that the onset and exacerbation of neuropsychiatric symptoms are closely linked to the female reproductive life cycle, including premenstrual dysphoric disorder, postpartum depression, and mood disturbances during the MT.⁶ These observations underscore the influence of hormonal fluctuations on brain function. Estrogen receptors (ER α and ER β) are widely distributed throughout the brain, including the hippocampus, amygdala, prefrontal cortex, and hypothalamus regions critical for mood regulation, cognition, and emotional processing.⁷ Estrogen modulates multiple neurotransmitter systems, including serotonergic, dopaminergic, and noradrenergic pathways, and exerts direct neurotrophic effects by promoting synaptic plasticity, axonal sprouting, and neuronal survival.⁸ Additionally, estrogen enhances cerebral blood flow through vasodilatory mechanisms and improves mitochondrial and antioxidant function within neural tissue.⁸ The decline and fluctuation of estrogen levels during the MT are therefore thought to contribute to increased vulnerability to neuropsychiatric symptoms in susceptible women.⁹ On this basis, hormone therapy (HT) has been proposed as a potential therapeutic option for alleviating mood and cognitive symptoms during perimenopause and early postmenopause in carefully selected patients, although its use should be individualised, considering symptom profile, timing, and overall risk-benefit balance.^{10,11}

Depression and Mood Disorders

Depression represents one of the most significant neuropsychiatric complications of the MT, with systematic evidence demonstrating substantially elevated vulnerability during perimenopause.¹² The prevalence of depression shows distinct patterns across menopausal stages, affecting 47.3% of perimenopausal women compared to 30.2% of postmenopausal women, suggesting that hormonal fluctuations rather than absolute hormone deficiency drive mood symptoms.¹³ The pathophysiology underlying menopausal depression involves complex alterations in multiple neurotransmitter systems. Estrogen profoundly modulates serotonin neurotransmission through the regulation of tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis, and modulation of serotonin receptor sensitivity.¹⁴ During perimenopause, declining estrogen levels correlate with increased monoamine oxidase A activity,

resulting in enhanced serotonin degradation and contributing to mood disturbances.¹⁵ The Study of Women's Health Across the Nation (SWAN) provides vital longitudinal data showing that perimenopause doubles the risk of depressive symptoms, with late perimenopause marking a peak vulnerability period.¹⁶ Psychiatric Morbidity During the MT. Psychiatric morbidity during the MT is highest in women with a prior history of mood disorders, especially major depressive disorder (MDD).¹⁷ A thorough and detailed clinical history is crucial to differentiate menopause-related mood changes from other common and potentially reversible causes of affective symptoms. These include untreated vasomotor symptoms, recurrence or new onset of major depression, nutritional deficiencies (notably iron, vitamin B12, and vitamin D), thyroid dysfunction, adverse effects of medications used for acute or chronic illnesses, and the impact of stressful life events.¹⁸ Psychosocial factors such as adjustment to age-related social changes, caregiving responsibilities, relationship transitions, and socioeconomic stressors further influence vulnerability to mood disturbances during this stage of life.¹⁹

Hormone Therapy and Mood: Studies evaluating the effects of HT on depressive symptoms during the MT have yielded mixed and sometimes conflicting results. Klaiber et al. reported a beneficial effect of high-dose estrogen therapy compared with placebo in both premenopausal and postmenopausal women with severe depression that was resistant to conventional antidepressant treatment.²⁰ More robust evidence emerged from a randomised, double-blind, placebo-controlled trial conducted by Soares and colleagues involving 50 perimenopausal women with depressive disorders. In this study,²⁶ women met criteria for major depressive disorder, 11 for dysthymic disorder, and 13 for minor depressive disorder. Treatment with transdermal estradiol resulted in a significant improvement in depressive symptoms compared with placebo. Notably, women receiving estradiol maintained antidepressant benefits after a four-week washout period, although somatic symptoms, particularly vasomotor complaints, tended to recur.²¹ Despite these positive findings, several other randomised and observational studies have failed to demonstrate a significant antidepressant effect of estrogen therapy, particularly in postmenopausal women or in those with established major depressive disorder.²² Consequently, whether depression during the MT represents a distinct clinical entity requiring hormone-based treatment remains unresolved. Current evidence supports the view that if a woman meets diagnostic criteria for a depressive disorder, standard psychiatric treatments such as antidepressant pharmacotherapy and psychotherapy remain the cornerstone of management, rather than estrogen therapy alone.¹¹ However, in women whose depressive symptoms occur in the context of significant vasomotor symptoms, HT may serve as a useful adjunctive therapy by improving sleep, quality of life, and treatment adherence, and may indirectly enhance recovery from depression.¹⁸ In cases of new-onset depressive symptoms temporally related to the MT, without a prior history of major depression, a therapeutic trial of HT may be considered, particularly when vasomotor symptoms are prominent.¹¹ If depressive symptoms persist beyond three months despite effective control of menopausal symptoms with HT, the indication for continued HT should be reassessed and alternative or additional psychiatric treatments initiated.²³ Non-pharmacological interventions constitute an essential component of management across the spectrum of depressive symptoms. These include structured physical activity, yoga and meditation, relaxation and breathing exercises, healthy dietary patterns (plant-based, low-fat, and reduced caffeine and alcohol intake), psychological counselling, social engagement, and creative activities. Such interventions have demonstrated efficacy in reducing depressive symptoms and improving overall quality of life, independent of their beneficial effects on vasomotor symptoms.²⁴

Anxiety Disorders and Panic Symptoms

Anxiety symptoms are common during the MT and may increase relative to premenopause. Longitudinal evidence from the SWAN study shows that women without prior anxiety are more likely to develop significant anxiety symptoms during perimenopause and into postmenopause compared with premenopause.²⁵ Meta-analytic prevalence estimates of anxiety symptoms suggest rates around ~54–55% in perimenopausal women and about ~52% in postmenopausal women, substantially higher than in premenopausal stages.²⁶ The hormonal instability characteristic of perimenopause negatively impacts limbic and prefrontal circuits, heightening vulnerability to anxiety disorders through disruption of estrogen receptor signalling.²⁷ Menopausal anxiety manifests through diverse symptomatology, including panic attacks, shortness of breath, fatigue, dizziness, chills, heart palpitations, chronic sweating, nausea, and muscle tension. These symptoms frequently overlap with vasomotor manifestations, complicating diagnosis and requiring careful clinical assessment. The dramatic fluctuations in estrogen and progesterone levels during perimenopause disrupt GABA balance between GABA-A and GABA-B receptors, contributing to anxiety symptom development.²⁷

Cognitive Dysfunction and Memory Impairment

Cognitive dysfunction represents one of the most distressing neurological manifestations of menopause, with subjective cognitive decline affecting 44-62% of women during the MT.²⁸ Most women in menopause (around 70%) report deterioration in memory functions, including mild cognitive impairment, particularly during the perimenopausal period.²⁹ Age-related patterns reveal that cognitive symptoms peak in the 50-54 age group, with memory problems affecting 78.4% of women in this age range, executive function decline affecting 65%, and processing speed decline affecting 55.2%.³⁰ These patterns correspond temporally with late perimenopause and early postmenopause, reflecting the most dramatic hormonal fluctuations during the transition. The most commonly reported cognitive complaints include problems with memory, especially difficulty remembering words, numbers, and appointments; disruptions in daily life activities; trouble concentrating; and difficulty switching between tasks.³⁰ Cognitive decline during menopause reflects direct consequences of decreased estradiol levels, with early and prolonged loss of ovarian-derived 17 β -estradiol representing the main cause of negative neurological outcomes.³¹ Estrogen receptors are broadly distributed throughout brain regions affecting memory, neuroprotection, and neurogenesis, coordinating regulation of metabolism, cerebral blood flow, nerve growth factors, and neurotransmitter synthesis.³¹ Recent neuroimaging studies provide compelling evidence of strong connections between menopause and Alzheimer's disease-related brain changes. Various imaging techniques consistently show that the MT is associated with significant alterations in brain structure and function, including decreased grey and white matter volumes, reduced glucose metabolism, and increased β -amyloid deposition.³² Mechanistically, the decrease in estrogen levels disrupts brain bioenergetics through mitochondrial dysfunction. Cerebral glucose hypometabolism in Alzheimer's-vulnerable regions correlates with reduced platelet mitochondrial cytochrome oxidase activity.²⁸ This hypometabolic state contributes to β -amyloid deposition, synaptic loss, and cognitive decline characteristic of menopausal brain changes.

Menopause and Cognition

Difficulty with concentration and memory is a common subjective complaint during the MT and early post menopause.³³ These cognitive concerns are often reported in conjunction with sleep disturbance, vasomotor symptoms, mood changes, and psychosocial stressors typical of midlife, all of which may contribute to perceived cognitive inefficiency.³⁴ Large population-based observational studies, including the Melbourne Women's Midlife Health Project and the Study of Women's Health Across the Nation (SWAN), have generally shown that the natural MT is not associated with a measurable decline in episodic memory or global cognitive performance.^{35,36} Cognitive abilities such as verbal memory, working memory, and processing speed appear largely stable across midlife in healthy women undergoing natural menopause.³⁷ However, not all cognitive domains have been equally studied, and it remains possible that subtle changes in specific functions such as verbal fluency or executive performance may occur in some women during the MT, potentially reflecting hormonal fluctuations or indirect effects of sleep and mood disturbance.³⁸ Importantly, current evidence does not support the notion that menopause itself causes clinically significant cognitive decline or dementia. In contrast, abrupt estrogen withdrawal, as occurs in surgical menopause following bilateral oophorectomy, may adversely affect cognitive performance.³⁹

Cognition and Hormone Therapy: Evidence regarding the effects of HT on cognition during and after the MT remains mixed. A meta-analysis examining randomised controlled trials concluded that HT may improve memory or selected cognitive skills in recently menopausal women, but does not confer cognitive benefit in asymptomatic women or in those well beyond menopause.⁴⁰ Overall, findings across studies are inconsistent, and many clinical trials conducted in relatively younger postmenopausal women have failed to demonstrate substantial effects of HT on global cognition, memory, or executive function.⁴¹ These conclusions, however, are limited by the relatively small number of trials and modest sample sizes. An important potential exception to this general pattern is estrogen therapy initiated immediately after bilateral oophorectomy. In this setting, limited clinical trial and observational evidence suggest that estrogen therapy may benefit cognitive performance, at least in the short term and in specific cognitive domains.³⁹ In particular, estrogen compared with placebo has been shown to improve episodic memory for verbal information, including tasks involving learning and recall of word lists and narratives.⁴² Further insight into timing effects has been provided by the Early versus Late Intervention Trial with Estradiol (ELITE), a double-blind, placebo-controlled randomised trial designed to test the "timing" or "critical window" hypothesis.⁴³ ELITE demonstrated that estradiol treatment did not exert a significant effect on global cognition when administered in the absence of cognitive or psychosocial stress. However, investigators noted that estradiol may modulate stress responsiveness, suggesting that

cognitive benefits could emerge under conditions of stress by attenuating hypothalamic–pituitary–adrenal (HPA) axis reactivity.⁴⁴ Importantly, differences were observed according to timing of initiation: women who began estradiol therapy within six years of menopause (“early initiation”) differed biologically from those who initiated therapy more than ten years after menopause (“late initiation”).⁴³ Across studies, the effects of HT on verbal appear to depend on several interacting factors, including the abruptness of estrogen withdrawal, the formulation and route of hormone therapy, the age and menopausal stage of the women studied, and baseline cognitive or stress status.^{42,45}

Migraine and Headache Disorders

Migraine headaches are three times more common in women than in men due to estrogen’s influence on headache pathophysiology.⁴⁶ The evolution of migraine across menopausal stages follows predictable patterns that follow the underlying hormonal changes and provide important clinical insights for management strategies. Many studies do show higher migraine prevalence or frequency during perimenopause versus premenopause, and lower prevalence post-menopause in population samples, but the specific percentages vary widely between studies and populations.⁴⁷ Data from systematic reviews show that migraine is more likely to worsen after surgical menopause compared with spontaneous menopause.³ These epidemiological patterns reflect the “estrogen withdrawal” hypothesis, which remains the predominant explanatory model for hormonally-triggered migraine attacks.³ The pathophysiology underlying menopausal migraine involves multiple interconnected mechanisms centred on estrogen’s effects on vascular tone, neural excitability, and neurotransmitter systems.⁴⁸ Estrogen induces vasodilation through mechanisms involving arterial endothelium and endothelial-independent actions, while progesterone demonstrates varying effects on arterial tone, including both smooth muscle relaxation and constriction.⁴⁹ The hormonal imbalance between estrogen and progesterone within the brain creates physiological conditions that alter migraine susceptibility.⁴⁹ While estrogen stimulates neural excitability, progesterone exhibits inhibitory actions in central neurons, creating a delicate balance that becomes disrupted during the MT.⁴⁶ Additionally, estrogen increases serotonin production, reduces serotonin reuptake, and decreases serotonin degradation, with consequent cyclical changes in serotonin levels in the trigeminal ganglia contributing to selective responses to estrogen withdrawal.⁴⁹

Clinical Characteristics: Migraine patterns undergo significant changes during perimenopause and menopause, with alterations in the estrogen and progesterone secretion creating particularly challenging clinical scenarios. Perimenopausal migraine is characterised by significant fluctuations in estrogen levels, accompanied by transient increases in vasomotor symptoms and altered migraine patterns. High estrogen levels during this period are associated with increased aura symptoms, while the achievement of physiological estrogen stabilisation typically reduces migraine burden in terms of intensity and frequency.⁵⁰ Women with histories of menstrual migraine demonstrate particular vulnerability to migraine exacerbation during the hormonally unstable perimenopausal period. Approximately 30% of women experience peak migraine symptoms during perimenopause, with prior migraine history representing a predominant risk factor for symptom worsening.⁵¹ The effects of exogenous hormones on migraine are heterogeneous. Use of oral contraceptive pills (OCPs) or menopausal hormone therapy (MHT/HT) has been reported to exacerbate migraine in some women while improving symptoms in others, depending on hormone formulation, dose, route of administration, and individual sensitivity to estrogen fluctuations.⁵² Continuous or transdermal estrogen regimens, which minimise hormonal variability, appear less likely to worsen migraine compared with cyclic or oral preparations.⁵³ Caution is warranted when prescribing combined estrogen-containing OCPs or systemic HT to women with migraine with aura. Substantial evidence indicates that migraine with aura is an independent risk factor for ischaemic stroke, and this risk is further increased by exposure to exogenous estrogen, particularly oral formulations.⁵⁴ Current guidelines therefore recommend avoiding combined hormonal contraception in women with migraine with aura and exercising caution with MHT, favouring the lowest effective dose and non-oral routes when hormone treatment is required.^{55,56}

Dementia (Major Neurocognitive Disorder)

The term dementia, while still widely used in clinical practice and public health, is increasingly replaced in formal diagnostic systems by Major Neurocognitive Disorder (Major NCD).⁵⁷ This terminology, introduced in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5 and DSM-5-TR), emphasises objective cognitive decline rather than age-associated stigma and reflects a spectrum of severity and aetiologies.⁵⁸ Major neurocognitive disorder is characterised by a chronic, usually progressive decline in one or more cognitive domains sufficient to interfere with independence in everyday activities. These domains include memory, executive function, language, attention, perceptual–motor function, and social cognition.⁵⁷ In addition to cognitive impairment, patients often

exhibit significant behavioural, psychological, and personality changes, ultimately accompanied by deterioration in physical and neurological function. Conceptually, major neurocognitive disorder may be regarded as a form of “chronic brain failure,” whereas delirium represents an “acute brain failure,” distinguished by fluctuating attention, altered consciousness, and typically reversible causes such as infection, metabolic disturbance, or drug toxicity.⁵⁸ Globally, dementia (major NCD) affects over 55 million people, a figure projected to exceed 139 million by 2050, largely due to population ageing.⁵⁹ Alzheimer’s disease (AD) remains the most common aetiology and is predicted to affect approximately 1 in 85 people worldwide by mid-century.⁶⁰ In India, current estimates suggest that 3.7–4 million individuals aged over 60 years live with dementia, with a higher burden among women than men. Prevalence varies by region, ranging from 0.6–3.5% in rural populations and 0.9–4.8% in urban populations, reflecting differences in longevity, education, vascular risk, and access to diagnosis.⁶¹ Major neurocognitive disorder results from structural or functional damage to brain cells, with different aetiologies producing characteristic clinical syndromes based on the brain regions involved. The condition is frequently multifactorial, with mixed pathologies being especially common in older adults.⁵⁷

Causes

- Alzheimer’s disease (60–80% of cases)
- Vascular neurocognitive disorder, often following ischaemic or haemorrhagic stroke
- Lewy body disease
- Frontotemporal lobar degeneration
- Parkinson’s disease related neurocognitive disorder

Importantly, some causes of cognitive impairment are potentially reversible, including hypothyroidism, vitamin B12 deficiency, depression (“pseudodementia”), normal pressure hydrocephalus, medication effects, and metabolic disturbances. Identification of these conditions is essential during evaluation.

Clinical Features: For a diagnosis of major neurocognitive disorder, there must be significant impairment in at least two cognitive domains, representing a decline from previous functioning and interfering with independence.⁵⁷

These Include:

- Memory
- Language and communication
- Attention and concentration
- Executive function (reasoning and judgement)
- Visual-spatial perception
- Ability to perform activities of daily living
- Most neurocognitive disorders are progressive. Early diagnosis allows identification of treatable conditions, initiation of symptomatic therapies, risk-factor modification, psychosocial support, and future care planning.⁶²

Alzheimer’s Disease

AD is the most common cause of major neurocognitive disorder and is characterised by a slowly progressive decline in memory, accompanied by impairment in other cognitive domains. Neuropathologically, AD is associated with diffuse cerebral atrophy, with prominent involvement of the hippocampus, entorhinal cortex, and temporoparietal association cortices. The hallmark microscopic features include extracellular deposits of β -amyloid plaques and intracellular neur fibrillary tangles composed of hyperphosphorylated tau protein, which together lead to synaptic dysfunction, neuronal loss, and network disintegration.^{57,63} β -Amyloid peptides are generated through abnormal proteolytic cleavage of amyloid precursor protein (APP), whereas tau pathology disrupts axonal transport and cytoskeletal stability. Degeneration of basal forebrain cholinergic neurons reduces cortical acetylcholine levels, contributing significantly to cognitive impairment. Importantly, neuropathological changes begin 10–20 years before the onset of clinical symptoms, supporting the concept of an AD continuum that extends from a preclinical stage to mild cognitive impairment and eventually overt dementia.^{63,64}

AD accounts for approximately 60–80% of dementia cases globally, making it a major public health challenge. Women have a higher lifetime risk of developing AD compared with men, a difference that is partly explained by greater longevity but may also reflect sex-specific biological vulnerability. Indian epidemiological studies report dementia prevalence ranging from 0.6% to 4.8%, with AD constituting the most common subtype.⁶⁵

Risk factors for AD can be broadly categorised into non-modifiable and modifiable factors. Non-modifiable risk factors include increasing age, female sex (odds ratio approximately 1.5), family history of dementia, carriage of the apolipoprotein E ϵ 4 allele, and genetic conditions such as Down syndrome.⁶⁵ Modifiable risk factors include mild cognitive impairment, vascular and metabolic disorders such as hypertension, diabetes, dyslipidemia, and obesity, as well as physical inactivity, smoking, depression, chronic stress, and traumatic brain injury. Lifestyle factors, including regular physical activity, a healthy diet, cognitive engagement, and optimal control of vascular risk factors, are consistently associated with reduced dementia risk.⁶²

AD typically presents insidiously, most often with episodic memory impairment, particularly affecting recent memory. As the disease progresses, additional cognitive domains become involved, including language (aphasia), motor planning (apraxia), object recognition (agnosia), and executive functioning. Neuropsychiatric symptoms such as depression, apathy, agitation, anxiety, sleep disturbance, and psychosis are common across disease stages and contribute substantially to caregiver burden, institutionalisation, and reduced quality of life.⁶⁶

The diagnosis of AD is primarily clinical and is supported by standardised cognitive testing and exclusion of alternative causes of cognitive impairment. The DSM-5-TR classifies AD under Major Neurocognitive Disorder due to AD.⁵⁷ The National Institute on Aging–Alzheimer’s Association (NIA-AA) 2018 research framework defines AD biologically using biomarkers, conceptualised within the AT(N) system.⁶⁴ Amyloid pathology (A) is indicated by reduced cerebrospinal fluid (CSF) A β 42 levels or positive amyloid PET imaging; tau pathology (T) by elevated CSF phosphorylated tau or tau PET positivity; and neurodegeneration (N) by structural MRI evidence of atrophy or hypometabolism on FDG-PET. Routine clinical evaluation should include laboratory testing for reversible causes of cognitive impairment, including thyroid dysfunction and vitamin B12 deficiency, as well as neuroimaging, with MRI preferred. Genetic testing, including APOE genotyping, is not recommended for routine clinical practice.⁶⁷

There is currently no curative therapy for AD, and management remains largely symptomatic and supportive. Pharmacological treatment includes cholinesterase inhibitors such as donepezil, rivastigmine, and galantamine, as well as the NMDA receptor antagonist memantine. These agents may provide modest symptomatic benefit or temporary stabilisation in mild to moderate disease, but do not alter disease progression.^{68,69} Non-pharmacological interventions are essential and include cognitive stimulation, behavioural strategies for managing neuropsychiatric symptoms, environmental modification, and structured caregiver education and support programmes.

Menopause, Hormone Therapy, and Alzheimer’s Disease: Estrogen exerts multiple neurobiological effects, including modulation of synaptic plasticity, cerebral blood flow, mitochondrial function, and neuroinflammation.⁹ Despite these mechanisms, HT is not recommended for the prevention or treatment of AD. The Women’s Health Initiative Memory Study (WHIMS) demonstrated an increased risk of dementia when estrogen therapy, with or without progestin, was initiated after the age of 65 years, particularly with combined estrogen–progestin regimens.⁷⁰ The “critical window hypothesis” proposes that initiation of hormone therapy near the time of menopause may have neutral or modest cognitive effects; however, current evidence is insufficient to support HT as a neuroprotective intervention.⁷¹ By the time AD becomes clinically manifest, extensive neuronal loss has already occurred, limiting the potential effectiveness of hormonal interventions.⁹

Prevention Strategies: It is estimated that up to 40% of dementia risk may be attributable to modifiable factors.⁶² Preventive strategies with the strongest evidence include regular physical activity, lifelong cognitive engagement, stress reduction, adequate sleep, adherence to a Mediterranean-style diet rich in fruits, vegetables, omega-3 fatty acids, and antioxidants, and aggressive management of vascular risk factors. Hormone therapy should not be used for dementia prevention.⁷⁰

Clinical Assessment and Diagnostic Considerations

Comprehensive Evaluation Framework: Assessment of neurological symptoms in menopausal women requires a systematic approach that incorporates multiple domains of neurological function.¹¹ Comprehensive evaluation should include detailed neurological histories focusing on headache patterns, cognitive complaints, sleep quality, mood symptoms, and sensory changes, alongside standardised assessment instruments for quantifying symptom

severity and functional impact.⁷² For headache assessment, detailed headache diaries tracking hormonal triggers, symptom patterns, and treatment responses provide crucial diagnostic information.¹³ Cognitive assessment should employ screening instruments such as the Montreal Cognitive Assessment (MoCA) or Mini-Mental State Examination (MMSE).^{73,74} Given the frequent overlap between cognitive complaints and mood symptoms, comprehensive psychiatric screening using instruments such as the Patient Health Questionnaire-9 (PHQ-9) and Generalised Anxiety Disorder-7 (GAD-7) is essential.^{75,76}

Red Flag Symptoms: The perimenopausal period poses diagnostic challenges due to multiple symptoms occurring simultaneously, requiring careful differentiation between menopause-related symptoms and other medical conditions. Red flag symptoms requiring immediate evaluation include sudden-onset severe headaches, headaches with neurological deficits, progressive cognitive decline exceeding expected patterns, new-onset seizures, and significant personality changes.⁷⁷ These symptoms may suggest secondary causes requiring neurological consultation and advanced imaging studies, stress, and support hormonal balance.

Clinical Practice Guidelines and Recommendations

Gynaecologists should implement systematic screening protocols for neurological symptoms in all perimenopausal and postmenopausal women.⁵⁵ Recommended approaches include annual assessment using validated instruments for mood (PHQ-9), anxiety (GAD-7), cognitive function (MoCA), and sleep quality (Pittsburgh Sleep Quality Index), supplemented by detailed symptom histories focusing on headache patterns, cognitive complaints, and functional impairments.

Early identification enables timely intervention and may prevent symptom progression and functional deterioration. Assessment should include evaluation of individual risk factors, prior neurological and psychiatric histories, current medications, and psychosocial stressors to guide personalised treatment.

Treatment decisions should consider the interconnected nature of neurological symptoms during menopause, with multimodal approaches often providing superior outcomes compared to single-domain interventions. For women with multiple neurological symptoms, HT may provide broad-spectrum benefits when not contraindicated, while targeted interventions may be appropriate for specific symptom domains. Treatment modifications may be necessary as women progress through different menopausal stages, with particular attention to the transitional periods between perimenopause and postmenopause.

SYNOPSIS

- Neurological manifestations represent core features of the MT, encompassing headaches, cognitive dysfunction, sleep disorders and mood changes that significantly impact women's quality of life and functional capacity.
- These symptoms reflect neurobiological changes resulting from estrogen withdrawal and disruption of multiple brain systems rather than normal ageing processes.
- Understanding the patterns of neurological symptoms across menopausal stages is essential for optimal clinical management.
- Migraine headaches show distinct evolutionary patterns with improvement in natural menopause but significant worsening with surgical menopause.
- Cognitive dysfunction peaks during the 50-54 age range corresponding to late perimenopause, while sleep disorders and mood symptoms show variable patterns requiring individualised assessment and treatment approaches.
- Evidence-based treatment approaches include HT as first-line treatment for multiple neurological domains, particularly to be initiated during the critical window of early menopause.
- Non-hormonal treatment options include targeted pharmacological interventions, cognitive-behavioural therapies, and lifestyle modifications, with combined approaches often providing superior outcomes compared to single-modality treatments.
- For gynaecologists, systematic screening for neurological symptoms, comprehensive assessment using validated instruments, and individualised treatment selection based on patient characteristics are essential components of optimal care, also we need to recognise neurological symptoms as legitimate medical concerns requiring evidence-based intervention rather than dismissal as normal ageing.

RESEARCH AGENDA

Identification of distinct neuropsychiatric vulnerability phenotypes using multimodal biomarkers, and determine whether early, phenotype-guided interventions can prevent persistent psychiatric disorders and adverse brain ageing outcomes.

REFERENCES

1. Brinton, R. D., Yao, J., Yin, F., Mack, W. J. & Cadenas, E. Perimenopause as a neurological transition state. *Nat. Rev. Endocrinol.* 11, 393–405 (2015). <https://doi.org/10.1038/nrendo.2015.82>
2. Genazzani, A. R. et al. Endocrinology of MT and Its Brain Implications. *CNS Spectr.* 10, 449–457 (2005). <https://doi.org/10.1017/s1092852900023142>
3. Sacco, S. et al. Migraine in menopausal women: a systematic review. *Int. J. Womens Health* 773 (2015) doi:10.2147/IJWH.S70073.
4. Bansal, R. & Aggarwal, N. Menopausal hot flashes: A concise review. *J. Midlife Health* 10, 6 (2019). https://doi.org/10.4103/jmh.jmh_7_19
5. Albert, P. R. Why is depression more prevalent in women? *Journal of Psychiatry and Neuroscience* 40, 219–221 (2015). <https://doi.org/10.1503/jpn.150205>
6. Steiner, M., Dunn, E. & Born, L. Hormones and mood: from menarche to menopause and beyond. *J. Affect. Disord.* 74, 67–83 (2003). [https://doi.org/10.1016/s0165-0327\(02\)00432-9](https://doi.org/10.1016/s0165-0327(02)00432-9)
7. McEwen, B. S. & Milner, T. A. Understanding the broad influence of sex hormones and sex differences in the brain. *J. Neurosci. Res.* 95, 24–39 (2017). <https://doi.org/10.1002/jnr.23809>
8. Woolley, C. S. Effects of estrogen in the CNS. *Curr. Opin. Neurobiol.* 9, 349–354 (1999). [https://doi.org/10.1016/s0959-4388\(99\)80051-8](https://doi.org/10.1016/s0959-4388(99)80051-8)
9. Brinton, R. D. Estrogen-induced plasticity from cells to circuits: predictions for cognitive function. *Trends Pharmacol. Sci.* 30, 212–222 (2009). <https://doi.org/10.1016/j.tips.2008.12.006>
10. Gordon, J. L. et al. Efficacy of Transdermal Estradiol and Micronized Progesterone in the Prevention of Depressive Symptoms in the Menopause Transition. *JAMA Psychiatry* 75, 149 (2018). <https://doi.org/10.1001/jamapsychiatry.2017.3998>
11. Maki, P. M. et al. Guidelines for the Evaluation and Treatment of Perimenopausal Depression: Summary and Recommendations. *J. Womens Health (Larchmt)*. 28, 117–134 (2019).
12. Badawy, Y., Spector, A., Li, Z. & Desai, R. The risk of depression in the menopausal stages: A systematic review and meta-analysis. *J. Affect. Disord.* 357, 126–133 (2024). <https://doi.org/10.1016/j.jad.2024.04.041>
13. Fang, Y. et al. Mapping global prevalence of menopausal symptoms among middle-aged women: a systematic review and meta-analysis. *BMC Public Health* 24, 1767 (2024). <https://doi.org/10.1186/s12889-024-19280-5>
14. Amin, Z. et al. Estradiol and Tryptophan Depletion Interact to Modulate Cognition in Menopausal Women. *Neuropsychopharmacology* 31, 2489–2497 (2006). <https://doi.org/10.1038/sj.npp.1301114>
15. Rekkas, P. V. et al. Greater Monoamine Oxidase A Binding in Perimenopausal Age as Measured With Carbon 11–Labeled Harmine Positron Emission Tomography. *JAMA Psychiatry* 71, 873 (2014). <https://doi.org/10.1001/jamapsychiatry.2014.250>
16. Bromberger, J. T. et al. Depressive symptoms during the MT: The Study of Women's Health Across the Nation (SWAN). *J. Affect. Disord.* 103, 267–272 (2007). <https://doi.org/10.1016/j.jad.2007.01.034>
17. Freeman, E. W. et al. Hormones and Menopausal Status as Predictors of Depression in Women in Transition to Menopause. *Arch. Gen. Psychiatry* 61, 62 (2004). <https://doi.org/10.1001/archpsyc.61.1.62>
18. Joffe, H. et al. Vasomotor symptoms are associated with depression in perimenopausal women seeking primary care. *Menopause* 9, 392–398 (2002). <https://doi.org/10.1097/00042192-200211000-00003>
19. Bromberger, J. T. & Kravitz, H. M. Mood and Menopause: Findings from the Study of Women's Health Across the Nation (SWAN) over 10 Years. *Obstet. Gynecol. Clin. North Am.* 38, 609–625 (2011). <https://doi.org/10.1016/j.ogc.2011.05.011>
20. Klaiber, E. L. Estrogen Therapy for Severe Persistent Depressions in Women. *Arch. Gen. Psychiatry* 36, 550 (1979). <https://doi.org/10.1001/archpsyc.1979.01780050060006>
21. de Novaes Soares, C., Almeida, O. P., Joffe, H. & Cohen, L. S. Efficacy of Estradiol for the Treatment of Depressive Disorders in Perimenopausal Women. *Arch. Gen. Psychiatry* 58, 529 (2001). <https://doi.org/10.1001/archpsyc.58.6.529>
22. Morrison, M. F. et al. Lack of efficacy of estradiol for depression in postmenopausal women: a randomized, controlled trial. *Biol. Psychiatry* 55, 406–412 (2004). <https://doi.org/10.1016/j.biopsych.2003.08.011>
23. Soares, C. N. Depression and Menopause. *Medical Clinics of North America* 103, 651–667 (2019). <https://doi.org/10.1016/j.mcna.2019.03.001>
24. Gartlehner, G. et al. Pharmacological and non-pharmacological treatments for major depressive disorder: review of systematic reviews. *BMJ Open* 7, e014912 (2017). <https://doi.org/10.1136/bmjopen-2016-014912>
25. Bromberger, J. T. et al. Does risk for anxiety increase during the MT? Study of Women's Health Across the Nation. *Menopause* 20, 488–495 (2013). <https://doi.org/10.1097/gme.0b013e3182730599>
26. Nik Hazlina, N. H., Norhayati, M. N., Shaiful Bahari, I. & Nik Muhammad Arif, N. A. Prevalence of Psychosomatic and Genitourinary Syndrome Among Menopausal Women: A Systematic Review and Meta-Analysis. *Front. Med. (Lausanne)*. 9, (2022). <https://doi.org/10.3389/fmed.2022.848202>
27. Parikh MD, D. P. et al. Menopausal [INCOMPLETE REFERENCE — full citation text missing; please supply]
28. Conde, D. M. et al. Menopause and cognitive impairment: A narrative review of current knowledge. *World J. Psychiatry* 11, 412–428 (2021). <https://doi.org/10.5498/wjp.v11.i8.412>
29. Sochocka, M. et al. Cognitive Decline in Early and Premature Menopause. *Int. J. Mol. Sci.* 24, 6566 (2023). <https://doi.org/10.3390/ijms24076566>

30. Maki, P. M. & Jaff, N. G. Brain fog in menopause: a health-care professional's guide for decision-making and counseling on cognition. *Climacteric* 25, 570–578 (2022). <https://doi.org/10.1080/13697137.2022.2122792>
31. Maioli, S., Leander, K., Nilsson, P. & Nalvarte, I. Estrogen receptors and the aging brain. *Essays Biochem.* 65, 913–925 (2021). <https://doi.org/10.1042/ebc20200162>
32. Briceno Silva, G. et al. Influence of the Onset of Menopause on the Risk of Developing Alzheimer's Disease. *Cureus* <https://doi.org/10.7759/cureus.69124> (2024) doi:10.7759/cureus.69124.
33. Weber, M. T., Rubin, L. H. & Maki, P. M. Cognition in perimenopause. *Menopause* 20, 511–517 (2013). <https://doi.org/10.1097/gme.0b013e31827655e5>
34. Maki, P. M. & Henderson, V. W. Cognition and the menopause transition. *Menopause* 23, 803–805 (2016). <https://doi.org/10.1097/gme.0000000000000681>
35. Guthrie, J., Dennerstein, L., Taffe, J., Lehert, P. & Burger, H. The MT: a 9-year prospective population-based study. The Melbourne Women's Midlife Health Project. *Climacteric* 7, 375–389 (2004). <https://doi.org/10.1080/13697130400012163>
36. Greendale, G. A. et al. Menopause-associated symptoms and cognitive performance: results from the study of women's health across the nation. *Am. J. Epidemiol.* 171, 1214–24 (2010). <https://doi.org/10.1093/aje/kwq067>
37. Henderson, V. W. & Sherwin, B. B. Surgical versus natural menopause. *Menopause* 14, 572–579 (2007). <https://doi.org/10.1097/gme.0b013e31803df49c>
38. Epperson, C. N., Sammel, M. D. & Freeman, E. W. Menopause Effects on Verbal Memory: Findings From a Longitudinal Community Cohort. *J. Clin. Endocrinol. Metab.* 98, 3829–3838 (2013). <https://doi.org/10.1210/jc.2013-1808>
39. Rocca, W. A., Grossardt, B. R. & Shuster, L. T. Oophorectomy, estrogen, and dementia: A 2014 update. *Mol. Cell. Endocrinol.* 389, 7–12 (2014). <https://doi.org/10.1016/j.mce.2014.01.020>
40. Yesufu, A., Banelow, S. & Hogervorst, E. Meta-Analyses of the Effect of Hormone Treatment on Cognitive Function in Postmenopausal Women. *Women's Health* 3, 173–194 (2007). <https://doi.org/10.2217/17455057.3.2.173>
41. Espeland MA. Conjugated Equine Estrogens and Global Cognitive Function in Postmenopausal Women<SUBTITLE>Women's Health Initiative Memory Study</SUBTITLE> *JAMA* 2004;291:2959. <https://doi.org/10.1001/jama.291.24.2959>
42. Phillips S. Effects of estrogen on memory function in surgically menopausal women. *Psychoneuroendocrinology* 1992;17:485–95. [https://doi.org/10.1016/0306-4530\(92\)90007-t](https://doi.org/10.1016/0306-4530(92)90007-t)
43. Henderson VW, St. John JA, Hodis HN, McCleary CA, Stanczyk FZ, Shoupe D, et al. Cognitive effects of estradiol after menopause. *Neurology* 2016;87:699–708. <https://doi.org/10.1212/wnl.0000000000002980>
44. Henderson VW, Hodis HN, St. John JA, McCleary CA, Stanczyk FZ, Shoupe D, et al. The critical window hypothesis: implications of cognitive outcomes from the ELITE clinical trial. *Maturitas* 2015;81:102. <https://doi.org/10.1016/j.maturitas.2015.02.070>
45. Sherwin BB. Estrogen and Cognitive Functioning in Women. *Endocrine Reviews* 2003;24:133–51. <https://doi.org/10.1210/er.2001-0016>
46. Sacco S, Ricci S, Degan D, Carolei A. Migraine in women: the role of hormones and their impact on vascular diseases. *The Journal of Headache and Pain* 2012;13:177–89. <https://doi.org/10.1007/s10194-012-0424-y>
47. Wang S, Fuh J, Lu S, Juang K, Wang P. Migraine Prevalence During MT. *Headache: The Journal of Head and Face Pain* 2003;43:470–8. <https://doi.org/10.1046/j.1526-4610.2003.03092.x>
48. MacGregor EA. Migraine and the menopause. *British Menopause Society Journal* 2006;12:104–8. <https://doi.org/10.1258/136218006778234048>
49. Martin VT, Behbehani M. Ovarian Hormones and Migraine Headache: Understanding Mechanisms and Pathogenesis—Part 2. *Headache: The Journal of Head and Face Pain* 2006;46:365–86. <https://doi.org/10.1111/j.1526-4610.2006.00370.x>
50. Waliszewska-Prosoł M, Grandi G, Ornello R, Raffaelli B, Straburzyński M, Tana C, et al. Menopause, Perimenopause, and Migraine: Understanding the Intersections and Implications for Treatment. *Neurology and Therapy* 2025;14:665–80. <https://doi.org/10.1007/s40120-025-00720-2>
51. Pavlović JM. The impact of midlife on migraine in women: summary of current views. *Women's Midlife Health* 2020;6. <https://doi.org/10.1186/s40695-020-00059-8>
52. Granella F, Sances G, Pucci E, Nappi R, Ghiotto N, Nappi G. Migraine with aura and reproductive life events: a case control study. *Cephalalgia* 2000;20:701–7. <https://doi.org/10.1046/j.1468-2982.2000.00112.x>
53. MacGregor EA, Frith A, Ellis J, Aspinall L, Hackshaw A. Prevention of menstrual attacks of migraine. *Neurology* 2006;67:2159–63. <https://doi.org/10.1212/01.wnl.0000249114.52802.55>
54. Champaloux SW, Tepper NK, Monsour M, Curtis KM, Whiteman MK, Marchbanks PA, et al. Use of combined hormonal contraceptives among women with migraines and risk of ischemic stroke. *American Journal of Obstetrics and Gynecology* 2017;216:489.e1-489.e7. <https://doi.org/10.1016/j.ajog.2016.12.019>
55. Sacco S, Merki-Feld GS, Aegidius KL, Bitzer J, Canonico M, et al. Hormonal contraceptives and risk of ischemic stroke in women with migraine: a consensus statement from the European Headache Federation (EHF) and the European Society of Contraception and Reproductive Health (ESC). *The Journal of Headache and Pain* 2017;18. <https://doi.org/10.1186/s10194-017-0815-1>
56. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause* 2022;29:767–94. <https://doi.org/10.1097/gme.0000000000002028>
57. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders* 2022. <https://doi.org/10.1176/appi.books.9780890425787>
58. Sachdev PS, Blacker D, Blazer DG, Ganguli M, Jeste DV, Paulsen JS, et al. Classifying neurocognitive disorders: the DSM-5 approach. *Nature Reviews Neurology* 2014;10:634–42. <https://doi.org/10.1038/nrneurol.2014.181>
59. World Health Organization. Global status report on the public health response to dementia: web annex: methodology for producing global dementia cost estimates. Geneva: World Health Organization; 2021. <https://iris.who.int/handle/10665/344479>
60. Brookmeyer R, Johnson E, Ziegler-Graham K, Arrighi HM. Forecasting the global burden of Alzheimer's disease. *Alzheimer's & Dementia* 2007;3:186–91. <https://doi.org/10.1016/j.jalz.2007.04.381>
61. Shaji KS, Jotheeswaran AT, Girish N, Bharath S, Dias A, Pattabiraman M, et al. The Dementia India Report: Prevalence, Impact, Costs and Services for Dementia. New Delhi: Alzheimer's and Related Disorders Society of India; 2010. Available from:

- <https://www.mhinnovation.net/sites/default/files/content/document/Dementia-India-Report.pdf> [Accessed 12th February 2026].
62. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, et al. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet* 2020;396:413–46. [https://doi.org/10.1016/s0140-6736\(20\)30367-6](https://doi.org/10.1016/s0140-6736(20)30367-6)
 63. Knopman DS, Amieva H, Petersen RC, Chételat G, Holtzman DM, Hyman BT, et al. Alzheimer disease. *Nature Reviews Disease Primers* 2021;7:33. <https://doi.org/10.1038/s41572-021-00275-0>
 64. Jack CR, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeberlein SB, et al. NIA-AA Research Framework: Toward a biological definition of Alzheimer's disease. *Alzheimer's & Dementia* 2018;14:535–62. <https://doi.org/10.1016/j.jalz.2018.02.018>
 65. Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, et al. Understanding the impact of sex and gender in Alzheimer's disease: A call to action. *Alzheimer's & Dementia* 2018;14:1171–83. <https://doi.org/10.1016/j.jalz.2018.04.008>
 66. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. *BMJ* 2015;350:h369. <https://doi.org/10.1136/bmj.h369>
 67. McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Kawas CH, et al. The diagnosis of dementia due to Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & Dementia* 2011;7:263–9. <https://doi.org/10.1016/j.jalz.2011.03.005>
 68. Birks J, Harvey R. Donepezil for dementia due to Alzheimer's disease. *Cochrane Database of Systematic Reviews* 2003;(3):CD001190. <https://doi.org/10.1002/14651858.cd001190>
 69. Singh B, Day CM, Abdella S, Garg S. Alzheimer's disease current therapies, novel drug delivery systems and future directions for better disease management. *Journal of Controlled Release* 2024;367:402–24. <https://doi.org/10.1016/j.jconrel.2024.01.047>
 70. Shumaker SA, Legault C, Rapp SR, Thal L, Wallace RB, Ockene JK, et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a randomized clinical trial. *JAMA* 2003;289:2651–62. <https://doi.org/10.1001/jama.289.20.2651>
 71. Henderson VW. Alzheimer's disease: Review of hormone therapy trials and implications for treatment and prevention after menopause. *The Journal of Steroid Biochemistry and Molecular Biology* 2014;142:99–106. <https://doi.org/10.1016/j.jsbmb.2013.05.010>
 72. Smith-Merry J, Mellifont D, Gillespie J, Salvador-Carulla L. Recovery-Oriented Community Mental Health Models: An Evidence Check Rapid Review Brokered by the Sax Institute for the Agency for Clinical Innovation. Sydney: Sax Institute; 2016. Available from: https://aci.health.nsw.gov.au/_data/assets/pdf_file/0019/395002/SAX-Recovery-oriented-community-mental-health-models-report.pdf [Accessed 12th February 2026].
 73. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal of the American Geriatrics Society* 2005;53:695–9. <https://doi.org/10.1111/j.1532-5415.2005.53221.x>
 74. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatric Research* 1975;12:189–98. [https://doi.org/10.1016/0022-3956\(75\)90026-6](https://doi.org/10.1016/0022-3956(75)90026-6)
 75. Kroenke K, Spitzer RL, Williams JBW. The PHQ-9: validity of a brief depression severity measure. *Journal of General Internal Medicine* 2001;16:606–13. <https://doi.org/10.1046/j.1525-1497.2001.016009606.x>
 76. Spitzer RL, Kroenke K, Williams JBW, Löwe B. A Brief Measure for Assessing Generalized Anxiety Disorder: The GAD-7. *Archives of Internal Medicine* 2006;166:1092–7. <https://doi.org/10.1001/archinte.166.10.1092>
 77. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia* 2018;38:1–211. <https://doi.org/10.1177/0333102417738202>

SLEEP DISORDERS

Keywords: Menopause, insomnia, obstructive sleep apnoea, restless leg syndrome

16

INTRODUCTION

Sleep abnormalities associated with menopause cause significant morbidity and represent one of the most challenging aspects of the menopause transition (MT). These sleep disturbances encompass a wide spectrum of disorders, including insomnia, sleep apnoea, increased nocturnal awakenings, poor sleep quality, and early morning awakening patterns. Together, these conditions lead to non-restorative sleep, increased daytime sleepiness, and diminished quality of life (QoL).¹ The prevalence and severity of these sleep disorders make them a critical public health concern. Considering that more than half of postmenopausal women suffer from various forms of sleep disorders, and given the increasing life expectancy, with women spending a significant amount of their lives in the postmenopausal state, it is imperative to understand this complex aspect of menopause comprehensively.² Early recognition, intervention, and appropriate treatment strategies can have a lasting positive impact on both immediate quality of life and long-term health outcomes. The MT is characterised by significant hormonal fluctuations that affect multiple physiological systems, with sleep regulation being particularly vulnerable.³ Understanding the intricate relationship between hormonal changes and sleep architecture is essential for developing effective therapeutic approaches and improving the overall well-being of menopausal women.

PHYSIOLOGY OF SLEEP

Sleep is broadly classified into rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. NREM sleep is subdivided into four stages (N1–N4), each characterised by distinct electroencephalographic (EEG) patterns, eye movements, and skeletal muscle tone, progressing from light sleep to deep slow-wave sleep.^{4,5} During both NREM and REM sleep, significant physiological changes occur across multiple systems, including the cardiovascular system, autonomic nervous system activity, respiratory regulation, cerebral blood flow, renal function, and endocrine secretion.^{4,6} Sleep is regulated by the interaction of two fundamental processes, the circadian rhythm and the homeostatic sleep drive. The circadian rhythm is governed by a central biological pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which coordinates sleep–wake timing by regulating melatonin secretion, core body temperature, alertness, and hormonal rhythms.^{7,8} The homeostatic mechanism reflects the progressive accumulation of sleep pressure during wakefulness, mediated in part by neurochemicals such as adenosine, and dissipates during sleep, thereby determining sleep intensity and duration.⁹

GENDER AND SLEEP DISORDERS

Sleep abnormalities demonstrate considerable variability across the MT, ranging from 16 to 47% in perimenopausal women and 35 to 60% in postmenopausal women.¹⁰ This wide range reflects the heterogeneous nature of sleep disturbances and the complex interplay of factors contributing to sleep dysfunction at this life stage.¹¹ One-fourth to half of all postmenopausal women will suffer from sleep disturbances. The prevalence of sleep disturbance is higher in perimenopausal, postmenopausal, and surgical menopausal women than in premenopausal women.¹¹ There is an independent relationship between menopausal stages and sleep disturbance beyond the effects of ageing and other confounders, although the magnitude of the relationship is small. Culture, ethnicity, or both may affect sleep disturbance levels across menopausal stages.¹¹ In surveys reported in medical literature, some women consistently report more sleep problems than men across all age groups.¹² Sleep disturbances in women can be affected by several factors throughout different age groups, starting from hormonal changes during menstrual cycles, pregnancy, and menopause, to medical and psychosocial factors such as gender specific roles and responsibilities in our society.¹³ Women are more likely than men to complain of insomnia, headache, irritability and fatigue than the “typical” symptoms of loud snoring and breathing cessation during sleep.¹² Hormones play an important role in women’s sleep. Reproductive hormones were found to protect against sleep apnoea in premenopausal women.¹⁴ Pregnancy is another period when the prevalence of sleep apnoea and Restless leg syndrome (RLS) increases due to hormonal effects.¹³ Progesterone stimulates benzodiazepine and gamma-aminobutyric acid (GABA) receptors, inducing sleep

and acting as an anxiolytic. Premenstrual fall in progesterone levels is associated with sleep disturbances.¹⁵ Estrogen is involved in the metabolism of norepinephrine, serotonin, and acetylcholine. It increases REM sleep and total sleep time and decreases sleep latency and spontaneous arousals. It is known to affect the thermoregulation centre, to regulate the timing of the lowest body temperature at night, and to improve sleep. It may also have an antidepressant effect due to its involvement in 5-hydroxytryptamine (5-HT) and neurotransmitter regulation, and because it is a GABA agonist, which translates into good-quality sleep.¹⁵

MELATONIN

Melatonin is an integral component of the biological circadian clock system. The synthesis and release of melatonin follow a precise temporal pattern, with light exposure inhibiting and darkness stimulating its production. The primary neural control originates from the suprachiasmatic nucleus of the hypothalamus, which serves as the master circadian pacemaker.¹⁶ With increasing age, melatonin levels decline even in healthy individuals. Studies have shown that melatonin levels are significantly lower in postmenopausal women than in premenopausal women. The relationship between melatonin and sleep disturbances in menopause is therefore complicated by the confounding effect of ageing. Nevertheless, this reduction disrupts circadian rhythms and alters sleep-wake cycles.¹⁷

HORMONAL CHANGES

Estrogen has been shown to have numerous positive effects on sleep regulation and architecture. These beneficial effects include reduced sleep latency (the time required to fall asleep), fewer arousals and awakenings after sleep onset, and increased total sleep time. Additionally, estrogen plays a crucial role in thermoregulation by reducing nocturnal body temperature fluctuations, which can significantly affect sleep quality and continuity.¹⁸ The neurochemical effects of estrogen extend to its modulation of key neurotransmitter pathways, particularly the noradrenergic and serotonergic systems. Through these mechanisms, estrogen exerts antidepressant effects that contribute to improved mood and, consequently, better sleep quality.¹⁸ Progesterone, conversely, demonstrates distinct anxiolytic and sedative properties through its interaction with GABA receptors in the central nervous system. GABA is the primary inhibitory neurotransmitter in the brain, and progesterone's enhancement of GABAergic activity promotes relaxation and sleep initiation.¹⁸

MOOD ABNORMALITIES

The loss of hormonal support in postmenopausal women leads to a complex constellation of symptoms that significantly impact overall well-being. These symptoms include vasomotor symptoms (VMS) such as hot flashes and night sweats, sexual dysfunction, cognitive complaints including memory difficulties and concentration problems, cardiovascular symptoms, musculoskeletal pains, and bone density changes.³ The psychological impact of these physical symptoms cannot be underestimated. For example, women experiencing VMS often report increased irritability, heightened anxiety levels, and mood instability.¹⁹ Sleep abnormalities and poor daytime quality of life, including workplace performance problems, concentration difficulties, and reduced social functioning, significantly accentuate mood disturbances. This creates a self-perpetuating cycle where mood disturbances worsen sleep quality, which in turn exacerbates mood symptoms. Breaking this cycle often requires comprehensive treatment approaches that address both sleep and mood components simultaneously.²⁰

INSOMNIA AND MENOPAUSE

Insomnia represents one of the most prevalent and troublesome symptoms of menopause, affecting approximately 46 to 48% of menopausal women.²¹ The clinical definition of insomnia encompasses difficulty initiating or maintaining sleep, or both, despite adequate opportunity and appropriate circumstances for sleep. The condition must result in clinically significant daytime impairment to meet diagnostic criteria.²² Chronic insomnia is specifically characterised by symptoms occurring at least three times per week for a minimum duration of three months.²³ Epidemiological data reveal important patterns in the development of menopausal insomnia. Women with a past history of insomnia at any point in their lives demonstrate an increased risk of developing incident insomnia during the postmenopausal period.²⁴ The pathogenesis of insomnia in menopause is distinctly multifactorial, involving complex interactions between biological, psychological, and environmental factors. Circadian rhythm disruptions, hormonal fluctuations, thermoregulatory disturbances (including hot flashes and night sweats), and mood abnormalities all contribute synergistically to the development and maintenance of insomnia.^{12,13,15} Refer to Table 1 for the causes of insomnia.

Understanding these multiple contributing factors is essential for developing comprehensive treatment strategies. Sleep maintenance insomnia, characterised by frequent nocturnal awakenings and difficulty returning to sleep, is more commonly reported than difficulty falling asleep initially, resulting in fragmented, non-restorative sleep.²⁵ The consequences of chronic insomnia in menopausal women extend far beyond nighttime sleep difficulties. Increased daytime sleepiness significantly impairs daily functioning, reducing workplace efficiency and performance and impairing decision-making.²⁶ The persistent fatigue with poor sleep quality contributes to increased levels of anxiety and depression, creating additional layers of complexity in the clinical presentation.²⁰ Long-term health consequences of chronic insomnia in postmenopausal women are particularly concerning as persistent sleep deprivation and poor sleep quality have also been linked to increased cardiovascular morbidity.²⁷ Polysomnographic studies, while providing objective measures of sleep parameters, have faced challenges in demonstrating consistent correlations between specific insomnia parameters, such as Wake After Sleep Onset (WASO) and hormonal changes in menopause. This lack of consistent correlation may be attributed to the difficulty of standardising sleep studies, given the dynamic and variable hormonal changes that occur across different stages of menopause, which pose methodological challenges.²⁵

Table 1: Aetiology of Insomnia During Menopause

Category	Aetiological Factors	Mechanism / Contribution to Insomnia
Hormonal changes	Decline in estrogen and progesterone	Alters thermoregulation, circadian rhythm, neurotransmitters (serotonin, GABA), and sleep architecture
Vasomotor symptoms	Hot flashes, night sweats	Cause nocturnal awakenings, sleep fragmentation, reduced sleep efficiency
Psychological factors	Depression, anxiety, stress, mood lability	Increase sleep latency, early morning awakenings, hyperarousal
Circadian rhythm changes	Altered melatonin secretion, aging SGN	Phase shifts, reduced sleep drive, difficulty maintaining sleep
Primary sleep disorders	Obstructive sleep apnoea, restless legs syndrome, periodic limb movement disorder	Phase shifts, reduced sleep drive, difficulty maintaining sleep
Medical Comorbidities	Chronic pain, arthritis, gastro-oesophageal reflux disease (GERD), urinary symptoms like Frequency/urgency/nocturia, thyroid disorders	Nighttime discomfort and repeated awakenings
Medications & substances	Details in the text, caffeine, alcohol	Interfere with sleep onset and continuity
Lifestyle & behavioural factors	Physical inactivity, poor sleep hygiene, irregular sleep schedules	Conditioned insomnia, reduced sleep quality
Aging-related changes	Reduced slow-wave sleep, increased arousals	Lighter, more fragmented sleep independent of menopause
Social Factors	Empty nest syndrome, Marital disharmony, financial constraints and family problems	Stress

Screening, Investigations, And Diagnosis Of Insomnia In Menopause

Routine screening for sleep disturbances should form an integral part of consultations for women presenting with menopausal symptoms. Targeted questioning regarding sleep onset latency, sleep maintenance, early morning awakening, sleep quality, and daytime impairment should be systematically incorporated, preferably using validated sleep questionnaires such as the Insomnia Severity Index and Pittsburgh Sleep Quality Index.^{28,29} Despite significant advances in objective sleep assessment, insomnia remains predominantly a clinical diagnosis, based on subjective patient complaints and established diagnostic criteria.³⁰ Although polysomnography (PSG), comprising electroencephalography, electrooculography, and electromyography, provides a detailed assessment of sleep architecture, it is not routinely recommended for uncomplicated insomnia. PSG is indicated when comorbid sleep disorders such as obstructive sleep apnoea, periodic limb movement disorder, parasomnias, or treatment-refractory insomnia are suspected.^{31,32} A comprehensive and individualised clinical history is fundamental to diagnosis and management. Clinicians should actively evaluate for symptoms of other sleep disorders, including snoring, witnessed apnoeas, nocturnal choking, restless legs symptoms, and involuntary limb movements.³² Menopause-related symptoms, particularly the frequency and severity of vasomotor symptoms, mood changes, fatigue, and urogenital complaints. Menstrual history and bleeding patterns to determine the stage of menopausal transition.¹ Psychiatric comorbidities, notably depression and anxiety, which are highly prevalent during menopause and strongly associated with insomnia.³³ Validated psychometric instruments, such as the Hamilton Depression Rating Scale (HDRS) and Hamilton Anxiety Rating Scale (HAM-A), may be used to identify coexisting mood and anxiety disorders that contribute to sleep disturbance.³⁴ Sleep diaries and standardised questionnaires further aid in defining sleep patterns, chronicity, severity, and treatment response.^{28,31} When insomnia is identified during menopause, secondary causes must be excluded, including common medical conditions (for example, sleep-disordered breathing, chronic pain syndromes, thyroid dysfunction) and psychiatric disorders.^{30,31} The decision to undertake objective investigations should be guided by clinical presentation, symptom severity, and the presence of red flag features, with diagnostic testing used judiciously.

General And Psychological Therapy

Treatment of insomnia in menopause requires a multi-pronged therapeutic approach that addresses the various contributing factors. Cognitive Behavioural Therapy for Insomnia (CBT-I) has demonstrated significant efficacy in improving multiple sleep parameters, including sleep quality, sleep onset latency, wake after sleep onset, and overall sleep efficiency. Refer to Table 2. CBT-I techniques include sleep restriction therapy, stimulus control, relaxation training, and cognitive restructuring to address maladaptive thoughts and behaviours related to sleep.³⁵

Table 2: Cognitive Behavioural Therapy for Insomnia

Elements	Description
Cognitive therapy	Aimed at changing patient's belief and attitudes about insomnia
CBTI	Combined cognitive therapy and behavioural techniques; the behavioural component may include stimulus control and/or sleep restriction therapy with or without use of relaxation therapy
Sleep hygiene education	Making patient aware of health practices and environment, but not a standard recommendation for using it as single therapy
Relaxation training	Progressive muscle relaxation and guided imagery rehearsal
Stimulus-control therapy	Training patient to reassociate bed and bedroom with sleep and reestablish a consistent sleep-wake schedule
Sleep-restriction therapy	Limiting time in bed, creating mild sleep deprivation, and then lengthening sleep time as sleep efficiency improves
Paradoxical Intention	Instructing patient to passively remain awake and avoid any effort to fall asleep; the goal is to eliminate performance anxiety
Biofeedback	Visual or auditory feedback to help control physiological variable to reduce arousal
Multicomponent therapy	Multiple behavioural techniques without cognitive therapy

(CBT: Cognitive-behavioural therapy; CBTI: Cognitive-behavioural therapy for insomnia).

SLEEP HYGIENE MEASURES

- Proper sleep scheduling and maintaining a regular sleep-wake schedule are crucial. Consistently going to bed and waking up at the same times helps synchronise the circadian rhythm.
- Avoid stimulants: Limiting caffeine, nicotine, and alcohol for at least 4–6 h before bedtime can enhance sleep onset and quality.
- Avoid using your bed for activities such as watching television, using smartphones, or reading to reinforce the connection between bed and sleep.
- Avoid stimulating activity close to bedtime: Exercise or heavy meals should be avoided within 2 h of sleep onset.
- Create a restful environment: Dim lighting, a quiet room, and a cool temperature (18°C–21°C) enhance sleep quality.
- Engaging in prayer, meditation, gratitude journaling, or positive thought exercises before sleep reduces cognitive arousal and nighttime repetitive negative thinking (rumination).
- Avoid spending too much time in bed: Limiting bedtime to the actual sleep duration helps improve sleep efficiency.^{36,37}

HORMONAL THERAPY

Until the early 2000s, menopausal hormone therapy (HT) was widely recommended as a first-line treatment for menopausal insomnia, largely based on multiple placebo-controlled trials demonstrating subjective improvement in sleep quality, particularly in women with coexisting vasomotor symptoms.³⁸ However, subsequent studies evaluating objective sleep parameters using polysomnography have yielded inconsistent results, likely attributable to heterogeneity in HT formulations, dosages, routes of administration, age at initiation, type of menopause, and baseline symptom burden.^{1,39} Several more recent trials and meta-analyses have concluded that HT confers a modest or no significant benefit on objectively measured sleep outcomes, especially when insomnia occurs independent of vasomotor symptoms.^{40,41} Concerns regarding the long-term risks of HT, particularly breast cancer, cardiovascular disease, stroke, and venous thromboembolism, intensified following the Women's Health Initiative (WHI) trials, leading to a paradigm shift in HT use.⁴² Consequently, individualised risk–benefit assessment and detailed counselling are mandatory prior to initiating HT. Factors such as personal and family history, contraindications (breast or ovarian cancer, thromboembolic disease), age, time since menopause, and treatment duration must be carefully considered.⁴³ Given the multifactorial etiology of insomnia in menopausal women, including psychological, medical, and primary sleep disorders, caution is advised against prescribing HT solely for insomnia.^{41,43} In a WHI-linked randomised trial, continuous combined therapy with conjugated equine estrogen (CEE) 0.625 mg and medroxyprogesterone acetate (MPA) 2.5 mg in women aged 50–79 years resulted in only a small short-term improvement in sleep disturbance at one year, with no sustained benefit at three years among 1,511 participants.⁴⁴ Improvements were primarily attributed to reductions in moderate-to-severe vasomotor symptoms, with minimal independent effects on insomnia.⁴⁵ HT was associated with improvements in self-reported sleep quality compared with placebo, though objective sleep measures (like polysomnography) did not show significant change. Specific HT regimens differed in effect, with 17β-estradiol and conjugated equine estrogens showing benefit on subjective sleep measures. Transdermal administration had stronger associations with improved sleep quality than oral routes. Combining estrogen with micronized progesterone was more effective for sleep disturbance relief than estrogen alone.³⁹ Differences among hormonal preparations appear clinically relevant. Studies suggest that micronised progesterone (MP) may exert sedative and anxiolytic effects via GABA-A receptor modulation, resulting in improved sleep continuity.⁴⁶ Randomised trials have demonstrated improvements in subjective and objective sleep quality with oral MP 300 mg, particularly in postmenopausal women with insomnia.^{46,47} Additionally, some studies report better sleep outcomes with CEE plus micronized progesterone compared to CEE plus MPA or dydrogesterone.⁴⁸ Other evidence indicates that while combined HT may alleviate climacteric symptoms and improve psychological well-being, it may have little or no effect on polysomnographically determined sleep architecture.⁴⁹ Combination therapy using oral estrogen with hypnotics has shown benefit in peri- and postmenopausal women in select populations, suggesting a potential adjunctive role

rather than monotherapy for HT in insomnia management.⁵⁰ The Radiological Evaluation and Breast Density (READ) study provided further insight into the role of HT discontinuation. Among women with a mean age of 60 years, temporary cessation of HT for 1–2 months was associated with worsening sleep quality, including difficulty initiating sleep, frequent awakenings, early morning awakening, non-restorative sleep, and reduced sleep satisfaction.⁵¹ These findings support the observation that withdrawal of HT may exacerbate sleep disturbances in some postmenopausal women. Emerging evidence suggests that HT may improve sleep primarily through reductions in vasomotor symptoms and anxiolytic effects, rather than through direct modulation of sleep architecture.^{40,41} Although tibolone has shown conflicting results, some recent studies indicate potential benefit in menopausal insomnia, particularly in women with prominent climacteric symptoms.⁵² In summary, hormone therapy is not recommended as first-line treatment for insomnia alone, but may be considered in symptomatic menopausal women with significant vasomotor symptoms, following individualised risk assessment. Current guidelines advocate using the lowest effective dose for the shortest duration, emphasising non-hormonal and behavioural therapies as primary treatment strategies for menopausal insomnia.⁵³

NONHORMONAL AND PSYCHIATRIC THERAPY

Antidepressant medications such as escitalopram have demonstrated benefits in improving sleep quality in postmenopausal women. These medications address both the underlying mood disturbances and their impact on sleep regulation.⁵⁴ Short-term treatment with sedative medications, including benzodiazepines such as lorazepam (0.5–2 mg) or diazepam (2–5 mg) and nonbenzodiazepine GABA-A receptor agonists such as zolpidem (5–10 mg), should be reserved for short-term treatment of severe insomnia that is unresponsive to behavioural and nonhormonal measures. Treatment should generally be limited to 2–4 weeks and not exceed 3 months without specialist review. Therapy should employ the lowest effective dose, with regular reassessment, and consider intermittent or alternate-night dosing for maintenance, in order to minimise dependence, tolerance, and cognitive adverse effects.^{55,56} Alternative pharmacological approaches include prolonged-release melatonin formulations and melatonin receptor agonists such as ramelteon, which have shown efficacy in improving insomnia symptoms, may be considered for up to 3–6 months in selected women, with a structured follow-up every 3–6 months. Long-term, open-ended use >12 months lacks robust data and should only continue with periodic clinical review.^{17,57,58} These medications represent safer alternatives to traditional benzodiazepines and Z-drugs such as zolpidem, particularly in older adults who may be more susceptible to adverse effects from sedative medications.⁵⁹ Dual orexin receptor antagonists (DORAs) block orexin receptor type 1 (OX1R) and type 2 (OX2R) and promote sleep through a decrease in arousal signalling, which, as has been noted, is a different therapeutic approach for insomnia.⁶⁰ Lemborexant, daridorexant, and suvorexant have favourable safety profiles and are potential future options for insomnia in midlife women; they can be continued long-term with monitoring.⁶¹ Nonhormonal agents: selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and gabapentin (preferred) have demonstrated moderate efficacy in improving sleep and reducing nocturnal vasomotor events.^{62,63}

COMPLEMENTARY AND MULTIDISCIPLINARY APPROACHES IN MENOPAUSAL

INSOMNIA

Several complementary therapies have been evaluated for the management of insomnia and climacteric symptoms, with variable evidence. Therapeutic massage has demonstrated modest subjective improvements in sleep quality and menopausal symptoms in small trials, likely mediated through relaxation and reduced autonomic arousal, although high-quality evidence remains limited.^{64,65}

The efficacy of soy isoflavones in improving sleep is inconsistent, with systematic reviews showing no clear benefit for insomnia, despite modest effects on some menopausal symptoms.⁶⁶ Current evidence is insufficient to support routine use of herbal remedies for menopausal insomnia due to heterogeneity and methodological limitations of existing studies.⁶⁷ In contrast, mind–body interventions such as yoga have shown more consistent benefits, with meta-analyses demonstrating improvements in subjective sleep quality, anxiety, and overall menopausal symptoms.⁶⁸ Evidence for tai chi remains limited but suggests potential benefit. Given the multifactorial nature of menopausal insomnia, a multidisciplinary approach involving gynaecologists, mental health professionals, and sleep specialists is recommended, particularly for treatment-resistant cases.⁴¹

CARDIOMETABOLIC RISKS LINKED TO SLEEP IN MENOPAUSE

Sleep duration and quality affect metabolic health. Short or disrupted sleep can worsen insulin sensitivity, appetite regulation, blood pressure, and inflammatory profiles, which are already vulnerable during menopause.⁶⁹ Sleep disorder prevalence increases with menopause, potentially compounding cardiometabolic risk. Menopause-related estrogen decline may amplify the harmful effects of poor sleep on cardiometabolic pathways, though mechanisms are still under study.⁷⁰ Both sleep health and cardiometabolic assessments are critical in midlife women. Integrating sleep screening into menopause care could help identify women at risk for cardiometabolic diseases.⁶⁹ The AHA statement emphasises that both short- and long-duration sleep and sleep disorders such as sleep-disordered breathing (SDB) and insomnia are associated with adverse cardiometabolic risk profiles and outcomes. Sleep restriction has a negative impact on energy balance, but it is less clear whether treating sleep disorders has a positive impact on obesity risk. Treating those with sleep disorders may provide clinical benefits, particularly for blood pressure.⁶⁹ Interventions that improve sleep duration/quality, sleep hygiene, cognitive-behavioural therapy for insomnia, and treatment of sleep-disordered breathing may potentially benefit cardiometabolic outcomes, though more menopause-specific research is needed. Menopausal women often experience changes in sleep that intersect with rising cardiometabolic risk. Addressing sleep health in this group could be a strategic point of intervention to improve long-term cardiometabolic outcomes. Sleep isn't just rest; it's a modifiable lifestyle factor with robust links to cardiometabolic health.⁷⁰

RESTLESS LEGS SYNDROME (RLS)

Restless Legs Syndrome presents as an irresistible urge to move the limbs, typically the legs, while attempting to fall asleep or during periods of rest. The condition is characterised by uncomfortable, abnormal sensations in the lower limbs that are temporarily relieved by movement and show a circadian pattern, with symptoms worsening during evening and nighttime hours. RLS shows a notable female predominance across all age groups, suggesting hormonal influences on its pathophysiology.⁷¹

BOX 1: DIAGNOSTIC CRITERIA FOR RESTLESS LEG SYNDROME

1. An urge to move the legs, usually accompanied or caused by uncomfortable and unpleasant sensations in the legs, (sometimes, the urge to move is present without the uncomfortable sensations and sometimes the arms or other body parts are involved in addition to the legs.)
2. The urge to move or unpleasant sensations begin or worsen during periods of rest or inactivity such as lying down or sitting.
3. The urge to move or unpleasant sensations are partially or totally relieved by movement, such as walking or stretching, at least as long as the activity continues.
4. The urge to move or unpleasant sensations are worse in the evening or at night than during the day or only occur in the evening or at night. (When symptoms are extremely severe, the worsening at night may not be noticeable but must have been present previously.)

Sources: South Med J © 2013 Lippincott Williams & Wilkins, International Restless Leg Syndrome Study Group criteria for restless leg syndrome.

The relationship between reproductive hormones and RLS presents a fascinating paradox in women's health. Both pregnancy and menopause, representing opposite ends of the reproductive hormone spectrum, are strongly associated with increased RLS prevalence. This observation has led researchers to propose that RLS in women may be more dependent on hormonal fluctuations and transitions than on absolute hormone levels, highlighting the importance of hormonal stability in symptom management.⁷¹ Epidemiological studies provide valuable insights into the prevalence and risk factors for RLS in postmenopausal women. A comprehensive Iranian population study demonstrated that 16.02% of postmenopausal women suffer from RLS, representing a significant public health burden. The study identified several important risk factors associated with increased RLS prevalence, including higher body mass index, lower socioeconomic status, anaemia, and a history of smoking, diabetes mellitus, and hypertension.⁷² Interestingly, the same study revealed that hormone replacement therapy was associated with reduced RLS risk, providing additional evidence for the hormonal basis of the condition.⁷² This finding suggests that maintaining adequate estrogen levels may have protective effects against RLS development or may help in symptom

management for women already affected by the condition.⁷¹ RLS is managed by first identifying and correcting reversible causes, particularly iron deficiency, as low brain iron is central to RLS pathophysiology.⁷³ Clinical guidelines recommend measuring serum ferritin in all patients and initiating iron therapy when ferritin is <75 ng/mL, with intravenous iron reserved for moderate–severe or refractory cases.⁷⁴ For persistent symptoms, α 2- δ calcium-channel ligands such as gabapentin or pregabalin are now preferred first-line pharmacologic agents because randomised trials show effective symptom control with a lower risk of augmentation compared with dopamine agonists.⁷⁵

Dopamine agonists (pramipexole, ropinirole) are effective but are recommended as second-line due to long-term risks of augmentation and impulse-control disorders. These strategies are supported by evidence-based recommendations from the International Restless Legs Syndrome Study Group and the American Academy of Sleep Medicine.⁷⁶

PERIODIC LIMB MOVEMENT DISORDER

Periodic Limb Movements (PLM) are characterised by abnormal, involuntary, repetitive movements of the lower limbs during sleep, typically occurring in clusters throughout the night. These movements can significantly disrupt sleep architecture and have been objectively associated with reduced sleep efficiency in polysomnographic studies. The movements typically involve dors flexion of the foot, extension of the big toe, and sometimes flexion of the knee and hip, occurring in stereotyped patterns every 20-40 seconds during episodes.⁷⁷ In postmenopausal women, the occurrence and severity of PLMs demonstrate significant correlations with vasomotor symptoms, which serve as markers for estrogen deficiency and hormonal dysregulation.²⁸ This relationship suggests that the hormonal changes characteristic of menopause may directly contribute to the development or exacerbation of PLM disorder.⁷⁸ Clinical evidence supporting the basis of PLMs comes from studies demonstrating that hormone replacement therapy can improve PLM frequency and severity in postmenopausal women. This therapeutic response further supports the role of menopausal reduction of sex steroids in the etiopathogenesis of the disorder and suggests that hormone replacement therapy may be beneficial for women with significant PLM-related sleep disturbances.⁷⁹ Treatment of PLM disorder focuses primarily on dopaminergic medications, with dopamine receptor agonists such as pramipexole representing an effective therapeutic option.⁷⁶

SLEEP DISORDERED BREATHING

Sleep-disordered breathing encompasses a range of respiratory problems that occur during sleep, significantly affecting sleep quality and overall health. This category includes obstructive sleep apnoea (OSA), central sleep apnoea (CSA), and hypopnoea events, each with distinct pathophysiological mechanisms but overlapping clinical presentations and consequences. Sleep disordered breathing is identified and quantified through polysomnographic evaluation, which measures recurrent episodes of reduced amplitude in respiratory, chest and abdominal movements during hypopnoea events, and complete cessation of respiratory activity during apnoea episodes. The frequency of these respiratory events is quantified using the apnoea- hypopnoea index (AHI), which represents the number of apnoea and hypopnoea events per hour of sleep.⁸⁰ This standardised measure allows for consistent diagnosis and severity assessment across different sleep laboratories and clinical settings. Obstructive sleep apnoea represents by far the most common form of sleep disordered breathing and is characterised by repeated mechanical obstruction of the upper airway during sleep. This obstruction typically manifests clinically as loud, disruptive snoring, often accompanied by witnessed breathing pauses and gasping or choking episodes. The clinical significance of OSA extends far beyond its immediate effects on sleep quality and daytime alertness.⁸¹ OSA can have profound and far-reaching impacts on multiple organ systems, affecting not only sleep quality, daytime sleepiness, and quality of life but also producing serious long-term health consequences. The cardiovascular system is particularly vulnerable, with OSA contributing to hypertension, coronary artery disease, heart failure, and arrhythmias. The brain is similarly affected, with OSA increasing the risk of stroke and cognitive impairment.⁸²

HORMONAL INFLUENCES ON SLEEP DISORDERED BREATHING

The relationship between hormonal changes and sleep-disordered breathing in menopause is supported by compelling clinical evidence. Both surgical menopause (hysterectomy) and oophorectomy (surgical removal of ovaries) are associated with significantly increased risk of developing OSA, suggesting that the abrupt loss of reproductive hormones may precipitate or worsen sleep-disordered breathing.⁸³ Statistical analyses show that OSA is approximately 4.5 times more prevalent in postmenopausal women compared to women in their reproductive years, representing one of the most dramatic increases in disease prevalence associated with the menopausal transition. Gender distribution of OSA provides additional insights into hormonal influences. While OSA is generally more

common in males across most age groups, this gender difference becomes progressively less pronounced with advancing age especially after menopause.⁸⁴ Age-related factors must be carefully considered when analysing OSA prevalence in menopause, as the general prevalence of OSA increases with advancing age in both men and women. Since menopause itself is an age-related phenomenon, separating the specific effects of hormonal changes from general aging effects requires sophisticated and complex approaches.⁸³ The physiological mechanisms by which estrogen deficiency contributes to OSA development operate through multiple pathways. Peripherally, estrogen changes affect body fat distribution, with postmenopausal women showing increased visceral fat deposition that can contribute to OSA.^{83,85} Sex hormones also exert significant effects on the neuromuscular control of pharyngeal muscles, which are crucial for maintaining upper airway patency during sleep.³⁷ The loss of this activity in postmenopausal women, therefore, leads to an increased tendency toward upper airway collapse during sleep. This mechanism helps explain the increased prevalence of OSA in postmenopausal women and supports the rationale for hormone replacement therapy in selected cases.⁸⁶

TREATMENT MODALITIES

Continuous positive airway pressure (CPAP) and automatic CPAP (Auto-CPAP) devices represent the gold standard and mainstay of treatment for moderate to severe OSA. These devices work by providing a continuous flow of pressurised air through a mask worn during sleep, effectively opening the upper airway and preventing obstruction.⁸⁷ Auto-CPAP devices offer the additional advantage of automatically adjusting pressure levels throughout the night based on real-time assessment of airway resistance and breathing patterns.⁸⁸ Despite the proven efficacy of CPAP therapy, compliance issues regarding regular nightly usage remain a significant clinical challenge. The equipment can initially feel cumbersome and uncomfortable, and many patients experience discomfort with mask fit, air pressure, or claustrophobia. Long-term adherence to CPAP therapy requires ongoing support, education, and, at times, equipment modifications to optimise comfort and effectiveness.⁸⁹ HT has demonstrated objective benefits in reducing OSA severity, as measured by significant reductions in the apnoea-hypopnoea index. This therapeutic response aligns with the pathogenetic understanding of reduced sex hormone levels contributing to OSA development in menopause. The improvements seen with hormone therapy support the biological plausibility of hormonal mechanisms in menopausal OSA and provide a rationale for considering hormone replacement in appropriately selected patients.⁹⁰

SYNOPSIS

- A detailed assessment of menopausal symptoms should always include questions about sleep patterns. Sleep questionnaires or sleep diaries can be useful to assess sleep in detail.
- Adverse lifestyle factors, social factors and risk factors should be considered and treated accordingly.
- If insomnia is identified, medical or psychiatric causes of insomnia should be ruled out and, if present, treated accordingly. If specific neurological or breathing disorders are suspected, further investigations and referrals to specialists should be initiated.
- Sleep hygiene measures and lifestyle modifications should be recommended as first-line treatment. Psychological treatments such as CBT should also be considered.
- Prior to considering treatment with HT, it is vital to take a detailed personal and family history, counsel patients regarding the effects and side effects of HT and exclude contraindications such as breast and ovarian cancer.
- Presently, prescribing HT solely for the treatment of insomnia is controversial, but it is given when associated with vasomotor symptoms. Optimisation of treatment should be based on clinical improvement, and patients should be closely monitored.
- If insomnia is resistant to lifestyle modifications and HT, then hypnotics, benzodiazepines or melatonin agonists can be used in the short-term, but there is no definite or convincing evidence to suggest their efficacy. These should only be prescribed under supervision or after liaison with psychiatrists or sleep experts.
- No recommendations can be made about the use of herbal remedies for insomnia as there is insufficient evidence. Mind-body therapies such as yoga and tai chi have some evidence but need further rigorous studies to prove their effectiveness.

- A multidisciplinary approach should be adopted to treat such patients, with effective communication among the various professionals involved.
- Voluntary organisations and support groups are often useful for patients to meet other patients who suffer from similar problems.
- Insomnia during menopause is treatable and should not be considered as an inevitable consequence of menopause. Clinicians should make every attempt possible to treat insomnia symptoms as these can result in a significant adverse impact on daily functioning and quality of life.
- Women presenting with typical or atypical symptoms of OSA should be screened with a comprehensive sleep evaluation and sleep study. Cardiovascular risks of untreated OSA are high and are treatable. CPAP therapy is the first line of management, and other treatment options should be discussed if they fail to improve with optimal PAP therapy.
- RLS is common among women of all ages, but it is more frequent during pregnancy. Correcting iron deficiency and using dopaminergic medications can be helpful in treatment

RESEARCH AGENDA

Develop predictive models to identify women likely to respond to hormone therapy vs CBT-I vs non-hormonal drugs.

REFERENCES

1. Baker FC, de Zambotti M, Colrain IM, Bei B. Sleep problems during the menopausal transition: prevalence, impact, and management challenges. *Nature and Science of Sleep* 2018;Volume 10:73–95. <https://doi.org/10.2147/nss.s125807>
2. Salari N, Hasheminezhad R, Hosseini-Far A, Rasoulpoor S, Assefi M, Nankali S, et al. Global prevalence of sleep disorders during menopause: a meta-analysis. *Sleep and Breathing* 2023;27:1883–97. <https://doi.org/10.1007/s11325-023-02793-5>
3. Monteleone P, Mascagni G, Giannini A, Genazzani AR, Simoncini T. Symptoms of menopause — global prevalence, physiology and implications. *Nature Reviews Endocrinology* 2018;14:199–215. <https://doi.org/10.1038/nrendo.2017.180>
4. Principles and Practice of Sleep Medicine 2005. <https://doi.org/10.1016/b0-7216-0797-7/x5001-0>
5. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. *Das AASM-Manual Zum Scoring von Schlaf Und Assoziierten Ereignissen* 2007. https://doi.org/10.1007/978-3-7985-1852-0_1
6. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-Nerve Activity during Sleep in Normal Subjects. *New England Journal of Medicine* 1993;328:303–7. <https://doi.org/10.1056/nejm199302043280502>
7. Moore RY. Suprachiasmatic nucleus in sleep–wake regulation. *Sleep Medicine* 2007;8:27–33. <https://doi.org/10.1016/j.sleep.2007.10.003>
8. Czeisler CA, Gooley JJ. Sleep and Circadian Rhythms in Humans. *Cold Spring Harbor Symposia on Quantitative Biology* 2007;72:579–97. <https://doi.org/10.1101/sqb.2007.72.064>
9. Borbély AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. *Journal of Sleep Research* 2016;25:131–43. <https://doi.org/10.1111/jsr.12371>
10. Tandon VR, Sharma S, Mahajan A, Mahajan A, Tandon A. Menopause and Sleep Disorders. *Journal of Mid-Life Health* 2022;13:26–33. https://doi.org/10.4103/jmh.jmh_18_22
11. Jeon G-H. Insomnia in Postmenopausal Women: How to Approach and Treat It? *Journal of Clinical Medicine* 2024;13:428. <https://doi.org/10.3390/jcm13020428>
12. Troia L, Garassino M, Volpicelli AI, Fornara A, Libretti A, Surico D, et al. Sleep Disturbance and Perimenopause: A Narrative Review. *Journal of Clinical Medicine* 2025;14:1479. <https://doi.org/10.3390/jcm14051479>
13. Dorsey A, de Lecea L, Jennings KJ. Neurobiological and Hormonal Mechanisms Regulating Women's Sleep. *Frontiers in Neuroscience* 2021;14. <https://doi.org/10.3389/fnins.2020.625397>
14. Brown AMC, Gervais NJ. Role of Ovarian Hormones in the Modulation of Sleep in Females Across the Adult Lifespan. *Endocrinology* 2020;161. <https://doi.org/10.1210/endocr/bqaa128>
15. Maki PM, Panay N, Simon JA. Sleep disturbance associated with the menopause. *Menopause* 2024;31:724–33. <https://doi.org/10.1097/gme.0000000000002386>
16. Gamble KL, Berry R, Frank SJ, Young ME. Circadian clock control of endocrine factors. *Nature Reviews Endocrinology* 2014;10:466–75. <https://doi.org/10.1038/nrendo.2014.78>
17. Jehan S, Jean-Louis G, Zizi F, Auguste E, Pandi-Perumal SR, Gupta R, et al. Sleep, Melatonin, and the Menopausal Transition: What Are the Links? *Sleep Science* 2017;10:11–8. <https://doi.org/10.5935/1984-0063.20170003>
18. Lee J, Han Y, Cho HH, Kim M-R. Sleep Disorders and Menopause. *Journal of Menopausal Medicine* 2019;25:83. <https://doi.org/10.6118/jmm.19192>
19. Augoulea A, Moros M, Lykeridou A, Kaparos G, Lyberi R, Panoulis K. Psychosomatic and vasomotor symptom changes during transition to menopause. *Menopausal Review* 2019;18:110–5. <https://doi.org/10.5114/pm.2019.86835>
20. Caruso D, Masci I, Cipollone G, Palagini L. Insomnia and depressive symptoms during the menopausal transition: theoretical and therapeutic implications of a self-reinforcing feedback loop. *Maturitas* 2019;123:78–81. <https://doi.org/10.1016/j.maturitas.2019.02.007>

21. Bruyneel M. Sleep disturbances in menopausal women: Aetiology and practical aspects. *Maturitas* 2015;81:406–9. <https://doi.org/10.1016/j.maturitas.2015.04.017>
22. Mai E, Buysse DJ. Insomnia: Prevalence, Impact, Pathogenesis, Differential Diagnosis, and Evaluation. *Sleep Medicine Clinics* 2008;3:167–74. <https://doi.org/10.1016/j.jsmc.2008.02.001>
23. Naha S, Sivaraman M, Sahota P. Insomnia: A Current Review. *Mo Med*. 2024;121:44–51.
24. Luo M, Li J, Tang R, Li HJ, Liu B, Peng Y, et al. Insomnia symptoms in relation to menopause among middle-aged Chinese women: Findings from a longitudinal cohort study. *Maturitas* 2020;141:1–8. <https://doi.org/10.1016/j.maturitas.2020.06.010>
25. Baker FC, Lampio L, Saareanta T, Polo-Kantola P. Sleep and Sleep Disorders in the Menopausal Transition. *Sleep Medicine Clinics* 2018;13:443–56. <https://doi.org/10.1016/j.jsmc.2018.04.011>
26. Ahmady F, Niknami M, khalesi ZB. Quality of sleep in women with menopause and its related factors. *Sleep Science* 2022;15:209–14. <https://doi.org/10.5935/1984-0063.20220021>
27. Lao XQ, Liu X, Deng H-B, Chan T-C, Ho KF, Wang F, et al. Sleep Quality, Sleep Duration, and the Risk of Coronary Heart Disease: A Prospective Cohort Study With 60,586 Adults. *Journal of Clinical Sleep Medicine* 2018;14:109–17. <https://doi.org/10.5664/jcsm.6894>
28. Bastien C. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine* 2001;2:297–307. [https://doi.org/10.1016/s1389-9457\(00\)00065-4](https://doi.org/10.1016/s1389-9457(00)00065-4)
29. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Research* 1989;28:193–213. [https://doi.org/10.1016/0165-1781\(89\)90047-4](https://doi.org/10.1016/0165-1781(89)90047-4)
30. Sateia MJ. International classification of sleep disorders-third edition: highlights and modifications. *Chest* 2014;146(5):1387–1394. <https://doi.org/10.1378/chest.14-0970>
31. Kryger MH, Roth T, Goldstein CA, Dement WC. Principles and Practice of Sleep Medicine. 7th ed. Elsevier; 2022.
32. Epstein LJ, Kristo D, Strollo PJ, Friedman N, Malhotra A, et al. Clinical Guideline for the Evaluation, Management and Long-term Care of Obstructive Sleep Apnea in Adults. *Journal of Clinical Sleep Medicine* 2009;5:263–76. <https://doi.org/10.5664/jcsm.27497>
33. Freeman EW. Associations of depression with the transition to menopause. *Menopause* 2010;17:823–7. <https://doi.org/10.1097/gme.0b013e3181db9f8b>
34. HAMILTON M. THE ASSESSMENT OF ANXIETY STATES BY RATING. *British Journal of Medical Psychology* 1959;32:50–5. <https://doi.org/10.1111/j.2044-8341.1959.tb00467.x>
35. Trauer JM, Qian MY, Doyle JS, Rajaratnam SMW, Cunnington D. Cognitive Behavioral Therapy for Chronic Insomnia. *Annals of Internal Medicine* 2015;163:191–204. <https://doi.org/10.7326/m14-2841>
36. Meeta M, Digumarti L, Agarwal N, Vaze N, Shah R, Malik S. Clinical practice guidelines on menopause: *An executive summary and recommendations: Indian menopause society 2019–2020. *Journal of Mid-Life Health* 2020;11:55. https://doi.org/10.4103/jmh.jmh_137_20
37. Kline CE, Irish LA, Buysse DJ, Kravitz HM, Okun ML, Owens JF, et al. Sleep Hygiene Behaviors Among Midlife Women with Insomnia or Sleep- Disordered Breathing: The SWAN Sleep Study. *Journal of Women's Health* 2014;23:894–903. <https://doi.org/10.1089/jwh.2014.4730>
38. Polo-Kantola P, Erkkola R, Irjala K, Pullinen S, Virtanen I, Polo O. Effect of short-term transdermal estrogen replacement therapy on sleep: a randomized, double-blind crossover trial in postmenopausal women. *Fertility and Sterility* 1999;71:873–80. [https://doi.org/10.1016/s0015-0282\(99\)00062-x](https://doi.org/10.1016/s0015-0282(99)00062-x)
39. Pan Z, Wen S, Qiao X, Yang M, Shen X, Xu L. Different regimens of menopausal hormone therapy for improving sleep quality: a systematic review and meta-analysis. *Menopause* 2022;29:627–35. <https://doi.org/10.1097/gme.0000000000001945>
40. Cintron D, Lipford M, Larrea-Mantilla L, Spencer-Bonilla G, Lloyd R, Gionfriddo MR, et al. Efficacy of menopausal hormone therapy on sleep quality: systematic review and meta-analysis. *Endocrine* 2016;55:702–11. <https://doi.org/10.1007/s12020-016-1072-9>
41. The 2023 nonhormone therapy position statement of The North American Menopause Society. *Menopause* 2023;30:573–90. <https://doi.org/10.1097/gme.0000000000002200>
42. Rossouw JE, Prentice RL, Manson JE, Wu L, Barad D, Barnabei VM, et al. Postmenopausal Hormone Therapy and Risk of Cardiovascular Disease by Age and Years Since Menopause. *JAMA* 2007;297. <https://doi.org/10.1001/jama.297.13.1465>
43. Practice Bulletin No. 141. Obstetrics & Gynecology 2014;123:202–16. <https://doi.org/10.1097/01.aog.0000441353.20693.78>
44. Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women: Principal Results From the Women's Health Initiative Randomized Controlled Trial. *JAMA* 2002;288:321–33. <https://doi.org/10.1001/jama.288.3.321>
45. Tranah GJ, Parimi N, Blackwell T, Ancoli-Israel S, Ensrud KE, Cauley JA, et al. Postmenopausal hormones and sleep quality in the elderly: a population based study. *BMC Women's Health* 2010;10. <https://doi.org/10.1186/1472-6874-10-15>
46. Friess E, Tagaya H, Trachsels L, Holsboer F, Rupprecht R. Progesterone-induced changes in sleep in male subjects. *American Journal of Physiology-Endocrinology and Metabolism* 1997;272:E885–91. <https://doi.org/10.1152/ajpendo.1997.272.5.e885>
47. Nolan BJ, Liang B, Cheung AS. Efficacy of Micronized Progesterone for Sleep: A Systematic Review and Meta-analysis of Randomized Controlled Trial Data. *The Journal of Clinical Endocrinology & Metabolism* 2020;106:e942–51. <https://doi.org/10.1210/clinem/dgaa873>
48. Leeangkoonsathian E, Pantasri T, Chaovitsere S, Morakot N. The effect of different progestogens on sleep in postmenopausal women: a randomized trial. *Gynecological Endocrinology* 2017;33:933–6. <https://doi.org/10.1080/09513590.2017.1333094>
49. Polo-Kantola P. Climacteric symptoms and sleep quality. *Obstetrics & Gynecology* 1999;94:219–24. [https://doi.org/10.1016/s0029-7844\(99\)00284-7](https://doi.org/10.1016/s0029-7844(99)00284-7)
50. Terauchi M, Obayashi S, Akiyoshi M, Kato K, Matsushima E, Kubota T. Effects of oral estrogen and hypnotics on Japanese peri- and postmenopausal women with sleep disturbance. *Journal of Obstetrics and Gynaecology Research* 2011;37:741–9. <https://doi.org/10.1111/j.1447-0756.2010.01424.x>
51. Tom SE, Anderson ML, Landis CA, Aiello Bowles EJ, Woods NF, Reed SD, et al. Sleep problems after short-term hormone therapy suspension. *Menopause* 2011;18:1184–90. <https://doi.org/10.1097/gme.0b013e31821d6d33>
52. Song Z, Li C, Jin F, Sun D, Tao M. Comparative Effectiveness of Tibolone and Combined Hormone Therapy in Relieving Menopausal Insomnia. *Women's Health Reports* 2025;6:1163–71. <https://doi.org/10.1177/26884844251387909>

53. Rees M, Abernethy K, Bachmann G, Bretz S, Ceausu I, Durmusoglu F, et al. The essential menopause curriculum for healthcare professionals: A European Menopause and Andropause Society (EMAS) position statement. *Maturitas* 2022;158:70–7. <https://doi.org/10.1016/j.maturitas.2021.12.001>
54. Ensrud KE, Joffe H, Guthrie KA, Larson JC, Reed SD, Newton KM, et al. Effect of escitalopram on insomnia symptoms and subjective sleep quality in healthy perimenopausal and postmenopausal women with hot flashes. *Menopause* 2012;19:848–55. <https://doi.org/10.1097/gme.0b013e3182476099>
55. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults: An American Academy of Sleep Medicine Clinical Practice Guideline. *Journal of Clinical Sleep Medicine* 2017;13:307–49. <https://doi.org/10.5664/jcsm.6470>
56. Krystal AD. Current, Emerging, and Newly Available Insomnia Medications. *The Journal of Clinical Psychiatry* 2015;76:e1045–e1045. <https://doi.org/10.4088/jcp.14046tx2c>
57. Dobkin RD, Menza M, Bienfait KL, Allen LA, Marin H, Gara MA. Ramelteon for the treatment of insomnia in menopausal women. *Menopause International* 2009;15:13–8. <https://doi.org/10.1258/mi.2009.009002>
58. Rosenberg RP, Benca R, Doghramji P, Roth T. A 2023 Update on Managing Insomnia in Primary Care. *The Primary Care Companion For CNS Disorders* 2023;25. <https://doi.org/10.4088/pcc.22nr03385>
59. An JH, Park MJ, Fava M, Mischoulon D, Kim H, Jang J, et al. Comparisons Between Successful Versus Unsuccessful Switches From Benzodiazepines or Zolpidem (Z-Drug) to Controlled-Release Melatonin in Patients With Major Depressive Disorder and Insomnia. *Frontiers in Psychiatry* 2020;11. <https://doi.org/10.3389/fpsy.2020.00444>
60. Rosenberg R, Citrome L, Drake CL. Advances in the Treatment of Chronic Insomnia: A Narrative Review of New Nonpharmacologic and Pharmacologic Therapies. *Neuropsychiatric Disease and Treatment* 2021;Volume 17:2549–66. <https://doi.org/10.2147/ndt.s297504>
61. Kishi T, Ikuta T, Citrome L, Sakuma K, Hatano M, Hamanaka S, et al. Comparative efficacy and safety of daridorexant, lemborexant, and suvorexant for insomnia: a systematic review and network meta-analysis. *Translational Psychiatry* 2025;15. <https://doi.org/10.1038/s41398-025-03439-8>
62. Huang AJ, Faubion S, Grady D. Nonhormonal Treatment of Menopausal Vasomotor Symptoms. *JAMA Internal Medicine* 2025;185:874. <https://doi.org/10.1001/jamainternmed.2025.0990>
63. McCormick CA, Brennan A, Hickey M. Managing vasomotor symptoms effectively without hormones. *Climacteric* 2020;23:532–8. <https://doi.org/10.1080/13697137.2020.1789093>
64. Oliveira DS, Hachul H, Goto V, Tufik S, Bittencourt LRA. Effect of therapeutic massage on insomnia and climacteric symptoms in postmenopausal women. *Climacteric* 2011;15:21–9. <https://doi.org/10.3109/13697137.2011.587557>
65. Hachul H, Oliveira DS, Bittencourt LRA, Andersen ML, Tufik S. The beneficial effects of massage therapy for insomnia in postmenopausal women. *Sleep Science* 2014;7:114–6. <https://doi.org/10.1016/j.slsci.2014.09.005>
66. Taku K, Melby MK, Kronenberg F, Kurzer MS, Messina M. Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity. *Menopause* 2012;19:776–90. <https://doi.org/10.1097/gme.0b013e3182410159>
67. Khadivzadeh T, Abdolhian S, Ghazanfarpour M, Kargarfard L, Dizavandi FR, Khorsand I. A Systematic Review and Meta-analysis on the Effect of Herbal Medicine to Manage Sleep Dysfunction in Peri- and Postmenopause. *Journal of Menopausal Medicine* 2018;24:92. <https://doi.org/10.6118/jmm.2018.24.2.92>
68. Cramer H, Lauche R, Langhorst J, Dobos G. Effectiveness of Yoga for Menopausal Symptoms: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *Evidence-Based Complementary and Alternative Medicine* 2012;2012:1–11. <https://doi.org/10.1155/2012/863905>
69. St-Onge M-P, Grandner MA, Brown D, Conroy MB, Jean-Louis G, Coons M, et al. Sleep Duration and Quality: Impact on Lifestyle Behaviors and Cardiometabolic Health: A Scientific Statement From the American Heart Association. *Circulation* 2016;134. <https://doi.org/10.1161/cir.0000000000000444>
70. Sparks JR, Wang X. Menopause-Related Changes in Sleep and the Associations with Cardiometabolic Health: A Narrative Review. *Healthcare* 2025;13:2085. <https://doi.org/10.3390/healthcare13172085>
71. Seeman MV. Why Are Women Prone to Restless Legs Syndrome? *International Journal of Environmental Research and Public Health* 2020;17:368. <https://doi.org/10.3390/ijerph17010368>
72. Bagheri R, Abedi P, Mousavi P, Azimi N. The prevalence of restless legs syndrome and its relationship with demographic characteristics and medical disorders in postmenopausal Iranian women. *Health Care for Women International* 2018;39:1317–25. <https://doi.org/10.1080/07399332.2018.1435662>
73. Trenkwalder C, Allen R, Högl B, Paulus W, Winkelmann J. Restless legs syndrome associated with major diseases. *Neurology* 2016;86:1336–43. <https://doi.org/10.1212/wnl.0000000000002542>
74. Allen RP, Picchietti DL, Auerbach M, Cho YW, Connor JR, Earley CJ, et al. Evidence-based and consensus clinical practice guidelines for the iron treatment of restless legs syndrome/Willis-Ekbom disease in adults and children: an IRLSSG task force report. *Sleep Medicine* 2018;41:27–44. <https://doi.org/10.1016/j.sleep.2017.11.1126>
75. Winkelmann JW, Armstrong MJ, Allen RP, Chaudhuri KR, Ondo W, Trenkwalder C, et al. Practice guideline summary: Treatment of restless legs syndrome in adults [RETIRED]. *Neurology* 2016;87:2585–93. <https://doi.org/10.1212/wnl.0000000000003388>
76. Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults—an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. *Sleep* 2012;35(8):1039–62. <https://doi.org/10.5664/sleep.1988>
77. Alessandria M, Provini F. Periodic Limb Movements during Sleep: A New Sleep-Related Cardiovascular Risk Factor? *Frontiers in Neurology* 2013;4. <https://doi.org/10.3389/fneur.2013.00116>
78. Wesström J, Ulfberg J, Sundström-Poromaa I, Lindberg E. Periodic Limb Movements Are Associated with Vasomotor Symptoms. *Journal of Clinical Sleep Medicine* 2014;10:15–20. <https://doi.org/10.5664/jcsm.3348>
79. Hachul H, Bittencourt LRA, Andersen ML, Haidar MA, Baracat EC, Tufik S. Effects of hormone therapy with estrogen and/or progesterone on sleep pattern in postmenopausal women. *International Journal of Gynecology & Obstetrics* 2008;103:207–12. <https://doi.org/10.1016/j.ijgo.2008.07.009>
80. Berry RB, Budhiraja R, Gottlieb DJ, Gozal D, Iber C, Kapur VK, et al. Rules for Scoring Respiratory Events in Sleep: Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. *Journal of Clinical Sleep Medicine* 2012;8:597–619. <https://doi.org/10.5664/jcsm.2172>
81. Jordan AS, McSharry DG, Malhotra A. Adult obstructive sleep apnoea. *The Lancet* 2014;383:736–47. [https://doi.org/10.1016/s0140-6736\(13\)60734-5](https://doi.org/10.1016/s0140-6736(13)60734-5)

82. Drager LF, McEvoy RD, Barbe F, Lorenzi-Filho G, Redline S. Sleep Apnea and Cardiovascular Disease. *Circulation* 2017;136:1840–50. <https://doi.org/10.1161/circulationaha.117.029400>
83. Wang Y, Liu H, Zhou B, Yue W, Wang M, Hu K. Menopause and obstructive sleep apnea: revealing an independent mediating role of visceral fat beyond body mass index. *BMC Endocrine Disorders* 2025;25. <https://doi.org/10.1186/s12902-025-01850-2>
84. Odai T, Terauchi M, Umeki H, Miyasaka N, Somekawa Y. Sleep apnea in postmenopausal women is associated with joint pain severity and fatigability: a cross-sectional study. *Menopause* 2022;29:680–6. <https://doi.org/10.1097/gme.0000000000001974>
85. BIXLER EO, VGONTZAS AN, LIN H-M, TEN HAVE T, REIN J, VELA-BUENO A, et al. Prevalence of Sleep-disordered Breathing in Women. *American Journal of Respiratory and Critical Care Medicine* 2001;163:608–13. <https://doi.org/10.1164/ajrccm.163.3.9911064>
86. Popovic RM, White DP. Upper airway muscle activity in normal women: influence of hormonal status. *Journal of Applied Physiology* 1998;84:1055–62. <https://doi.org/10.1152/jappl.1998.84.3.1055>
87. Qiu Z-H, Liang S-F, Deng X-B, Wei Q-S, Luo Y-M, Wang L, et al. Treatment of obstructive sleep apnea with a simple CPAP device. *Sleep and Breathing* 2023;27:2351–9. <https://doi.org/10.1007/s11325-023-02823-2>
88. Messineo L, White DP, Hete B, Knepper M, Berry R, Noah WH. Auto-adjusting positive airway pressure: the fine line between engineering and medicine. *Sleep and Breathing* 2025;29. <https://doi.org/10.1007/s11325-025-03409-w>
89. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: Clinical and empiric insights for developing CPAP adherence interventions. *Sleep Medicine Reviews* 2011;15:343–56. <https://doi.org/10.1016/j.smr.2011.01.003>
90. Shahar E, Redline S, Young T, Boland LL, Baldwin CM, Nieto FJ, et al. Hormone Replacement Therapy and Sleep-disordered Breathing. *American Journal of Respiratory and Critical Care Medicine* 2003;167:1186–92. <https://doi.org/10.1164/rccm.200210-1238oc>

Section 4

SKELETOMUSCULAR SYSTEM

17. Postmenopausal Osteoporosis

18. Frailty and Sarcopenia

19. Osteoarthritis

POSTMENOPAUSAL OSTEOPOROSIS

Keywords: Definition, risk factors, diagnosis, management, postmenopausal osteoporosis

17

INTRODUCTION

Menopause is associated with estrogen deficiency-induced alterations in bone remodelling, leading to accelerated bone resorption that exceeds bone formation.¹ Peak bone mass (PBM) is achieved in early adulthood, typically by the third decade of life.¹ Thereafter, bone mass declines gradually with ageing. The MT is characterised by a distinct phase of accelerated bone loss due to estrogen deficiency, with the most rapid loss occurring during the late perimenopause and early postmenopausal years. During the first 5–7 years after menopause, women may lose approximately 10–20% of trabecular bone and 5–10% of cortical bone, leading to a substantial increase in the risk of osteoporosis and fragility fractures.² Postmenopausal osteoporosis (PMO), often termed a “silent” disease, is a chronic condition and carries a high lifetime risk of fragility fractures. Such fractures are associated with significant mortality, loss of independence, and a substantial social and economic burden.³ Long-term, sometimes lifelong, management may be required.

EPIDEMIOLOGY

In a meta-analysis of 40 studies (31 from Asia, 5 from Europe, and 4 from the Americas) comprising 79,127 participants, the global prevalence of osteoporosis in older adults was estimated at 21.7%. When stratified by sex, the overall prevalence was 35.3% in older women and 12.5% in older men. Among regions, Asia demonstrated the highest prevalence of osteoporosis in older populations, estimated at 24.3%.⁴ Global estimates suggest that up to 1 in 2 women over the age of 50 years, may experience an osteoporosis-related fracture during their remaining lifetime, with India reporting the highest disability-adjusted life years (DALYs) rates.⁵ Indian data consistently show that fragility fractures, particularly hip fractures, occur about a decade earlier (mean age 65–71 years) than in Western populations (>75–80 years). However, most available datasets include both men and women, so these studies provide robust evidence of earlier fracture onset in the Indian population but may underestimate the sex-specific burden and predictors of PMO.^{6–8} In a tertiary-care hospital-based study of peri-menopausal women (40–49 years), nearly one in five had vertebral fractures, and these women had lower AMH levels, suggesting that declining ovarian reserve may parallel skeletal fragility.⁹ This earlier onset aligns with epidemiological evidence showing that approximately 1 in 3 postmenopausal women has osteoporosis, and nearly 1 in 2 has osteopenia, often manifesting in the 50s–60s.^{10–14} Early menopause in Indian women, in comparison with their Caucasian counterparts, may significantly contribute to PMO in the Indian context, since there is an inverse correlation between years since menopause and bone mineral density (BMD). Hospital and community-based studies further implicate low body mass index (BMI), poor sleep, elevated triglycerides, increased C-reactive protein (CRP), and early menopause as significant risk factors.^{13,15–17} Nutritional deficits are widespread: about 3 in 4 women consume less calcium than the RDA, and 2 in 3 are vitamin D deficient. These “twin nutrient deficiencies,” compounded by demographic ageing and lifestyle risk factors, contribute to the earlier onset of osteoporosis and fragility fractures in Indian women.^{18–20} The burden of fragility fractures is rising steeply due to demographic ageing and nutritional factors. In particular, hypovitaminosis D and low dietary calcium intake from childhood contribute to reduced PBM and earlier onset of osteoporosis.^{10,14,21} Over 70% of Indian women and many clinicians have poor awareness of PMO, significantly limiting prevention and treatment efforts.^{22–24} The Indian Menopause Society (IMS) 2020 Clinical practice guidelines on PMO: recognises PMO as a major national concern, and urges early screening, lifestyle counselling, and timely preventive strategies tailored to Indian women.²⁵ Gynaecologists are the first line of defence for skeletal and musculoskeletal health in midlife women. Routine gynecological visits should integrate bone health assessment, lifestyle counselling, and timely preventive or therapeutic interventions.²⁶

DEFINITIONS

Osteoporosis: The World Health Organization (WHO) defines osteoporosis as “a systemic skeletal disease characterised by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fractures involving the wrist, spine, hip, pelvis, ribs, or humerus”.²⁷ The National

Institute of Health (NIH) defines osteoporosis as “a disease characterised by decreased bone strength and an increased propensity to fractures”.²⁸

Bone mass is measured as BMD by Dual-energy X-ray Absorptiometry (DXA), and micro-architectural deterioration of bone tissue is quantified indirectly using the trabecular bone score (TBS) derived from DXA and, more precisely, by high-resolution peripheral Quantitative Computed Tomography (QCT) or histomorphometry.^{29,30}

Primary Osteoporosis

Type I (Postmenopausal Osteoporosis): Occurs in women after menopause due to estrogen deficiency. It predominantly affects trabecular bone, with accelerated bone loss of 1–2% (up to 5%) annually in the first 5–7 years post-menopause.

Type II (Senile Osteoporosis): Age-related bone loss at 1% per year, affecting both cortical and trabecular bone in men and women.²⁵

Secondary Osteoporosis: results from identifiable secondary causes, such as endocrine disorders (hyperthyroidism, hyperparathyroidism, Cushing’s), medication use (especially glucocorticoids), chronic systemic illnesses, and malabsorption syndromes that impair bone metabolism or limit peak bone mass acquisition.^{31,32}

Premenopausal Osteoporosis: is defined by a low BMD (Z-score < -2.0) with or without fragility fractures in women before menopause.^{33–35} The majority of cases are secondary, linked to gynaecological, endocrine, metabolic, or systemic causes, and therefore warrant thorough evaluation before pharmacological treatment. Drug therapy is considered only for women with recurrent fractures, progressive bone loss, or irreversible secondary causes.^{33–35}

Idiopathic Premenopausal Osteoporosis (IPO): is a rare diagnosis, established only when no secondary cause of low bone mass or fragility fracture can be identified after comprehensive evaluation. Its pathogenesis remains incompletely understood, likely reflecting heterogeneous mechanisms, including genetic predisposition, impaired bone formation, altered bone microarchitecture, and intrinsic skeletal factors.^{36–38}

Fragility Fracture/Osteoporotic Fracture: defined by the WHO as “a fracture caused by injury, which would be insufficient to fracture normal bone: the result of reduced compressive and/or torsional strength of bone.” Clinically, a fragility fracture can be defined as one which occurs as a result of minimal trauma, such as a fall from a standing height or less, or no identifiable trauma.³⁹

Types Of Fragility Fractures: Fragility fractures most commonly involve the hip, vertebrae, and distal radius, though other sites such as the humerus, pelvis, ribs, and pubic rami may also be affected following minimal trauma.^{40,41} Fragility fractures are caused by both BMD-related and non-BMD-related factors, resulting from a complex interplay of osteoporosis, sarcopenia, frailty, nutritional deficits, comorbidities, and falls.^{42,43}

Osteomalacia: is defined as a condition in which there is impaired mineralisation of the bone matrix (osteoid) in mature skeletons, most commonly due to Vitamin D deficiency or disordered phosphate metabolism, leading to bone pain, muscle weakness, and increased fracture risk, particularly Looser’s zones (pseudofractures).²⁵

PATHOGENESIS

Osteoporotic fractures result from the interaction of three principal factors: skeletal strength, fall risk, and the impact of the fall.

Skeletal strength: is determined by bone mass, bone geometry, microarchitecture, and tissue properties (bone quality). Refer to Figure 1.³⁸ Low BMD is the strongest and most consistently validated independent predictor of fracture risk.⁴⁴ As BMD decreases, less force is required to cause a fracture.³⁸ BMD is most accurately measured by DXA, which forms the basis of the operational definition of osteoporosis.⁴⁴ Although trauma is integral to fracture occurrence, reduced skeletal strength markedly lowers the threshold for fracture, even with minimal loading.^{38,45}

Fall risk is influenced by neuromuscular factors such as muscle mass, strength, balance, and coordination, as well as age, frailty, comorbidities, medications, and environmental hazards.⁴⁵ In individuals with very low BMD, minimal trauma such as coughing, bending, twisting, or lifting may result in vertebral compression fractures or hip fractures.^{38,45} Fall risk is primarily assessed through clinical history and physical examination.⁴⁵

Impact of fall: The likelihood of fracture following a fall depends on the energy transmitted to the skeleton, which is modified by the height, direction, and angle of the fall, as well as by external protective factors such as hip protectors.⁴⁵

Interventions that reduce impact energy or improve protective responses can lower fracture risk independently of BMD.⁴⁵

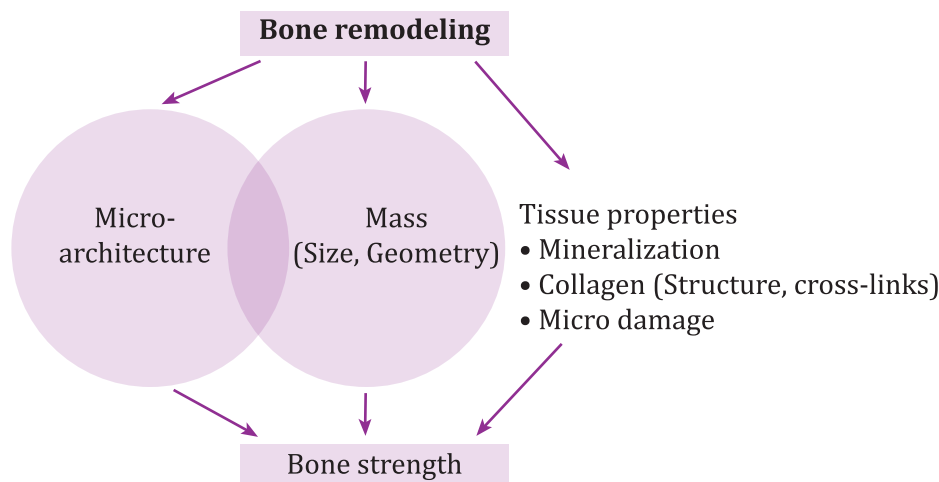


Figure 1: Factors determining bone strength

RISK FACTORS FOR POSTMENOPAUSAL OSTEOPOROSIS AND FRAGILITY FRACTURES

Risk factors predisposing to osteoporotic fractures are multifactorial and cumulative, and are identified through clinical history and physical examination. Refer to Figure 2 for the pathogenesis of a fragility fracture. It is important to distinguish between factors that primarily reduce bone mass and those that increase fracture risk independently of BMD, such as an increased risk of falling. These BMD-independent clinical risk factors have been well characterised and currently form the basis for fracture risk assessment. Major risk factors, as defined by the WHO, are as follows:⁴⁶

- *Age*: Advancing age is the single most significant risk factor.
- *Low BMI*: Although low BMI is a significant risk factor for hip fracture, the value of BMI in predicting other fractures is much reduced when adjusted for BMD.
- *Prior history of a fracture*: Doubles the risk of further fracture. This is more pronounced after a vertebral fracture following a prior spine fracture. The risks are, in part, independent of BMD.
- *Parental history of hip fracture*: It is a significant risk factor that is largely independent of BMD.
- *Smoking*: It is a risk factor that is in part dependent on BMD.
- *Glucocorticoid*: The fracture risk associated with glucocorticoid use does not depend solely on bone loss; other BMD-independent risks have been identified.
- *Alcohol*: Alcohol intake and fracture risk are dose-dependent. Consumption of 3 or more units daily is associated with a dose-dependent increase in fracture risk.
- *Rheumatoid arthritis*: increases fracture risk independently of BMD.

Peak Bone Mass (PBM): is the highest level of bone mass achieved as a result of normal growth. It is an important predictor of the onset of primary osteoporosis. It is influenced by genetic, hormonal, racial, nutritional, and lifestyle factors, as well as physical activity. Environmental factors modulate the genetic potential for achieving PBM.^{47,48} PBM is attained by 25–30 years, with 40–50% achieved by age 18. Women reach skeletal maturity with 10–15% lower bone mass than men. Asian Indians have significantly lower PBM compared to some other races.^{49–52}

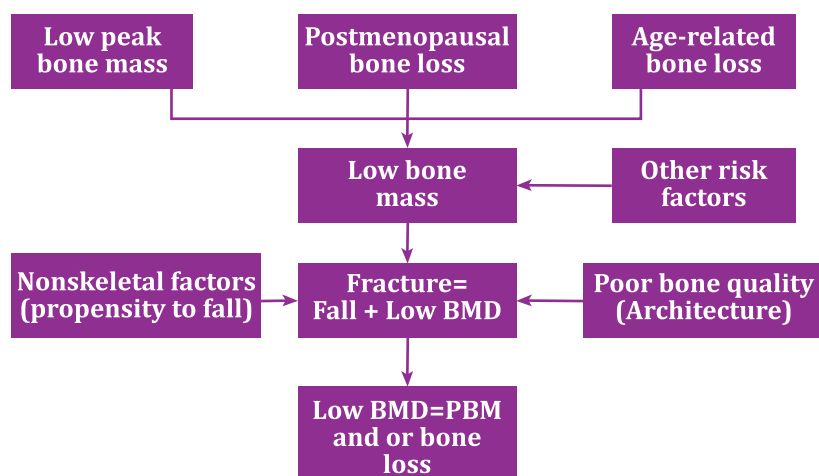


Figure 1: Factors determining bone strength

Marwaha and colleagues have evaluated the impact of lifestyle on BMD and osteoporosis in Indian Jawans and Indian sportswomen, highlighting that good nutrition, favourable bone biochemical parameters, adequate sun exposure, and sustained physical activity from a younger age contribute to higher peak bone mass than in age-matched sedentary controls.⁵¹ This underscores the urgent need for government and nongovernment organisations to promote community- and school-based educational programmes on nutrition, physical activity, and adequate outdoor exposure, to address these modifiable risk factors for osteoporosis.

Non-modifiable risk factors: include age, sex, race, ethnicity, and genetics. They have a major influence on achieving PBM.

Modifiable risk factors: include environmental factors such as poor nutritional status, low dietary calcium, reduced sunlight exposure, vitamin D deficiency, lack of exercise, low BMI, smoking, excessive intake of alcohol/caffeine/salt, and the risk of falls.^{46,53}

*Risk factors for falls:*⁵⁴ include previous history of falls, neurologic disorders (Parkinson's disease, peripheral neuropathy, stroke, dementia), impaired gait and balance (or both), impaired vision, impaired hearing, frailty and deconditioning, proximal myopathy, sarcopenia, medications, and environmental factors (poor lighting, stairs, slippery floors, rugs/toys/small pets on the floor).⁵⁴

Medical conditions and medications associated with low bone mass: Many diseases and disorders, as well as several commonly used medications, are associated with osteoporosis and increased fracture risk.⁵⁵ Refer to Table 1 for medical conditions that may be associated with an increased risk of osteoporosis.

Table 1: Medical conditions that may be associated with an increased risk of osteoporosis

AIDS/HIV	Hyperparathyroidism	Pernicious anemia
Amyloidosis	Hypogonadism, primary and secondary (amenorrhea)	Rheumatoid arthritis
Ankylosing spondylitis	Hypophosphatasia	Severe liver disease, especially primary biliary cirrhosis
Chronic obstructive pulmonary disease	Idiopathic scoliosis	Spinal cord transection
Congenital porphyria	Inadequate diet	Sprue
Cushing's syndrome	Inflammatory bowel disease	Stroke (CVA)
Eating disorders (anorexia nervosa)	Insulin-dependent diabetes mellitus	Thalassemia
Female athlete triad	Lymphoma and leukemia	Thyrotoxicosis
Gastrectomy	Malabsorption syndromes	Tumor secretion of parathyroid hormone related peptide
Gaucher's disease	Mastocytosis	Weight loss
Hemochromatosis	Multiple myeloma	
Hemophilia	Multiple sclerosis	
(AIDS: Acquired immunodeficiency syndrome; HIV: Human immunodeficiency virus; CVA: Cerebrovascular accident).		

FRACTURE RISK ASSESSMENT TOOLS FOR INDIAN WOMEN

Any of the following tools may be used to identify women at risk for osteoporosis: FRAX, OSTA, SCORE, and DXA. Tools like OSTA and SCORE are rapid, inexpensive, and easy to use in the rural Indian setting.

World Health Organisation Fracture Risk Assessment Tool (FRAX®)

FRAX integrates key clinical risk factors with or without BMD to estimate the 10-year probability of hip and major osteoporotic fractures. FRAX is an internationally validated model used in over 100 countries, offering population-specific calibration and valuable fracture-probability estimates. It is the preferred first-line tool, particularly valuable for guiding management in intermediate-risk women.^{40,59,60} FRAX is country-specific, and an Indian FRAX model is available online (www.shf.ac.uk/FRAX).⁶¹ Assessment is made after calculating the 10-year probability of a major osteoporotic fracture using FRAX without BMD, and categorising into low, intermediate, high, and very high risk categories. Refer to Figure 4.

Advantage: It can also be used without BMD to identify cases at risk of fractures. Given the limited availability of DXA machines in India, it is helpful to use FRAX without BMD in the Indian context.

Limitations: The Indian FRAX® model, derived from a small north-Indian cohort, lacks nationwide calibration and is likely to underestimate true fracture risk. It omits falls risk, lumbar spine BMD, and regional skeletal variation, and requires online access, limiting its applicability in rural settings.^{6,62} Given the heterogeneity of the Indian scenario, intervention thresholds and management may need to be individualised. Heterogeneity across regions of the country and the prevalence of nutritional and other risk factors specific to the Indian population have not been accounted for in the FRAX calculation. Moreover, the diversity of the Indian population makes it difficult to develop a universally acceptable FRAX model for India. FRAX with BMD tends to be more reliable at predicting hip fracture than FRAX without BMD and adjusted FRAX in Asia.⁶³

FRAXplus: an upgrade to the widely used FRAX fracture risk assessment tool, developed to address several limitations of the original model. (<https://www.fraxplus.org/frax-plus>)

The Osteoporosis Self- Assessment Tool for Asians (OSTA)

The OSTA score is a simple, non-BMD screening tool that uses only age and weight. It stratifies women into low, intermediate, and high-risk categories; validated in Indian and other Asian populations. The Osteoporosis Self-assessment Tool for Asians (OSTA) chart (Figure 3) is suitable for community-based and preliminary risk assessment, helping sensitise women to their osteoporosis risk. The OSTA is practical for primary-care screening when DXA is unavailable and has a high negative predictive value for excluding severe osteoporosis.⁶⁴ The OSTA index is the calculated numerical value derived from the formula: $\text{OSTA Index} = (\text{body weight (kg)} - \text{age (year)}) \times 0.2$ (the resulting number is usually rounded to the nearest integer. Women are stratified into three groups based on their OSTA index. Refer to Table 3.

Table 3: OSTA Scoring System

OSTA Score	LOW	MODERATE	HIGH
OSTA Index	> -1	-1 to -4	< -4

As OSTA cannot estimate fracture probability or guide precise treatment thresholds, it should be used for initial triage.⁶⁴ In a cross-sectional study of rural south Indian postmenopausal women, the OSTA score had a sensitivity of 88.5% and a specificity of 41.7% for femoral neck osteoporosis, making it a useful tool for identifying women at high risk of osteoporosis.⁶⁵ The risk of osteoporosis in the high-, medium- and low-risk categories was found to be 61%, 15% and 3%. A systematic review and meta-analysis of the performance of clinical risk assessment instruments for screening for DXA-determined osteoporosis or low bone density concluded that OSTA, generally performed as well as, or better than more complex instruments.⁶⁶

Limitations: The OSTA considers only two variables and therefore omits many established clinical risk factors such as history of low-trauma fractures, long-term corticosteroid use, rheumatoid arthritis, and other secondary causes of bone loss. OSTA also does not account for fracture history severity or other demographic and lifestyle risk factors, and it should not replace DXA or comprehensive clinical assessment in individual risk evaluation.⁶⁷

Weight (kg)	40-44 88-98	45-49 99-109	50-54 110-119	55-59 120-130	60-64 131-141	65-69 142-152	70-74 153-164	75-79 165-174	80-84 175-185	85-89 186-196	196-94 196-208
40-44											
45-49											
50-54											
55-59											
60-64											
65-69											
70-74											
75-79											
80-84											
85-89											
90-94											
95-99											

Figure 3: Osteoporosis Self-assessment Tool for Asians (OSTA) Koh, L et al.*

A Simple Tool to Identify Asian Women at Increased Risk of Osteoporosis. *Osteoporos Int* 12, 699–705 (2001).
<https://doi.org/10.1007/s001980170070>

Simple Calculated Osteoporosis Risk Estimation (SCORE)

SCORE is a simple questionnaire-based clinical risk assessment tool for identifying postmenopausal women at risk of

low BMD. It was derived and validated in a large cohort of 1,279 postmenopausal women aged >45 years across multiple centres in the US. The scoring system included age, weight, race, estrogen use, history of rheumatoid arthritis, and history of nontraumatic fractures. A SCORE value ≥ 6 is associated with low BMD (T-score ≤ -2) and indicates the need for osteoporosis evaluation with DXA. The tool has high sensitivity for detecting low bone mass, making it useful as a screening instrument, although its specificity is modest.⁶⁸ In a large cohort of rural Indian postmenopausal women, the SCORE screening tool showed good sensitivity and AUC for predicting femoral neck osteoporosis, suggesting its usefulness as a screening tool in resource-limited settings.⁶⁵

Score: A. Race not black: 5 points, B. Rheumatoid Arthritis: 4 points, C. Fracture after age 45 of wrist, hip or rib: 4 points per Fracture, D. Age over 65: Calculate $3 \times (1\text{st digit of age})$ (for example, for age 70 = 21), E. Weight: Calculate $(-1 \times \text{weight in pounds})/10$ (for example, for weight 200 pounds: -20), F. Estrogen therapy never used: 1 point.

Interpretation:

A. Score of 6 or above is associated with T-Score below -2

B. Osteoporosis testing with DXA Scan is recommended if Score of 6 or above

Efficacy: Test Sensitivity: 91%, Test Specificity: 40% SCORE Calculator is available from:

<https://www.medcentral.com/calculators/endocrinology/osteoporosis-risk-score-simple-calculated-osteoporosis-risk-estimation>.

Proposed Strategy for using OSTA and FRAX in India

A stepwise, resource-sensitive framework combining OSTA and FRAX enables rational, tiered risk assessment in Indian practice:

Primary Screening: OSTA functions as a first-line, low-cost community screening tool that can be easily applied by paramedical staff or frontline health workers in primary care and outreach settings to identify women at potential risk. It requires only age and weight, making it practical where DXA or internet access is unavailable, and suitable for busy clinical environments with limited physician time.

Secondary Risk Stratification: FRAX without BMD serves as a secondary stratifier for women categorised as intermediate- or high-risk by OSTA. It is an internationally validated model used in over 100 countries, offering population-specific calibration and valuable fracture-probability estimates. However, its web-based format and detailed data requirements may limit use in resource-constrained or high-volume practices.

Definitive Risk Quantification: FRAX with BMD using DXA remains the definitive risk quantifier for individualised treatment planning and establishing pharmacologic intervention thresholds, ideally performed in secondary or tertiary care centres with standardised DXA facilities.

Bone Density Measurement and Dual-Energy X-Ray Absorptiometry

Assess fracture risk using DXA, including BMD, vertebral fracture assessment (VFA), and TBS. The current gold standard for BMD assessment is DXA. BMD values are expressed as T-scores (SD difference from the young adult mean) or Z-scores (SD difference from the age- and sex-matched mean). Diagnosis is based on central DXA of the spine, total hip, and neck of the femur. If this is not feasible, the lower one-third of the radius (33%) is measured. The lowest BMD score across all sites is used for diagnosis.⁶⁹

Indications for Dual-Energy X-Ray Absorptiometry²⁵

- All postmenopausal women > 5 years since menopause.
- Postmenopausal women < 5 years since menopause who have additional clinical risk factors for osteoporosis.
- Women in the MT with secondary causes of bone loss (such as endocrine, metabolic, or medication-related).
- Presence of radiological osteopenia or vertebral compression fracture.
- Women with fragility fractures confirmed by radiology or DXA.
- Prior to initiating pharmacotherapy for osteoporosis, establish a diagnostic and therapeutic baseline.
- Emerging indication: Assessment of total body composition (fat and lean mass) for metabolic and sarcopenic risk evaluation.

It is suggested to conduct central DXA of the spine and hip in all women 5 years beyond the natural age of menopause, and in women less than 5 years since menopause with one high clinical risk or more than two clinical risk factors. The Indian-specific basis for these recommendations is based on the following:

- For each SD decrease in BMD, fracture risk doubles.
- The early age of natural menopause is 46.7 years in Indian women.
- The average life expectancy of a woman in India is 73.6 years.⁷⁰
- Accrual of low PBM.
- Early age of presentation of fracture.
- Accelerated bone loss occurs in the first 5 years after menopause, and trabecular bone is affected more.
- Stratification by age shows that the prevalence of low bone mass exceeds 40% from age 40 and increases to more than 80% by age 65.

Follow-Up and Monitoring with Dual-Energy X-Ray Absorptiometry

For monitoring treatment and comparing DXA results, accurate comparisons can be made only when the scans are performed on the same machine and when comparing values from the same sites. To monitor therapy, the interval to the next DXA should depend on the calculated individual risk and is typically scheduled between 1 and 5 years later. The lumbar spine (L1–L4) is the preferred primary site for BMD monitoring, with the hip (total hip and femoral neck) serving as the secondary site. Both sides should be measured routinely for comprehensive treatment monitoring.

- Measurement error must be considered when interpreting serial BMD assessments to determine whether the change is real rather than a random fluctuation or artefact.
- Each centre should determine its precision error to estimate the least significant change (LSC) (the change in BMD required to have 95% confidence that the change is real).⁷¹
- Most osteoporosis therapies do not cause large increases in BMD, and the antifracture effect of treatment is only partly explained by the relatively small BMD gains.
- Stabilisation of BMD without further decline is a marker of effective treatment and reflects reduced bone turnover and fracture risk.⁷²

DIAGNOSIS AND CATEGORISATION OF POSTMENOPAUSAL OSTEOPOROSIS

Diagnosis and categorisation of osteoporosis in postmenopausal women is established by the presence of a fragility fracture (clinical or radiological) and/or by a BMD T-score ≤ -2.5 at the lumbar spine, total hip, or femoral neck. The lowest BMD T-score among measured sites should be used for diagnosis.⁷³ For each standard deviation decrease in BMD, there is a doubling of fracture risk. Refer to Table 4, WHO Classification of Osteoporosis, for detailed BMD-based categories.⁷³

Table 4. Diagnosis of PMO with and without fractures [WHO categories for diagnosis of osteoporosis]

	T-score (SD)
Normal	Equal to -1.0 or higher
Low Bone Mass (Osteopenia)	Between -1.0 and -2.5
Osteoporosis	Equal to -2.5 or lower
Severe Osteoporosis	Equal to -2.5 or lower with fracture

The reference range for calculating the T-score in postmenopausal women is based on the NHANES III Caucasian female reference database (age 20–29 years).⁷³ Global organisations, WHO, IOF, ISCD, and NOF, and Indian professional bodies, such as the Indian Menopause Society (IMS) and the Indian Society for Bone and Mineral Research (ISBMR), currently recommend using the NHANES III Caucasian female reference database for T-score calculation.^{25,40,41,73-75}

However, this reference standard may overestimate the prevalence of osteoporosis in Indian women. The ETHNICA 2025 study demonstrated that when Indian normative (ICMR) reference data were applied instead of Caucasian values, the estimated prevalence of osteoporosis declined from 26.6% to 18%, highlighting substantial ethnic calibration bias.⁷⁶ This finding underscores the urgent need for nationally validated BMD reference standards correlated with fracture outcomes, to serve as the scientific basis for diagnostic thresholds and treatment eligibility criteria in Indian women.^{25,40,41,73,75,77}

The ISCD diagnostic criteria for osteoporosis in postmenopausal women and in men aged 50 and older are a T-score of -2.5 or less at the lumbar spine, total hip, or femoral neck. In certain circumstances, the 33% radius (also called 1/3 radius) may be utilised.⁶⁹

Z-score: Indicates how many SDs an individual's BMD differs from the mean for age and sex. Primarily used in children, adolescents, and premenopausal women. A Z-score < -2 is considered "low for age".⁶⁹

Categorising PMO based on FRAX/OSTA and BMD by DXA

For categorising PMO based on FRAX/DXA and BMD, refer to Table 5.

Table 5: Categorising fracture risk based on FRAX/OSTA and BMD by DXA

Normal	Equal to -1.0 or higher	FRAX-Low, OSTA -LOW	Low risk
Low Bone Mass (Osteopenia)	Between -1.0 and -2.5	FRAX-<20% MOF or <3% HPF, OSTA -Moderate	Upper or lower percentile of Low Risk
Low Bone Mass	Between -1.0 and -2.5	FRAX->20% MOF or >3% HPF, OSTA---High	High Risk
Osteoporosis	Equal to -2.5 or lower	FRAX->20% MOF or >3% HPF, OSTA---High	High Risk
Severe Osteoporosis	Equal to -3 or lower, with fracture	FRAX->30% MOF or >4.5% HPF	Very High Risk

MOF: Major osteoporotic fracture, HF: Hip fracture, FRAX: Fracture risk assessment tool, OSTA: Osteoporosis self-assessment tool for Asians, SD: Standard deviation

CLINICAL EVALUATION

Women without fractures

Women with fractures

Typical presentations: include sudden severe pain following low-energy (minimal) trauma, groin/lateral hip pain with inability to bear weight and possible limb shortening (hip). Distal forearm pain with swelling and deformity after falling on an outstretched hand (wrist). Sudden severe mid-back pain after minimal trauma, or insidious chronic mid-back discomfort that may radiate around the abdomen, should prompt spine imaging.

Related symptoms: Generalised bone pain should raise suspicion of osteomalacia or skeletal metastasis.^{78,79}

Vitamin D deficiency symptoms include proximal muscle weakness leading to difficulty with squatting, climbing stairs, and rising from low chairs. Tenderness may be elicited over the pretibial region and sternum.^{25,80}

Calcium deficiency symptoms: include muscle spasms, twitches, cramps, numbness, or tingling in the fingers, toes, or around the mouth.²⁵

Sarcopenia and frailty: share many symptoms most notably muscle weakness, slowness, fatigue, and weight loss, but frailty also encompasses broader issues like exhaustion, cognitive decline, and increased vulnerability to stressors. Early recognition of these symptoms is crucial for intervention and prevention of further decline.⁸¹

Fall Risk Assessment

A multifactorial fall risk assessment is a structured, individualised evaluation of factors that increase the risk of falling, aimed at guiding targeted prevention strategies.⁸² Key components include: assessment of previous falls, gait, balance and mobility, muscle strength and functional ability, medication review (particularly psychotropics and polypharmacy), vision, medical and neurological conditions, postural hypotension, foot problems and footwear, use of assistive devices, and environmental hazards, especially within the home.^{83,84}

Physical examination

Physical examination should include annual height and weight measurement, assessment of balance and gait (including the Get-Up-and-Go test), and routine dental evaluation. A prospective height loss of ≥ 4 cm from peak adult height, or a current–previous height difference of ≥ 2 cm accompanied by other risk factors (such as kyphosis, back pain, or glucocorticoid use), should prompt evaluation for vertebral fracture or underlying osteoporosis.^{25,85} The occiput-to-wall distance in a standing position is ideally zero; inability to touch the occiput to the wall while standing implies a thoracic fracture. Inability to insert four fingers between the lowest rib and iliac crest implies a lumbar fracture. Kyphosis and Dowager’s hump are seen in the late stage of osteoporosis.^{25,85}

INVESTIGATIONS

Laboratory Tests

Lab tests are done essentially to rule out secondary causes. Complete blood picture, erythrocyte sedimentation rate (ESR), CRP, blood sugar, serum calcium, serum creatinine, serum albumin, alkaline phosphatase, thyroid-stimulating hormone (TSH), 25-hydroxy vitamin D, preferably fasting serum phosphorus, parathyroid hormone PTH (based on clinical judgement).^{25,86}

Radiography

An X-ray of the thoracolumbar spine (lateral view) is the preferred position for detecting altered vertebral architecture.²⁵ X-ray abnormality is a feature of advanced bone disease. It is recommended that X-rays be used in all the diagnostic protocols for osteoporosis. Up to two-thirds of vertebral fractures are asymptomatic and remain undiagnosed if spine imaging is not performed. Since they are mostly clinically silent, their presence predisposes a person to further fragility fractures of the vertebra or even the hip. Diagnosis of vertebral fractures on lateral X-ray of the spine is therefore clinically important and should ideally use a standardised semiquantitative method. Conventional radiographic techniques are easily available and useful for epidemiological screening. However, they cannot be used for monitoring response to drug therapy. Adequate care should be taken while utilising radiographic techniques since numerous physical factors, such as inconsistencies in beam quality, instability of the X-ray source, film response, processing conditions, radiation scattering conditions, and beam hardening effects, may influence the radiographic image and have an adverse effect on the precision and accuracy of the method. VFA performed using lateral spine imaging during DXA is a validated, low-radiation technique for detecting prevalent vertebral fractures, many of which are clinically silent.^{87,88} Since vertebral fractures are the strongest predictors of future osteoporotic fractures, their identification has major implications for diagnosis, fracture risk stratification, and treatment decisions.^{87,88}

Trabecular Bone Score (Tbs): Emerging Role In India

TBS, derived from lumbar spine DXA images, is an adjunctive tool for assessing bone microarchitecture and for refining fracture risk, independent of areal BMD. TBS is particularly useful in postmenopausal women with discordance between BMD and clinical fracture risk, and in conditions associated with impaired bone quality, such as type 2 diabetes mellitus, long-term glucocorticoid use, and secondary osteoporosis.^{29,89}

TBS interpretation: TBS > 1.310 : normal microarchitecture, low fracture risk; TBS 1.230–1.309: partially degraded microarchitecture; TBS < 1.230 : degraded microarchitecture, high fracture risk.

Peripheral DXA (X-ray-based) may be used as a mass screening tool due to its high negative predictive value.⁹⁰

Quantitative Ultrasound (QUS)

QUS is a portable, inexpensive, radiation-free tool with utility for preliminary osteoporosis screening in community and rural settings in India. However, it cannot be used for diagnosis or monitoring therapy. Among Taiwanese postmenopausal women, QUS outperformed OSTA in those aged 45–65 years, whereas OSTA outperformed QUS in those aged 66–80 years.^{91–93} WHO's diagnostic criteria of -2.5 standard deviation (SD) below PBM do not apply for non-DXA techniques. In the absence of calibrated ultrasound machines, it is not recommended for population screening. In areas with endemic fluorosis (rampant in several parts of India), it is not advisable to use ultrasound-based bone densitometry to diagnose osteoporosis.

Quantitative Computed Tomography And Magnetic Resonance Imaging

Quantitative computed tomography (QCT) and magnetic resonance imaging (MRI) give an additional advantage of three-dimensional (3D) structural assessment of bone tissue.

Bone Turnover Markers

Bone turnover markers (BTMs) are valuable adjuncts in the management of osteoporosis. However, they are not recommended for the routine clinical diagnosis of osteoporosis.^{25,94} Their principal utility lies in monitoring treatment adherence and early therapeutic response, and in refining fracture risk prediction and treatment efficacy, thereby supporting timely clinical decision-making and potentially improving patient outcomes.^{25,94} Normal values are reference values established in healthy premenopausal women aged 30–45 years.⁹⁵ This may help identify women at greatest risk, who would benefit from therapeutic intervention at menopause. While BMD provides a static picture of bone, BTMs provide a dynamic measure of bone turnover, distinguish between fast and slow bone losers during the menopause transition, and may aid decision-making. The broad guidelines to be followed are:

A. Type of marker

- *Bone resorption*: Serum carboxy-terminal cross-linked telopeptide (CTX) of type 1 collagen or urine CTX.
- *Bone formation*: N-terminal propeptide of type 1 procollagen (PINP), bone-specific alkaline phosphatase or osteocalcin.

B. Use one marker of bone resorption and one marker of bone formation. More specifically, markers for bone resorption when on antiresorptives and bone formation markers when on anabolic agents.

C. Timing of sample:

- Serum: Morning (before 9 am) after an overnight fast.
- Urine: Either first or second morning void, with creatinine correction after an overnight fast. Try to use the same laboratory services and the same assay or method for monitoring.

D. Intervals of measurement:

- *Resorption markers*: Before starting treatment and 3 or 6 months after treatment initiation.
- *Formation markers*: Before starting treatment and 6 months after treatment initiation.

E. Further monitoring is not required if the drug is found efficacious.

F. Try to use the same laboratory services and the same assay or method for monitoring measurement intervals, and compare differences against the least significant change, expressed as percentages or absolute values.

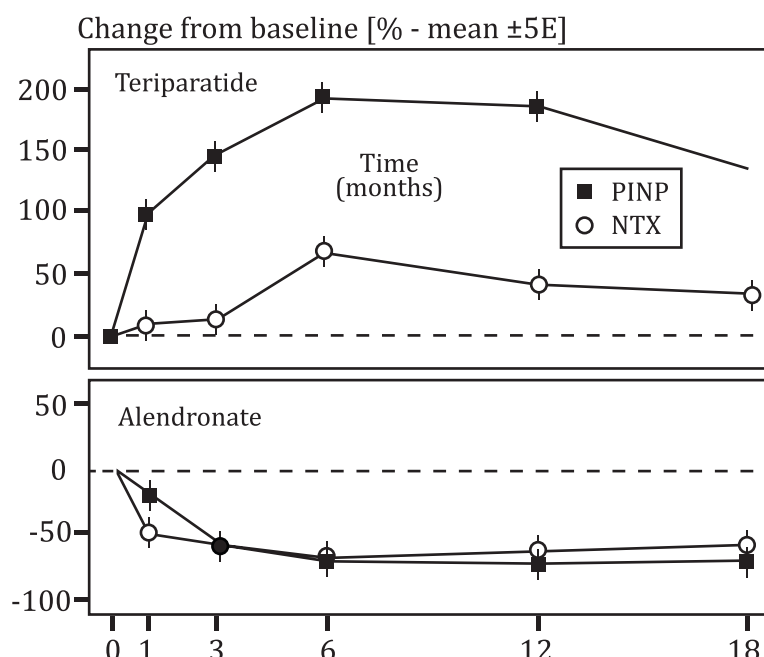


Figure 4: Typical BTM Changes After Therapy vs Anti-Resorptive Therapy [Ariot et al.* (2005) JBMR 20: 1244-53] Percent change from baseline in markers of bone formation (PINP; ■) and bone resorption (NTx; ○) in the alendronate (ALN) and teriparatide (TPTD) treatment groups of the biopsy subset. *p < 0.05; †p < 0.01; ‡p < 0.001 from baseline.^{96*}

Interpretation of Results: The results for markers during treatment should be interpreted using the 'least significant change' (LSC). LSC is the minimum change to be at least 95% sure that the change is real and not preanalytical /or analytical factors. The LSC is about 25% for most bone formation markers and 40-65% for most resorption markers. (Refer to Figure 4) When there is little or no change in the markers during treatment, check for compliance, that is, if the patient is taking medicine as prescribed and rule out secondary causes of osteoporosis.

Key Findings from a consensus paper by The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), International Osteoporosis Foundation (IOF), and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) (2025):⁹⁷

- Increased concentrations of BTMs are linked to higher fracture risk in postmenopausal women.
- PINP and β -CTX-I measured in blood are associated with fracture risk; however, further research is needed to integrate them into fracture risk assessment models.
- Treatment-induced changes in PINP and β -CTX-I significantly reduce fracture risk and improve treatment adherence.
- In patients with chronic kidney disease (CKD), renal retention may affect total PINP and β -CTX-I levels, necessitating alternative markers, such as bone alkaline phosphatase (BALP), intact PINP, and tartrate-resistant acid phosphatase 5b (TRACP5b). These show promise in assessing bone turnover in CKD-related osteoporosis and are recommended for inclusion in observational and interventional studies.

MANAGEMENT OF POSTMENOPAUSAL OSTEOPOROSIS

A population-based and a personalised approach is to be implemented to prevent and treat PMO. This target is achieved by primary prevention (population-based), intervention, and rehabilitation (individualised). Osteoporosis is a long-term condition for which there is currently no cure; therefore, lifelong treatment, more than one medication, and monitoring may be needed to treat the disease and to decrease fracture risk.

Prevention Versus Treatment of Postmenopausal Osteoporosis

It is good to understand the terms prevention and treatment in the context of osteoporosis. Prevention refers to interventions aimed at halting or slowing bone loss in postmenopausal women with low bone mass (T-score between -1.0 and -2.5) and increased fracture risk. Treatment refers to the use of pharmacological agents to reduce fracture risk in women with established osteoporosis (T-score $\leq$ -2.5 or presence of a fragility fracture).²⁵

Treatment Failure

As osteoporosis drug therapies do not totally eliminate fracture risk, it is often unclear whether sustaining a fracture while on therapy is considered a failure of therapy.⁹⁸ In general, loss of BMD greater than the least significant change (usually 5% in the lumbar spine, 4% in the total hip, and 5% in the femoral neck) over 2 years and BTM decrease on antiresorptive drugs less than the least significant change is defined as “failure” of therapy.⁹⁹ Two or more fractures while on therapy is considered as treatment failure, especially vertebral fractures.⁹⁸ In clinical practice, the occurrence of one fracture while on effective therapy and in a compliant patient needs consideration.^{98,99}

Fracture Risk

Fracture risk is defined by BMD (both primary and secondary causes) and clinical risk factors for osteoporotic fracture. For treatment purposes, combining BMD with clinical risk factors provides a better estimate of fracture risk. Hence, it will be easier to use a risk assessment tool such as FRAX, with or without BMD. We should not treat T-scores in isolation; we must consider a patient’s full clinical status when making therapeutic decisions.

Treatment Recommendation Based on Fracture Risk Assessment Tool

The interventional threshold for initiating treatment is >3% for hip and >20% for major fractures, as shown in Figure 5.

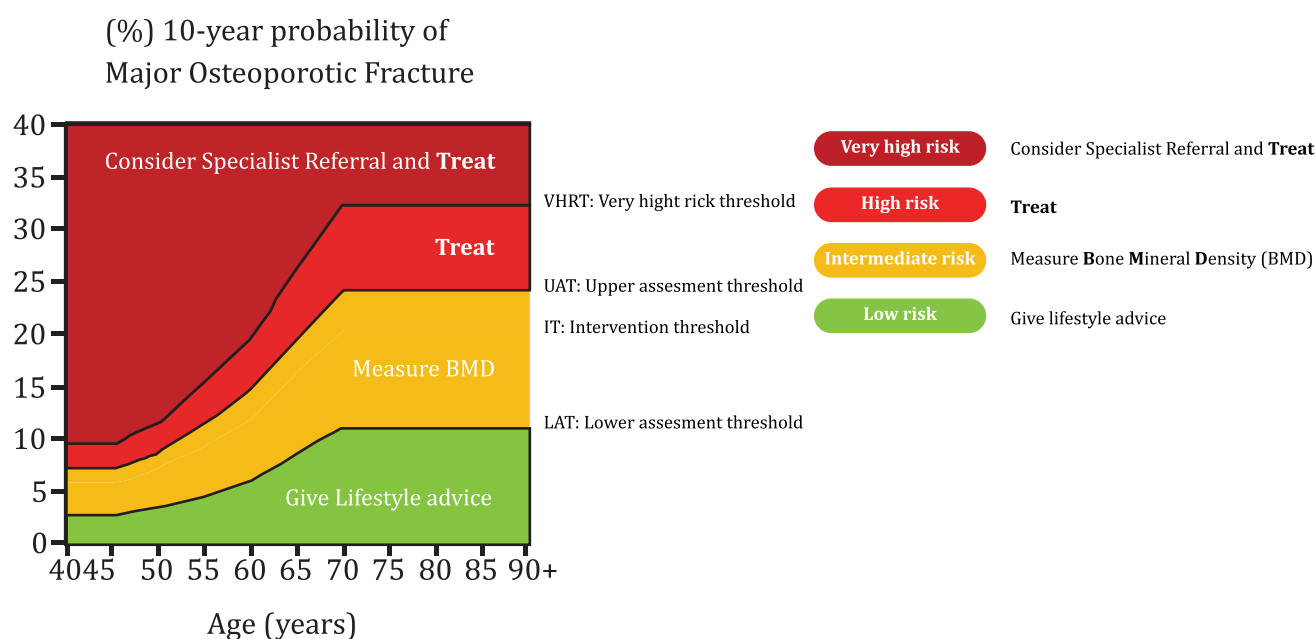


Figure 5: Based on FRAX with and without BMD the chart gives a 10-year probability of major osteoporotic fracture and suggests an interventional threshold to guide treatment decisions. Adapted from NOGG-UK clinical guideline for the prevention and treatment of osteoporosis/Celia L. Gregson et al. /Archives of Osteoporosis (2022) 17: 58/ <https://doi.org/10.1007/s11657-022-01061-5/>

Treatment Recommendation Based on Osteoporosis Self-Assessment Tool for Asians

The risk of osteoporosis in the high-, medium- and low-risk categories was found to be 61%, 15% and 3%.

High-risk patients: to measure BMD, if possible, and consider drug treatment even if BMD is not available. (About 61% of individuals in the high-risk group have osteoporosis).

Moderate risk patients: to measure BMD and consider drug treatment if BMD is low. (About 15% of individuals in the moderate-risk group have osteoporosis)

Low-risk patients: not to measure BMD unless other risk factors are present.

Precautions: Calculation assumes no other risk factors for osteoporosis. Significantly increased risks are associated with rheumatoid arthritis, fracture of the wrist, hip or rib after age 45, other risks such as low-trauma related fractures or long-term corticosteroids.⁶⁴

Treatment Recommendation Based on BMD, FRAX and OSTA

Table 6 gives a comprehensive management plan based on the outcomes of the assessment of BMD/FRAX/OSTA.

Table 6: Treatment Recommendations Based on BMD /FRAX /OSTA

BMD	Fracture risk (BMD+CRF)/ CRF by FRAX and or OSTA	Treatment decision	Choice of therapy
Low bone mass	Low	TLM/ reassess after 5 years	TLM
Low bone mass	Upper percentile of low risk	Treat if risk with/without BMD is above IT	Early PM-MHT,BP; Late PM -BP
Osteoporosis	High	Treat	Early PM- MHT, BP, DU; Late PM-BP,DU,TER,RZ
Severe Osteoporosis	Very high risk	Refer to specialist	Early PM-BP, DU, TER,RZ; Late PM -BP, DU, TER,RZ

BMD: Bone mineral density, **CRF:** Clinical risk factors, **TLM:** Therapeutic lifestyle management, **PM:** Postmenopause, **MHT:** Menopause hormone therapy, **BP:** Bisphosphonates, **DU:** Denosumab, **TER:** Teriparatide, **RZ:** Romosozumab, **IT:** Interventional threshold, **FRAX:** Fracture Risk Assessment Tool, **OSTA:** Osteoporosis self-assessment tool for Asians

Universal Recommendations

Universal Recommendations include therapeutic lifestyle management (TLM), Calcium, Vitamin D, physical activity and exercise, prevention of falls and education and psychological support.

Therapeutic Lifestyle Management

TLM includes a balanced diet, adequate physical activity, exposure to sunlight, and avoidance of bone-depleting agents. Balanced diet: Daily salt intake should not exceed 5 gm (1 tsp). Protein should be 1 gm/kg body weight. Decrease caffeine intake (<3 cups/day), limit alcohol, and avoid tobacco use. Maintain good oral hygiene and receive routine dental check-ups.²⁵

Calcium

Assess total calcium intake from dietary sources using the National Osteoporosis Foundation (NOF) Calcium Calculator (Refer to Table 7).

Table 7. Quick Dietary Calcium Assessment Chart

Source	Calcium (mg)*	Number of servings	Total Calcium (mg)
Dairy sources	300-520 /1 glass milk	x	
	300/1 katori curds	x	
Non dairy	200-300	x	

Total intake of calcium in mg. *Approximate estimates. Calculate the total daily dietary intake by entering the sources and the number of servings from dairy and nondairy sources before supplementation.

Encourage achieving the recommended calcium intake primarily through daily foods (Ref Table 7), emphasising that this is an achievable target for every Indian through simple, locally available options.¹⁰⁰ Adequate calcium intake (>800 mg/day) can be achieved through culturally appropriate, affordable Indian diets without routine supplementation. Refer to Table 8.

Table 8: Indian Foods with Calcium Rich Content

No	Dietary product	Serving	Calcium (mg)
1	Milk/curd (buffalo)	1 glass (250ml)	520
2	Milk/curd (cow)	1 glass (250ml)	300
3	Milk/curd (low fat)	1 glass (250ml)	300
4	Khoa	100 gms	600
5	Paneer	100 gms	320
6	Cheese slice	20 gms	160
7	Ragi	100 gms	360
8	Horse gram whole/ rajma	100 gms	280
9	Soyabean	100 gms	240
10	Moth bean/ bengal gram (whole)	100 gms	200
11	Red/green/blackgram/chickpeas	100 gms	100-120
12	Drum stick leaves	100 gms	300
13	Radish leaves/ methi leaves	100 gms	270
14	Mint/parsley	100 gms	200
15	Okra(bhindi)	100 gms	85
16	Cabbage	100 gms	60
17	Dried figs	5 whole	95
18	Almonds	1 handful 25 gms	60
19	Sesmae seeds (til)	15 gms, 1 tbsp	90
20	Cumin	6 gms, 0.4 tbsp	60
21	Orange	1 medium size	50
22	Fish rohu	25 gms	160

T. Longvah, R. Ananthan, K. Bhaskarachary and K. Venkaiah, Indian Food Composition. Tables, 2017 by National Institute of Nutrition, Indian Council of Medical Research.

Aim for 3–4 calcium sources daily, for example, 1 glass milk + 1 katori greens + 1 tbsp sesame + 1 dal = 800 mg calcium. Add sesame/curry leaf/mint/coriander/chutney. Dairy foods also add 6–8 g of protein per serving, supporting bone and muscle strength.

Enhance calcium intake: Resource-limited diets that include ragi, pulses, leafy greens, and sesame/curry leaves chutney can meet daily needs.¹⁰¹ Mixed diets with milk, curd, greens, dal, peanuts and small fish (sardines with bones) yield similar adequacy.¹⁰¹ Affluent/health-conscious diets using fortified milk, paneer, sesame, nuts, and diverse greens easily reach RDA goals.^{101,102}

Low sodium intake improves calcium balance primarily by reducing urinary calcium loss, rather than by directly increasing intestinal calcium absorption. Sodium and calcium share common renal tubular reabsorption pathways; therefore, a high sodium intake increases calciuria, with approximately 1 mmol (40 mg) of calcium lost for every additional 100 mmol of urinary sodium excretion. Restricting salt intake to ≤ 5 g/day (1 teaspoon) helps conserve calcium, reduce hypercalciuria, and support bone health, particularly in postmenopausal women, and individuals at increased risk of osteoporosis.¹⁰³

Adequate dietary protein intake (1 g/kg/day) is also beneficial for skeletal health, as protein enhances intestinal calcium absorption, increases circulating insulin-like growth factor-1 (IGF-1), and supports muscle strength and balance, thereby indirectly reducing fracture and fall risk. Although very high protein intake may increase urinary calcium excretion, this effect is largely offset when calcium intake is sufficient. By contrast, low protein intake is consistently associated with reduced calcium absorption, sarcopenia, and increased fracture risk.¹⁰⁴

Milk is a nutrient-dense food that provides highly bioavailable calcium, high-quality protein, phosphorus, and bioactive components, all of which are relevant to skeletal health. A 2022 meta-analysis of randomised controlled trials (RCTs) found that, milk supplementation in adults produced small but significant increases in lumbar spine and hip BMD, along with favourable reductions in bone turnover markers and parathyroid hormone, and modest increases in IGF-1, indicating an improved balance of bone remodelling rather than a large anabolic effect.¹⁰⁵ These findings support milk as a useful dietary contributor to bone health across the life course, particularly during peak bone mass acquisition and in older adults, where adequate protein also supports muscle strength and fall prevention. However, the magnitude of benefit is modest, and milk should be viewed as part of a total dietary pattern, not as an essential or exclusive strategy. Adequate calcium and protein requirements can also be met through non-dairy dietary sources (fortified foods, legumes, nuts, small fish with bones, and green vegetables) or supplements when needed. Current evidence therefore supports encouraging milk when culturally acceptable and tolerated, while emphasising that dietary diversity, rather than reliance on a single food source, is central to lifelong bone health.^{105,106}

Calcium Requirements in Indian Postmenopausal Women: Discrepancies and Evolving Guidelines,

Recommended dietary allowance of calcium

The ICMR RDA (2010) recommended 600 mg/day of calcium for postmenopausal women. This value was based on a sound factorial approach: obligatory urinary/fecal/dermal losses, balance studies, limited Indian absorption data, and adaptation of FAO/WHO/UNU norms with adjustments for Indian dietary bioavailability. This was aligned with global practice, where calcium RDAs are derived from balance studies rather than fracture outcome data.^{72,107–110} Importantly, calcium requirements vary with ethnicity, habitual protein intake, vitamin D status, and other confounders, underscoring the need for population specific recommendations.¹⁰⁷ Average intake in India remains around 400 mg/day, which is well below both global and Indian targets.

The ICMR 2020 Expert Group revised the RDA upward to 1200 mg/day for women >50 years, using updated factorial modelling and population distribution (EAR + RDA framework). While biologically reasonable, this threshold would necessitate near-universal supplementation, which may not be practical or cost-effective in the Indian setting.¹¹¹ IMS 2020 guideline adopted ≥ 800 mg/day as a pragmatic recommendation, achievable through food-based sources with selective supplementation.^{25,100} Refer to Table 8.

Vitamin D

Recommended dietary allowance (RDA) of Vitamin D. Refer Table 9.

Table 9: Recommended dietary allowance (RDA) of Vitamin D

Life stage group	RDA (IU)	Upper limit
Adults (18 years and above)	1500-2000	10,000
Pregnancy and lactation	1500-2000	10,000
Children and adults at risk*	2-3 times the normal requirement for their age	

US Endocrine Society 2011 recommended dietary allowance

*Obesity, HIV infection, on glucocorticoids, anticonvulsant, antifungal and antiviral therapy. A desirable range is between 30 and 60 ng/mL, although levels up to 100 ng/mL are unlikely to result in Vitamin D toxicity. Except in granuloma disorders, wherein it is advisable to maintain the serum levels of 25(OH) D up to >30 ng/mL

The recommended daily intake of vitamin D for Indian adults is 1000–2000 IU, aligning with Endocrine Society and Indian (ICMR, ESI, IMS) guidance, which target serum 25(OH)D $\geq$ 30 ng/mL; Institute of Medicine (IOM) values (600–800 IU/day) may be inadequate in India due to widespread deficiency and limited sunlight exposure.^{25,111,113-115} Sunlight is the preferred natural source of vitamin D. Exposure of 15–30% of body surface area (face, neck, arms, and forearms) without sunscreen for about 30 minutes between 10 am and 3 pm, depending on season, latitude, altitude, air pollution, and skin pigmentation, can maintain adequate vitamin D synthesis. This exposure is roughly equivalent to an oral intake of 340–490 IU/day, given that 100 IU increases serum 25(OH)D by 1 ng/mL.^{19,112,116}

Physical Activity / Exercise

Appropriate resistance, weight-bearing aerobics, and core-stabilising exercises are needed to maintain bone health. Brisk walking 4–5 times/week for 30 min is healthy, but on its own, it is not sufficient for bone health.^{117,118} Balance exercises are necessary to prevent falls. Patients with severe osteoporosis should avoid forward flexion, heavy lifting, and side-bending exercises, as these activities can exert compressive forces on the spine and increase fracture risk.¹¹⁹⁻¹²¹

Prevention of Falls

Fall prevention is essential in older adults with osteoporosis because falls lead to fractures, functional decline, loss of independence, and adverse psychosocial outcomes. Frailty increases the risk of falls and fractures, underscoring the importance of early risk identification and intervention. Multifactorial risk assessment and tailored interventions remain the most consistently effective strategies to prevent falls. These strategies incorporate a history of falls, medication review, medical comorbidities, vision, gait and balance, cardiovascular status, including orthostatic hypotension, and neurological and musculoskeletal evaluations.⁸³ Home hazard assessment and modification, balance and strength training, and individualised physical therapy are recommended to reduce fall risk and related injuries.^{83,84} Balance-focused exercise training, such as Tai Chi and functional balance programmes, is particularly effective;¹²² exercise alone reduces falls primarily when balance and postural control are specifically trained, whereas strength or flexibility training without balance components is less consistent in reducing falls.^{83,122}

Multifactorial fall prevention should combine targeted exercise, medication review to reduce or withdraw sedatives, antidepressants, antihypertensives, and hypoglycemic agents, vision correction, and environmental modifications such as improved lighting, removal of tripping hazards, installation of handrails and grab bars, and appropriate footwear.^{83,122} Recent network meta-analysis evidence in patients with osteoporosis confirms that exercise and exercise combined with medication are among the most effective interventions for reducing falls.^{123,124} While exercise appears to be the preferred intervention for fracture prevention, the quality of evidence remains low, and further high-quality trials are needed.^{125,126}

Although existing evidence supports the effectiveness of fall prevention interventions in community-dwelling older adults, further research is needed to better capture patient-important outcomes, particularly fall-related fractures, functional consequences, and potential adverse effects. There is also a need for studies that explicitly address equity-deserving and underrepresented populations, as well as for evaluations of digitally delivered or virtual fall-prevention programmes that may improve access and scalability.¹²⁷

Education and Psychological support

Education and psychosocial support addressing emotional and psychological aspects form an essential component of

the comprehensive management of PMO. Lifestyle counselling should routinely include smoking cessation and reduction of alcohol intake, as both adversely affect bone and mental health.⁴⁰ Treatment of osteoporosis has been associated with improvements in health-related quality of life (QoL) and psychological well-being, likely mediated through reduced fracture risk, pain relief, and improved physical function. Such benefits have been reported with pharmacological therapies, including raloxifene, denosumab, and hormone therapy where appropriate, as well as exercise-based interventions.¹²⁸⁻¹²⁹ Conversely, certain agents have been linked to neuropsychiatric adverse effects; strontium ranelate, in particular, has been associated with central nervous system and cognitive side effects, warranting caution, especially in women with pre-existing neuropsychiatric vulnerability.¹³⁰ Wherever possible, medications with known bone-depleting or adverse neurocognitive effects should be avoided or minimised, and in women with risk factors for secondary osteoporosis, standard universal preventive and therapeutic recommendations should be consistently applied.

Nutritional Pharmacological Management

Nutritional Supplementation: Combined calcium and vitamin D supplementation (1000–1200 mg Ca + 800–1000 IU D₃/day) reduces hip and total fracture risk in older adults.¹³¹⁻¹³⁴

Calcium: supplementation is indicated to correct calcium and vitamin D deficiency and forms an integral component of established osteoporosis management when dietary intake is inadequate. The recommended total daily calcium intake (diet + supplements) is 1000–1200 mg/day for osteoporosis.¹³⁵ Current evidence indicates that calcium intake within the tolerable upper intake level (2000–2500 mg/day) is not associated with an increased risk of cardiovascular disease or nephrolithiasis in generally healthy adults.¹³⁶ Calcium absorption is saturable, and intake should be limited to ≤500 mg per dose, obtained from food and/or supplements, with calcium sources distributed throughout the day to optimise absorption. Dietary calcium restriction is no longer recommended for patients with hypercalciuria; instead, adequate calcium intake combined with low sodium intake is advised to reduce urinary calcium loss. Excessive calcium intake (>2500 mg/day) should be avoided, as it may impair renal function and reduce the absorption of other minerals such as iron, zinc, and magnesium.¹³⁶ When calcium supplementation is medically necessary, it should preferably be taken with meals, and patients, especially those at risk, should be monitored for hypercalciuria. Calcium absorption may be reduced when calcium supplements are taken concurrently with high fibre or high-fat meals, iron or zinc supplements, oxalate-rich foods such as spinach, excess alcohol, or antacids. Moderate tea and coffee consumption is compatible with optimal bone health, provided total calcium intake is adequate, and calcium supplements are not taken simultaneously with caffeinated beverages.^{137,138} Decrease caffeine intake to < 3 cups/day.¹³⁷ A cup (150 mL) of brewed coffee contains 80–120 mg of caffeine, and instant coffee 50–65 mg, while tea contains 30–65 mg of caffeine.¹³⁷

Several commonly prescribed medications, including thyroid hormone preparations, corticosteroids, tetracyclines, bisphosphonates, and anticonvulsants, can have reduced absorption or altered efficacy when co-administered with calcium; therefore, these medications should be taken at least 2–4 hours apart from calcium supplements. Calcium intake should be individualised and physiologic ≤500 mg per dose, 800–1200 mg/day total, taken with meals, and spaced from interfering nutrients or drugs. Dietary restriction is not advised, and excessive intake (>2500 mg/day) should be avoided.^{40,131}

Vitamin D: Vitamin D deficiency is widespread across India, with prevalence estimates ranging from 20% to 100%, higher among women and residents of northern and eastern regions due to limited sun exposure and cultural clothing practices.^{139,140} Vitamin D is obtained from sunlight, fortified foods, and supplements, but most Indians receive inadequate sun exposure, and current food fortification levels are insufficient to meet the RDA. According to ICMR-NIN (2024) and Food Safety and Standards Authority of India (FSSAI) standards, fortified edible oil provides approximately 110–160 IU/day, while fortified milk provides 200 IU/day, assuming average adult intake of 25–30 g oil + 250 mL milk/day, together covering only about two-thirds of the RDA.^{139,141,142} Hence, supplementation is advisable in high-risk groups (indoor workers, elderly, obese or malabsorptive states). Gupta's review underlines that even apparently healthy Indians show low serum 25-hydroxyvitamin D (25OHD) levels, supporting universal supplementation, initial correction followed by maintenance dosing until widespread and effective food fortification becomes a reality.^{139,143}

Measurement of serum 25OHD is recommended in individuals at risk of vitamin D deficiency, including those with osteoporosis, fragility fractures, malabsorption, chronic kidney or liver disease, obesity, or limited sun exposure. Routine screening of the general population is not recommended.^{111,144} Cholecalciferol is preferred for correcting and maintaining vitamin D deficiency; aim for a serum 25(OH)D level of 40–60 ng/mL. Doses ≤ 4000 IU/day are safe; toxicity occurs with >10,000 IU/day.^{145,146} Cholecalciferol (vitamin D₃) is available in oral tablets, capsules, granules, 261

nano-emulsions, and spray forms, typically in doses of 1000 IU, 2000 IU, and 60,000 IU. Intramuscular preparations (300,000–600,000 IU per ampoule) are cost-effective and particularly useful in patients with malabsorption, poor adherence, or intolerance to oral therapy, though they may cause injection-site discomfort and yield variable serum 25(OH)D levels. The choice between daily and bolus dosing remains a topic of debate. The Endocrine Society (USA) recommends daily dosing for physiological mimicry, yet adherence challenges are common with long-term daily use. Bolus regimens, weekly or monthly, are supported by vitamin D's long half-life and comparable ability to sustain 25(OH)D and parathyroid hormone (PTH) levels over time, as excess vitamin D is stored in adipose tissue and released gradually. Thus, daily, weekly, or monthly schedules may be selected based on patient preference, likelihood of adherence, and clinical context, provided the total cumulative dose remains within recommended limits.^{114,144,147}

Management of Vitamin D deficiency (<20 ng/ml/ <50 nmol/L): Cholecalciferol (vitamin D3), 60,000 IU/ orally once a week for twelve weeks, preferably with milk or 2000 IU/day.

Vitamin D insufficiency (20–30 ng/ml/50–75 nmol/L): Cholecalciferol (vitamin D3), 60,000 IU/ orally once a week for eight weeks, preferably with milk or 2000 IU/day. One IM injection of 6,00,000 IU is given to correct the deficiency (not to be repeated before three months and may be given after confirmation of persistent low levels of vitamin D). Caution: Always combine with adequate calcium intake (dietary or supplemental) for bone benefits. Higher doses may be required in obesity, malabsorption, and chronic kidney disease.

Maintenance therapy: All regimes are to be followed by maintenance therapy. Cholecalciferol 60,000 IU once a month in summer or twice a month in winter. Vitamin D supplements of 2,000 IU/day, or Injection of Cholecalciferol 3,00,000 IU IM, twice a year or 6,00,000 IU IM once a year.^{113,148,149}

Vitamin D derivatives: Calcitriol (0.25–0.5 µg/day) & Alfacalcidol, the active form of vitamin D, are reserved only for patients with chronic renal and hepatic disease, with impaired activation of vitamin D. Alfacalcidol is a synthetic analogue of the active vitamin D metabolite calcitriol (1,25-dihydroxyvitamin D3), and it is metabolised to calcitriol by its 25-hydroxylation in the liver. It is less potent than calcitriol. The use of vitamin D derivatives requires monitoring of serum and, possibly, urine calcium. There is the risk of hypercalcaemia and hypercalciuria. Adverse effects of prolonged hypercalcaemia include impairment of renal function and nephrocalcinosis. Their use mandates monitoring of calcium and renal function due to the risk of hypercalcaemia, hypercalciuria, and nephrocalcinosis.^{150,151}

Vitamin K supplementation: 180–350 µg/day of Vitamin K2–7 may be considered along with calcium, magnesium, Vitamin D, and a balanced diet. The current RDA (WHO/FAO) of 65–80 µg/day is considered inadequate. Suggested intake is ≥100 µg/day throughout life, with higher doses when indicated. Vit. K supports both bone health and cardiovascular health in women with osteoporosis.¹⁵²

PHARMACOLOGICAL MANAGEMENT OF POSTMENOPAUSAL OSTEOPOROSIS

Indications For Pharmacotherapy

Categorisation by fracture risk: Management is stratified into low, intermediate, high, or very high-risk categories based on BMD and clinical risk factors. In the absence of DXA, treatment decisions are based on FRAX and OSTA outcomes. Refer to Table 5.

Choice of Medication

The choice of medication depends on the level of fracture risk, drug-related (risk-benefit), patient profile (age, years since menopause, symptoms, comorbidities), and environmental factors (economic and social). Patients should be educated about PMO and its treatment, and empowered to participate in shared decision-making to improve adherence. Calcium and Vitamin D co-therapy is mandatory to optimise outcomes.^{25, 153} There are no direct head-to-head RCTs comparing the fracture-reduction efficacy of different osteoporosis drugs; available evidence is derived primarily from placebo-controlled studies and indirect comparisons. Details of individual drug efficacy, safety, and indications are summarised in the accompanying tables.⁹⁴

Indications for Referral to an Endocrinologist

Referral to an endocrinologist is indicated for special group of patients such as when a premenopausal woman or a patient with normal BMD sustains a fragility fracture, recurrent fractures or continued bone loss despite treatment, unexpectedly low BMD or atypical biochemical findings (such as abnormal alkaline phosphatase or phosphorus), breast cancer survivors on endocrine therapy, non-responders to treatment or patients with comorbid conditions complicating management such as renal dysfunction, hyperparathyroidism, or malabsorption.⁷²

Management According to Risk for Fracture

Very high risk for fracture: Patients at very high fracture risk should be referred to a specialist. The indications are the presence of single but important clinical risk factors, such as a recent vertebral fracture (within the last 2 years), ≥ 2 vertebral fractures (whenever they have occurred), very low BMD T score, and treatment with high-dose glucocorticoids (≥ 7.5 mg/day of prednisolone or equivalent over 3 months).¹⁵³ Following a recent hip fracture, intravenous zoledronic acid is an effective first-line treatment option, with evidence demonstrating reduction in subsequent fractures and mortality.¹⁵⁴ Teriparatide, abaloparatide or romosozumab are first-line treatment options in postmenopausal women at very high fracture risk, particularly in those with vertebral fractures.^{72,94,155,156}

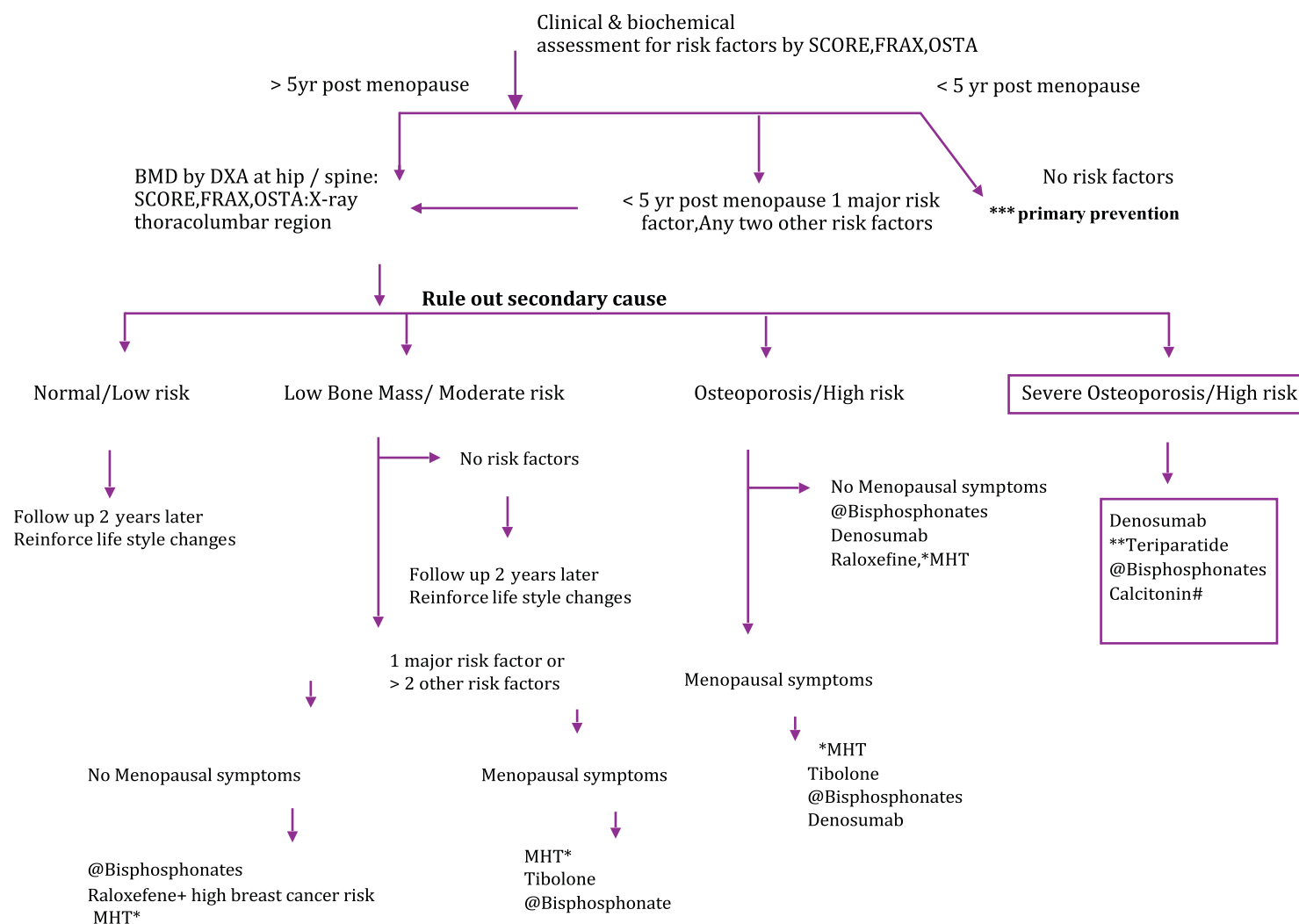
High risk for fracture: In early menopause (within 10 yrs of menopause) - First-line management is MHT / or bisphosphonates or denosumab. Second line options are teriparatide, abaloparatide or romosozumab, particularly in those with vertebral fractures. In late menopause (>10 years postmenopause), the first-line management is bisphosphonates/ denosumab. Second line teriparatide, abaloparatide, or romosozumab, particularly in those with vertebral fractures.

Intermediate risk for fracture: In early menopause (within 10 yrs of menopause) - First line of management is MHT/ or bisphosphonates. In case of contraindications, intolerance, or patient preference for ease and compliance, denosumab may be offered. In late menopause (> 10 yrs postmenopause) - bisphosphonates. In cases of contraindications, intolerance/ treatment failure, or patient preference for ease and compliance, denosumab may be offered.

Low risk of fracture: TLM Refer Flow chart 1 and 2 for managing osteoporosis.

Flowchart 1: Algorithm for Assessing and Managing Bone Health in an asymptomatic woman

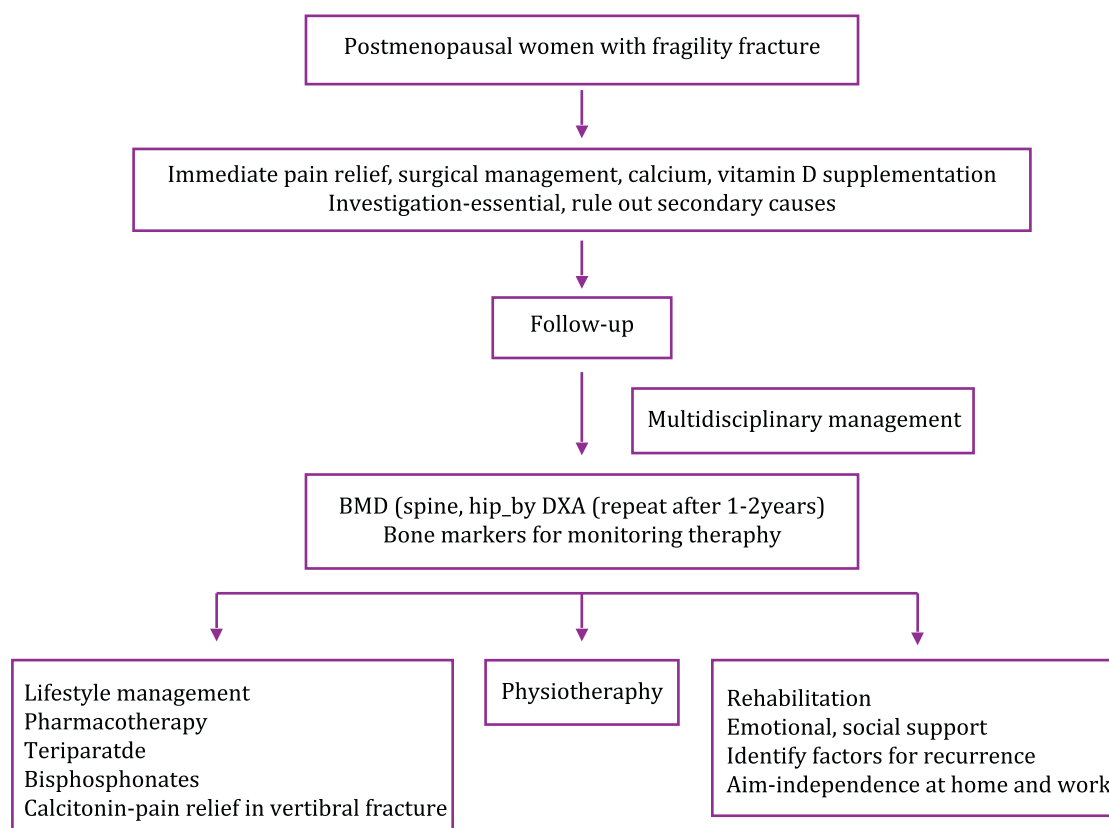
Asymptomatic Post Menopausal Woman



*** Primary Prevention for all --Nutrition ,Lifestyle Modification,Adequate Vitamin D and Calcium, Excercise, Avoid bone depleting agents	
@Bisphosphonates - Drug holiday after 3yrs for IV,5 years for oral (at low risk) - Consider continuation after a drug holiday - Raloxefine - effective on vertebral fractures	Denosumab-long term,On discontinuation add Bisphosphonates
*Hormone therapy To be used within 10 yrs of menopause - Pre initiation workup - Review annually - Individualize therapy	** Teriparatide – can be used upto 2 years Calcitonin# Analgesic , short term for three months in vertebral fractures .5yrs postmenopause
SCORE, Simple Calculated Osteoporosis Risk Estimation) FRAX, Fracture Risk Assessment Tool OSTA-The Osteoporosis Self-Assessment Tool for Asians	

Meeta, Harinarayan CV, Marwah R, Sahay R, Kalra S, Babhulkar S. Clinical practice guidelines on postmenopausal osteoporosis: Indian Menopause Society,2020

Management After Fracture



Flow chart 2. Management After Fracture

Follow-Up and Monitoring

Patients should be monitored every 3–6 months initially for 2–3 visits, and thereafter annually for clinical assessment, evaluation of adherence, and monitoring of adverse effects. Monitoring should include symptom review; assessment of compliance, health status, and fall risk; and secondary causes. Maintain calcium and vitamin D status and/or drug-specific laboratory investigations, and perform periodic BMD measurement every 1–2 years where feasible.⁷² During bisphosphonate or denosumab therapy, report any oral symptoms such as dental mobility, pain, or swelling, any unexplained thigh, groin, or hip pain, and if such symptoms develop, the femur should be imaged.

Investigations During Osteoporosis Therapy

Appropriate biochemical and clinical monitoring during osteoporosis therapy is essential to ensure safety, adherence, and optimal treatment response.

Teriparatide: Serum calcium and serum creatinine should be assessed at baseline, 1 month after initiation, and every 6 months thereafter to detect hypercalcaemia or renal impairment.⁷⁵

Denosumab: Serum calcium and 25-OHD levels should be measured before each 6-monthly injection, as hypocalcemia may occur, particularly in patients with vitamin D deficiency or renal impairment.^{157,158}

Zoledronic acid: Renal function and serum calcium should be checked before each annual infusion due to the risk of acute kidney injury and hypocalcaemia.¹⁵⁹

Alendronate: Routine biochemical monitoring is not required; however, symptom review, adherence assessment, and evaluation for gastrointestinal intolerance should be performed every 6–12 months.⁹⁴

Follow-up and Monitoring with DXA: Refer to Bone Density Measurement and Dual-Energy X-Ray Absorptiometry under Screening and Diagnosis.

Bone turnover markers: Refer to BTM under Investigations.

Non-response to osteoporosis therapy

Non-response may result from poor adherence, inadequate calcium or vitamin D status, unrecognised secondary osteoporosis, interfering medications, or suboptimal drug selection and monitoring strategies. Identification and correction of these factors are essential before changing therapy.^{72,160}

Duration of Therapy

The duration of therapy must be individualised based on the patient's profile, the drug used, and the patient's response to therapy. Oral bisphosphonates (alendronate, ibandronate and risedronate) for at least 5 years, zoledronate for at least 3 years and then re-assess fracture risk. Longer treatment durations of at least 10 years with oral therapy and 6 years with zoledronate in special situations. Teriparatide for 24 months (can be given only once in lifetime), abaloparatide for 18 months, and romosozumab for 12 months. Denosumab safety and efficacy is established for 10 yrs.

Bisphosphonate Holiday

In postmenopausal women with osteoporosis taking bisphosphonates (BP), fracture risk should be reassessed after 3–5 years (3 years for IV, 5 years for oral). Women who remain at high risk for fracture, including older women, low hip T-score, high fracture risk score, previous major osteoporotic fracture, or who fracture on therapy, should continue therapy for up to 10 years (oral) or 6 years (IV), with periodic reassessment.^{94,161} The risk of atypical femoral fracture (AFF), but not osteonecrosis of the jaw (ONJ), increases with longer duration of BP therapy. In women at low-to-moderate fracture risk, after 3 to 5 years of BP treatment, a drug holiday of 2 to 3 years can be considered. Owing to prolonged skeletal retention, anti-fracture efficacy is largely maintained for several years after discontinuation, while AFF risk declines.^{161,162} Bisphosphonate therapy should be reinitiated if fracture risk increases, BMD declines beyond the least significant change (LSC) on DXA, bone turnover markers rise significantly, or a new fragility fracture occurs.¹⁶¹

Sequential Regimens

Sequential therapy in osteoporosis refers to the planned transition between different pharmacologic classes to optimise BMD gains and reduce fracture risk over time. Selection of an optimal sequential therapy approach requires an individualised assessment based on baseline fracture risk, prior therapy, patient characteristics, and long-term

treatment goals. Current evidence supports anabolic first strategies as the most effective approach for maximising skeletal benefits.¹⁶³

Anabolic-to-Antiresorptive Sequences (Preferred): Initiation with an anabolic agent (teriparatide or romosozumab), followed by antiresorptive therapy (bisphosphonate or denosumab), is recommended to consolidate and maintain BMD gains and ensure long-term fracture protection.^{94,164}

Antiresorptive to Antiresorptive Sequences: The transition from bisphosphonates to denosumab may be considered in patients with an inadequate response or intolerance to bisphosphonates. Denosumab discontinuation is most critical and requires mandatory sequential therapy due to rapid bone loss and an increased risk of rebound vertebral fractures in case of delay or lack of an alternative therapy 6 months after the last denosumab dose. Denosumab must always be followed by bisphosphonate, preferably zoledronate or oral alendronate in patients with adequate renal function.¹⁶⁵⁻¹⁶⁷

Hormone-Based Sequential Approaches: Transition from estrogen therapy, MHT, or raloxifene to a bisphosphonate may be appropriate when HT is discontinued due to age, duration of use, or emerging contraindications.

Between-Anabolic Agent Transitions: Recent evidence suggests superior efficacy with the teriparatide-to-romosozumab sequence.

Combination Regimens

Simultaneous combination therapy is not routinely recommended because of insufficient safety and cost-effectiveness data. Combination regimens are typically reserved for very high-risk patients (such as multiple prior fractures, extremely low BMD, imminent fracture risk). The duration of concurrent therapy is individualised. Anabolic agents are restricted to 12–24 months, while antiresorptives continue as per standard long-term maintenance protocols. When combination or overlapping therapy is used, patients should be monitored for hypercalcaemia, orthostatic hypotension (with PTH analogues), renal function, and strict adherence to dosing intervals should be ensured. Tailoring combination therapy requires a multidisciplinary assessment and balancing fracture risk reduction with cost, safety, and patient preferences.¹⁶⁸

Specific combination therapies include teriparatide + denosumab combination¹⁶⁹ and HT + bisphosphonate combinations.¹⁷⁰ Among available studies, the teriparatide + denosumab regimen has produced the greatest BMD improvements (DATA and DATA-Switch trials),^{171,172} though evidence on fracture outcomes remains limited; such combinations should therefore be reserved for selected very high-risk patients under specialist supervision. Combining estrogen with bisphosphonates results in modestly greater increases in spine and hip BMD and greater suppression of bone turnover markers than monotherapy; however, convincing evidence for additional fracture risk reduction is limited.¹⁷³

Menopause Hormone Therapy for Postmenopausal Osteoporosis

There is strong evidence supporting menopausal hormone therapy (MHT) for the primary prevention of PMO in early postmenopausal women.

The Rationale

Estrogen deficiency at the menopause transition produces a rapid rise in bone remodelling, with resorption outpacing formation, leading to accelerated loss of trabecular and cortical bone. This biologic “high-turnover window” is most pronounced in the early postmenopause and precisely the period when MHT most reliably suppresses bone turnover, preserves microarchitecture, increases BMD, and reduces incident fractures in otherwise healthy women. RCTs and meta-analyses consistently show that systemic estrogen therapy either estrogen alone (ET, for women without a uterus) or estrogen–progestogen therapy (EPT, for women with a uterus) prevents bone loss at the spine and hip and reduces osteoporotic fractures even in women not selected for low baseline BMD.¹⁷⁴⁻¹⁷⁷

Effect of MHT on BMD of Lumbar Spine and Hip

Early studies demonstrated that estrogen therapy suppresses bone turnover and prevents postmenopausal bone loss at the lumbar spine and hip.¹⁷⁵ Subsequent RCTs and meta-analyses confirmed that MHT significantly increases BMD at the lumbar spine, femoral neck, and forearm compared with placebo or no treatment, with gains maintained during continued therapy.¹⁷⁶⁻¹⁷⁸ The PEPI trial showed significant gains in spine and hip BMD over 2 years with estrogen-based regimens versus placebo, alongside suppression of remodelling markers; importantly, BMD benefit wanes after discontinuation, reinforcing that protection is largely treatment-dependant.¹⁷⁶ Meta-analytic data similarly

demonstrate an approximately 6–7% increase in lumbar spine BMD and approximately 4% increase in hip BMD by about 2 years compared with control, with broadly consistent effects across estrogen formulations and with/without a progestogen.¹⁷⁷

Menopause Hormone Therapy and Fracture Reduction

The most robust fracture evidence comes from the WHI randomised trials, which uniquely enrolled generally healthy postmenopausal women not selected for osteoporosis. In the WHI trial, conjugated equine estrogen and medroxyprogesterone acetate (CEE+MPA), hormone therapy (HT) increased BMD and reduced fractures, with benefits observed across examined subgroups.¹⁷⁴ A subsequent WHI analysis showed a synergistic effect of HT combined with calcium and vitamin D supplementation, resulting in a 41% reduction in fracture risk (HR 0.59; 95% CI 0.38–0.93).¹⁷⁹ In the WHI estrogen therapy (ET) trial (CEE in hysterectomised women), estrogen also reduced fracture risk and increased BMD.¹⁸⁰ These results underpin the key clinical point for PMO prevention: MHT reduces vertebral, hip, and other osteoporotic

fractures by approximately 20–40% in randomised data, including women at relatively low baseline fracture risk. A meta-analysis of 28 RCTs confirmed the anti-fracture efficacy of HT, reporting a 26% reduction in total fractures, a 28% reduction in hip fractures, and a 37% reduction in vertebral fractures, particularly when HT is initiated before age 60, regardless of baseline BMD.¹⁸¹ They concluded that protection may attenuate after cessation and when therapy is initiated later.¹⁸¹ These effects are also seen with low-dose and ultra-low-dose transdermal estradiol, which significantly increases BMD and lowers turnover markers in early postmenopausal women, supporting bone-protective use when symptom control and tolerability permit.¹⁸²

Impact of Estrogen Formulation and Dose on BMD

Refer to Chapter 37 for Low-Dose MHT.

Any systemic estrogen dose that suppresses bone turnover is effective for preventing postmenopausal bone loss. Although most trials evaluated standard oral estrogen doses, both lower-dose and transdermal estrogen therapies significantly improve BMD. RCTs demonstrate comparable increases in spine and hip BMD with oral CEE, oral estradiol, and transdermal estradiol, with consistent suppression of bone turnover.^{178,183} Importantly, low-dose and ultra-low-dose transdermal estradiol regimens significantly increase BMD and reduce BTMs in early postmenopausal women, supporting their role in long-term bone protection with improved tolerability.¹⁸² While fracture-reduction data for low-dose and transdermal estrogen are limited, several low-dose oral and transdermal estrogen formulations are approved for osteoporosis prevention based on demonstrated BMD efficacy.¹⁸⁴ The evidence is that standard doses (oral CEE 0.625 mg, oral estradiol 1–2 mg, transdermal estradiol 50 µg) have the strongest fracture-reduction evidence. Low-dose and ultra-low-dose estrogen regimens (oral CEE 0.3 mg, oral estradiol 0.5 mg, transdermal estradiol 14–25 µg) effectively maintain BMD and are acceptable for long-term continuation. Hence, the dose, route and duration need to be individualised. The addition of a progestogen for endometrial protection does not diminish skeletal benefits.¹⁷⁶ Overall, available evidence indicates that bone protection is a class effect of estrogen, largely independent of route of administration, with formulation choice based on age, time since menopause, comorbidities, and safety considerations rather than skeletal efficacy alone.¹⁸⁵

Effect of Menopause Hormone Therapy on Postmenopausal Osteoporosis, Low Bone Mineral Density and Post-Fracture Outcomes

Osteoporosis: MHT is effective for both prevention and treatment of PMO. Large RCTs and meta-analyses demonstrate significant reductions in vertebral, hip, and non-vertebral fractures with estrogen-based therapy.^{174,178} Recent analyses confirm a reduction in fracture risk regardless of baseline FRAX probability, supporting its anti-fracture efficacy.¹⁸⁶

Low BMD: In women with osteopenia, MHT slows bone loss, preserves BMD, and reduces progression to osteoporosis. Notably, fracture reduction with MHT has been observed even in women without densitometric osteoporosis, supporting its role in appropriately selected younger postmenopausal women at intermediate fracture risk.^{174,185}

Post-fracture: Evidence supporting MHT for secondary fracture prevention is limited, as no RCT has been specifically designed for this indication. Although subgroup analyses from the WHI demonstrate continued improvements in BMD and reductions in fracture risk with MHT in women with prior fractures, these findings are based on primary prevention trials. Accordingly, anti-osteoporotic agents with proven fracture-specific efficacy remain first-line therapy for secondary fracture prevention.^{154,174,186} MHT may be considered in recently menopausal, symptomatic

women after an individualised risk–benefit assessment.^{185,186}

On the basis of accumulated evidence, MHT may be considered as a first-line treatment in younger postmenopausal women (<60 years or within 10 years of menopause) who are at intermediate and high fracture risk after full risk assessment, provided there are no contraindications.^{174,176,182,183,186-188} Continued use after 60 years is a shared decision based on an individual risk–benefit analysis. MHT should not be started solely for bone protection after 10 years of menopause. Extended use of MHT in women with reduced bone mass is an option after considering the risk–benefit analysis compared to the other available therapies for osteoporosis.^{185,189}

Tibolone

Refer to Chapter 39.

Raloxifene

Refer to Chapter 40.

Premature ovarian insufficiency(POI) and Early Menopause

HT should be offered to women with POI and early menopause (and it can be recommended until the age of natural menopause).¹⁹⁰⁻¹⁹²

Menopause Hormone Therapy Vs Bisphosphonates

Both MHT and BPs effectively reduce osteoporotic fracture risk, but their clinical roles differ according to menopausal stage, risk category, and symptom profile.^{72,159,174,187,193} BPs do not confer the systemic short or long-term health benefits of MHT in eligible women, particularly regarding cardiometabolic, urogenital, cognitive, and overall quality-of-life outcomes.^{72,159,174,187,193} BPs demonstrate additional systemic benefits, including reduced post-fracture mortality, lower risk of bone metastases and recurrence in postmenopausal breast cancer, anti-inflammatory effects, and possible cardiovascular and survival advantages in older adults. These effects are most consistent in postmenopausal women and fracture survivors.^{154,194-197}

Treatment Duration

Early initiation of HT near the onset of menopause and continuation beyond 10 years does not confer the same risk as initiating HT more than 10 years after menopause or after age 60, when cardiovascular and thromboembolic risks increase. Current evidence does not support a mandatory upper limit for HT duration or routine discontinuation in asymptomatic women in the absence of new medical contraindications.¹⁹⁸ In the context of osteoporosis prevention and treatment, decisions regarding treatment duration should be individualised and based on age at menopause, timing of HT initiation, evolving risk factors, and ongoing benefit–risk assessment. An individualised approach using shared decision-making is recommended to balance symptom control, fracture prevention, and long-term safety.^{198,199}

Bone Effects After Discontinuation of Menopause Hormone Therapy

Women who discontinued HT during or after the PEPI randomised trial experienced BMD loss at rates comparable to untreated postmenopausal women (approximately 1% in the first year and approximately 0.5% annually thereafter). Continued HT beyond 3 years did not result in additional BMD gains. These findings indicate that HT discontinuation is not associated with accelerated bone loss, and that most skeletal benefit is achieved within the initial years of therapy.²⁰⁰ However, evidence suggests that some benefits on bone density and microarchitecture preservation, as assessed by TBS, may persist for a period after withdrawal, particularly following long-term use.^{201,202} Importantly, large prospective data from the WHI study indicate no significant increase in fracture risk, either sustained or transient, for former HT users compared with former placebo users after stopping MHT, despite declines in BMD.²⁰³

More robust long-term follow-up evidence comes from the PERF study: after 2–3 years of HT in early postmenopause, women retained higher BMD than placebo recipients for years afterward, and had a lower risk of osteoporotic fractures (reported OR about 0.48) despite bone loss resuming at typical postmenopausal rates after withdrawal supporting the concept that early limited exposure may yield longer-lasting skeletal advantage in some women.

However, newer large-scale real-world evidence from a 2025 nested case–control analysis using routinely collected primary care data, Vinogradova and colleagues reported that fracture protection diminishes rapidly within about a year of stopping, followed by a medium-term elevation in fracture risk compared with never-users, before a later attenuation suggesting persistent beneficial effects on bone ageing in those who survive into older age.²⁰⁴

Observational data indicate that women with continuous or remote past MHT use exhibit less age-related thoracic hyperkyphosis in advanced age compared with never-users, suggesting a potential protective role of HT on spinal posture and vertebral integrity in later life.²⁰⁵

These findings support the role of MHT as an effective anti-resorptive therapy during use, while highlighting the need for reassessment of fracture risk and consideration of alternative osteoporosis therapies after cessation. It is recommended that women who discontinue ET/HT undergo a BMD assessment. If the T score is below -2.0, another therapy, such as a BP, can be used to prevent further bone loss. In conclusion, HT, alendronate, and risedronate may be considered as initial options for most early postmenopausal women with low or moderate fracture risk. In women who are intolerant of oral BPs or in whom they are contraindicated, intravenous BPs or denosumab should be considered. Women with breast cancer risk and with osteoporosis of the spine may be benefited with raloxifene.

Bps are recommended as the first-line drugs for treating postmenopausal women in the management of osteoporosis. In older postmenopausal women, injectable agents such as denosumab, zoledronic acid, or teriparatide can be considered as initial therapy for those who have the highest fracture risk, older women who have had multiple vertebral fractures or hip fractures, or those who have very low T-scores, those who have upper gastrointestinal problems, and those might not tolerate or absorb oral medication and patient preference. BPs are recommended as the first-line drugs for treating postmenopausal women, with proven efficacy in the prevention of vertebral and nonvertebral fractures. Refer to Table 10 for positioning, efficacy, and precautions, and to Table 11 for advantages, disadvantages, contraindications, and adverse effects of the medications.

Table 10. Osteoporosis Drug Chart – Positioning, Efficacy and Precautions

Drug	Dosage	Route	Position in therapy	Vertebral*	Hip*	Non-vertebral*	Precautions
Alendronate	5/10 mg daily	Oral	1 st line	Yes, 50%	Yes, 51-56%	Yes, 49%	Hypocalcemia, Vit. D status, should not be used in patients with eGFR below 30ml/min, pregnancy, lactation, pediatric, ONJ, AFF
Alendronate	35/70 mg/ weekly				Yes, 51-56%		Hypocalcemia, Vit. D status, should not be used in patients with eGFR below 30ml/min, pregnancy, lactation, pediatric, ONJ, AFF
Alendronate	150 mg monthly				Yes, 51-56%		Hypocalcemia, Vit. D status, should not be used in patients with eGFR below 30ml/min, pregnancy, lactation, pediatric, ONJ, AFF
Risedronate	5 mg daily	Oral	1 st line	Yes, 41-49%	Yes, 30%	Yes, 36%	Hypocalcemia, Vit. D status, should not be used in patients with eGFR below 30ml/min, pregnancy, lactation, pediatric, ONJ, AFF
Risedronate	35 mg weekly			Yes, 41-49%			Hypocalcemia, Vit. D status, should not be used in patients with eGFR below 30ml/min, pregnancy, lactation, pediatric, ONJ, AFF

Risedronate	150 mg monthly			Yes, 41-49%			Hypocalcemia, Vit. D status, should not be used in patients with eGFR below 30ml/min, pregnancy, lactation, pediatric, ONJ, AFF
Zolendronate	5 mg	IV	1 st line	Yes, 70%	Yes, 41%	Yes, 25%	Hypocalcemia, Vit. D status, should not be used in patients with eGFR below 30 ml/min, pregnancy, lactation, pediatric, ONJ, AFF
Teriparatide	20 mcg	SC	For severe osteoporosis	Yes, 65%	Insufficient data	Yes, 53%	Hypocalcemia, Vitamin D status, Hypersensitivity, local tissue damage, pregnancy, lactation, pediatric,
Romozumab	210 mg monthly × 12 months	SC	For severe osteoporosis	60%	38%	25%	Hypocalcemia, Vit. D status, Established CVD should not be used in patients with eGFR below 30 ml/min, pregnancy, lactation, pediatric, ONJ, AFF
Denosumab	60 mg	SC	1 st line	Yes, 68%	Yes, 40%	Yes, 20%	Hypocalcemia, Vit. D status, pregnancy, lactation, pediatric,
MHT	Various regimes	Various regimes	1 st line with menopausal symptoms (<10 years menopause)	Yes, 30-70%	Yes, 40%	Yes, 27%	Blood clots, Cancer (such as breast, uterine, or endometrial), Heart or liver disease, Heart attack, Known or suspected pregnancy, Stroke
Raloxifene	60 mg	Oral	At risk of breast cancer, without VMS, <10 years menopause	40%	No	No	With a low risk of DVT and for whom bisphosphonates or denosumab are not appropriate, or with a high risk of breast cancer
Tibolone	2.5 mg	Oral	1 st line <10 years menopause	Yes, 50%	Yes, 26%	Yes, 26%	To stop tibolone a few weeks before any operation to reduce the risk of a blood clot, drug interaction with warfarin
Calcitonin	200 IU	Nasal spray	2 nd line	Yes, 21%	No	No	Serious hypersensitivity reactions, including fatal anaphylaxis, reported; consider skin testing prior to treatment

Table 11. Advantages, Disadvantages, Contraindications and Adverse Effects of Bisphosphonates

Drug	Advantages	Disadvantages	Contraindications	Common Adverse effects
Alendronate	Most commonly used drug	Inconvenient administration - Stay upright for 30 min on intake, drink lots of water; no food before taking the drug, drug holiday may be needed after 3-5 years	Hypocalcemia, Hypersensitivity, compromised renal function, Upper GI disease - Abnormalities of the esophagus which delay esophageal emptying such as stricture of achalasia, patients at increased risk of aspiration	Dyspepsia, esophagitis abdominal pain, musculoskeletal pain
Risedronate		Inconvenient administration - Stay upright for 30 min on intake, drink lots of water; no food before taking the drug, drug holiday may be needed after 3-5 years	Hypocalcemia, hypersensitivity, compromised renal function, Upper GI disease - Abnormalities of the esophagus which delay esophageal emptying such as stricture of achalasia, patients at increased risk of aspiration	Rash, abdominal pain, dyspepsia, diarrhea, arthralgia
Zoledronate	1 st line drug, Once a year	anaphylaxis, including fatal events	Hypocalcemia, hypersensitivity, compromised renal function	Acute reaction (flu such as symptoms, fever, myalgia) may occur within 3 days of infusion, hypotension, fatigue, eye inflammation, more nausea, vomiting, abdominal pain

POST-FRACTURE OSTEOPOROSIS MANAGEMENT

All patients with fractures should undergo BMD testing post-surgery. Osteoporosis therapy should be started to prevent subsequent fractures. Teriparatide can be started postoperatively to stimulate bone formation. It accelerates fracture healing by enhancing callus formation. Denosumab is fracture-neutral, does not affect healing, and can be started before or after 6 weeks and combined with teriparatide. Bisphosphonates: start 4–6 weeks post-fracture. The patient should be calcium and vitamin D-replete. Anabolic steroids may be used in very old frail women with sarcopenia for 6 months.²⁰⁶

REHABILITATION

Phase-wise physiotherapy is based on the severity of osteoporosis and hip/spine involvement. The use of strengthening, resistance, and weight-bearing exercises depends on age and the severity of osteoporosis. A combined approach is followed using occupational and diet therapy.

ECONOMICS OF OSTEOPOROSIS

Advising lifestyle measures to all postmenopausal women, such as increasing dietary calcium intake and physical activity, improves bone health and is a cost-effective approach. Supplementation with calcium and vitamin D, with a prescription to those with inadequate intake, to help prevent osteoporosis and related fractures. Screening postmenopausal women for osteoporosis/osteopenia by DXA at the hip/spine and relevant biochemical tests is a cost-effective strategy. Furthermore, treating women diagnosed with osteoporosis represents an effective and economically justified intervention.

GLUCOCORTICOID-INDUCED OSTEOPOROSIS

GIOP is the most common secondary cause of osteoporosis and contributes significantly to fracture risk.²⁰⁷ All patients receiving chronic oral glucocorticoids (even low doses ≥ 2.5 –5 mg prednisolone equivalent for ≥ 3 months) should be evaluated for fracture risk and considered for preventive therapy.²⁰⁸ Bone loss begins early (often within the first 3–6 months) and is dose-dependant, occurring even with low doses of glucocorticoids. These adverse effects are due to inhibition of bone formation accompanied by an early but transient increase in bone resorption.²⁰⁹ In patients initiating high-dose glucocorticoids, anti-osteoporosis therapy should be started promptly to mitigate rapid bone loss; oral bisphosphonates are typically first-line, with intravenous options considered when oral therapy is unsuitable.²⁰⁸ Inhaled corticosteroids at standard doses generally have minimal systemic effects on bone, but higher doses can still affect bone density, and this is influenced by dose and adrenal suppression.

Prevention and Management

- Baseline BMD assessment (DXA) and fracture risk evaluation is recommended for patients anticipated to require ≥ 3 months of glucocorticoid therapy.
- Calcium and vitamin D supplementation is advised for all patients on glucocorticoids or other high-risk medications (such as anticonvulsants, antiretrovirals, thyroid therapy)
- Antiresorptive therapy: Oral bisphosphonates (such as alendronate, risedronate) are recommended first-line for GIOP prevention and treatment in adults at increased fracture risk, with evidence demonstrating preservation or modest increases in BMD.
- Teriparatide has been shown in clinical studies to increase BMD more than bisphosphonates in GIOP as it directly counteracts GIOP pathophysiology, and may be preferred in certain patients who are at high-or very high risk for fracture.^{208,210}
- Duration of therapy: Antiresorptive therapy is generally continued while glucocorticoid therapy is ongoing, with periodic reassessment of fracture risk.

SYNOPSIS

- Postmenopausal osteoporosis is a chronic systemic skeletal disorder resulting from estrogen deficiency after menopause, characterised by reduced bone mass, impaired bone microarchitecture, and increased fragility fracture risk, particularly at the spine, hip, and distal forearm.
- Peak bone mass is achieved by the third decade, after which age-related bone loss occurs; the menopausal transition is marked by a distinct phase of accelerated bone loss, with up to 10–20% trabecular and 5–10% cortical bone loss within the first 5–7 years after menopause, substantially increasing fracture risk.
- PMO represents a major global and Indian public health burden, with fractures occurring earlier in Indian women, compounded by lower peak bone mass, earlier menopause, nutritional deficiencies, and limited awareness; up to one in two women over 50 years may experience a fragility fracture during their lifetime.
- Fracture risk in PMO is multifactorial, arising from the interaction of reduced skeletal strength (low BMD and poor bone quality), increased fall risk (sarcopenia, frailty, comorbidities), and fall impact, explaining why many fractures occur in women with osteopenia rather than DXA-defined osteoporosis.
- Diagnosis and risk stratification rely on an integrated approach, combining clinical risk factors, fracture history, and BMD measured by DXA; osteoporosis is defined by a T-score ≤ -2.5 or the presence of a fragility fracture, with vertebral fracture assessment and trabecular bone score providing additional risk refinement.
- Selective screening and case finding strategies are recommended rather than population-wide DXA screening, using tools such as FRAX (with or without BMD) and OSTA to identify women at increased fracture risk, particularly in resource-limited settings.
- Management of PMO is lifelong and multifaceted, encompassing therapeutic lifestyle measures (adequate calcium and vitamin D intake, weight-bearing and resistance exercise, fall prevention, smoking cessation), correction of secondary causes, and pharmacologic therapy tailored to fracture risk and menopausal status.

- MHT is an effective option for primary prevention of bone loss and fractures in eligible early postmenopausal women, while nonhormonal antiresorptive or anabolic agents are preferred in older women, those at high or very high fracture risk, or when MHT is contraindicated.
- Treatment selection, duration, and monitoring should be individualised, guided by age, time since menopause, fracture risk category, comorbidities, patient preference, and periodic reassessment using BMD, clinical risk factors, and adherence, with the goal of reducing fractures, preserving function, and improving QoL.

RESEARCH AGENDA

What are real-world Indian rates and predictors of atypical femoral fracture, ONJ, and hypocalcemia, and how do these compare with global estimates?

EDITOR'S NOTE

This chapter is based on the monograph on “Clinical Practice Guidelines on Postmenopausal Osteoporosis” by the Indian Menopause Society. Available at www.indianmenopausesociety.org.

REFERENCES

1. Riggs BL, Khosla S, Melton LJ. Sex Steroids and the Construction and Conservation of the Adult Skeleton. *Endocrine Reviews* 2002;23:279-302. <https://doi.org/10.1210/edrv.23.3.0465>
2. Finkelstein JS, Brockwell SE, Mehta V, Greendale GA, Sowers MR, Ettinger B, et al. Bone Mineral Density Changes during the Menopause Transition in a Multiethnic Cohort of Women. *The Journal of Clinical Endocrinology & Metabolism* 2008;93:861-8. <https://doi.org/10.1210/jc.2007-1876>
3. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster J-Y, Borgstrom F, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporosis International* 2008;19:399-428. <https://doi.org/10.1007/s00198-008-0560-z>
4. Salari N, Darvishi N, Bartina Y, Larti M, Kiaei A, Hemmati M, et al. Global prevalence of osteoporosis among the world older adults: a comprehensive systematic review and meta-analysis. *Journal of Orthopaedic Surgery and Research* 2021;16. <https://doi.org/10.1186/s13018-021-02821-8>
5. Liang H, Chen S, Shi M, Xu J, Zhao C, Yang B, et al. Global epidemiology and burden of osteoporosis among postmenopausal women: insights from the Global Burden of Disease Study 2021. *Npj Aging* 2025;11. <https://doi.org/10.1038/s41514-025-00269-2>
6. Dhanwal DK, Dennison EM, Harvey NC, Cooper C. Epidemiology of hip fracture: Worldwide geographic variation. *Indian Journal of Orthopaedics* 2011;45:15-22. <https://doi.org/10.4103/0019-5413.73656>
7. Dash SK, Panigrahi R, Palo N, Priyadarshi A, Biswal M. Fragility Hip Fractures in Elderly Patients in Bhubaneswar, India (2012-2014). *Geriatric Orthopaedic Surgery & Rehabilitation* 2014;6:11-5. <https://doi.org/10.1177/2151458514555570>
8. Bhadada S, Dhibar D, Gogate Y, Aggarwal S, Garg S, Bhansali A. Predictors and outcome of fragility hip fracture: A prospective study from North India. *Indian Journal of Endocrinology and Metabolism* 2019;23:282. https://doi.org/10.4103/ijem.ijem_648_18
9. Kuriakose C, Cherian KE, Jebasingh F, Kapoor N, Asha HS, Jose A, et al. The prevalence of vertebral fractures among Indian perimenopausal women and its association with ovarian biomarkers. *Journal of Bone and Mineral Metabolism* 2021;40:142-9. <https://doi.org/10.1007/s00774-021-01266-7>
10. Shatrugna V, Kulkarni B, Kumar PA, Rani KU, Balakrishna N. Bone status of Indian women from a low-income group and its relationship to the nutritional status. *Osteoporosis International* 2005;16:1827-35. <https://doi.org/10.1007/s00198-005-1933-1>
11. Anupama DS, Noronha JA, Acharya KKV, Prabhu MM, Shetty J, Shankar R, et al. Burden of Osteopenia and Osteoporosis Among Postmenopausal Women in India: A Systematic Review and Meta-Analysis. *Journal of Mid-Life Health* 2022;13:107-14. https://doi.org/10.4103/jmh.jmh_207_21
12. Babhulkar S, Seth S. Prevalence of osteoporosis in India: an observation of 31238 adults. *International Journal of Research in Orthopaedics* 2021;7:362-8. <https://doi.org/10.18203/issn.2455-4510.intjresorthop20210630>
13. Khinda R, Valecha S, Kumar N, Walia JPS, Singh K, Sethi S, et al. Prevalence and Predictors of Osteoporosis and Osteopenia in Postmenopausal Women of Punjab, India. *International Journal of Environmental Research and Public Health* 2022;19:2999. <https://doi.org/10.3390/ijerph19052999>
14. Bhatia M, Mishra A, Sukla P. Post-menopausal osteoporosis: prevalence of risk factors and probable symptoms. *International Journal of Community Medicine And Public Health* 2018;5:5253. <https://doi.org/10.18203/2394-6040.ijcmph20184799>
15. Singh M. Early age of natural menopause in India, a biological marker for early preventive health programs. *Climacteric* 2012;15:581-6. <https://doi.org/10.3109/13697137.2011.643514>
16. Gupta A. Osteoporosis in India—the nutritional hypothesis. *National Medical Journal of India* 1996;9:268-74. PMID: 9111786.
17. Agrawal AC, Garg AK. Epidemiology of Osteoporosis. *Indian Journal of Orthopaedics* 2023;57:45-8. <https://doi.org/10.1007/s43465-023-01012-3>
18. Harinarayan C, Ramalakshmi T. Patterns of dietary calcium intake in south Indian rural, urban and metropolitan city subjects. *Journal of Clinical and Scientific Research* 2015;4:143. <https://doi.org/10.15380/2277-5706.jcsr.15.003>
19. Harinarayan CV, Ramalakshmi T, Prasad UV, Sudhakar D. Vitamin D status in Andhra Pradesh: a population based study. *Indian Journal of Medical Research* 2008;127:211-8. PMID: 18497434.
20. Sreenivasulu K, Banerjee M, Tomo S, Shukla K, Selvi MK, Garg MK, et al. Seasonal variation and Vitamin-D status in ostensibly healthy Indian population: An experience from a tertiary care institute. *Metabolism Open* 2024;23:100298. <https://doi.org/10.1016/j.metop.2024.100298>
21. Harinarayan CV, Akhila H. Modern India and the Tale of Twin Nutrient Deficiency—Calcium and Vitamin D—Nutrition Trend Data 50 Years-Retrospect, Introspect, and Prospect. *Frontiers in Endocrinology* 2019;10:493. <https://doi.org/10.3389/fendo.2019.00493>

22. Thakur P, Kuriakose C, Cherian KE, Asha HS, Kapoor N, Paul TV. Knowledge gap regarding osteoporosis among medical professionals in Southern India. *Journal of Evaluation in Clinical Practice* 2020;26:272–80. <https://doi.org/10.1111/jep.13164>
23. Kale A, Khandelwal N, Sirohi B, Shaki O, Rai S. Knowledge, Attitudes, Practices, and Awareness Levels Among Indian Postmenopausal Women About Osteoporosis and Its Relationship With Sociodemographic Factors: A Cross-Sectional Study From Northern India. *Cureus* 2024;16:e59606. <https://doi.org/10.7759/cureus.59606>
24. Kadam N, Chiplonkar S, Khadilkar A, Khadilkar V. Low knowledge of osteoporosis and its risk factors in urban Indian adults from Pune city, India. *Public Health Nutrition* 2019;22:1292–9. <https://doi.org/10.1017/s1368980018003634>
25. Meeta M, Harinarayan C, Marwah R, Sahay R, Kalra S, Babhulkar S. Clinical practice guidelines on postmenopausal osteoporosis: *An executive summary and recommendations – Update 2019–2020. *Journal of Mid-Life Health* 2020;11:96–112. https://doi.org/10.4103/jmh.jmh_143_20
26. Yordanov A, Vasileva-Slaveva M, Tsoneva E, Kostov S, Yanachkova V. Bone Health for Gynaecologists. *Medicina* 2025;61:530. <https://doi.org/10.3390/medicina61030530>
27. Compston J. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis (WHO Technical Report Series No 843). *Annals of the Rheumatic Diseases* 1995;54:548. <https://doi.org/10.1136/ard.54.7.548>
28. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis Prevention, Diagnosis, and Therapy. *JAMA* 2001;285:785–95. <https://doi.org/10.1001/jama.285.6.785>
29. Silva BC, Leslie WD, Resch H, Lamy O, Lesnyak O, Binkley N, et al. Trabecular Bone Score: A Noninvasive Analytical Method Based Upon the DXA Image. *Journal of Bone and Mineral Research* 2014;29:518–30. <https://doi.org/10.1002/jbmr.2176>
30. Boutroy S, Bouxsein ML, Munoz F, Delmas PD. In Vivo Assessment of Trabecular Bone Microarchitecture by High-Resolution Peripheral Quantitative Computed Tomography. *The Journal of Clinical Endocrinology & Metabolism* 2005;90:6508–15. <https://doi.org/10.1210/jc.2005-1258>
31. Mirza F, Canalis E. MANAGEMENT OF ENDOCRINE DISEASE: Secondary osteoporosis: pathophysiology and management. *European Journal of Endocrinology* 2015;173:R131–51. <https://doi.org/10.1530/eje-15-0118>
32. Briot K, Roux C. Glucocorticoid-induced osteoporosis. *RMD Open* 2015;1:e000014. <https://doi.org/10.1136/rmdopen-2014-000014>
33. Pepe J, Body J-J, Hadji P, McCloskey E, Meier C, Obermayer-Pietsch B, et al. Osteoporosis in Premenopausal Women: A Clinical Narrative Review by the ECTS and the IOF. *The Journal of Clinical Endocrinology & Metabolism* 2020;105:2487–506. <https://doi.org/10.1210/clinem/dgaa306>
34. Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, et al. Official Positions of the International Society for Clinical Densitometry and Executive Summary of the 2007 ISCD Position Development Conference. *Journal of Clinical Densitometry* 2008;11:75–91. <https://doi.org/10.1016/j.jocd.2007.12.007>
35. Cohen A. Premenopausal Osteoporosis. *Endocrinology and Metabolism Clinics of North America* 2017;46:117–33. <https://doi.org/10.1016/j.ecl.2016.09.007>
36. Gourlay ML, Brown SA. Clinical Considerations in Premenopausal Osteoporosis. *Archives of Internal Medicine* 2004;164:603. <https://doi.org/10.1001/archinte.164.6.603>
37. Rubin MR, Schussheim DH, Kulak CAM, Kurland ES, Rosen CJ, Bilezikian JP, et al. Idiopathic osteoporosis in premenopausal women. *Osteoporosis International* 2004;16:526–33. <https://doi.org/10.1007/s00198-004-1716-0>
38. Seeman E. Bone quality: the material and structural basis of bone strength. *Journal of Bone and Mineral Metabolism* 2008;26:1–8. <https://doi.org/10.1007/s00774-007-0793-5>
39. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: Synopsis of a WHO report. *Osteoporosis International* 1994;4:368–81. <https://doi.org/10.1007/bf01622200>
40. Kanis JA, Cooper C, Rizzoli R, Reginster J-Y. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporosis International* 2018;30:3–44. <https://doi.org/10.1007/s00198-018-4704-5>
41. Bhadada SK, Chadha M, Sriram U, Pal R, Paul TV, Khadgawat R, et al. The Indian Society for Bone and Mineral Research (ISBMR) position statement for the diagnosis and treatment of osteoporosis in adults. *Archives of Osteoporosis* 2021;16:102. <https://doi.org/10.1007/s11657-021-00954-1>
42. Shilpa K, Norman G. Prevalence of frailty and its association with lifestyle factors among elderly in rural Bengaluru. *Journal of Family Medicine and Primary Care* 2022;11:2083–9. https://doi.org/10.4103/jfmpc.jfmpc_1679_21
43. S. RS, Lanjewar S, Narlawar UW, P. T, U. IAG, P. AK. Prevalence of frailty among rural community-dwelling elderly: a cross-sectional study in central India. *International Journal Of Community Medicine And Public Health* 2024;12:298–303. <https://doi.org/10.18203/2394-6040.ijcmph20244035>
44. Professor Kanis JA, Melton LJ, Christiansen C, Johnston CC, Khaltayev N. The diagnosis of osteoporosis. *Journal of Bone and Mineral Research* 1994;9:1137–41. <https://doi.org/10.1002/jbmr.5650090802>
45. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. *The Lancet* 2002;359:1761–7. [https://doi.org/10.1016/s0140-6736\(02\)08657-9](https://doi.org/10.1016/s0140-6736(02)08657-9)
46. Ghannam NN. Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis (WHO Technical Report Series No 843). *Annals of Saudi Medicine* 1994;14:527. <https://doi.org/10.5144/0256-4947.1994.527>
47. Chevalley T, Rizzoli R. Acquisition of peak bone mass. *Best Practice & Research Clinical Endocrinology & Metabolism* 2022;36:101616. <https://doi.org/10.1016/j.beem.2022.101616>
48. Akhiarova K, Khusainova R, Minniakhmetov I, Mokrysheva N, Tyurin A. Peak Bone Mass Formation: Modern View of the Problem. *Biomedicine* 2023;11:2982. <https://doi.org/10.3390/biomedicine11112982>
49. Hereford T, Kellish A, Samora JB, Reid Nichols L. Understanding the importance of peak bone mass. *Journal of the Pediatric Orthopaedic Society of North America* 2024;7:100031. <https://doi.org/10.1016/j.jposna.2024.100031>
50. Marwaha RK, Tandon N, Shivaprasad C, Kanwar R, Mani K, Aggarwal R, et al. Peak Bone Mineral Density of Physically Active Healthy Indian Men With Adequate Nutrition and No Known Current Constraints to Bone Mineralization. *Journal of Clinical Densitometry* 2009;12:314–21. <https://doi.org/10.1016/j.jocd.2009.05.004>

51. Marwaha RK, Puri S, Tandon N, Dhir S, Agarwal N, Bhadra K, Saini N. Effects of sports training & nutrition on bone mineral density in young Indian healthy females. *Indian Journal of Medical Research* 2011;134:307–13. PMID: 21985813
52. Shatrugna V, Ammini AC, Tandon N, Goswami R, Gupta N, Bhatia E, et al. Population based reference standards of Peak Bone Mineral Density of Indian males and females – an ICMR multi-centre task force study. Indian Council of Medical Research (ICMR). [Internet]. 2023. Available from: https://www.icmr.gov.in/icmrobject/static/icmr/dist/images/pdf/reports/ICMR_Tech_Report_BMDRefStds2010.pdf [Accessed 6 Feb 2026]
53. Vaishya R, Iyengar KP, Jain VK, Vaish A. Demystifying the Risk Factors and Preventive Measures for Osteoporosis. *Indian Journal of Orthopaedics* 2023;57:94–104. <https://doi.org/10.1007/s43465-023-00998-0>
54. Camacho PM, Petak SM, Binkley N, Clarke BL, Harris ST, Hurley DL, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis —2016. *Endocrine Practice* 2016;22 (Suppl 4):1–42. <https://doi.org/10.4158/ep161435.gl>
55. Compston JE, McClung MR, Leslie WD. Osteoporosis. *The Lancet* 2019;393:364–76. [https://doi.org/10.1016/s0140-6736\(18\)32112-3](https://doi.org/10.1016/s0140-6736(18)32112-3)
56. Barker DJ. The fetal and infant origins of adult disease. *BMJ* 1990;301:1111–1111. <https://doi.org/10.1136/bmj.301.6761.1111>
57. Baird J, Kurshid MA, Kim M, Harvey N, Dennison E, Cooper C. Does birthweight predict bone mass in adulthood? A systematic review and meta-analysis. *Osteoporosis International* 2011;22:1323–34. <https://doi.org/10.1007/s00198-010-1344-9>
58. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporosis International* 2006;17:1726–33. <https://doi.org/10.1007/s00198-006-0172-4>
59. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX™ and the assessment of fracture probability in men and women from the UK. *Osteoporosis International* 2008;19:385–97. <https://doi.org/10.1007/s00198-007-0543-5>
60. Vandenput L, Johansson H, McCloskey EV, Liu E, Åkesson KE, Anderson FA, et al. Update of the fracture risk prediction tool FRAX: a systematic review of potential cohorts and analysis plan. *Osteoporosis International* 2022;33:2103–36. <https://doi.org/10.1007/s00198-022-06435-6>
61. Rajan R, Paul J, Cherian KE, Asha HS, Kapoor N, Paul TV. FRAX® with or without BMD and TBS predicts fragility fractures in community-dwelling rural southern Indian postmenopausal women. *Archives of Osteoporosis* 2020;15:82. <https://doi.org/10.1007/s11657-020-00756-x>
62. Dhanwal DK, Siwach R, Dixit V, Mithal A, Jameson K, Cooper C. Incidence of hip fracture in Rohtak district, North India. *Archives of Osteoporosis* 2013;8:135. <https://doi.org/10.1007/s11657-013-0135-2>
63. Jha D, Chandran M, Hong N, Rhee Y, Baek S, Ferguson SJ, et al. Discriminatory Accuracy of Fracture Risk Assessment Tool in Asian Populations: A Systematic Review and Meta-Analysis. *Journal of Bone Metabolism* 2024;31:296–315. <https://doi.org/10.11005/jbm.24.781>
64. Koh LKH, Ben Sedrine W, Torralba TP, Kung A, Fujiwara S, Chan SP, et al. A Simple Tool to Identify Asian Women at Increased Risk of Osteoporosis. *Osteoporosis International* 2001;12:699–705. <https://doi.org/10.1007/s001980170070>
65. Cherian KE, Kapoor N, Shetty S, Naik D, Thomas N, Paul TV. Evaluation of Different Screening Tools for Predicting Femoral Neck Osteoporosis in Rural South Indian Postmenopausal Women. *Journal of Clinical Densitometry* 2018;21:119–24. <https://doi.org/10.1016/j.jocd.2017.08.002>
66. Nayak S, Edwards DL, Saleh AA, Greenspan SL. Systematic review and meta-analysis of the performance of clinical risk assessment instruments for screening for osteoporosis or low bone density. *Osteoporosis International* 2015;26:1543–54. <https://doi.org/10.1007/s00198-015-3025-1>
67. Chin K-Y. A review on the performance of osteoporosis self-assessment tool for Asians in determining osteoporosis and fracture risk. *Postgraduate Medicine* 2017;129:734–46. <https://doi.org/10.1080/00325481.2017.1353394>
68. Lydick E, Cook K, Turpin J, Melton M, Stine R, Byrnes C. Development and validation of a simple questionnaire to facilitate identification of women likely to have low bone density. *American Journal of Managed Care* 1998;4:37–48. PMID: 10179905
69. Shuhart C, Cheung A, Gill R, Gani L, Goel H, Szalat A. Executive Summary of the 2023 Adult Position Development Conference of the International Society for Clinical Densitometry: DXA Reporting, Follow-up BMD Testing and Trabecular Bone Score Application and Reporting. *Journal of Clinical Densitometry* 2024;27:101435. <https://doi.org/10.1016/j.jocd.2023.101435>
70. Mishra V. India's Projected Aged Population (65+), Projected Life Expectancy at Birth and Insecurities Faced by Aged Population. *Ageing International* 2019;45:72–84. <https://doi.org/10.1007/s12126-019-09350-0>
71. Shepherd JA. Positions of The International Society for Clinical Densitometry and Their Etiology: A Scoping Review. *Journal of Clinical Densitometry* 2023;26:101369. <https://doi.org/10.1016/j.jocd.2023.101369>
72. Gregson CL, Armstrong DJ, Avgerinou C, Bowden J, Cooper C, Douglas L, et al. The 2024 UK clinical guideline for the prevention and treatment of osteoporosis. *Archives of Osteoporosis* 2025;20:119. <https://doi.org/10.1007/s11657-025-01588-3>
73. World Health Organization. Guidelines for preclinical evaluation and clinical trials in osteoporosis. [Internet]. Geneva: World Health Organization; 1998. Available from: <https://iris.who.int/handle/10665/42088> [Accessed 6 Feb 2026]
74. International Society for Clinical Densitometry. 2019 ISCD Official Positions – Adult. [Internet]. 2019. Available from: <https://iscd.org/wp-content/uploads/2021/09/2019-Official-Positions-Adult-1.pdf> [Accessed 6 Feb 2026]
75. Cosman F, de Beur SJ, LeBoff MS, Lewiecki EM, Tanner B, Randall S, et al. Clinician's Guide to Prevention and Treatment of Osteoporosis. *Osteoporosis International* 2014;25:2359–81. <https://doi.org/10.1007/s00198-014-2794-2>
76. Kandasamy N, Karjala SL, Jayakumar D, Machiraju PK, Kalathur HK, Balakrishnan L. Estimation of T scores with Hologic using NatIve vs. Caucasian data in IndiAns (ETHNICA): a single centre retrospective study. *BMC Musculoskeletal Disorders* 2025;26:448. <https://doi.org/10.1186/s12891-025-08599-8>
77. International Society for Clinical Densitometry. 2023 ISCD Official Positions – Adult. [Internet]. 2023. Available from: <https://iscd.org/official-positions-2023/> [Accessed 6 Feb 2026]
78. Bhan A, Rao AD, Rao DS. Osteomalacia as a Result of Vitamin D Deficiency. *Endocrinology and Metabolism Clinics of North America* 2010;39:321–31. <https://doi.org/10.1016/j.ecl.2010.02.001>
79. Coleman RE. Metastatic bone disease: clinical features, pathophysiology and treatment strategies. *Cancer Treatment Reviews* 2001;27:165–76. <https://doi.org/10.1053/ctrv.2000.0210>
80. Beaudart C, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slomian J, et al. The Effects of Vitamin D on Skeletal Muscle Strength, Muscle Mass, and Muscle Power: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. *The Journal of Clinical Endocrinology & Metabolism* 2014;99:4336–45. <https://doi.org/10.1210/jc.2014-1742>

81. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age and Ageing* 2019;48:16–31. <https://doi.org/10.1093/ageing/afy169>
82. Nicholson WK, Silverstein M, Wong JB, Barry MJ, Chelmow D, et al. Interventions to Prevent Falls in Community-Dwelling Older Adults: US Preventive Services Task Force Recommendation Statement. *JAMA* 2024;332:51–7. <https://doi.org/10.1001/jama.2024.8481>
83. Gillespie LD, Robertson MC, Gillespie WJ, Sherrington C, Gates S, Clemson LM, et al. Interventions for preventing falls in older people living in the community. *Cochrane Database of Systematic Reviews* 2012;2012:CD007146. <https://doi.org/10.1002/14651858.cd007146.pub3>
84. Campbell AJ, Robertson MC. Rethinking individual and community fall prevention strategies: a meta-regression comparing single and multifactorial interventions. *Age and Ageing* 2007;36:656–62. <https://doi.org/10.1093/ageing/afm122>
85. Siminoski K, Jiang G, Adachi JD, Hanley DA, Cline G, Ioannidis G, et al. Accuracy of height loss during prospective monitoring for detection of incident vertebral fractures. *Osteoporosis International* 2005;16:403–10. <https://doi.org/10.1007/s00198-004-1709-z>
86. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Guideline Update. *The Journal of Clinical Endocrinology & Metabolism* 2020;105:587–94. <https://doi.org/10.1210/clinem/dgaa048>
87. Schousboe JT, Vokes T, Broy SB, Ferrar L, McKiernan F, Roux C, et al. Vertebral Fracture Assessment: The 2007 ISCD Official Positions. *Journal of Clinical Densitometry* 2008;11:92–108. <https://doi.org/10.1016/j.jocd.2007.12.008>
88. Lewiecki EM, Laster AJ. Clinical Applications of Vertebral Fracture Assessment by Dual-Energy X-Ray Absorptiometry. *The Journal of Clinical Endocrinology & Metabolism* 2006;91:4215–22. <https://doi.org/10.1210/jc.2006-1178>
89. Aggarwal T, Shah R, Pal R, Rastogi A, Singla V, Bhadda SK. Trabecular Bone Score in Asian-Indian Post-menopausal Women Across the Spectrum of Hyperglycaemia: Insights from a Cross-Sectional Study. *Indian Journal of Endocrinology and Metabolism* 2025;29:43–8. https://doi.org/10.4103/ijem.ijem_310_24
90. Hans D, Downs RW, Duboeuf F, Greenspan S, Jankowski LG, Kiebzak GM, et al. Skeletal Sites for Osteoporosis Diagnosis: The 2005 ISCD Official Positions. *Journal of Clinical Densitometry* 2006;9:15–21. <https://doi.org/10.1016/j.jocd.2006.05.003>
91. Hans D, Métrailler A, Gonzalez Rodriguez E, Lamy O, Shevroja E. Quantitative Ultrasound (QUS) in the Management of Osteoporosis and Assessment of Fracture Risk: An Update. *Bone Quantitative Ultrasound*. 2022;7–34. https://doi.org/10.1007/978-3-030-91979-5_2
92. Bala S, Prabha M, Krishna T. Prevalence and risk factors of low bone mineral density with quantitative ultrasonography among south Indian postmenopausal women. *International Journal of Community Medicine and Public Health*. 2016;3(7):1735–40. <https://doi.org/10.18203/2394-6040.ijcmph20162034>
93. Liu D-H, Lin C-S, Wu P-C. Osteoporosis self-assessment tool for Asians and calcaneal quantitative ultrasound for identifying primary osteoporosis in Taiwanese postmenopausal women. *Frontiers in Endocrinology*. 2025;16:1639176. <https://doi.org/10.3389/fendo.2025.1639176>
94. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2019;104(5):1595–622. <https://doi.org/10.1210/jc.2019-00221>
95. Eastell R, Pigott T, Gossiel F, Naylor KE, Walsh JS, Peel NFA. DIAGNOSIS OF ENDOCRINE DISEASE: Bone turnover markers: are they clinically useful? *European Journal of Endocrinology*. 2018;178(1):R19–31. <https://doi.org/10.1530/eje-17-0585>
96. Arlot M, Meunier PJ, Boivin G, Haddock L, Tamayo J, Correa-Rotter R, et al. Differential Effects of Teriparatide and Alendronate on Bone Remodelling in Postmenopausal Women Assessed by Histomorphometric Parameters. *Journal of Bone and Mineral Research*. 2005;20(7):1244–53. <https://doi.org/10.1359/jbmr.050309>
97. Bhattoa HP, Vasikaran S, Trifonidi I, Kapoula G, Lombardi G, Jorgensen NR, et al. Update on the role of bone turnover markers in the diagnosis and management of osteoporosis: a consensus paper from The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), International Osteoporosis Foundation (IOF), and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC). *Osteoporosis International*. 2025;36(4):579–608. <https://doi.org/10.1007/s00198-025-07422-3>
98. Diez-Perez A, Adachi JD, Agnusdei D, Bilezikian JP, Compston JE, et al. Treatment failure in osteoporosis. *Osteoporosis International*. 2012;23(12):2769–74. <https://doi.org/10.1007/s00198-012-2093-8>
99. Bonnick SL, Shulman L. Monitoring Osteoporosis Therapy: Bone Mineral Density, Bone Turnover Markers, or Both? *The American Journal of Medicine*. 2006;119(4 Suppl 1):S25–31. <https://doi.org/10.1016/j.amjmed.2005.12.020>
100. Meeta M. How Much Calcium Does an Indian Postmenopausal Woman Need? *Journal of Mid-Life Health*. 2022;13(1):9–14. https://doi.org/10.4103/jmh.jmh_70_22
101. Gopalan C, Rao BSN, Deosthale YG, Pant KC. Nutritive Value of Indian Foods. Rev. ed. Hyderabad: National Institute of Nutrition, Indian Council of Medical Research; 1989.
102. Longvah T, Ananthan R, Bhaskarachary K, Venkaiah K. Indian Food Composition Tables. Hyderabad: National Institute of Nutrition, Indian Council of Medical Research; 2017.
103. Friedman PA. Codependence of renal calcium and sodium transport. *Annual Review of Physiology*. 1998;60:179–97. <https://doi.org/10.1146/annurev.physiol.60.1.179>
104. Kerstetter JE, O'Brien KO, Insogna KL. Dietary protein, calcium metabolism, and skeletal homeostasis revisited. *The American Journal of Clinical Nutrition*. 2003;78(3):584S–592S. <https://doi.org/10.1093/ajcn/78.3.584S>
105. Hidayat K, Chen J-S, Wang T-C, Liu Y-J, Shi Y-J, Su H-W, et al. The Effects of Milk Supplementation on Bone Health Indices in Adults: A Meta-Analysis of Randomized Controlled Trials. *Advances in Nutrition*. 2022;13(4):1186–99. <https://doi.org/10.1093/advances/nmab136>
106. Weaver CM, Gordon CM, Janz KF, Kalkwarf HJ, Lappe JM, Lewis R, et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporosis International*. 2016;27(4):1281–386. <https://doi.org/10.1007/s00198-015-3440-3>
107. Indian Council of Medical Research. Nutrient requirements and recommended dietary allowances for Indians: a report of the Expert Group of the Indian Council of Medical Research. New Delhi: Indian Council of Medical Research; 2010.
108. Joint FAO/WHO Expert Consultation. Carbohydrates in human nutrition: report of a joint FAO/WHO expert consultation, Rome, 14-18 April 1997. Geneva: World Health Organization; 1998.

109. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary Reference Intakes for Calcium and Vitamin D. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Washington (DC): National Academies Press (US); 2011. <https://doi.org/10.17226/13050>
110. National Nutrition Monitoring Bureau (NNMB). Diet and Nutritional Status of Population and Prevalence of Hypertension among Adults in Rural Areas. NNMB Technical Report No. 24. Hyderabad: National Institute of Nutrition, Indian Council of Medical Research; 2006. [cited 6 Feb 2026]. Available from: <https://www.nin.res.in/downloads/NNMBReport06Nov20.pdf>
111. Indian Council of Medical Research. Nutrient Requirements for Indians: Recommended Dietary Allowances and Estimated Average Requirements. A Report of the Expert Group. Hyderabad: ICMR-National Institute of Nutrition; 2020. Available from: <https://www.nin.res.in>
112. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. The American Journal of Clinical Nutrition. 1995;61(3 Suppl):638S–645S. <https://doi.org/10.1093/ajcn/61.3.638S>
113. Kalra S, Zargar AH, Das AK, Baidya A, Dasgupta A, Selvan C, et al. Prevention and Treatment of Vitamin D Deficiency in India: An Expert Group Consensus. Indian Journal of Endocrinology and Metabolism. 2025;29(1):13–26. https://doi.org/10.4103/ijem.ijem_264_24
114. Demay MB, Pittas AG, Bikle DD, Diab DL, Kiely ME, Lazaretti-Castro M, et al. Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline. The Journal of Clinical Endocrinology & Metabolism. 2024;109(8):1907–47. <https://doi.org/10.1210/clinem/dgae290>
115. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, et al. The 2011 report on Dietary Reference Intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. The Journal of Clinical Endocrinology & Metabolism. 2011;96(1):53–8. <https://doi.org/10.1210/jc.2010-2704>
116. Babu US, Calvo MS. Modern India and the vitamin D dilemma: evidence for the need of a national food fortification program. Molecular Nutrition & Food Research. 2010;54(8):1134–47. <https://doi.org/10.1002/mnfr.200900480>
117. Cheng L, Chang S, He B, Yan Y. Effects of Tai Chi and brisk walking on the bone mineral density of perimenopausal women: A randomised controlled trial. Frontiers in Public Health. 2022;10:948890. <https://doi.org/10.3389/fpubh.2022.948890>
118. Martyn-St James M, Carroll S. Meta-analysis of walking for preservation of bone mineral density in postmenopausal women. Bone. 2008;43(3):521–31. <https://doi.org/10.1016/j.bone.2008.05.012>
119. Giangregorio LM, Papaioannou A, MacIntyre NJ, Ashe MC, Heinonen A, Shipp K, et al. Too Fit To Fracture: exercise recommendations for individuals with osteoporosis or osteoporotic vertebral fracture. Osteoporosis International. 2014;25(3):821–35. <https://doi.org/10.1007/s00198-013-2523-2>
120. Sinaki M. Exercise for patients with osteoporosis: management of vertebral compression fractures and trunk strengthening for fall prevention. PM & R. 2012;4(11):882–8. <https://doi.org/10.1016/j.pmrj.2012.10.008>
121. Sinaki M, Itoi E, Wahner HW, Wollan P, Gelzcer R, Mullan BP, et al. Stronger back muscles reduce the incidence of vertebral fractures: a prospective 10 year follow-up of postmenopausal women. Bone. 2002;30(6):836–41. [https://doi.org/10.1016/s8756-3282\(02\)00739-1](https://doi.org/10.1016/s8756-3282(02)00739-1)
122. Sherrington C, Fairhall NJ, Wallbank GK, Tiedemann A, Michaleff ZA, Howard K, et al. Exercise for preventing falls in older people living in the community. Cochrane Database of Systematic Reviews. 2019;1(1):CD012424. <https://doi.org/10.1002/14651858.CD012424.pub2>
123. Zhang W, Li X, He Q, Wang X. Effects of exercise on bone metabolism in postmenopausal women: a systematic review and meta-analysis of randomised controlled trials. Frontiers in Endocrinology. 2025;16:1597046. <https://doi.org/10.3389/fendo.2025.1597046>
124. Granacher U, Gollhofer A, Hortobagyi T, Kressig RW, Muehlbauer T. The importance of trunk muscle strength for balance, functional performance, and fall prevention in seniors: a systematic review. Sports Medicine. 2013;43(7):627–41. <https://doi.org/10.1007/s40279-013-0041-1>
125. Wei S, He Y, Liu K, Wang R, Wang Y. Priority interventions for the prevention of falls or fractures in patients with osteoporosis: A network meta-analysis. Archives of Gerontology and Geriatrics. 2024;127:105558. <https://doi.org/10.1016/j.archger.2024.105558>
126. Dautzenberg L, Beglinger S, Tsokani S, Zevgiti S, Rajmanna RCMA, Rodondi N, et al. Interventions for preventing falls and fall-related fractures in community-dwelling older adults: A systematic review and network meta-analysis. Journal of the American Geriatrics Society. 2021;69(10):2973–84. <https://doi.org/10.1111/jgs.17375>
127. Pillay J, Gaudet LA, Saba S, Vandermeer B, Ashiq AR, Wingert A, et al. Falls prevention interventions for community-dwelling older adults: systematic review and meta-analysis of benefits, harms, and patient values and preferences. Systematic Reviews. 2024;13(1):289. <https://doi.org/10.1186/s13643-024-02681-3>
128. Lee D-Y, Chung Y-S. Quality of life and patient satisfaction with raloxifene/cholecalciferol combination therapy in postmenopausal women. Scientific Reports. 2022;12(1):7142. <https://doi.org/10.1038/s41598-022-11298-2>
129. Hayashi S, Fukuda K, Maeda T, Chinzei N, Kihara S, Miura Y, et al. Denosumab Treatment Improved Health-Related Quality of Life in Osteoporosis: A Prospective Cohort Study. JBMR Plus. 2019;3(7):e10191. <https://doi.org/10.1002/jbm4.10191>
130. Jonville-Bera AP, Autret-Leca E. [Adverse drug reactions of strontium ranelate(Protelos®) in France]. La Presse Médicale. 2011;40(10):e453–62. <https://doi.org/10.1016/j.lpm.2011.07.010>
131. Yao P, Bennett D, Mafham M, Lin X, Chen Z, Armitage J, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. JAMA Network Open. 2019;2(12):e1917789. <https://doi.org/10.1001/jamanetworkopen.2019.17789>
132. Yakabe M, Hosoi T, Matsumoto S, Fujimori K, Tamaki J, Nakatoh S, et al. Prescription of vitamin D was associated with a lower incidence of hip fractures. Scientific Reports. 2023;13(1):12889. <https://doi.org/10.1038/s41598-023-40259-6>
133. Dawson-Hughes B. Effect of vitamin D on risk of falls and fractures - The contribution of recent mega-trials. Metabolism Open. 2024;23:100300. <https://doi.org/10.1016/j.metop.2024.100300>
134. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and Calcium to Prevent Hip Fractures in Elderly Women. New England Journal of Medicine. 1992;327(23):1637–42. <https://doi.org/10.1056/NEJM199212033272305>
135. Weaver CM, Alexander DD, Boushey CJ, Dawson-Hughes B, Lappe JM, LeBoff MS, et al. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. Osteoporosis International. 2016;27(1):367–76. <https://doi.org/10.1007/s00198-015-3386-5>
136. Chung M, Tang AM, Fu Z, Wang DD, Newberry SJ. Calcium Intake and Cardiovascular Disease Risk: An Updated Systematic Review and Meta-analysis. Annals of Internal Medicine. 2016;165(12):856–66. <https://doi.org/10.7326/M16-1165>

137. Heaney RP. Effects of caffeine on bone and the calcium economy. *Food and Chemical Toxicology*. 2002;40(9):1263–70. [https://doi.org/10.1016/s0278-6915\(02\)00094-7](https://doi.org/10.1016/s0278-6915(02)00094-7)
138. Hallstrom H, Byberg L, Glynn A, Lemming EW, Wolk A, Michaelsson K. Long-term coffee consumption in relation to fracture risk and bone mineral density in women. *American Journal of Epidemiology*. 2013;178(6):898–909. <https://doi.org/10.1093/aje/kwt062>
139. Ritu G, Gupta A. Vitamin D deficiency in India: Prevalence, causalities and interventions. *Nutrients*. 2014;6(2):729–75. <https://doi.org/10.3390/nu6020729>
140. Harinarayan CV. Prevalence of vitamin D insufficiency in postmenopausal south Indian women. *Osteoporosis International*. 2005;16(4):397–402. <https://doi.org/10.1007/s00198-004-1703-5>
141. Food Safety and Standards Authority of India. Food Safety and Standards (Fortification of Foods) Regulations, 2018. New Delhi: FSSAI; 2018. [cited 6 Feb 2026]. Available from: https://www.fssai.gov.in/upload/uploadfiles/files/Compendium_Food_Fortification_Regulations_30_09_2021.pdf
142. Marwaha RK, Dabas A, Puri S, Kalaivani M, Dabas V, Yadav S, et al. Efficacy of Daily Supplementation of Milk Fortified With Vitamin D2 for Three Months in Healthy School Children: A Randomized Placebo Controlled Trial. *Indian Pediatrics*. 2021;58(9):820–5. <https://doi.org/10.1007/s13312-021-2300-9>
143. Goswami R, Gupta N, Ray D, Singh N, Tomar N. Pattern of 25-hydroxy vitamin D response at short (2 month) and long (1 year) interval after 8 weeks of oral supplementation with cholecalciferol in Asian Indians with chronic hypovitaminosis D. *British Journal of Nutrition*. 2008;100(3):526–9. <https://doi.org/10.1017/s0007114508921711>
144. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Evaluation, Treatment, and Prevention of Vitamin D Deficiency: an Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2011;96(7):1911–30. <https://doi.org/10.1210/jc.2011-0385>
145. Ortiz-Prado E, Vasconez-Gonzalez J, Izquiero-Condoy JS, Suarez-Sangucho IA, Prieto-Marin JG, Villarreal-Burbano KB, et al. Cholecalciferol (vitamin D3): efficacy, safety, and implications in public health. *Frontiers in Nutrition*. 2025;12:1579957. <https://doi.org/10.3389/fnut.2025.1579957>
146. Marwaha RK, Dabas A. Interventions for Prevention and Control of Epidemic of Vitamin D Deficiency. *The Indian Journal of Pediatrics*. 2019;86(6):532–7. <https://doi.org/10.1007/s12098-019-02857-z>
147. Zhuang Y, Zhu Z, Chi P, Zhou H, Peng Z, Cheng H, et al. Efficacy of intermittent versus daily vitamin D supplementation on improving circulating 25(OH)D concentration: a Bayesian network meta-analysis of randomised controlled trials. *Frontiers in Nutrition*. 2023;10:1168115. <https://doi.org/10.3389/fnut.2023.1168115>
148. Meeta M, Digumarti L, Agarwal N, Vaze N, Shah R, Malik S. Clinical Practice Guidelines on Menopause: *An Executive Summary and Recommendations: Indian Menopause Society 2019–2020. *Journal of Mid-Life Health*. 2020;11(2):55–95. https://doi.org/10.4103/jmh.JMH_137_20
149. Giustina A, Bilezikian JP, Adler RA, Banfi G, Bikle DD, Binkley NC, et al. Consensus Statement on Vitamin D Status Assessment and Supplementation: Whys, Whens, and Hows. *Endocrine Reviews*. 2024;45(5):625–54. <https://doi.org/10.1210/endrev/bnae009>
150. Vieth R. Vitamin D Toxicity, Policy, and Science. *Journal of Bone and Mineral Research*. 2007;22(Suppl 2):V64–8. <https://doi.org/10.1359/jbmr.07s221>
151. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. *The American Journal of Clinical Nutrition*. 2008;88(2):491S–499S. <https://doi.org/10.1093/ajcn/88.2.491S>
152. Emaus N, Gjesdal CG, Almas B, Christensen M, Grimsgaard AS, Berntsen GKR, et al. Vitamin K2 supplementation does not influence bone loss in early menopausal women: a randomised double-blind placebo-controlled trial. *Osteoporosis International*. 2010;21(10):1731–40. <https://doi.org/10.1007/s00198-009-1126-4>
153. Kanis JA, Harvey NC, McCloskey EV, Bruyere O, Veronese N, Lorentzon M, et al. Algorithm for the management of patients at low, high and very high risk of osteoporotic fractures. *Osteoporosis International*. 2020;31(1):1–12. <https://doi.org/10.1007/s00198-019-01263-x>
154. Lyles KW, Col -Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C, et al. Zoledronic Acid and Clinical Fractures and Mortality after Hip Fracture. *New England Journal of Medicine*. 2007;357(18):1799–809. <https://doi.org/10.1056/NEJMoa074941>
155. Cosman F, Lewiecki EM, Eastell R, Ebeling PR, Jan De Beur S, Langdahl B, et al. Goal-directed osteoporosis treatment: ASBMR/BHOF task force position statement 2024. *Journal of Bone and Mineral Research*. 2024;39(10):1393–405. <https://doi.org/10.1093/jbmr/zjae119>
156. Saag KG, Petersen J, Brandi ML, Karaplis AC, Lorentzon M, Thomas T, et al. Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis. *New England Journal of Medicine*. 2017;377(15):1417–27. <https://doi.org/10.1056/NEJMoa1708322>
157. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *New England Journal of Medicine*. 2009;361(8):756–65. <https://doi.org/10.1056/NEJMoa0809493>
158. Tsourdi E, Langdahl B, Cohen-Solal M, Aubry-Rozier B, Eriksen EF, Guanabens N, et al. Discontinuation of Denosumab therapy for osteoporosis: A systematic review and position statement by ECTS. *Bone*. 2017;105:11–17. <https://doi.org/10.1016/j.bone.2017.08.003>
159. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA, et al. Once-Yearly Zoledronic Acid for Treatment of Postmenopausal Osteoporosis. *New England Journal of Medicine*. 2007;356(18):1809–22. <https://doi.org/10.1056/NEJMoa067312>
160. Lewiecki EM. Nonresponders to osteoporosis therapy. *Journal of Clinical Densitometry*. 2003;6(4):307–14. <https://doi.org/10.1385/jcd.6.4.307>
161. Adler RA, El-Hajj Fuleihan G, Bauer DC, Camacho PM, Clarke BL, Clines GA, et al. Managing Osteoporosis in Patients on Long-Term Bisphosphonate Treatment: Report of a Task Force of the American Society for Bone and Mineral Research. *Journal of Bone and Mineral Research*. 2016;31(1):16–35. <https://doi.org/10.1002/jbmr.2708>
162. Schilcher J, Koeppen V, Aspenberg P, Michaelsson K. Risk of atypical femoral fracture during and after bisphosphonate use. *Acta Orthopaedica*. 2015;86(1):100–7. <https://doi.org/10.3109/17453674.2015.1004149>
163. Fassio A, Gatti D, Biffi A, Ronco R, Porcu G, Adami G, et al. The sequential antifracture treatment: a meta-analysis of randomised clinical trials. *Therapeutic Advances in Musculoskeletal Disease*. 2024;16:1759720X241234584. <https://doi.org/10.1177/1759720X241234584>
164. Cosman F, Oates M, Betah D, Timoshanko J, Wang Z, Ferrari S, et al. Romosozumab followed by denosumab versus denosumab only: a post hoc analysis of FRAME and FRAME extension. *Journal of Bone and Mineral Research*. 2024;39(9):1268–77. <https://doi.org/10.1093/jbmr/zjae116>
165. Cruchelow KR, Peter ME, Chakrabarti A, Gipson HM, Gregory WT, DeClercq J, et al. Denosumab treatment lapses, discontinuation, and off-treatment fracture risk: A retrospective study of patients with osteoporosis in a real-world clinical setting. *Bone*. 2023;177:116925. <https://doi.org/10.1016/j.bone.2023.116925>

166. Burckhardt P, Faouzi M, Buclin T, Lamy O. Fractures After Denosumab Discontinuation: A Retrospective Study of 797 Cases. *Journal of Bone and Mineral Research*. 2021;36(9):1717–28. <https://doi.org/10.1002/jbmr.4335>
167. Solling AS, Harslof T, Langdahl B. Treatment With Zoledronate Subsequent to Denosumab in Osteoporosis: A 2-Year Randomized Study. *Journal of Bone and Mineral Research*. 2021;36(7):1245–54. <https://doi.org/10.1002/jbmr.4305>
168. Zhang C, Song C. Combination Therapy of PTH and Antiresorptive Drugs on Osteoporosis: A Review of Treatment Alternatives. *Frontiers in Pharmacology*. 2020;11:607017. <https://doi.org/10.3389/fphar.2020.607017>
169. Sun Y, Li Y, Li J, Xie X, Gu F, Sui Z, et al. Efficacy of the Combination of Teriparatide and Denosumab in the Treatment of Postmenopausal Osteoporosis: A Meta-Analysis. *Frontiers in Pharmacology*. 2022;13:888208. <https://doi.org/10.3389/fphar.2022.888208>
170. Harris ST, Eriksen EF, Davidson M, Ettinger MP, Moffett Jr AH, Baylink DJ, et al. Effect of Combined Risedronate and Hormone Replacement Therapies on Bone Mineral Density in Postmenopausal Women. *The Journal of Clinical Endocrinology & Metabolism*. 2001;86(5):1890–7. <https://doi.org/10.1210/jcem.86.5.7505>
171. Leder BZ, Tsai JN, Uihlein AV, Burnett-Bowie SA, Zhu Y, Foley K, et al. Two years of Denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomised controlled trial. *The Journal of Clinical Endocrinology & Metabolism*. 2014;99(5):1694–700. <https://doi.org/10.1210/jc.2013-4440>
172. Tsai JN, Uihlein AV, Burnett-Bowie SM, Neer RM, Derrico NP, Lee H, et al. Effects of Two Years of Teriparatide, Denosumab, or Both on Bone Microarchitecture and Strength (DATA-HRQCT study). *The Journal of Clinical Endocrinology & Metabolism*. 2016;101(5):2023–30. <https://doi.org/10.1210/jc.2016-1160>
173. Greenspan SL, Resnick NM, Parker RA. Combination Therapy With Hormone Replacement and Alendronate for Prevention of Bone Loss in Elderly Women: A Randomized Controlled Trial. *JAMA*. 2003;289(19):2525–33. <https://doi.org/10.1001/jama.289.19.2525>
174. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ, et al. Effects of Estrogen Plus Progestin on Risk of Fracture and Bone Mineral Density: The Women's Health Initiative Randomized Trial. *JAMA*. 2003;290(13):1729–38. <https://doi.org/10.1001/jama.290.13.1729>
175. Lindsay R, Hart DM, Aitken JM, Macdonald EB, Anderson JB, Clarke AC. Long-term prevention of postmenopausal osteoporosis by estrogen. Evidence for an increased bone mass after delayed onset of estrogen treatment. *The Lancet*. 1976;1(7968):1038–41. [https://doi.org/10.1016/S0140-6736\(76\)92217-0](https://doi.org/10.1016/S0140-6736(76)92217-0)
176. Writing Group for the PEPI Trial. Effects of Hormone Therapy on Bone Mineral Density: Results From the Postmenopausal Estrogen/Progestin Interventions (PEPI) Trial. *JAMA*. 1996;276(17):1389–96. <https://doi.org/10.1001/jama.1996.03540170033029>
177. Wells G, Tugwell P, Shea B, Guyatt G, Peterson J, Zytaruk N, et al. V. Meta-analysis of the efficacy of hormone replacement therapy in treating and preventing osteoporosis in postmenopausal women. *Endocrine Reviews*. 2002;23(4):529–39. <https://doi.org/10.1210/er.2001-5002>
178. Torgerson DJ, Bell-Syer SE. Hormone replacement therapy and prevention of vertebral fractures: a meta-analysis of randomised trials. *BMC Musculoskeletal Disorders*. 2001;2:7. <https://doi.org/10.1186/1471-2474-2-7>
179. Robbins JA, Aragaki A, Crandall CJ, Manson JE, Carbone L, Jackson R, et al. Women's Health Initiative clinical trials: interaction of calcium and vitamin D with hormone therapy. *Menopause*. 2014;21(2):116–23. <https://doi.org/10.1097/GME.0b013e3182963901>
180. Jackson RD, Wactawski-Wende J, LaCroix AZ, Pettinger M, Yood RA, Watts NB, et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomised trial. *Journal of Bone and Mineral Research*. 2006;21(6):817–28. <https://doi.org/10.1359/jbmr.060312>
181. Zhu L, Jiang X, Sun Y, Shu W. Effect of hormone therapy on the risk of bone fractures: a systematic review and meta-analysis of randomised controlled trials. *Menopause*. 2016;23(4):461–70. <https://doi.org/10.1097/GME.0000000000000519>
182. Ettinger B, Ensrud KE, Wallace R, Johnson KC, Cummings SR, Yankov V, et al. Effects of Ultralow-Dose Transdermal Estradiol on Bone Mineral Density: A Randomized Clinical Trial. *Obstetrics & Gynecology*. 2004;104(3):443–51. <https://doi.org/10.1097/01.AOG.0000137833.43248.79>
183. Kiel DP, Felson DT, Anderson JJ, Wilson PWF, Moskowitz MA. Hip Fracture and the Use of Estrogens in Postmenopausal Women. *New England Journal of Medicine*. 1987;317(19):1169–74. <https://doi.org/10.1056/NEJM198711053171901>
184. Levin VA, Jiang X, Kagan R. Estrogen therapy for osteoporosis in the modern era. *Osteoporosis International*. 2018;29(5):1049–55. <https://doi.org/10.1007/s00198-018-4414-z>
185. Rozenberg S, Al-Daghri N, Aubertin-Leheudre M, Brandi ML, Cano A, Collins P, et al. Is there a role for menopausal hormone therapy in the management of postmenopausal osteoporosis? *Osteoporosis International*. 2020;31(12):2271–86. <https://doi.org/10.1007/s00198-020-05497-8>
186. Lorentzon M, Johansson H, Harvey NC, Liu E, Vandenput L, Crandall CJ, et al. Menopausal hormone therapy reduces the risk of fracture regardless of falls risk or baseline FRAX probability—results from the Women's Health Initiative hormone therapy trials. *Osteoporosis International*. 2022;33(11):2297–305. <https://doi.org/10.1007/s00198-022-06483-y>
187. Women's Health Initiative Steering Committee. Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy: The Women's Health Initiative Randomized Controlled Trial. *JAMA*. 2004;291(14):1701–12. <https://doi.org/10.1001/jama.291.14.1701>
188. Torgerson DJ, Bell-Syer SEM. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomised trials. *JAMA*. 2001;285(22):2891–7. <https://doi.org/10.1001/jama.285.22.2891>
189. Tremollieres FA, Chabbert-Buffet N, Plu-Bureau G, Rousset-Jablonski C, Lecerf JM, Duclos M, et al. Management of postmenopausal women: College National des Gynecologues et Obsteticiens Francais (CNGOF) and Groupe d'Etude sur la Menopause et le Vieillissement (GEMVi) Clinical Practice Guidelines. *Maturitas*. 2022;163:62–81. <https://doi.org/10.1016/j.maturitas.2022.05.008>
190. Goncalves CR, Vasconcellos AS, Rodrigues TR, Comin FV, Reis FM. Hormone therapy in women with premature ovarian insufficiency: a systematic review and meta-analysis. *Reproductive BioMedicine Online*. 2022;44(6):1143–57. <https://doi.org/10.1016/j.rbmo.2022.02.006>
191. Sullivan SD, Sarrel PM, Nelson LM. Hormone replacement therapy in young women with primary ovarian insufficiency and early menopause. *Fertility and Sterility*. 2016;106(7):1588–99. <https://doi.org/10.1016/j.fertnstert.2016.09.046>
192. Ishizuka B. Current Understanding of the Etiology, Symptomatology, and Treatment Options in Premature Ovarian Insufficiency (POI). *Frontiers in Endocrinology*. 2021;12:626924. <https://doi.org/10.3389/fendo.2021.626924>
193. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *The Lancet*. 1996;348(9041):1535–41. [https://doi.org/10.1016/s0140-6736\(96\)07088-2](https://doi.org/10.1016/s0140-6736(96)07088-2)

194. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Adjuvant bisphosphonate treatment in early breast cancer: meta-analyses of individual patient data from randomised trials. *The Lancet*. 2015;386(10001):1353–61. [https://doi.org/10.1016/S0140-6736\(15\)60908-4](https://doi.org/10.1016/S0140-6736(15)60908-4)
195. Hewitt RE, Lissina A, Green AE, Slay ES, Price DA, Sewell AK. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral blood $\gamma\delta$ T cells in response to aminobisphosphonates is inhibited by statins. *Clinical and Experimental Immunology*. 2005;139(1):101–11. <https://doi.org/10.1111/j.1365-2249.2005.02665.x>
196. Kunzmann V, Bauer E, Feurle J, Weissinger F, Tony HP, Wilhelm M. Stimulation of $\gamma\delta$ T cells by aminobisphosphonates and induction of antiplasma cell activity in multiple myeloma. *Blood*. 2000;96(2):384–92. <https://doi.org/10.1182/blood.v96.2.384>
197. Peris P, Monegal A, Gunañabens N. Bisphosphonates in inflammatory rheumatic diseases. *Bone*. 2021;146:115887. <https://doi.org/10.1016/j.bone.2021.115887>
198. "The 2022 hormone therapy position statement of The North American Menopause Society" Advisory Panel. The 2022 hormone therapy position statement of The North American Menopause Society. *Menopause*. 2022;29(7):767–94. <https://doi.org/10.1097/GME.0000000000002028>
199. Stuenkel CA, Davis SR, Gompel A, Lumsden MA, Murad MH, Pinkerton JV, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2015;100(11):3975–4011. <https://doi.org/10.1210/jc.2015-2236>
200. Greendale GA, Espeland M, Slone S, Marcus R, Barrett-Connor E. Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study. *Archives of Internal Medicine*. 2002;162(6):665–72. <https://doi.org/10.1001/archinte.162.6.665>
201. Bagger YZ, Tank LB, Alexandersen P, Hansen HB, Mollgaard A, Ravn P, et al. Two to three years of hormone replacement treatment in healthy women have long-term preventive effects on bone mass and osteoporotic fractures: the PERF study. *Bone*. 2004;34(4):728–35. <https://doi.org/10.1016/j.bone.2003.12.021>
202. Papadakis G, Hans D, Gonzalez-Rodriguez E, Vollenweider P, Waeber G, Marques-Vidal PM, et al. The Benefit of Menopausal Hormone Therapy on Bone Density and Microarchitecture Persists After its Withdrawal. *The Journal of Clinical Endocrinology & Metabolism*. 2016;101(12):5004–11. <https://doi.org/10.1210/jc.2016-2695>
203. Watts NB, Cauley JA, Jackson RD, LaCroix AZ, Lewis CE, Manson JE, et al. No Increase in Fractures After Stopping Hormone Therapy: Results From the Women's Health Initiative. *The Journal of Clinical Endocrinology & Metabolism*. 2017;102(1):302–8. <https://doi.org/10.1210/jc.2016-3270>
204. Vinogradova Y, Iyen B, Masud T, Taylor L, Kai J. Discontinuation of menopausal hormone therapy and risk of fracture: nested case-control studies using routinely collected primary care data. *The Lancet Healthy Longevity*. 2025;6(7):100729. <https://doi.org/10.1016/j.lanhl.2025.100729>
205. Woods GN, Huang M-H, Cawthon PM, McDaniel-Davidson C, Fink HA, Kado DM. Patterns of menopausal hormone therapy use and hyperkyphosis in older women. *Menopause*. 2018;25(7):738–43. <https://doi.org/10.1097/GME.0000000000001070>
206. Oh YK, Moon NH, Shin WC. Management of Osteoporosis Medication after Osteoporotic Fracture. *Hip & Pelvis*. 2022;34(4):191–202. <https://doi.org/10.5371/hp.2022.34.4.191>
207. Tanaka Y, Soen S, Hirata S, Okada Y, Fujiwara S, Tanaka I, et al. The 2023 Guidelines for the management and treatment of glucocorticoid-induced osteoporosis. *Journal of Bone and Mineral Metabolism*. 2024;42(2):143–54. <https://doi.org/10.1007/s00774-024-01502-w>
208. Humphrey MB, Russell L, Danila MI, Fink HA, Guyatt G, Cannon M, et al. 2022 American College of Rheumatology Guideline for the Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Care & Research*. 2023;75(12):2405–19. <https://doi.org/10.1002/acr.25240>
209. Compston J. Glucocorticoid-induced osteoporosis: an update. *Endocrine*. 2018;61(1):7–16. <https://doi.org/10.1007/s12020-018-1588-2>
210. Saag KG, Shane E, Boonen S, Marin F, Donley DW, Taylor KA, et al. Teriparatide or alendronate in glucocorticoid-induced osteoporosis. *New England Journal of Medicine*. 2007;357(20):2028–39. <https://doi.org/10.1056/NEJMoa071408>