

CLINICAL PRACTICE GUIDELINES FOR MENOPAUSE

2026

PART - 2

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



Indian
Menopause Society

CLINICAL PRACTICE GUIDELINES FOR MENOPAUSE

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Section 9

MANAGEMENT OPTIONS

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ART OF COUNSELLING

Keywords: Counselling, strategies, explaining risk and benefits

33

INTRODUCTION

The menopausal transition (MT) is a unique opportunity for caregivers to promote preventive health care for women. At this stage, education, counselling, and the addressing of fears and concerns about menopause and ageing should be integral to menopause management.¹ Counselling is an important tool in both the prevention and management of menopausal issues, and menopause sensitisation should begin at age 35 and be reinforced at every opportunity for contact.

COUNSELLING

The objective is to empower women to make informed, shared decisions about their physical, mental, and emotional health.²⁻⁵

COUNSELLOR

A counsellor can be a clinician, advanced practice nurse, health educator, or other professional who provides comprehensive counselling to women about the ageing process and the management of menopausal problems. It would be appropriate to provide training courses for counsellors to enable them to conduct menopause counselling.⁶

The prerequisites of an efficient counsellor are:

- *Knowledge:* Needs updating on issues of women's health
- *Communication skills:* Translating and providing clinical information and numerical data in an easy-to-understand and simple language
- *Attitude:* Sincere, empathetic, honest and effective, with an opinion that takes into account the individual woman's medical, socioeconomic, family and emotional background.⁷

Methods

Face-to-face contact (one-to-one or group) between a patient and a counsellor. However, there are many ways to provide information to patients, such as classes or support groups, print materials, audio and video decision-making tools, telephone resource lines, and online tools.

Strategies to be a successful counsellor⁸

- *Avoid:* tapping fingers, pens, or pencils; clenching fists; yawning; tapping your feet; crossing your arms; writing or prescribing while the woman has not yet finished speaking.
- *Do:* Put women at ease by adopting a concerned, friendly demeanour; maintain eye contact; take no phone calls during the interview; avoid judgmental statements and questions.
- *Listening and Hearing:* Listening requires concentration, complex information gathering and mental function. Hearing is a simple, effortless prerequisite for listening.

General Strategies for Menopause

Learn to be firm when the conversation moves beyond the health problem. Develop a satisfactory clinical relationship through communication and active listening.⁸

- First, listen to the woman's reason for visiting and understand her awareness and attitude towards menopause.
- Encourage women to speak by asking open-ended questions and allowing sufficient time. Short sentences are easy to understand and support learning. Understand the woman's demographics, menopause experience, symptom experience, and concurrent medical concerns

- Personalise the discussions based on the woman's health, social beliefs and values, spirituality, experience, and family history. Consider the woman's preferences, values, and key concerns, including family members' experiences and concerns about breast cancer.
- Educate the woman about relevant health conditions, such as heart disease, diabetes, urogenital health, sexuality and osteoporosis, and explain how these conditions could affect her quality of life in the future.
- Leading questions about vaginal itching, burning, and difficulty during intercourse need to be handled subtly.
- Consider the practical issues the woman may face if medication is part of her management plan, such as cost, convenience, and side effects that might affect her desire to continue therapy.
- Ensure that the scientific information presented to the woman is objective.
- Consider using high-quality decision-making tools, educational materials, and programmes to enhance the office visit counselling session.
- Consider the practical issues the woman may face if medication is part of her management plan, such as cost, convenience, and side effects that might affect her desire to continue therapy. Consider her attitudes, beliefs, and preferences about vasomotor symptoms (VMS) and VMS treatment options, the importance of quality of life (QoL), and tolerance for risks and adverse events (AEs).
- Discuss the known risks and benefits associated with each option, and present in lay terminology information about the strength of the existing evidence.
- Make an effort to address all of the patient's questions, including those about recommended treatments.
- Maintain privacy, treat the woman's questions respectfully.
- Share the decision-making process. Elicit and include women's preferences in any recommendation.
- Schedule regular follow-up visits, periodically evaluate treatment continuation, and adjust treatment as needed.

COUNSELLING ON LIFESTYLE

Lifestyle therapy should be the first course of treatment and include counselling on dietary patterns, physical activity, exercise, addictions (tobacco, gutka, paan, alcohol), stress management, relaxation techniques, and sleep hygiene. Counselling should aim to promote behavioural changes to achieve mental, physical and emotional health.⁹

COUNSELLING ON MEDICATION¹⁰

Guidance on medication safety should be explained to the woman. Women should be advised as follows:

- Know your medicines, including their names, the reasons for taking them, and possible side effects.
- Keep a current list of all your medicines.
- Keep your medicines in a cool, dry place unless you are given different instructions.
- Store your medicines in one location. Please keep them in a safe place out of children's reach.
- Take your medicines exactly as directed.
- Continue taking your medicines until your healthcare provider tells you to stop.
- Ask your pharmacist or healthcare provider before taking any over-the-counter medicines.
- Double-check your prescriptions when you pick them up at the pharmacy. Make sure your name, the medicine name and the dosage are correct.
- Check the expiry dates. Do not use medicines that are old or expired.
- Use the same pharmacy, if possible.
- Do not share your medicines with anyone.
- Contact your healthcare provider if you have any problems with your medication.

Counselling To Prevent Cancer in Middle Age

Preventative measures and being proactive in managing a balanced, healthy lifestyle will significantly reduce the risk of cancer, according to the World Cancer Research Fund (WCRF) and the American Institute of Cancer Research (AICR):¹¹

- *Maintain a healthy weight:* This may help lower the risk of various types of cancer, including breast, prostate, lung, colon and kidney cancers.
- *Maintain a healthy weight:* This may help lower the risk of various types of cancer, including breast, prostate, lung, colon and kidney cancers.
- *Get fit:* Regular exercise, including 30 minutes of vigorous activity a day. Physical activity on its own has been shown to reduce the risk of most cancers, especially breast cancer, and keeping fit helps lower body mass index and insulin resistance.
- *Do not smoke:* Smoking is linked to various types of cancer, including lung, head and neck, and bladder cancers. Chewing tobacco has been linked to oral and pancreatic cancers. Exposure to passive smoke might increase the risk of lung cancer. Stopping smoking can reduce the risk of dying from cancer by more than 20%. Advice to eat five portions of fruit or vegetables a day: making healthy food choices might help reduce the risk of cancer. A balanced diet includes fruits, vegetables, and other plant-based foods such as whole grains and beans.
- *Follow a low-fat diet:* High-fat diets tend to be higher in calories and may increase the risk of obesity, which in turn can increase cancer risk. Health authorities recommend an average daily intake of 2,000 calories for an average woman. As one approaches middle age, the body changes and needs fewer calories to maintain one's weight. Diet strongly influences the risk of colorectal, breast and endometrial cancers; changes in dietary habits might reduce the colorectal cancer burden by up to 70%.
- *Moderate alcohol intake:* The risk of cancer of the breast, colon, lung, kidney, esophagus and liver increases with the amount of alcohol consumed and the frequency of drinking. Low-risk women are advised to limit their daily alcohol intake to no more than one unit to reduce the risk of endometrial cancer.
- *Protect from the sun:* Skin cancer is a common type of cancer and one of the most preventable. Avoid the midday sun when its rays are strongest, and stay in the shade when outdoors to reduce unnecessary risks. When applying sunscreen, use generous amounts and reapply frequently.
- *Get immunised:* Infections such as hepatitis B and human papillomavirus (HPV) are associated with an increased risk of cancer. Ensure immunisation status is up to date and properly documented. Additionally, identify and treat *Helicobacter pylori* infection to reduce the risk of gastric cancer.
- *Practice safe sex and use condom:* An effective cancer prevention tactic is to avoid risky behaviours that can lead to sexually transmitted infections, which, in turn, might increase the risk of cancer.
- *Visit healthcare professional:* Regular self-examination and screening for various types of cancer can increase chances of detecting cancer early, when treatment is most likely to be successful. A systematic follow-up at least once a year by a trained practitioner is recommended for each woman in midlife and beyond. This will allow evaluation of individual risks for each potential age-related disease.

WOMEN SHOULD BE AWARE OF UNUSUAL SYMPTOMS LASTING FOR MORE THAN TWO WEEKS

- Abnormal vaginal bleeding, abdominal or pelvic pain, swelling, abnormal vaginal discharge, blood in urine or stools, and changes in appetite, bowel habits, abdominal bloating, indigestion or nausea can reveal endometrial, ovarian or colon cancer and warrant a visit to the health care provider.
- Breast nipple discharge, a lump, or a skin abnormality on the surface of the breast can indicate breast cancer.
- Unusual cough, shortness of breath, coughing up blood, or throat pain can indicate lung cancer.
- The occurrence of venous thrombosis in women without a family history may indicate cancer and requires further investigation.

STRATEGIES TO EXPLAIN RISK BENEFIT FOR SCREENING, MANAGEMENT AND FOLLOW-UP

“Medicine is a science of uncertainty and an art of probability,”

Sir William Osler

Living with uncertainty is a constant fact of life for both physicians and patients. Effective clinical decision-making depends not only on the evidence itself but also on how risk is communicated. Clinicians should provide all necessary information to support truly informed decision-making and must be skilled at presenting risk to patients in an accurate, transparent, and meaningful way. Risk ratios should be expressed as absolute numbers rather than percentages, with a consistent, easily understandable denominator such as 100, 1,000, or 10,000. For example, stating that a headache occurs in 12 out of 1,000 women without a drug, compared with 20 out of 1,000 women using the drug, conveys risk more clearly than presenting a percentage increase alone. Percentages should be avoided where possible; instead of saying “20% of women develop a headache,” it is preferable to say “2 out of every 100 women may develop a headache.”

An alternative and often simpler approach is to describe risk using standardised qualitative terms, very rare, rare, uncommon, common, and very common, based on the Council for International Organisations of Medical Sciences (CIOMS) classification of adverse event frequency. In 1998, the CIOMS Task Force proposed a structured framework to help both healthcare professionals and the public interpret risk, linking these descriptors to defined numerical ranges.¹² Refer to Table 1

Women’s Health Initiative - Example of Harm Resulting from Poor Risk Communication

The greatest harm in menopause care arose not from flawed science but from the incomplete interpretation and early communication of data from an otherwise well-conducted trial, the Women’s Health Initiative (WHI). At the time of its initial release in 2002, risks were predominantly communicated as percentage increases in relative risk rather than as absolute event rates.¹³ This approach led both clinicians and the public to overestimate harms and to conclude that menopause hormone therapy (MHT) carried more risks than benefits.

For example, presenting a “26% increased risk” without context obscured the fact that the absolute annual risk increase was fewer than 1 additional event per 1,000 women. A modest and statistically marginal finding was thus transformed into what appeared to be a categorical contraindication. In the WHI combined estrogen–progestin arm, a relative risk of 1.26 for coronary heart disease translated to approximately 8 additional cases per 10,000 women per year, while a relative risk of 1.24 for breast cancer similarly represented 8 additional cases per 10,000 women per year. Conversely, in the estrogen arm, women aged 50–59 years from pooled & long-term follow-up data had reduced all-cause mortality (hazard ratio 0.70), although this benefit was not emphasised in the original publications.

For perspective, the annual risk of death from motor vehicle accidents is approximately 11 per 10,000 individuals, a figure rarely perceived as prohibitive in daily life. The WHI’s disproportionate emphasis on relative risk fundamentally altered clinical practice and public perception, leading to widespread avoidance of MHT and unintended long-term consequences for women’s health.

Visual aids are excellent methods of communicating possible outcomes. Using pictographs is an especially effective way to convey risk information and can help patients make unbiased decisions, and simple plain language.

In a study of predictors of intentions to use HT in clinical postmenopausal women, Simpson used the Health Belief Model to explain the cognitive factors that influence health-promoting decision-making, and this model has been used to predict adherence to or intentions to use medications or HT. After controlling for all variables, the main predictor of intention to use HT was that the benefits outweigh the risks. This study underscores the importance of counselling on risk-benefit analysis in simple terminology.¹⁴ Self-efficacy means one’s belief in their ability to do something has a major component in compliance.

Ask about the prescription and over-the-counter medicines the woman is taking. Polypharmacy is a major problem, and misuse of vitamins is commonplace. In India, we prescribe the pharmacological names rather than the generic names, which may result in duplicate prescriptions for supplements across formulations.

Table 1. CIOMS definitions of adverse events

TERM	NUMBER	COLLOQUIAL
Very common	1/1 - 1/10	A person in family
Common	1/10 to 1/100	A person in street
Uncommon	1/100 to 1/10,000	A person in village
Rare	1/10,000 to 1/1,0000	A person in small town
Very rare	Less than 1/10,000	A person in large town
RCOG Clinical Governance Advice.		

OBSTACLES TO ACCEPTANCE & CONTINUATION OF HORMONE THERAPY

Obstacles to acceptance of HT and to the continuation of therapy appear to be the same among Indian women as those reported worldwide.^{14,15} These are:

- The idea of long-term therapy
- The frequency of administration is daunting.
- The fear of cancer is the most frequent reason for refusal of HT, whereas vaginal bleeding is the most frequent reason for discontinuation. The other side effects are nausea, weight gain, headache and bleeding
- Cost of therapy
- Number of visits to the clinic for monitoring purposes
- Limited experience of physicians in counselling about menopause and HT
- Lack of time on the part of the healthcare provider
- Health-care professionals consider HT counselling with low priority
- Substantial variations exist in HT counselling practices. Lack of awareness and motivation among patients. Assess women's understanding of instructions and capacity to follow them.
- Patient management and therapy should be reviewed. annually with risk-benefit counselling
- Some women are naturalist and suspicious.
- Patterns of HT use differ between surgically and naturally menopausal women. For example, the probability of starting HT is approximately 5 times higher among surgically menopausal women than among those undergoing the natural transition.

SOCIOCULTURAL ISSUES

Attitudes And Health-Seeking Behaviour, Barriers To The Implementation Of Menopause Care -

Refer to Chapter 1

Women in India have a positive attitude towards life and menopause, viewing it as part of the ageing process. Building on this attitude, health-care professionals need to be proactive in counselling, education and the implementation of current health programmes.

An American Association of Retired Persons survey found that only 35% of women aged 40–49 years had ever discussed menopause with their healthcare provider.¹⁶ Similarly, the EMPOWER survey showed that only 10–15% of

healthcare providers initiate conversations about menopause symptoms, specifically vulvovaginal atrophy.¹⁷ Menopause education may enhance knowledge and empower women to raise the topic of menopause during patient-provider interactions.

TRENDS IN PRESCRIPTION PATTERN

Hormone Therapy Prescriptions In India

HT is not commonly prescribed in India for three reasons. One is the expense, another is a mindset that opposes interfering with a natural phase of a woman's life, and the third is the problem of follow-up. Before discussing HT, it must be noted that this therapy in India is almost exclusively used in private medical practice. Even within this, it is estimated that only about one per cent of postmenopausal urban women are on HT.

A 2010 study found that 69.04% of gynaecologists prescribed HT, and 61.9% would consider using HT for themselves. Alternative therapies were used in 83.48% of their prescribing practices. The reason cited by 71% for preferring alternative therapies was that they were safer and less controversial.¹⁸ The trend has not changed over the years. A 2025 dual survey (Meeta et al.) of > 32,000 women from under-resourced Indian communities and > 1,200 gynaecologists from the Indian Menopause Society (IMS) identified critical gaps in awareness and understanding of menopause and HT among underprivileged Indian women, as well as in gynaecologists' prescribing patterns. Responses from gynaecologists showed that systemic HT was prescribed by 62.4% of health care professionals (HCPs) and vaginal estrogen therapy by 86.0%. Although 95% of gynaecologists were aware of the indications, risks, and benefits of HT, 57% used alternative therapies as first-line therapy and 71% used them as adjuncts to HT.¹⁹

A recent study found that HT practice varies with years of experience: 83.1% of gynaecologists with 0-3 years of experience recommended systemic estrogen combined with progestogen for vasomotor symptoms, whereas this figure dropped to 77.2% among the more experienced (7-10 years) cohort. Conversely, younger gynaecologists were less likely to support the early initiation of HT, with only 30.4% in favour, compared to 48.9% among those with 7-10 years of experience.²⁰

Hormone Therapy Prescriptions In The United States (US)

In the 1970s, an estimated 30% of postmenopausal women used HT, and by the early 2000s, that number had increased to over 40%.²¹ In 2003, following the WHI findings, the food and drug administration (FDA) began approving class-wide labelling changes for estrogen plus progestogen and estrogen-alone products approved for VMS, genitourinary syndrome (GSM) and the prevention of postmenopausal osteoporosis. These changes would eventually include a Boxed Warning for an increased risk of serious adverse events, including cardiovascular disorders, invasive breast cancer, and probable dementia. Use among postmenopausal women declined from about 27% to about 5% between 1999 and March 2020.²¹ Until 2002, MHT use was highest among women aged 52 to 65 years, shifting to the youngest age group after 2005. Consistent with evolving clinical guidelines, the use of vaginal formulations increased during the study period, whereas the use of high- and standard-dose oral formulations decreased sharply. In addition, in 2000, 45.7% of women received HT prescriptions from family physicians and 40.9% from gynaecologists; by 2009, more than 60% of women received their HT from gynaecologists.²²

The FDA and Black Box Warning

The FDA held an Expert Panel on 17 July 2025 to discuss the risks and benefits of HT. Following the Expert Panel meeting, the FDA requested broad public input on the risks and benefits of HT. On 10 November 2025, the agency agreed to remove black box warnings from all estrogen-containing hormone therapy products.

The changes to the black box apply to all HTs (systemic and local vaginal products):

- Removal of the recommendation to use the lowest effective dose for the shortest possible duration
- Removal of the probable dementia warning
- Addition of consideration of starting HT for moderate to severe VMS in women < 60 years old or < 10 years since menopause. Addition of WHI data for women 50-59 years old.
- Maintain the boxed warning for endometrial cancer for HT products containin only systemic estrogen.

For local vaginal estrogen products: In the labelling as a whole, condense safety information and prioritise the information most relevant to the local vaginal formulation. Vaginal estrogen does not carry the risks of stroke, blood clots, or cancer. A new study reinforces that point, suggesting that among older women who have had one stroke, those using vaginal estrogen tablets aren't more likely to have a second stroke than those who don't use them.^{23,24}

Post-COVID, prescriptions have been on the rise, from 2021 (29.3 per 1,000) to 2025 (50.4 per 1,000). HT prescribing rose by 72%, the largest increase over time. These findings suggest a growing clinical use of HT among menopausal women in recent years, potentially reflecting updated clinical guidance from global societies and shifting perceptions of the benefit-risk balance. These data come from Cosmos, a dataset created in collaboration with a community of Epic health systems, representing more than 300 million patient records from 1,800 hospitals and more than 41,000 clinics across all 50 U.S. states, Canada, Lebanon, and Saudi Arabia. This study was conducted by two independent teams, each composed of a clinician and research scientists. The two teams reached similar conclusions.²⁵

Prescription Pattern from Europe

A survey of more than 2,500 German gynaecologists was conducted in 2010; the average age of the doctors was 51. Nearly all were willing to recommend HT for hot flushes, whether to a partner or a patient. However, there was some disconnect regarding other potential uses. For example, 59% of doctors said they would take hormones to ward off osteoporosis or recommend them to their partners. But only three-quarters of that 59% had suggested the same to at least some patients. Doctors may be more willing to use HT themselves or, in the case of male physicians, to recommend it to their wives rather than to prescribe it to their patients, as the survey suggests. This differential prescribing pattern reflects the shift from evidence-based to experience-based practice. Annual trends in HT prescribing in Wales were similar to those in England. A study by the National Health Service (NHS) England found that HT prescribing increased by 47% from 2021/2022 to 2022/2023.²⁶ Between 2019 and 2023, the number of menopausal patients and the total number of treatment drug prescriptions increased across nine cities nationwide. Estradiol, dydrogesterone, and tibolone were the main sex hormone drugs used to treat menopause.²⁶

SUGGESTIONS TO IMPROVE UPTAKE AND COMPLIANCE

Confidence Building in Prescription

The IMS has been working towards a holistic approach to menopause management and is active in organising national, zonal, and local educational programmes for professionals. Yearly all-India quiz for postgraduates and the menopause credential examination for clinicians are conducted. Publications: A quarterly "Journal of Midlife Health"; special issues in 2020 and 2026 on the executive summary of the clinical practice guidelines on menopause and osteoporosis are available on an open-access site at the IMS and the journal website.^{27,28} A monograph on "Clinical Practice Guidelines on Management of Menopause" and a monograph on "Clinical Practice Guidelines on Management of Osteoporosis" are available at www.indianmenopausesociety.org. More educational programmes are needed on the finer aspects of prescribing HT. Faith and confidence in any treatment modality are important for prescribing; these can be achieved through experience, the integration of knowledge with evidence (clinical practice guidelines), and materials supporting the use of therapy for the appropriate indication and population.

- Formation of urban and rural menopause clinics. Refer to Chapter 57
- A menopause clinic may be run as a separate, focused special clinic. It should offer a comprehensive, specialised, woman-friendly approach under one roof
- Formation of Club-35 PLUS for women in cities and towns, with periodic meetings organised under the IMS.
- Periodic bone mineral density (BMD) screening camps, pap smear camps, and breast health camps at medical centres directed at women over 40 years old.
- Good communication between healthcare providers and patients is encouraged.
- Provide balanced information about menopause to women and their families
- Conducting a widespread awareness campaign in the country
- Posters and educational materials should be provided to "ASHA" health workers in villages in the local language.

STATISTICS FOR THE CLINICIAN^{29,30}

The rapid accumulation of biomedical information has sparked considerable interest in evidence-based medicine and the use of quantitative evidence. Statistics is mainly used in research to investigate causality, to draw conclusions about how changes in predictor (independent variable) values affect dependent variables (responses). In the era of evidence-based practice, the clinician must understand basic terminology and interpret numbers.

Sample Size

Statistical inference allows conclusions about a population to be drawn from a representative sample. Sampling is commonly used because studying the entire population is often impractical, time-consuming, or costly. For valid inference, the sampled population should closely resemble the target population.

When estimating sample size, several key factors must be considered:

- *Significance level (α):* This is the risk of concluding that a treatment effect exists when, in reality, there is no true difference. It is conventionally set at 5%.
- *Type II error (β):* This is the risk of failing to detect a true difference when one actually exists.
- *Statistical power:* Power ($1 - \beta$) is the study's ability to detect a clinically meaningful difference when it truly exists and indicates the likelihood of correctly rejecting the null hypothesis.
- *Clinically meaningful difference:* The expected difference between groups should be defined and should be of practical or clinical relevance.
- *Outcome variability:* An estimate of the standard deviation or the proportion of the primary outcome is required. When prior data are unavailable, estimates may be drawn from the published literature or from reasonable assumptions.

Risk calculations

Risk calculations describe the likelihood of an outcome occurring given a specific exposure. They help researchers explore possible links between an exposure and an outcome and allow epidemiologists to estimate how much a disease or event may be attributable to that exposure. Risk estimates are also useful in clinical practice, helping health-care providers and patients weigh the potential benefits and risks of treatment.

Importantly, a statistical association does not necessarily imply causation or clinical relevance. Associations that are weak, reported in a single study, or derived from poorly designed studies should be interpreted with caution. Robust evidence, ideally from well-conducted randomised controlled trials, is required before concluding that a cause-and-effect relationship exists.

For example, women using estrogen-progestogen therapy (EPT) for a period of time have been shown to have a small increase in the risk of being diagnosed with breast cancer. However, EPT has not been shown to initiate breast cancer. It is thought that EPT may promote the growth of existing, undetected cancers, leading to earlier diagnosis rather than causing new disease.

Understanding commonly used measures such as relative risk and absolute risk is essential for effective patient communication. Interpretation of these measures should always be accompanied by an assessment of statistical significance to place risk estimates in an appropriate clinical context.

Relative Risk

Relative risk (RR) estimates the risk of developing a disease among individuals exposed to a particular factor compared with those who are not exposed. It reflects the strength of association between an exposure and an outcome.

$RR = \text{Incidence in exposed group} / \text{Incidence in non-exposed group}$ Example:

- Incidence of lung cancer among smokers = $70 / 7,000 = 10$ per 1,000
- Incidence of lung cancer among non-smokers = $3 / 3,000 = 1$ per 1,000 $RR = 10 / 1 = 10$

This means that smokers have a tenfold higher risk of developing lung cancer than non-smokers.

In observational research, small relative risks should be interpreted with caution. Relative risks of 2–3 or less in cohort studies, and odds ratios of 3–4 or less in case–control studies, may be affected by bias or confounding and do not necessarily indicate a causal relationship.

Attributable Risk

Attributable risk (AR) indicates the extent to which the disease under study can be attributed to the exposure.

$$AR = (\text{Incidence among exposed} - \text{incidence among nonexposed}) / \text{incidence among exposed} \times 100$$

$AR = (10 - 1) / 10 = 90\%$. Here, 90% indicates that 90% of the lung cancer cases among smokers were due to smoking. This suggests the amount of disease that might be eliminated if the factors under study could be controlled or eliminated.

Unlike relative risk, attributable risk reflects the public health impact. Relative risk quantifies the strength of the association between an exposure and an outcome, whereas attributable risk estimates the extent of the disease burden that could be reduced by prevention or risk factor control. Attributable risk concerns exposure to a disease-causing agent or risk factor (assuming a causal relationship): what's the risk of lung cancer in people who smoke? What's the risk of lung cancer in people who don't smoke? The attributable risk is the difference between the two. Absolute risk reduction is about intervention/prevention: what % of people who get a placebo vaccine go on to get COVID? What percentage of people who get a real vaccine end up getting COVID? Absolute risk reduction is the difference between the two.

P Value

It is the probability of obtaining a test statistic at least as extreme as the one observed, assuming the null hypothesis is true. $RR = (\text{Incidence among exposed} / \text{Incidence among nonexposed}) \times 100$. One often “rejects the null hypothesis” when the P value is less than the significance level α , which is often set at 0.05 or 0.01 in the study.

A P value of 0.01 indicates that, mathematically, there is a 1% or less probability (≤ 1 in 100) that the observed difference between two groups occurred by chance.

By convention, P is considered significant if it is less than 0.05. This means there is a 1 in 20 chance that the results occurred by chance. This becomes important when you consider that some analyses compare 25 or 30 characteristics of the WHI subjects. One must remember that 1 out of 20 comparisons will be statistically significant at the $P = 0.05$ level, but may be due to chance. As the P level declines, our confidence in the likelihood of the event being real increases. At $P = 0.01$, the results occur only 1 in 100 times by chance; at $P = 0.001$, only 1 in 1,000 times, and so on.

“Clinical significance” (or clinical relevance) is a separate issue and can be determined only by judgment. The take-home message for this point is that just because a comparison is statistically significant, it does not necessarily mean it is clinically significant for your patient's decision about using HT.

Statistical significance: For example, when $p = 0.05$, this means there is a 5% chance that the study's results are due to chance or coincidence and a 95% chance that they are truly related to the intervention being studied. Practical (or clinical) significance, whether the results are worth acting on, is entirely different. For example, a 6-month study of a weight-loss treatment using a large number of patients might show statistically significant weight loss of 1 pound, which is not practically significant for someone who needs to lose 30 pounds. Thus, statistical significance does not always imply clinical relevance, and P values should always be interpreted alongside effect size and clinical context.

What is an Odds Ratio?

An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR is the odds of an outcome occurring given a particular exposure, relative to the odds of the outcome occurring in the absence of that exposure. ORs are most commonly used in case-control studies; however, they can also be used in cross-sectional and cohort study designs (with some modifications and/or assumptions).

What is it used?

Odds ratios are used to compare the relative odds of the outcome of interest (such as a disease or disorder) occurring, given exposure to the variable of interest (such as a health characteristic or medical history). The OR can also be used to determine whether a particular exposure is a risk factor for a given outcome and to compare the magnitudes of various risk factors for that outcome.

OR=1: Exposure does not affect the odds of the outcome. OR > 1: Exposure is associated with higher odds of the outcome. OR < 1: Exposure is associated with lower odds of the outcome.

Hazard ratio

Hazard ratio (HR), RR, and OR assess the effect of an exposure or risk factor on an outcome or disease at a fixed point in time (such as after one year). Both RR and OR concern interventions and outcomes and thus report across the entire study period.

In contrast, the HR compares the rate at which an event occurs over time between two groups. It reflects the relative likelihood that an event will happen at any given point during the follow-up period, rather than at a single, fixed time point.

Hazard ratios are commonly used in time-to-event (survival) analyses, where both the occurrence and timing of events are important.

Confidence Interval

The 95% confidence interval (CI) is used to estimate the precision of the OR. The general formula for the CI is:

Mean $\pm$ (multiplying factor) $\times$ [standard deviation/ $\sqrt{(\text{sample size})}$], where the multiplying factor is obtained from the distribution the data follows.

The meaning of 95% CI is that if an experiment is repeated 100 times, 95 times the mean will fall between the upper and lower limit of CIs or that 95% of the intervals will contain the mean in the long run. In large-scale epidemiological studies, if the CI includes 1.0, the result is considered not statistically significant. A narrow CI indicates a more precise estimate. A wide CI reflects greater uncertainty, often due to a small sample size or data variability.

It is important to note, however, that unlike the p-value, the 95% CI does not report a measure's statistical significance. In practice, the 95% CI is often used as a proxy for statistical significance if it does not overlap the null value (e.g. OR = 1). Nevertheless, it would be inappropriate to interpret an OR with a 95% CI that spans the null value as indicating a lack of association between the exposure and outcome.

Number-Needed-to-Treat

There is a way to understand how much modern medicine offers individual patients. It is a simple statistical concept called the number-needed-to-treat (NNT). The NNT measures the impact of a medicine or therapy by estimating the number of patients who need to be treated to benefit one person. The concept is both statistical and intuitive, because we know that not everyone benefits from a medicine or intervention. Some benefit, some are harmed, and some are unaffected. The NNT tells us how many of each.

The number NNT is the statistical inverse of the absolute risk reduction (ARR), i.e., $1/\text{arr}$. In general, A is the intervention and B the control (e.g. A might be a 5-year treatment with a drug, while B is no treatment). A defined endpoint must be specified (e.g. the appearance of colon cancer in a five-year period). If the probabilities pA and pB of this endpoint under treatments A and B, respectively, are known, then the NNT is computed as $1/(pB - pA)$. NNT is a number between 1 and ∞ ; effective interventions have a low NNT. A negative number would not be presented as an NNT; instead, if the intervention is harmful, it is expressed as a number needed to harm (NNH). The units of the aforementioned probabilities are the number of events per subject; the inverse NNH is the number of subjects per event.

Implications of NNTs

The number needed to treat is useful for both policy and individual patient decisions. There are some important points to bear in mind, though.

NNTs can be calculated from any trial data that provide dichotomous outcomes; information is needed on how many patients achieve a particular treatment benefit, such as pain relief to a certain level or survival. So, some thought needs to go into defining a worthwhile outcome.

When calculating NNTs, all circumstances are important. These include the comparison (placebo or another active treatment), the drug dose and/or the duration of therapy, and the outcome.

Any NNT is a point estimate. All point estimates have uncertainty, usually reflected in the 95% CI. For example, an NNT

of 5.0 (3.6–7.2) means that, in 19 out of 20 replications, the result would fall between 3.6 and 7.2. The CI narrows as the amount of data increases, so large trials yield narrower intervals than small ones. NNTs calculated from systematic reviews of randomised controlled trials provide the highest level of evidence.

NNTs can be used to calculate different endpoints from the same studies.

Comparison across treatments may be sensible, but only when comparisons are on a like-for-like basis. So, comparing NNTs from, say, a lipid-lowering study with a 6-month outcome with those from another study with a 3-year outcome would be problematic.

NNTs can be used to express other features, such as harm. Adverse effects of treatment will increasingly be examined in this way, and we will begin to see the NNH and the NNT.

When (RRRs) were presented, more clinicians and policymakers were presented with research results in different formats, including NNTs, ARRs and relative risk reductions. Conservative decisions were made when treatment effects were expressed as NNTs, and they were then presented as RRRs or ARRs.

SYNOPSIS

The prerequisites of an efficient counsellor are:

- Knowledge: Need to be updated on issues of women's health
- Communication skills: Translating and providing clinical information and numerical data in an easy-to-understand and simple language.
- Attitude: Sincere, honest and effective, with an opinion that takes into account the individual woman's medical, socioeconomic, family and emotional background.
- Explain the risk-benefit in simple, understandable language.
- An update on management and treatment options is needed.

RESEARCH AGENDA

Effect of counselling on the uptake of HT in postmenopausal women.

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DIETARY THERAPY FOR MENOPAUSE

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Keywords: Menopause, diet quality, nutrient density, functional food, microbiome

INTRODUCTION

The nutrients we obtain through food significantly affect physical growth and development, the maintenance of normal body functions, physical activity, and overall health. Nutritious food is thus needed to sustain life and activity. Our diet must provide all essential nutrients in the required amounts. Requirements of essential nutrients vary with age, gender, physiological status and physical activity. A balanced diet, with judicious choices of a variety of foods, prevents adverse effects of nutritional deficiencies and ensures optimal growth and development.

Dietary intakes that are lower or higher than the body's requirements can lead to undernutrition (deficiency diseases) or overnutrition (diseases of affluence), respectively. Eating too little food during the vulnerable periods of life, such as infancy, childhood, adolescence, pregnancy and lactation and eating too much at any age can lead to harmful consequences. Appropriate dietary habits promote optimal growth and development and prevent malnutrition in all its forms, including undernutrition, micronutrient deficiencies, overweight, obesity (including abdominal and/or central obesity), and diet-related non-communicable diseases.¹

As women age, several factors influence their nutritional status.² Metabolic requirements tend to change after menopause due to the decline in ovarian function. Weight gain around menopause is common and may result from alterations in satiety signals, a reduction in basal metabolic rate, redistribution of body fat towards the abdomen, and a shift from the gynoid to the android pattern of fat distribution, which increases the risk of metabolic syndrome.³ Energy requirements also decline with age. The estimated daily energy requirement for women around midlife (approximately 40–50 years) is about 1600–1700 kcal per day, depending on physical activity levels. This requirement further decreases to around 1500 kcal per day after age 60.¹ Additionally, nutritional status may be affected by age-related illnesses or chronic diseases. Medications prescribed for various conditions may influence appetite, metabolism, and nutrient absorption, thereby altering nutritional balance. Social and psychosocial factors may also play a role. Women who are widowed, living alone, or experiencing bereavement may be less likely to prepare nutritional meals. Physical disability may limit access to fresh foods, leading to reliance on easily stored or processed foods. Furthermore, mental health conditions such as depression or cognitive decline may reduce the motivation or ability to maintain a healthy and nutritious diet.¹

NUTRITION BASICS

Food provides the energy and nutrition required for cell growth, maintenance, survival and regeneration. Nutrients are broadly classified into macronutrients and micronutrients, and their composition in commonly consumed Indian foods has been documented in national food composition databases.⁴

Macronutrients: include carbohydrates, proteins, and fats. Carbohydrates are the body's preferred sources of energy, followed by fats. Proteins are specialised macronutrients essential for tissue building, repair, enzyme and hormone synthesis, and various regulatory functions.

Micronutrients: are substances vital to the body that are needed in small amounts. These are vitamins, minerals, trace elements, essential amino acids, and essential fatty acids, which must be obtained through the diet because the body cannot synthesise them. These nutrients are essential for the basic metabolism and regulatory functions of the body. Deficiencies in micronutrients such as iron, folate, and vitamin B12 can cause anaemia and cognitive deficits; adequate intake supports metabolic and neurological health.

CARBOHYDRATES

Glycemic Index and Glycemic Load¹

The *glycemic index (GI)* is a measure of how rapidly a carbohydrate -containing food raises blood glucose levels

compared with a reference food. Foods are classified based on their GI values as follows: low (≤ 55), medium (56–69), and high (≥ 70).

The glycemic load (GL) indicates how much a food raises blood glucose, taking into account both the type of carbohydrate (GI) and the amount consumed (portion size). GL is a more clinically relevant measure because it incorporates quantity. Diets emphasising low-GL foods can help improve glycemic control, reduce central adiposity, and support cardiometabolic health. GL is classified as low (≤ 10), moderate (11–19), and high (≥ 20). The aim is to choose low-GI foods in portions that keep the overall GL low.

Carbohydrates And Dietary Fibre

The quantity and quality of carbohydrates are important in a daily diet. The total carbohydrate intake should constitute approximately 50-60% of total daily caloric intake.^{1,3} Carbohydrates can be categorised as complex, simple, and refined. Refined carbohydrates are highly processed foods devoid of dietary fibre that have a high glycemic index (GI) and elevate glycemic load (GL), contributing to postprandial hyperglycemia and potentially insulin resistance. Complex carbohydrates from whole grains, pulses, and low-GI vegetables should be preferred over simple sugars and high-GI foods.⁵

Dietary fibre, a type of carbohydrate found in plant-based foods, differs in its digestibility, solubility and fermentability.⁶ Dietary fibre is classified as soluble and insoluble. Insoluble fibre is present in leafy vegetables, whole grains, millets, nuts, and oilseeds, whereas soluble fibre is found in fruits (guava, apple), pulses, dals, vegetables (peas, beans, lady's finger), cereals (barley, oats), and oilseeds flax, fenugreek). Fibre benefits both the gastrointestinal microbiota and systemic health, including reducing serum cholesterol and improving glycemic control. Dietary fibre intake should be encouraged at each meal. The recommended total dietary fibre intake is 25-40 g per day.⁵

Practical Guidance on Carbohydrate Selection

- The primary sources of complex carbohydrates should be whole-grain cereals such as unpolished rice, whole wheat, oats, broken wheat (dhaliya), millets, whole-grain pulses and sprouts, and soybeans. Natural simple carbohydrates, such as milk, fruit juice, and honey, and starchy vegetables like potatoes, are digested quickly. Refined carbohydrates, after processing (unhealthy carbs), have lower nutritional value. It includes polished rice, white bread, and maida (refined flour) based cereal preparations such as rumali roti, naan, pav, guthli, buns, and khari. Added simple sugars from aerated (carbonated) drinks, candy, HFSS foods (high-fat, sugar, and salt foods), ultra-processed foods, and bakery products contribute substantially to overall simple carbohydrate intake.
- Low-GI carbohydrate foods such as oats, unpolished rice, parboiled rice, whole pulses, beans, legumes, and all whole fruits with skin, such as guava and apple, should be preferred. High-GI and GL foods, such as refined flour, root vegetables such as yams, potatoes, tapioca, and colocasia (arbi), should be consumed in moderation.
- A minimum intake of four to five servings of vegetables and fruits per day is recommended, corresponding to approximately 400–500 g/day. This should include three to four servings of vegetables and one to two servings of fruits. One serving is defined as 100 g of raw vegetables, such as caul flower or brinjal, or 100 g of fruit, such as an apple.
- Simple sugars such as crystalline sugar, sugarcane juice, sweetened carbonated beverages, fruit juices, and sugar syrups should be avoided.

Refer to Table 1 for understanding the glycemic carbohydrates from commonly consumed foods, Table 2 for the glycemic carbohydrate content of commonly consumed Indian breakfast foods, Table 3 for the GI and GL of different food samples, and Table 4 for the GI and GL of commonly consumed Indian breakfast foods.

Table 1: Estimation of glycemic carbohydrates from commonly consumed foods (g/ 100g dry matter (DM)¹

Food sample	Glycemic carbohydrates (g/100g DM)
Rice	79.22 ± 0.67
Wheat flour	63.26 ± 0.23
Baley	64.99 ± 0.21
Red gram dhal	51.90 ± 1.03
Green gram dhal	51.24 ± 1.72
Bengal gram whole	52.33 ± 1.29
Masoor dhal	52.52 ± 0.83
Chana dhal	56.22 ± 0.62
Wheat + chana (60:40)	49.94 ± 1.27
Wheat + chana + barley (40:30:30)	46.89 ± 0.22
Mixed dhal	40.09 ± 1.56

Each value is the average of triplicate determinations ±, one SD

Source: S. Devindra et al., (2017). Estimation of glycemic carbohydrate and glycemic index/load of commonly consumed cereals, legumes and mixture of cereals and legumes. Int. J. Diab. Dev. Coun. 37(4):426-431.

(Source: Dietary Guidelines for Indians ICMR – NIN 2024)

Table 2: Glycemic carbohydrate content of commonly consumed Indian breakfast foods (g/100g)¹

Food sample	Glycemic carbohydrates (g/100g DM)
Idly sambar	58.98 ± 0.0
MLA Upama pesarattu	66.26 ± 2.7
Onion rava dosa	70.95 ± 0.5
Open dosa	70.33 ± 5.7
Paneer dosa	68.69 ± 0.6
Pesarattu	65.75 ± 0.1
Rava paneer dosa	65.17 ± 3.1
Set dosa	69.93 ± 0.2
Vegetable dosa	69.56 ± 2.9
Vada sambar	49.63 ± 1.5
Onion dosa	69.96 ± 0.3
Plain dosa	70.75 ± 0.3
MLA Dosa	70.13 ± 0.5
Bisibele bhath	56.99 ± 0.2
Open veg paneer dosa	66.34 ± 0.9
Tomato bhath	61.49 ± 2.0
Lemon rice	70.36 ± 0.1
Chapati	66.12 ± 2.2
Tomato rice	71.35 ± 0.2
Vegetable biryani	71.84 ± 3.1
Curd rice	70.96 ± 0.7
Parota	63.50 ± 1.3
Mysore bonda	70.38 ± 0.1

Each value is the average of triplicate determinations ±, one SD

Source: S. Devindra et al., (2017). Estimation of glycemic carbohydrate and glycemic index/load of commonly consumed cereals, legumes and mixture of cereals and legumes. Int. J. Diab. Dev. Coun. 37(4):426-431.

(Source: Dietary Guidelines for Indians ICMR – NIN 2024)

Table 3: Glycemic index and Glycemic load of different food sample^{1,7}

Name of foods	Glycemic index (GI)	Glycemic load (GL)
Rice	78.23 d $\pm$ 4.24	49.38 d $\pm$ 2.67
Wheat chapatti	65.66 b $\pm$ 4.22	32.83 b $\pm$ 2.11
Red gram	43.01 a $\pm$ 4.93	21.50 a $\pm$ 2.46
Green gram	42.45 a $\pm$ 4.05	21.22 a $\pm$ 2.02
Bengal gram	37.95 b $\pm$ 5.73	18.97 ac $\pm$ 2.86
Masoor dhal	42.15 a $\pm$ 3.26	21.07 a $\pm$ 1.63
Mix dhal	43.64 a $\pm$ 6.98	21.82 a $\pm$ 3.49
Wheat + chana dhal	32.37 c $\pm$ 9.10	16.18 ce $\pm$ 5.30
Wheat + chana dhal + barley	39.27 ac $\pm$ 5.20	19.63 ae $\pm$ 6.33

Value are mean and $\pm$, SD three separate determinations.

Values in the row with different letters are significantly different ($p < 0.05$)

Source: S. Devindra et al., (2017). Estimation of glycemic carbohydrate and glycemic index/load of commonly consumed cereals, legumes and mixture of cereals and legumes. *Int. J. Diab. Dev.Coun.*37(4):426-431.

(Source: Dietary Guidelines for Indians ICMR – NIN 2024)

Table 4: Glycemic index and Glycemic load of commonly consumed Indian breakfast foods¹

Name of the breakfast foods	Glycemic index (GI)	Glycemic load (GL)
Idly sambar	68.69 $\pm$ 5.8	34.34 $\pm$ 7.1
MLA Upma pesarattu	72.85 $\pm$ 5.8	36.42 $\pm$ 6.7
Onion rava dosa	66.43 $\pm$ 5.7	33.21 $\pm$ 5.3
Open dosa	77.33 $\pm$ 5.7	39.34 $\pm$ 3.5
Paneer dosa	71.47 $\pm$ 4.3	35.73 $\pm$ 3.7
Pesarattu	60.69 $\pm$ 5.7	33.70 $\pm$ 9.5
Rava paneer dosa	71.94 $\pm$ 6.2	35.97 $\pm$ 5.2
Set dosa	65.97 $\pm$ 5.7	32.98 $\pm$ 6.5
Vegetable dosa	63.97 $\pm$ 5.7	31.98 $\pm$ 6.5
Vada sambar	36.89 $\pm$ 5.7	18.44 $\pm$ 7.7
Onion dosa	79.69 $\pm$ 5.9	39.84 $\pm$ 4.8
Plain dosa	79.39 $\pm$ 6.8	39.69 $\pm$ 2.7

MLA dosa	71.17 ± 6.6	35.58. ± 5.4
Bisibele bhath	74.64 ± 5.8	32.59 ± 5.6
Open veg paneer dosa	70.98 ± 6.4	35.49 ± 6.8
Tomato bhath	68.57 ± 5.8	36.54 ± 7.3
Lemon rice	79.30 ± 5.9	39.65 ± 3.9
Chapati	62.43 ± 6.1	28.37 ± 5.3
Tomato rice	68.89 ± 6.2	34.44 ± 7.3
Vegetable biryani	74.53 ± 6.1	37.26 ± 7.3
Curd rice	64.94 ± 5.6	32.47 ± 7.5
Parota	62.48 ± 5.6	31.24 ± 6.3
Mysore bonda	61.41 ± 5.6	39.84 ± 4.8

Each value is the average of triplicate determinations ±, one SD

Source: Devindra S, et al., (2022). Glycemic carbohydrate, glycemic index, and glycemic load of commonly consumed South Indian breakfast foods. journal of food Science and Technology. 59,3619-3626. Doi.org/10.1007/s13197-022-05368-6

(Source: Dietary Guidelines for Indians ICMR – NIN 2024)

FATS

The “essential” limit of fat is the level adequate for energy needs (15% of total energy).¹ It prevents essential fatty acid (EFA) deficiency and facilitates optimal absorption of fat-soluble vitamins. High levels of saturated fatty acids (SFAs) and trans fatty acids (TFAs) promote dyslipidemia and atherosclerosis and should be avoided.⁸ Total fats (visible and invisible) should provide not more than 30% of total energy/day, and SFAs should provide not more than 7-10 % of total energy per day.⁸ For women with low-density lipoprotein cholesterol (LDL-C) ≥100mg/dL, SFAs should be < 7% of total energy intake/day.⁹ Essential polyunsaturated fatty acids (PUFA), such as linoleic acid (LA), an omega-6 fatty acid, should contribute approximately 3% of total daily energy intake. For a 2000 kcal diet, this corresponds to about 60 kcal, or approximately 6.6 g of n-6 PUFA per day.¹ Alpha-linolenic acid (ALA), an omega-3 fatty acid, should contribute approximately 0.6–1.2% of total daily energy intake. For a 2000 kcal diet, this corresponds to about 20 kcal, or approximately 2.2 g of n-3 PUFA per day. The optimal dietary ratio of LA to ALA is considered to be between 5:1 and 10:1.¹⁰ Cis monounsaturated fatty acids (MUFA) should contribute approximately 10–15% of total daily energy intake. For a 2000 kcal diet, this corresponds to about 200–300 kcal, equivalent to approximately 22–33 g of MUFA per day.¹¹ TFAs should provide <1% of total daily energy intake.¹¹ Dietary cholesterol intake should be limited to 200-300 mg/day.¹²

Practical Guidance on Fat Selection

- Fats have long carried a negative reputation and are often perceived as dietary villains. Consequently, many individuals attempting weight loss eliminate fats entirely from their diets in pursuit of rapid, significant weight reduction.
- Fats are indeed a rich source of energy.
- High intake of saturated and trans fats is associated with elevated blood cholesterol levels and promotes atherosclerotic plaque formation within blood vessels. Progressive vascular narrowing or occlusion may impair coronary blood flow, resulting in myocardial infarction, while obstruction of cerebral vessels can lead to ischemic stroke.¹⁰
- When taken in excess amounts, they increase the risk of obesity and cancer.
- However, one should not completely avoid fat in the diet as it has certain essential functions.

- Fats play a vital role in promoting the absorption of the four important fat-soluble vitamins (A, D, E and K).¹⁰
- Fats also provide a feeling of fullness and satisfaction, thereby delaying the onset of hunger.
- Fats, along with proteins, are major components of body fluids and cell membranes and play a vital role in cellular metabolic functions.¹⁰
- All fats are high in calories. To maintain and achieve a desirable body weight, we need to limit the amount of fat in our daily diets.
- The Dietary Guidelines for Indians, ICMR National Institute of Nutrition (NIN), 2024, recommend limiting total fat intake to 15-30 per cent of total calories. It is recommended that adult women and men with a sedentary lifestyle limit daily visible fat intake to 20g and 30g, respectively.¹

Dietary Cholesterol

Cholesterol is synthesised in the liver and plays an important role in the fluidity and permeability of the body's cell membranes. It is also a precursor to many hormones & vitamin D and aids cell signalling. In a normal, healthy state, the body produces adequate cholesterol to support these functions. Dietary cholesterol is the addition which needs to be regulated and rationed. It should be emphasised that cholesterol is present only in animal foods. It is also important to note that vegetable oils do not contain cholesterol, but the predominant fatty acid in the oil can help lower cholesterol. Thus, "promoting oils as cholesterol-free" is a misleading communication to the consumers.

Sources of cholesterol are milk & milk products, butter, ghee, egg yolks, liver, brain and other organ meats, red meat and poultry. Cholesterol intake should be restricted to less than 200 mg/day.¹ One can reduce both saturated fat and cholesterol intake by limiting consumption of high-fat animal foods like butter, ghee, meat, eggs, and organ meats, and by choosing low-fat (skimmed) milk instead of whole milk. However, ICMR -NIN guidelines (2024) recommend consumption of eggs (3eggs/ week) in view of the several nutritional advantages of eggs.¹

Types Of Fats

Saturated Fats

These fats include butter, ghee, cheese, whole milk, cream, egg yolks, lard, and the skin of poultry, red meat, and processed meats like sausages, ham, and bacon. Vegetable sources of saturated fat include coconut oil, cocoa butter, and palm kernel oil.¹⁰ Ghee, butter and coconut oil are easily digested and absorbed, hence recommended for infants, young children and in certain medical conditions. Saturated fats are associated with adverse cardiovascular effects, including elevated serum cholesterol levels, increased low-density lipoprotein (LDL), and an increased risk of coronary heart disease. Dietary saturated fat intake can be reduced by limiting butter and deep-fried foods, choosing low-fat or fat-free milk and dairy products, and minimising red meat intake.

Trans Fatty Acids

These are artificially hydrogenated fats. The hydrogenation of vegetable oils was introduced to produce solid fats, resulting in products such as margarine and vanaspati (partially hydrogenated vegetable oils). Initially, these fats were considered a healthier alternative to butter because they contain no dietary cholesterol. However, the hydrogenation process promotes the formation of TFAs. Clinical and epidemiological studies have demonstrated that TFAs adversely affect lipid profiles by increasing LDL-C and reducing high-density lipoprotein (HDL) cholesterol. Data from the Framingham Heart Study indicated that even a modest increase in margarine consumption was associated with a significantly higher risk of myocardial infarction. Furthermore, accumulating evidence suggests that TFA intake may contribute to adverse reproductive outcomes, increased risk of certain malignancies, including breast and colorectal cancer, higher rates of preeclampsia during pregnancy, impaired fetal development, and reduced insulin sensitivity in individuals with diabetes.¹⁰

The Dietary Guidelines for Indians, National Institute of Nutrition-ICMR (2024), recommend avoiding TFAs and limiting them to less than 1% of total fat intake in packaged foods.¹ Sources of TFAs are bakery products, margarine, vanaspati/dalda, ready-to-eat (processed) foods, deep-fried foods like samosas, bhajias, french fries, chips and sweets like jalebis, gulab jamuns. It is also desirable to opt for low-fat milk-based products. Recent evidence suggests that thermal processing of flax seeds, including roasting, which is often promoted for lipid-lowering benefits, may increase the formation of TFAs. Consequently, consuming roasted flax seeds may not confer the same health benefits as unprocessed flax seeds and should be approached with caution. The declaration of TFA content is mandatory for packaged foods.¹³ Thus, reading the food label for HFSS content and TFA before buying any product is desirable.

Unsaturated Fats:

Monounsaturated fatty acids (MUFA): do not raise cholesterol, improve insulin sensitivity and decrease clot formation and atherogenesis⁹; hence, it is recommended that 12-15% of total energy intake should be contributed from MUFA (visible and invisible fat sources).¹⁰ Invisible fat sources of MUFA include nuts like almonds, cashews, walnuts, pistachios, and groundnuts; oilseeds like sesame, chia, and pumpkin seeds; avocado; and visible fat sources like olive oil, groundnut oil, canola oil, rice bran oil, and peanut butter.

Polyunsaturated fatty acids (PUFA) are essential because they contain 'essential fatty acids' which cannot be synthesised by the body and have to be obtained from dietary sources. There are two groups of essential fatty acids: Omega-6 and Omega-3. Refer to Table 5

Omega-6 fatty acids: Omega-6 fatty acids lower total and LDL-C when taken instead of saturated fatty acids. They also support the cardiovascular, reproductive, immune, and nervous systems. Visible fat sources of omega-6-rich oils are safflower, sunflower, cottonseed, corn, and soybean oils; groundnut, rice bran, and sesame oils also provide moderate amounts of PUFA.1 Omega-6 is a PUFA that is readily available in most natural foods, but the balance between N6 and N3 in the total diet is more important.

Ideally, the ratio of N6: N3 in a diet should be 5-10.¹⁰

Omega-3 fatty acids: It is desirable to include more omega-3 fatty acid-rich sources in our diet, as they are present in selected foods. The invisible fat sources of omega 3 include pulses like black gram (kala chana), kidney beans (rajmah) & cowpea (lobia), mustard, fenugreek seeds and green leafy vegetables, millets like bajra, whole grain cereals like oats, wheat, egg, fatty fish like mackerel, sardines, and tuna, chicken and meat are good sources of omega -3 fatty acid.1 Refer to Table 5.

Table 5: Approximate quantity of foods required to furnish a minimum of 100mg n-3 PUFAs

Plant foods (ALA)	g	Vegetable (ALA)	g
Cereal/Millet	70	Mustard/Rapeseed	0.7
Wheat & Bajra	70	Soyabean	1.5
Oats	1.4	Canola	0.5
Wheat		Flaxseed	0.2
Pulses		LC n-3 PUFAs from animal foods	20-50
Black gram, Rajmah &	20	Fish	
Cowpea	7	Low/medium fat fish	
Soyabean	60	Oily fish(>5% fat)	10
Other pulses			
Vegetables		Poultry egg	
Green leafy	60	Standard	2-3 eggs
Purslane	25	DHA enrich (flaxseed)	1 egg
Radish seed(sprouted)	14	DHA enrich (meal from marine sources)	1/3rd egg
Spirulina (dried)	12	Chicken	100
Spices	5	Lean meats	
Fenugreek seed	2	Lamb, sheep, goat, beef, pork	150
Mustard seed			
Nuts	2		
Walnuts	25		
Almonds			
Unconventional oilseeds	0.5		
Flaxseed (linseed)	0.5		
Perilla seed			

(Source: Dietary Guidelines For Indians ICMR – NIN 2024)

Nuts and oilseeds, such as flax seeds (the richest vegetarian source of omega-3), walnuts, and pumpkin seeds, are considered good sources of omega-3 fatty acids. It is important to remember that the amount of nuts and oilseeds consumed in a daily diet should be aligned with the individual's total desired caloric intake. Refer to Table 6. The oils rich in omega-3 include mustard, soybean, canola, and flaxseed oils.⁴

Table 6 List of Omega 3 Rich Foods (per 100 gms) (Source: IFCT 2017)⁴

Food High in Omega 3	Serving size	Omega 3 (mg/100g)	Omega 3 (mg/ serving size)
Flaxseed	15 g	12956	1943
Walnut	15 g	8710	1306
Garden cress seeds	15 g	7484	1122
Salmon	100 g	1598	1598
Soyabean	30 g	1314	394
Hilsa	100 g	1157	1157
Sardine	100 g	614	614
Black gram (whole)	30 g	601	180
Rajmah	30 g	552	166
Drumstick leaves	100 g	446	446
Gogu leaves	100 g	434	434
Fenugreek leaves	100 g	362	362
Mackerel	100 g	332	332

Omega-3 fatty acids play a critical role in promoting metabolic health.¹¹ Studies show that long-chain derivatives of omega-3 fatty acids favour insulin sensitivity, maintain blood viscosity and blood pressure, and thus prevent arterial clogging. It also protects against diseases like arthritis and colitis, reducing the risk of cancer and Alzheimer's disease. Eating fish, prepared the low-fat way, 2 to 3 times a week, protects the heart.¹

Choice of cooking oils

To achieve the desired ratios of MUFA: PUFA and PUFA: SFA, it is advisable to consume more than one type of vegetable oil or blended oils. Refer to Figure 1 for the fatty acid composition of vegetable oils. NIN recommends using a blend of two or more vegetable oils for daily cooking. Hence, the choice of cooking oil should be as follows:^{1,14}

- Rice bran/Cotton seed + Safflower/Sunflower/Soyabean
- Groundnut/Sesame /Rice bran + Mustard
- Groundnut/Sesame/Rice bran + Canola
- Safflower / Sunflower + Groundnut/Sesame/ Rice bran
- Groundnut/Sesame/Rice bran +Soyabean

The plant oils, in addition, contain certain useful substances such as lignans (sesame oil), tocotrienols (palm oil), sterols, tocopherols (vitamin E), oryzanol and tocotrienols (rice bran oil), carotenoids, all of which reduce cholesterol and have antioxidant properties which repair oxidant damage due to ageing, inflammation that occurs in chronic diseases. Some useful components are lost during oil refining; advances in refining processes allow them to be preserved, fortified, and stabilised. Use of LoSorb technology reduces oil absorption, and use of filtered, cold-pressed oils limits heat-related damage.¹⁵

Frying and Reheating Of Oils

For frying, use oils with high smoke points and good stability. People often choose olive oil because they think it's healthy, but frying in it is not recommended because it has a low smoke point. The common practice of repeatedly using oil for frying is hazardous, as it generates free radicals and forms carcinogenic compounds such as acrylamide and trans fats, which are harmful to our health. When reheated, oil's viscosity increases, it becomes darker in colour, and it turns rancid. Therefore, it is advisable not to reheat oils. The oil once used for frying can be used for regular cooking and utilised quickly. All oils should be stored in dry and cool conditions to prevent rancidity.¹⁶

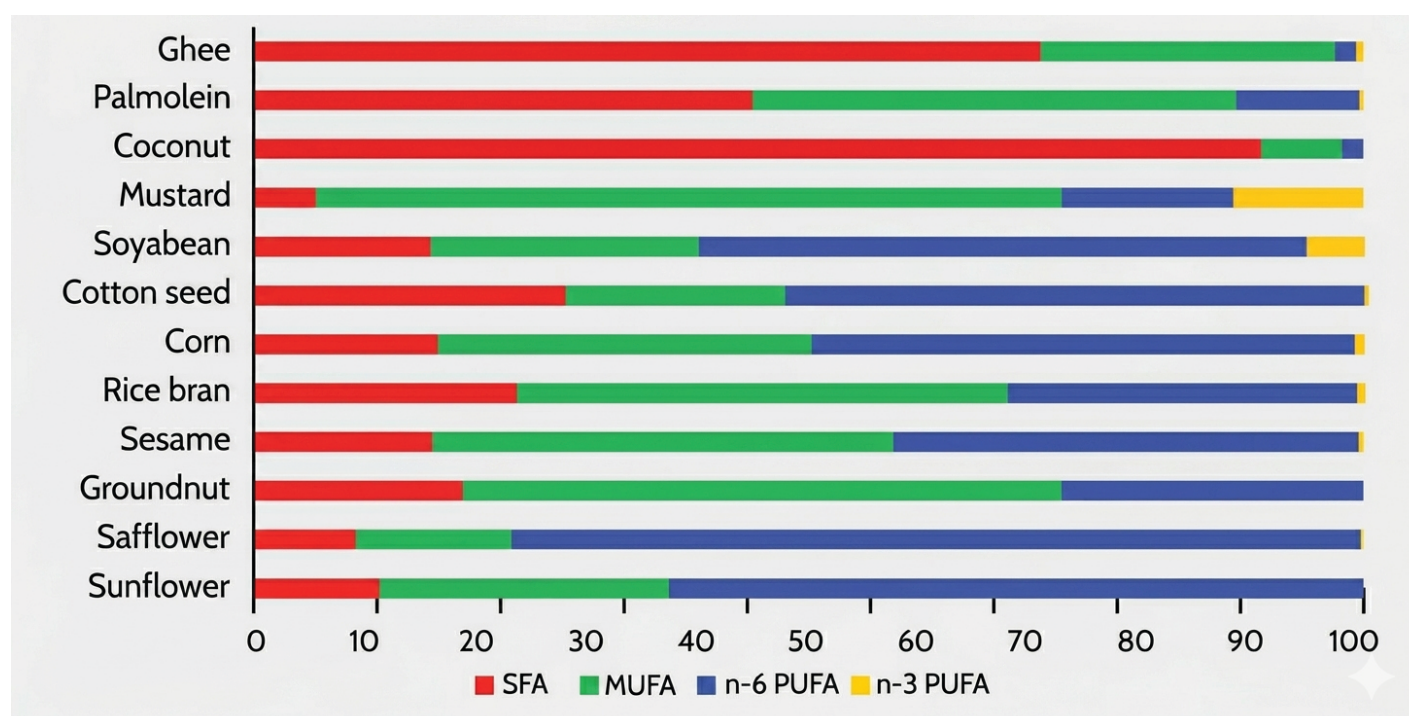


Figure 1: Fatty acid composition of vegetable oils (g/ 100g oils) (Source: Dietary Guidelines For Indians ICMR – NIN 2024)

Food-Based Guidelines to Ensure Optimal Fat Quality in Asian Indian Diets

Reliance on a single vegetable oil does not ensure an optimal intake of the various fatty acids (Fig. 1). Therefore, the use of two or more different vegetable oils in the diet is recommended to achieve a better balance of fatty acids. Accordingly, the recommended choices of cooking oils are as follows:¹¹

- If single oil is to be used, canola, olive, mustard and rice bran oil are good recommendations.
- A combination of oils such as safflower, sunflower, corn, soy, or mustard is essential to maintain a healthy n6/n3 ratio. A ratio between 5-10 is a good recommendation.
- Consumption of butter and ghee should be kept to a minimum.
- The use of vanaspati as a cooking medium should be strictly avoided.
- There should be regular consumption of foods with high ALA content (wheat, pearl millet, pulses, green leafy vegetables, fenugreek, flaxseed, mustard seeds) (Table 5).
- Substitution of part of visible fat and invisible fats from animal foods with whole nuts such as pistachios and almonds.

- Moderation in the use of animal foods (beef, pork, ham, eggs) containing high fat, SFAs and cholesterol.
- For non-vegetarians, consumption of 100-200 g of fish (4-6 pieces)/week.
- Choose low-fat dairy foods such as low-fat milk (fat < 1.5%) or curd made from such milk. The recommendation to prefer low-fat dairy foods would also reduce ruminant TFAs.

PROTEIN

The protein requirement, as indicated by the recent Dietary guidelines for Indians, ICMR, NIN, 2024 and 2007 WHO/FAO/UNU Expert Consultation, is 0.66 g/kg/day for healthy adult men and women.^{1,15} Since we use mixed proteins in India, adequate protein intake would be about 1 g/kg/day. The Estimated Average Requirement (EAR) of Protein is 36.3 g per day, with the protein-to-energy ratio (P: E) contributing to 10 to 15 per cent of total energy for the day in Indian menopausal women (40-50 years).⁴

Protein as a nutrient is present in all foods in varying degrees except pure sugar, oil and fats. The sources of protein are:

- Non-vegetarian: egg white, fish, and lean chicken;
- Vegetarian: Soya, pulses, and whole grains like channa, rajma, and green gram;
- Lacto-vegetarian: milk and low-fat dairy products.

Animal sources contain 20% protein; soybeans are the richest, at 40%. Pulses and millets contain 10% protein, and cereals contain 10%.

There are twenty amino acids in proteins; nine of them cannot be synthesised in the body and are called the essential amino acids (EAA).¹⁷ These are best obtained from eggs, dairy foods, meat, fish and poultry, which are typically considered to be complete proteins. Vegetarians, and especially vegans, often do not have a source of complete protein in their diets, but can easily obtain all of the essential amino acids by eating a variety of beans, grains, nuts, seeds, and vegetables.

Practical Guidance on Protein Selection

- To obtain high-quality proteins, the right combination of cereals, pulses, nuts, and seeds helps complement the EAA to favour optimal protein utilisation.
- Cereals (grains and millets) contain lysine, threonine, and tryptophan as limiting EAAs but are rich in methionine.
- Pulses have methionine as the limiting EAA, but are rich in lysine, threonine and tryptophan
- Nuts and seeds have lysine as the limiting EAA, but are rich in methionine.
- Thus, an appropriate combination of cereals and pulses in the ratio of 3:1 (raw food weight) can meet the requirements of all EAAs, including other amino acids.
- Adding 250 ml of milk to our daily diet can further increase EAA intake and help meet requirements in a lactovegetarian diet.¹
- Non-vegetarians can easily meet the recommended level (700 to 900 g/week; marine water fish, poultry, or lean meat) of flesh-food or egg consumption.¹
- To increase muscle mass, along with protein intake, exercise is also required. Regular physical activity prevents muscle atrophy.

MINERALS

Calcium

A major component of bones, calcium also plays an important role in the cardiovascular, nervous, and muscular systems. On an average, only about 20–40% of the calcium consumed is absorbed, and this absorption tends to decline with age. The factors that enhance calcium availability include lactose (milk sugar), vitamin D, and an appropriate calcium-to-phosphorus ratio. For this reason, milk is considered an excellent source of calcium. Other calcium-rich sources include sesame seeds (the richest source of calcium), ragi (a millet very rich in calcium), rajgira (a pseudo-millet high in calcium), some pulses like rajmah, black chana, cowpea, green leafy vegetables including colocasia

leaves (patra), drumstick leaves, fenugreek leaves (methi), radish leaves, and chaulai.⁴ These foods contain factors like phytates (millets, pulses), oxalates (green leafy vegetables and nuts and oilseeds) that inhibit absorption of calcium. But an intake of a diverse diet with all food groups will, in totality, favour calcium absorption in the body. Other factors that influence calcium availability include lack of exercise, medications, smoking, caffeine, and stress. Refer to Chapter 17 for calcium-rich foods.

Magnesium

Adequate magnesium intake may help reduce the risk or severity of menopause-associated conditions such as osteoporosis, fatigue, type 2 diabetes, coronary artery disease, anxiety, and depression. Examples of rich sources of magnesium include nuts, seeds, pulses, whole grains, millets, and dark green vegetables. Refer to Table 7.

Table 7 List of Magnesium Rich Foods (per 100 gms) (Source: IFCT 2017)⁴

Food High in Magnesium	Serving size	Magnesium (mg/100g)	Magnesium (mg/ serving size)
Pumpkin seeds	15 g	550	83
Watermelon seeds	15 g	515	77
Sunflower seeds	15 g	413	62
Flaxseeds	15 g	392	59
Sesam seeds, black	15 g	390	58.5
Fennel seeds	15 g	385	58
Moth beans	30 g	381	114
Amaranth seeds	30 g	325	98
Almond, Cashew nut	15 g	320	48
Soya bean, brown	30 g	259	78
Cowpea	30 g	213	64
Walnuts	15 g	180	27
Green gram, whole	30 g	198	60

Selenium

Helps to combat fibrocystic breast disease/ cancer. Examples of selenium-rich sources include wheat germ, tuna, tomatoes, and broccoli.

Manganese

Helps to combat atherosclerosis in later life. Rich sources of manganese include nuts, fruit, vegetables, and wholegrain cereals.⁴

Phosphorus

Helps in the prevention of osteoporosis. Rich sources include meat, fish, eggs, milk, grains, nuts, seeds and beans.⁴

Zinc

Helps to combat osteoporosis in later life. Dietary sources include wheat germ, pumpkin seeds, eggs.⁴

Iron

Deficiency of iron leads to anaemia. Examples of rich sources include green leafy vegetables, pomegranates, beetroots, nuts, eggs, and liver.

VITAMINS

Vitamin D

Over the past decade, growing scientific evidence has demonstrated that vitamin D plays a central role in multiple physiological processes and is essential across all age groups, particularly for women during the menopausal transition. Vitamin D has been associated with the prevention of cardiovascular disease, osteoporosis, diabetes, malignancy, and weight gain. Beyond skeletal health, vitamin D deficiency has been linked to a wide range of adverse outcomes, including autoimmune disorders, infections, type 2 diabetes, metabolic syndrome, hypertension, cardiovascular disease, cognitive decline, and cancer, conditions of increasing relevance as women approach menopause.

Vitamin D is critical for calcium absorption and bone health, facilitating intestinal calcium uptake and helping maintain stable serum calcium levels. The biologically active form of vitamin D is synthesised in the skin through exposure to ultraviolet B radiation, with sunlight exposure between approximately 11:00 am and 3:00 pm being most conducive to vitamin D production.¹⁸ Dietary sources of vitamin D are limited and include milk, eggs, dairy fats, and fatty fish such as tuna and salmon.

Given its essential role in bone metabolism, adequate vitamin D intake is particularly important for women over 40 and for those with risk factors for osteoporosis. The combined use of calcium and vitamin D remains a cornerstone strategy for preventing and managing bone loss. Additional micronutrients, including magnesium, manganese, copper, zinc, and boron, also contribute to bone health by supporting mineralisation, hormonal balance, and optimal vitamin D activity. Regular monitoring of vitamin D levels is therefore recommended for menopausal women, with supplementation undertaken under medical supervision when deficiency is identified.¹⁹

Vitamin A

This vitamin is necessary for the health and growth of the skin, eyes and mucous membranes. Vitamin A deficiency can lead to night blindness, increased susceptibility to infections and rough skin. Low levels of vitamin A contribute to heavy menstrual bleeding and age-related skin conditions, such as leukoplakia.²⁰ Sources include green leafy vegetables, orange and yellow vegetables and fruits, milk, eggs, and sheep liver.

Vitamin B Complex

Several B-complex vitamins play important roles during the menopausal transition by supporting metabolic, neurological, and psychological health. Adequate folate (vitamin B9) intake has been associated with a reduced risk of cervical dysplasia, particularly in women with low dietary intake.¹

B-complex vitamins function synergistically in glucose metabolism, hepatic function, and neurotransmitter synthesis, and deficiencies have been linked to fatigue, mood disturbances, emotional stress, and depressive symptoms.⁴

Dietary sources of folate include green leafy vegetables, nuts, legumes, and organ meats such as liver and kidney. Vitamin B3 (niacin) is obtained from animal sources, including meat, poultry, and fish, as well as plant-based sources such as whole grains, peanuts, legumes, oilseeds, mushrooms, potatoes, and leafy vegetables. Vitamin B6 is present in meat, poultry, fish, bananas, whole-grain cereals, and dairy products, while vitamin B12 is primarily derived from animal products, including fish, poultry, eggs, and milk, or from fortified foods.⁴ Adequate intake of B-complex vitamins is particularly relevant during menopause, when nutritional deficiencies may exacerbate fatigue, cognitive symptoms, and mood changes commonly experienced during this life stage.

Vitamin C

Vitamin C plays an important role in tissue repair and collagen synthesis, processes that become increasingly relevant with advancing age and during menopause. As collagen turnover declines over time, adequate vitamin C intake supports skin integrity, wound healing, and vascular health. Vitamin C also supports immune function and adrenal function, systems that may require greater support during midlife and the menopausal transition. Rich dietary sources include amla, guava, capsicum, cabbage, citrus fruits, broccoli, peppers, and tomatoes.⁴

Vitamin E

It has been studied for its potential role in alleviating certain menopausal symptoms, including vasomotor and psychological complaints, possibly due to its antioxidant properties and structural similarity to estrogen. In addition to its possible symptomatic benefits, vitamin E functions as a potent antioxidant, protecting cellular membranes from oxidative damage. Dietary sources rich in vitamin E include wheat germ oil, eggs, green leafy vegetables, cereals, dried beans, and nuts.⁴

SALT

Dietary sodium intake is a major determinant of both individual and population blood pressure levels, and reducing sodium consumption has been shown to lower blood pressure and reduce cardiovascular risk.²¹ In urban India, the prevalence of hypertension is rising, underscoring the importance of dietary salt reduction.²² The World Health Organisation recommends limiting salt intake to less than 5 g of sodium chloride per day (approximately 2 g of sodium or a teaspoon of salt).²³ Excess sodium intake among Asian Indians is often attributable to frequent consumption of salt-rich foods such as pickles, papads, namkeens, chutneys, bakery products, potato chips, popcorn, salty biscuits, preserved meats, soups, cheese, and fast foods.^{1,24}

Additional salt intake from discretionary sources, such as adding salt at the table, should be avoided. Processed and packaged foods may contain hidden sodium from additives such as sodium benzoate, monosodium glutamate, baking powder, and baking soda.⁴ Public health strategies should therefore emphasise limiting processed foods, and encouraging routine reading of food labels to identify sodium content in commercially prepared products.¹ Reducing dietary salt intake is particularly important in midlife women, as blood pressure and cardiovascular risk tend to increase after menopause.

EVIDENCE-BASED INDICATIONS FOR MICRONUTRIENT SUPPLEMENTATION

Vitamin A: Randomised controlled trials of β -carotene supplementation have not demonstrated an overall benefit in reducing the incidence of cancer or cardiovascular disease.^{25,26} While carotenoids obtained through a balanced diet may help protect against age-related DNA damage, long-term supplementation with high doses of vitamin A is associated with toxicity. Excess vitamin A intake has been linked to reduced bone mineral density and an increased risk of osteoporotic hip fractures, likely due to its antagonistic effects on vitamin D and calcium metabolism.²⁷

Vitamins C and E: Evidence suggests that vitamin C supplementation may reduce the risk of cortical cataracts.²⁸ and that topical application of vitamins C and E may offer protection against skin photoaging.²⁹ However, findings on the role of vitamins C and E in preventing cardiovascular disease and cancer are inconsistent.^{25,30} High supplemental doses of vitamin C may increase cardiovascular mortality in postmenopausal women with diabetes and may cause gastrointestinal disturbances or renal calculi.³⁰ Vitamin E can influence platelet aggregation and coagulation, though doses up to 600 IU have generally been well tolerated in healthy individuals.³¹ Despite its widespread use for alleviating hot flashes, evidence supporting vitamin E for menopausal symptom relief is limited. Only a small number of controlled trials have been conducted. While some reduction in hot-flush frequency has been observed, the magnitude of benefit appears modest.³² Meta-analyses have reported an increased risk of all-cause mortality with long-term vitamin E supplementation at doses ≥ 400 IU/day.³³ Vitamin E supplementation has not been shown to prevent cancer or major cardiovascular events and may increase the risk of heart failure in individuals with pre-existing vascular disease or diabetes.³⁴

Vitamin B-Complex: B-group vitamins are not stored in the body, and older menopausal women with reduced energy intake may be unable to meet their requirements through diet alone. Deficiencies in riboflavin, niacin, vitamins B6 and B12, and folate may contribute to oxidative stress. Age-related declines in dietary intake and reduced bioavailability of protein-bound vitamin B12 further increase the risk of deficiency. Folic acid supplementation has been shown to lower plasma homocysteine levels and improve insulin sensitivity and lipid metabolism, thereby potentially reducing cardiovascular risk.³¹ However, evidence on cancer prevention remains inconsistent.³²

Lycopene is a biologically active carotenoid that has been investigated for potential cardiometabolic and skeletal benefits in menopausal women. A randomised controlled trial evaluating LycoRed supplementation from the All India Institute of Medical Sciences (AIIMS), New Delhi, demonstrated favourable effects on lipid metabolism, including reductions in total and low-density lipoprotein cholesterol with increases in high-density lipoprotein cholesterol.³⁵ A

subsequent double-blind, placebo-controlled, multicentre randomised trial conducted by the Indian Menopause Society reported that higher intake of fruits and vegetables significantly increased circulating lycopene levels, which were inversely associated with inflammatory markers such as high-sensitivity C-reactive protein and markers of bone resorption.³⁶ Lycopene supplementation has also been associated with modest improvement in menopausal symptoms, including vasomotor complaints, fatigue, anxiety, and mood disturbances.³⁶ Experimental and clinical evidence further suggests a potential role for lycopene in reducing bone resorption and supporting bone health in postmenopausal women.³⁷

Zinc: supplementation may benefit older adults; however, prolonged supplementation can interfere with the absorption of other trace elements, including copper, and iron. Careful assessment of nutritional status is recommended before long-term use.³⁸

Iron: Most healthy older women meet the recommended dietary allowance for iron, and iron-deficiency anaemia is uncommon when intake is adequate. In this age group, anaemia is more often associated with chronic inflammation. Supplementation may be necessary in cases of low dietary intake, but excessive iron should be avoided due to its pro-oxidant effects.³⁹

Chromium: Although chromium supplementation has been proposed to improve glucose metabolism in postmenopausal women, there is currently insufficient evidence to support routine use, and no consensus recommendations have been established.³⁸

Copper: Copper is widely available in a variety of foods, and adequate intake is typically achieved through a balanced diet. Supplementation is rarely required in the absence of a documented deficiency.³⁹

Boron: The role of boron in human nutrition remains uncertain, and there is insufficient evidence to recommend routine supplementation.³⁸

Antioxidants: Endogenous and dietary compounds that protect cells against oxidative damage caused by free radicals generated during normal metabolic processes. Excessive free radical production has been implicated in cellular damage, accelerated ageing, and the development of chronic diseases. Environmental exposures such as air pollution, tobacco smoke, alcohol consumption, and psychological stress can further increase oxidative stress.⁴⁰

The body's antioxidant defence system comprises both enzymatic and non-enzymatic components. Enzymatic antioxidants rely on trace minerals, including selenium, zinc, copper, iron, chromium, and manganese, as essential cofactors. Non-enzymatic antioxidants are derived primarily from the diet and include vitamins C, A, and E, carotenoids such as lycopene and beta carotene, and other compounds such as glutathione, taurine, and cysteine. Epidemiological studies consistently show that higher consumption of fruits and vegetables is associated with a reduced risk of chronic diseases; however, these benefits are attributed to the combined effects of multiple bioactive compounds rather than any single antioxidant. Evidence supporting routine antioxidant supplementation for chronic disease prevention, including in postmenopausal women, remains limited and inconsistent.^{40,41}

FUNCTIONAL FOODS

Functional foods are defined as foods that provide health benefits beyond basic nutrition. Several categories are relevant to women's health:⁴²

Probiotics are live microorganisms that, when administered in adequate amounts (typically 10^9 – 10^{13} CFU per serving, as per FSSAI standards) 43, confer health benefits by maintaining or restoring a beneficial gut microbiota, thereby supporting digestion and immune function. Prebiotics are non-digestible food components that selectively stimulate the growth and activity of beneficial intestinal bacteria.⁴⁴

Synbiotics combine probiotics and prebiotics to achieve synergistic effects on gut health and immune regulation.⁴⁴

Natural Functional Foods

Certain commonly consumed foods possess antioxidant and anti-inflammatory properties:

- **Garlic** contains allicin, which supports immune function, reduces platelet aggregation⁴⁴ on, and may help reduce cardiovascular and cancer risk.⁴⁵
- **Ginger** contains bioactive compounds with antioxidant and anti-inflammatory properties and is a source of dietary fibre.⁴⁶

- *Green tea* is rich in polyphenols, which exhibit antioxidant activity and are associated with a reduced risk of cancer.^{47,48}
- *Fenugreek* (leaves and seeds) demonstrates antioxidant and anti-inflammatory effects and may aid in glycemic and lipid regulation.⁴⁹
- *Millet and whole grains* are high in dietary fibre and are associated with reduced risk of cardiovascular disease and certain cancers; oats are particularly rich in β -glucan, a cholesterol-lowering soluble fibre.⁵⁰

PHYTOCHEMICALS IN FRUITS AND VEGETABLES

Fruits and vegetables are rich in phytochemicals, polyphenols, vitamins, and dietary fibre, contributing to protection against cancer, hypertension, and cardiovascular disease.^{51,52} Consuming at least four to five servings of fruits and vegetables daily, particularly cruciferous vegetables such as broccoli, has been associated with a reduced risk of cancer.⁵² Tomatoes are a major source of lycopene, a potent antioxidant that supports immune function; cooking tomatoes enhances lycopene bioavailability.⁵³ Citrus fruits provide vitamin C, folate, soluble fibre, and limonoids, phytochemicals with demonstrated protective effects against several cancers.⁵⁴

Phytoestrogens

Phytoestrogens are naturally occurring plant-derived compounds that exhibit weak estrogenic or anti-estrogenic effects through interaction with estrogen receptors ER- α and ER- β .^{55,56} These compounds, particularly isoflavones, lignans, and coumestans, have been investigated for potential protective effects during menopause, including modulation of hormonal activity, improvement in lipid profiles, and possible cardiovascular and bone health benefits.^{55,56} Major dietary sources of phytoestrogens include soybeans and soy-based products (tofu, tempeh, soy milk), legumes (lentils, kidney beans, chickpeas, peas), and seeds and nuts flaxseeds, sesame seeds, sunflower seeds). Whole grains also provide lignans, while fruits and vegetables including berries, grapes, apples, cruciferous vegetables (broccoli, cauliflower, cabbage), and garlic contain smaller amounts of phytoestrogenic compounds.^{55,56}

Bioflavonoids

Bioflavonoids are a class of phytochemicals commonly found in citrus fruits, particularly in the pulp and pith. These compounds have antioxidant and anti-inflammatory properties and have been studied for their potential role in alleviating menopausal symptoms such as vasomotor instability, abnormal uterine bleeding, vaginal discomfort, anxiety, and mood disturbances.^{54,55}

Nutraceuticals

The term nutraceutical was first introduced by Stephen DeFelice in 1989 to describe food components that provide health benefits beyond basic nutrition.⁵⁷ Nutraceuticals encompass a broad range of products, including functional foods, probiotics, prebiotics, synbiotics, vitamin and mineral supplements, and herbal preparations.⁵⁸ These products are increasingly used as adjuncts to conventional therapy for the promotion of health and prevention of chronic diseases. Integration of nutraceutical approaches with conventional medical care may offer additional support in the management of menopausal symptoms and improvement in overall quality of life.^{58,59}

Phytoestrogens are among the most commonly used nutraceuticals as alternative or complementary therapies for menopausal symptom relief, particularly in women who are unable or unwilling to use hormone therapy. Certain herbal preparations, such as evening primrose oil, exhibit phytoestrogenic activity through mixed agonistic and antagonistic effects on estrogen receptors. *Asparagus racemosus* (Shatavari), an Ayurvedic medicinal plant, has been reported to possess phytoestrogenic properties and may support musculoskeletal health in postmenopausal women.⁵⁵

COMPOSITION OF AN IDEAL NUTRITIOUS DIET FOR MENOPAUSAL WOMEN

Fruits and vegetables are rich in phytochemicals, polyphenols, vitamins, and dietary fibre, contributing to protection against cancer, hypertension, and cardiovascular disease.^{51,52} Consuming at least four to five servings of fruits and vegetables daily, particularly cruciferous vegetables such as broccoli, has been associated with a reduced risk of cancer.⁵² Tomatoes are a major source of lycopene, a potent antioxidant that supports immune function; cooking tomatoes enhances lycopene bioavailability.⁵³ Citrus fruits provide vitamin C, folate, soluble fibre, and limonoids, phytochemicals with demonstrated protective effects against several cancers.⁵⁴

Energy Requirements

Energy intake should be individualised to maintain optimal health and body composition in menopausal women. Recommended energy requirements depend on the individual's physical activity level (sedentary, moderate, or heavy) and body build. Refer to Box 1. Maintaining an ideal body weight (IBW) corresponding to a body mass index (BMI) of 18–23 kg/m² is generally advised to reduce cardiometabolic and skeletal risks during menopause.⁴

Box 1. Calculation of Energy Requirement⁶⁰

Energy Requirement (Kcal/Kg IBW/day)			
Activity	Obese	Normal	Underweight
Sedentary	20-25	30	35
Moderate	30	35	40
Heavy	40	40	45-50

Source: Williams, 1989

Calculation of Ideal Body weight^{61,62} Refer to Box 2

- IBW Devine Formula 45.5 kg + 2.3 every inch over 5 feet
- Broca's Index: Height in cms -100 (for height above 150 cm)
- Lorentz formula for female Height < 150 cms = (Ht in cm -100) – (Ht in cms -150)

Box 2. Calculation of Energy Requirement⁶⁰

Build	
Medium	100 lbs. (45.5 kg) for first 5 ft. (152cm) height, plus 5 lb. (2.3 kg) for each additional inch
Small	Subtract 10 %
Large	Add 10 %

Source: Adapted from Committees of the American Diabetes Association Inc. and American Dietetic Association, 1977.

The body of a menopausal woman undergoes a number of physiological changes, including impaired nutrient absorption, altered body composition, insulin resistance, inflammation, and decreased bone density.⁵⁹ A balanced diet should provide no more than 45 per cent of calories from cereals and millets (nutri-cereals) and up to 15 per cent of calories from pulses, legumes, and meat, while the remaining calories should come from nuts, vegetables, fruits, and milk (see Table 6).^{3,58} Such a diverse and judicious choice of food groups will ensure approximately 50-55 per cent of total calories from carbohydrates,¹⁰⁻¹⁵ per cent from proteins, and 20-30 per cent from dietary fats, supporting energy needs and metabolic health in menopausal women.^{3,59} The food groups that give these nutrients are categorised into 10 Food Groups.¹ Refer to Table 8.

Table 8: Food Groups categorisation as per the nutrient content

1	Cereals and millets	Rice, wheat, millets and other cereals, etc.	
2	Pulses	Lentil, green gram, chickpea, rajma, cowpea, etc.	
3	Vegetables	Seasonal vegetables	
4	Nuts, oil seeds, oils and fats	Peanuts, walnuts, almonds, pistachio, hazel nuts, and other nuts, vegetable oils, etc.	
5	Green leafy vegetables (GLV)	Seasonal GLVs	
6	Fruits	Seasonal fruits	
7	Dairy	Milk, curd and butter milk	
8	Roots and tubers	Beetroot, radish, carrot, tapioca, sweet potato, etc.	
9	Flesh foods	Marine fish, poultry and lean cut meat	
10	Spices and herbs	Turmeric (haldi), ginger, mustard, pepper, cumin, corriander (dhania), etc.	

(Source: Dietary Guidelines For Indians ICMR – NIN 2024).

Adequate quantities of foods from at least 5-7 food groups should be consumed daily. The ‘My Plate for the Day’ published in the 2024 Dietary Guidelines for Indians by the ICMR-NIN provides simple guidance on achieving a balanced diet, sourcing energy from different food groups. With a reference of 2000 kcal per day, this can be customised for menopausal women to a 1660 kcal per day diet (Table 7). The proportions of each food group are important indicators of diversity and balance.¹

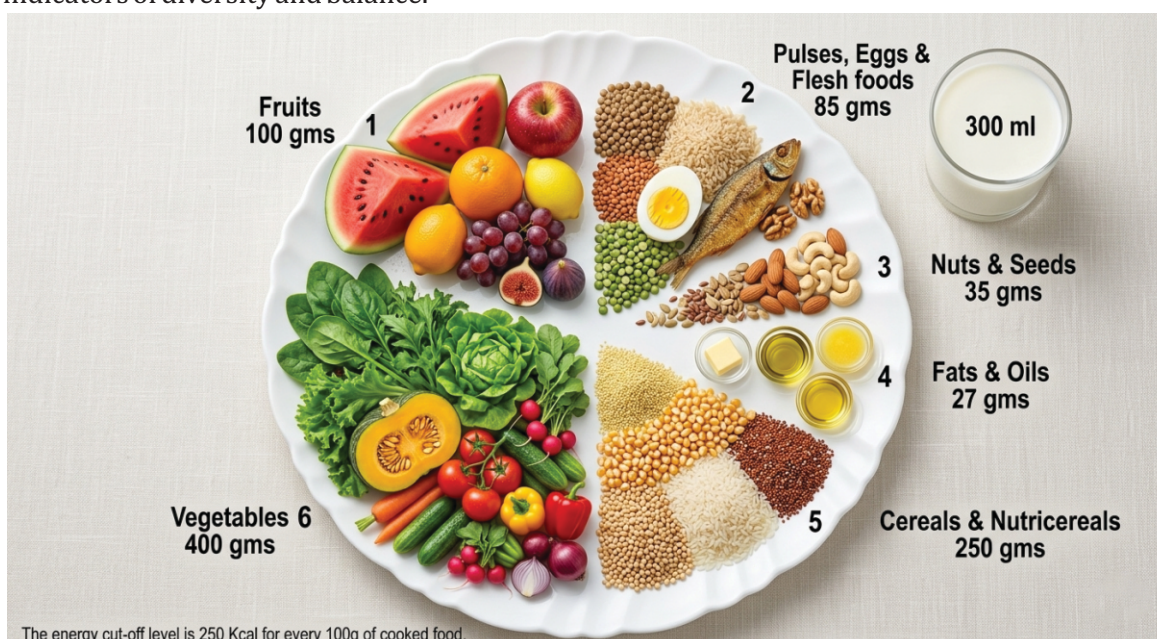


Figure 2: My Healthy Indian Plate of the Day. (Source: Dietary Guidelines For Indians ICMR –NIN 2024)

The plate clearly communicates: half the plate is filled with seasonal and coloured vegetables, tubers, and fruits; one quarter with whole-grain cereals; 30 per cent with nutrient-rich cereals; and one quarter with protein-rich foods and foods providing good-quality fats. Refer to Figure 2. Adequate amounts of foods from at least 5-7 food groups should be consumed daily. Refer to Table 6. Other foods may be consumed at least twice a week. This method of ensuring diversity and variety within groups will ensure adequate intake of most nutrients, such as essential amino acids, essential fatty acids, vitamins, minerals, phytonutrients, dietary fibre, and bioactive substances. Spices like turmeric, cumin, ginger, garlic, cinnamon, pepper, and cloves are rich in antioxidants and can be part of a balanced diet.¹

There is no clear consensus on protein intake in menopausal women because studies on nitrogen balance in the elderly have been difficult to replicate.^{63,64} Protein stores diminish with ageing due to a decline in lean body mass, and there is some disagreement over whether body protein synthesis may be reduced in the elderly. Serum albumin levels decline with age, and protein metabolism depends on kidney function, which may also be impaired.⁶⁴ Considering all these factors, it has been recommended that menopausal women consume 12% to 14% of their calories as protein, with larger amounts for those who are undernourished, and restricted intake in those with compromised kidney function.⁶³

Mediterranean Diet for Menopause

The Mediterranean Dietary Pattern is characterised by high consumption of olive oil, fruits, vegetables, whole grains, legumes and nuts; moderate consumption of dairy, fish, poultry and wine; and low intake of red meat, processed meat, and sweets.⁶⁵ A recent meta-analysis indicates that high adherence to the Mediterranean diet is associated with lower all-cause mortality, reduced cardiovascular mortality, and fewer non-fatal cardiovascular events in older adults.⁶⁶ An analysis of more than 1.5 million healthy adults demonstrated that following a Mediterranean diet was associated with a reduced risk of death from heart disease & cancer, as well as a reduced incidence of Parkinson's and Alzheimer's diseases.⁶⁷

The Dietary Guidelines for Americans recommends the Mediterranean diet as an eating plan that can help promote health and prevent disease. Refer to Figure 3

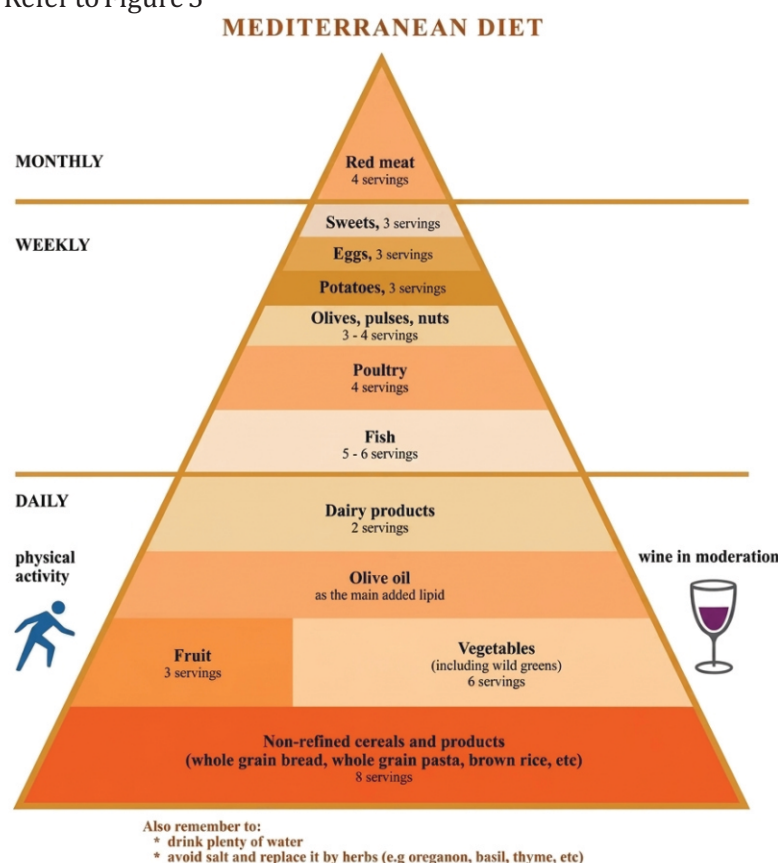


Figure 3: Mediterranean Diet Food Pyramid

Vegetables & Tubers	Artichokes, Arugula, Beets, Broccoli, Brussels Spouts, Cabbage, Carrots, Celery, Celeriac, Chicory, Collard Cucumber, Dandelion Greens, Eggplant, Fennel, Kale, Leeks, Lemons, Lettuce, Mache, Mushrooms, Mustard Greens, Nettles, Olives, Onions, (red, sweet, white) Peas, Peppers, Potatoes, Pumpkin, Purslane, Radishes, Rutabaga, Scallions, Shallots, Spinach, Sweet Potatoes, Turnips, Zucchini
Fruits	Avocados, Apples, Apricots, Cherries, Clementines, Dates, Figs, Grapefruit, Grapes, Oranges, Melons, Nectarines, Olives, Peaches, Pears, Potatoes, Pomegranates, Strawberries, Tangerines, Tomatoes
Grains	Breads, Barley, Buckwheat, Bulgur, Couscous, Durum, Farro, Millet, Oats, Polenta, Rice, Wheatberries
Fish & Seafood	Abalone, Cockles, Clams, Crab, Eel, Flounder, Lobster, Mackerel, Mussels, Octopus, Oysters, Salmon, Sardines, Sea Bass, Shrimp, Squid, Tilapia, Tuna, Whelk, Yellowtail
Poultry, Eggs, Cheese, & Yogurt	Chicken, Duck, Guinea Fowl Eggs (Chicken, Quail, and Duck) Cheeses (Examples Include: Brie, Chevre, Corvo, Feta, Haloumi, Manchego, Parmigiano-Reggiano, Pecorino, Ricotta) Yogurt, Greek Yogurt
Nuts, Seeds, & Legumes	Almonds, Beans (Cannellini, Chickpeas, Fava, Kidney, Green), Cashews, Hazelnuts, Lentils, Pine Nuts, Pistachios, Sesame Seeds (Tahini), Split Peas, Walnuts
Herbs & Spices	Anise, Basil, Bay Leaf, Chiles, Clove, Cumin, Fennel, Garlic, Lavender, Marjoram, Mint, Oregano, Parsley, Pepper, Pul Biber, Rosemary, Sage, Savory, Sumac, Tarragon, Thyme, Zatar
Meats & Sweets	Pork, Beef, Lamb, Mutton, Goat Sweets (Examples include: Baklava, Biscotti, Creme Caramel, Chocolate, Gelato, Fruit Tarts, Kunefe, Lokum, Mousse Au Chocolat, Sorbet, Tiramisu)
Water & Wine	Drink Plenty Of Water Wine In Moderation

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Figure 4: Food Ingredients included in the Mediterranean Diet

Portion guidance described in Mediterranean diet pyramids includes vegetables (a cup of raw leafy vegetables or half a cup of other vegetables), potatoes (100 g), legume (one cup [100 g] cooked), nuts (30 g), fruit (one apple/one banana/one orange/200 g of melon/watermelon/30 g of grapes), meat (60 g of cooked lean meat or fish), grains (half a cup [50-60 g] of cooked pasta or rice; one slice of bread [25 g]), dairy (one cup of milk or yoghurt; 30 g of cheese), eggs (one egg), wine (125 ml glass of average-strength red wine), olive oil (50 grams, or 3.5 tablespoons) Refer to Figure 4.

The Mediterranean Diet is considered beneficial for various metabolic disorders and healthy ageing. However, its adoption outside Mediterranean regions has been challenging due to food availability and cultural dietary practices. Efforts are underway to adapt the Mediterranean dietary pattern in Asian countries by emphasising locally available, seasonal functional foods that align with core Mediterranean principles to improve metabolic health outcomes.⁶⁸⁻⁷⁰

OTHER DIETARY HABITS

Water

Water is necessary for metabolism and physiological functions in the body and also serves as a source of essential minerals, including calcium, magnesium, and fluoride.⁷¹ Fluid requirements should vary by individual and by specific population. Advocacy by some individuals for excessive water intake is scientifically untenable. However, increased

water intake is recommended under special circumstances, such as vigorous work and outdoor activity in hot climates. An individual should have 1.5 - 2 litres (8 -10 glasses) of water every day; intake could be increased in hot climates.⁷²

Alcohol

Alcohol is not recommended as a health intervention, and individuals who do not currently drink should not start drinking for health benefits.⁷³ If alcohol is consumed, intake should be limited to no more than one standard drink per day for women and up to two drinks per day for men, where one standard drink is approximately 120 ml of wine, 300 ml of beer, or 30 ml of spirits.⁷³ Alcohol intake should be avoided in individuals with significant liver disease, uncontrolled hypertension, or serum triglyceride levels ≥ 500 mg/dL, as it may worsen these conditions.⁷³ Regular excessive alcohol use is harmful, increasing the risk of cardiovascular events, liver disease, and metabolic complications.⁷³

In Asian populations, alcohol consumption has been linked with increased risk of cerebrovascular disease in women, with light and heavy drinking associated with higher stroke incidence in Japanese women.⁷⁴ Additionally, lifestyle analyses in China, Japan, and Korea indicate that alcohol intake is significantly associated with increased breast cancer risk.⁷⁵

Food Choices While Eating Out

- Report of Joint WHO/FAO Expert Consultation on “Diet, Nutrition, and The Prevention of Chronic Diseases clearly stated that eating behaviours linked to overweight/obesity and consequent chronic diseases include snacking/eating frequency, binge-eating patterns, and eating out.⁷⁶ Some of the suggested steps include:
- Choose healthy snack options. Look at the ingredients of snacks (both packaged and freshly prepared) and try to identify foods high in bad fat (trans fat and saturated fat), simple sugars, refined maida and high amounts of salt (HFSS).
- Choose protein-dense ingredients like eggs, milk, paneer, curd, chicken, and fish, and select snacks that are low in fat and prepared by grilling, steaming, or simple cooking rather than frying.
- Order vegetable-based preparations without gravies. Prefer sautéed vegetables and salads without creamy dressings.
- A smaller portion while eating out should be preferred over a larger one. Follow a healthy plate model to guide your portions: more veggies, protein foods, and portioned cereals or other carbohydrate-rich foods.
- A paneer-based dessert or a fruit-based dessert is always preferred. Always share your dessert for portion control and good bonding.
- Avoid sweetened carbonated drinks and commercially available high-calorie drinks, and opt for beverages like buttermilk, coconut water, and fresh lime water.

Regular Breakfast

Eating breakfast is associated with healthier body weight and dietary patterns. A systematic review and metaanalysis of longitudinal observational studies found that skipping breakfast was prospectively linked with higher BMI and an increased risk of overweight and obesity across populations.⁷⁷ Another metaanalysis of crosssectional studies also reported that individuals who skipped breakfast had significantly greater odds of overweight/obesity compared with regular breakfast consumers.⁷⁸ Breakfast consumption has been shown to enhance satiety, stabilize postprandial glucose and insulin responses, and improve overall diet quality, all of which support healthier weight regulation.⁷⁹ Together, this evidence supports the inclusion of regular breakfast as part of healthy eating patterns for weight control. A healthy, regular breakfast should comprise the following:

- Good quality protein – Eggs, Chicken /Milk /Curd
- Dietary fibre – colored veggies and fruits
- Good quality fats – nuts and seeds
- Whole grain “rationed” carbohydrate source

Cooking Methods: Tips For Healthy Cooking

- Wash vegetables before cutting and preferably cut into long pieces. Do not soak in water for long.
- Use only sufficient water for cooking.
- Cook food in covered vessels on a slow fire.
- Prefer pressure/steam to deep fry and roasting.
- Avoid using baking soda and artificial colours.
- Do not reheat the leftover oil repeatedly.
- Fermented foods like idli, dosa, dhokla, and sprouts improve digestibility and enhance vitamin C and B-complex absorption, but they have a high glycemic response, so their intake should be limited or controlled.
- Correct cooking methods could minimise dietary fat intake. Deep-frying foods should be avoided. If such a cooking method is unavoidable, methods (such as blotting paper) should be used to drain excess oil from the fried food. Roasting or grilling not only eliminates added oil but may also allow any fat already present in food to drip away. Hence, the following methods are recommended: boiling, steaming, roasting, grilling, stewing, broiling, or preparing sauteed or poached dishes.

FAD DIETS

Menopause is commonly associated with weight gain and changes in body composition. In the absence of appropriate nutritional guidance, many individuals seek rapid solutions for weight loss and may adopt so-called fad diets. Although not a scientific term, fad diets are characterised by trendy dietary patterns that promise rapid weight reduction, often lacking robust scientific evidence. While initial weight loss may occur, its effects are usually short-lived and are often accompanied by nutritional inadequacy.

Fad diets typically gain popularity through social media and are marked by extreme dietary restrictions that prioritise aesthetic outcomes over health. Such restrictive practices can result in micronutrient deficiencies and may adversely affect chronic disease risk, particularly during menopause, when metabolic and hormonal changes increase vulnerability.

A ketogenic diet, which severely restricts carbohydrate intake while increasing fat intake to approximately 70–80% of total calories, may induce short-term weight loss through increased fat oxidation but also increases ketone body production. In susceptible individuals, excessive ketosis may result in metabolic complications, including ketoacidosis. The Atkins diet, which restricts carbohydrates to as little as 5% of total energy intake while allowing unrestricted protein and fat consumption, has also been promoted for rapid weight loss. Long-term adherence to these diets is difficult and unsupervised use may increase metabolic risks, including dyslipidemia.⁸⁰

The Palaeolithic (Paleo) diet, which emphasises foods presumed to have been consumed by early humans and excludes grains, legumes, dairy products, and processed foods. Although this dietary pattern may lead to short-term weight loss and improvements in certain metabolic parameters, adherence is challenging, and long-term exclusion of entire food groups may predispose to micronutrient deficiencies with potential adverse health consequences.⁸¹

Vegan diets, which eliminate all animal-derived foods, including meat, dairy products, and eggs, are often adopted for health, ethical, or cultural reasons. While well-planned vegan diets can be nutritionally adequate, inadequate intake of key micronutrients, particularly vitamin B12 and vitamin D, may occur if supplementation is not appropriately managed. This is particularly concerning during menopause, when nutritional needs increase due to changes in bone health and metabolism.⁸²

Extreme caloric restriction, such as very low calorie diets (VLCDs), typically providing less than 800 kcal/day, can produce rapid weight loss but may be associated with loss of lean body mass, metabolic adaptation, and risk of nutrient inadequacy if not medically supervised. Similarly, mono-diets, which involve the consumption of a single food or food group over prolonged periods, can lead to rapid but unhealthy weight loss accompanied by significant nutritional imbalance.⁸³

Intermittent fasting has become a popular dietary strategy that alternates between eating and fasting, with common

patterns including 16:8 or 20:4. While it may support weight loss and improve glycemic control in some individuals,⁸⁴ prolonged fasting may increase the risk of inadequate micronutrient intake if not carefully planned. During menopause, such risks warrant particular attention, as nutritional deficiencies may exacerbate fatigue, bone loss, and metabolic disturbances.

Refer to Table 9 for a nutrition plan for Indian Menopausal women (40-50 years) with a sedentary lifestyle.

“Let thy food be thy Medicine”.—Hippocrates

**Table 9: Nutrition plan for an Adult sedentary woman (1660 Kcal)
(My Indian Plate, ICMR-NIN, 2024)**

Food source	g/day
Cereals and millets	210 *(can be reduced)
Pulses (vegetarian), Egg and Flesh Foods(Lean/ not processed)	70
Nuts and Seeds	28
Vegetables (Seasonal and Coloured)	332
Fruit(Seasonal and Coloured)	85
Dairy products (low Fat)	250
Fats and oils	22.5 *(can be reduced)
Sugar (less than 5 percent of total Kcal)	*15
Salt	*4-5
Water	8–10 glasses

**Reduced considering a sedentary lifestyle. A regular increase in the number of steps through aerobic activity and resistance exercise is recommended. Limiting added salt and sugar is a recommendation. Modified and adapted from Dietary Guidelines for Indians (2024) 1*

MENOPAUSE AND THE MICROBIOME

Interest in the human microbiome has expanded considerably over the past two decades. Historically, microorganisms were classified within the plant kingdom, giving rise to the term microflora. With advances in taxonomy and molecular biology, microorganisms were reclassified into distinct kingdoms, and the term microbiota is now preferred to describe the collection of microorganisms residing in a specific anatomical niche. The microbiome refers to the ecological community of these microorganisms and their collective genomes within a defined environment.⁸⁵

The human microbiome consists predominantly of bacteria, but also includes viruses, fungi, and bacteroids. These organisms colonise various body sites and contribute significantly to local and systemic physiological functions, including immune modulation, metabolic activity, and maintenance of epithelial integrity. Disruption of this balanced ecosystem, termed dysbiosis, may result in pathological states. Traditional culture-based techniques substantially underestimate microbial diversity, as many microorganisms are not readily cultivated under standard laboratory conditions. The application of culture-independent methods, particularly 16S ribosomal RNA (rRNA) gene sequencing and metagenomic analysis, has enabled comprehensive characterisation of complex microbial communities.⁸⁵ These advances have transformed the understanding of host–microbe interactions across multiple organ systems.

Gut Microbiome and Menopause

The human gut microbiome comprises trillions of microorganisms, predominantly belonging to the phyla Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, and functions as a metabolically active organ that contributes to immune regulation, epithelial barrier integrity, bile acid metabolism, and short-chain fatty acid production.^{85,93} Beyond local gastrointestinal effects, the gut microbiome influences systemic metabolic and endocrine pathways.

Emerging evidence indicates that the estrogen decline associated with menopause significantly alters the composition and diversity of the gut microbiome. Postmenopausal women exhibit reduced microbial diversity and a shift toward a microbial profile more similar to that of age-matched men, suggesting a hormone-mediated restructuring of the gut ecosystem.^{86,87} These changes may contribute to increased systemic inflammation, metabolic dysregulation, adiposity, and cardiometabolic risk observed after menopause.

The gut microbiome influences estrogen metabolism through the estrobolome, a collection of bacterial genes encoding enzymes such as β -glucuronidase. These enzymes regulate enterohepatic recirculation of estrogens and circulating estradiol and estrone levels.⁹⁴ Alterations in estrobolome may therefore affect menopausal symptoms and drive estrogen-mediated pathologies,⁹⁵ with disruption of this microbial–hormonal axis potentially contributing to osteoporosis, metabolic syndrome, and hormone-dependent malignancies.⁹⁴

Interventional evidence supports this concept. In peri- and postmenopausal women, a probiotic formulation with β -glucuronidase activity significantly altered serum estrogen levels, suggesting that targeted manipulation of the gut microbiome may influence endocrine status.⁹⁶ Although preliminary, these findings provide proof-of-concept for microbiome-directed strategies in menopausal care.

Gut dysbiosis, characterised by reduced microbial diversity and altered metabolic activity, may contribute to hypoestrogenism and menopause-related mucosal and metabolic changes.^{87,94} Altered production of microbial metabolites, including short-chain fatty acids, may further modulate systemic inflammatory and metabolic pathways. Recent reviews further highlight the bidirectional gut–vaginal axis, wherein gut microbial communities may influence vaginal colonisation patterns and susceptibility to GSM. This reinforces the concept of menopause as a state of systemic microbial remodelling rather than isolated niche change.^{86,97}

Dietary modulation is a promising and practical therapeutic approach. Nutritional strategies aimed at improving microbial diversity and metabolic function, including prebiotics and probiotics, may complement MHT or, in selected cases, provide a supportive, standalone benefit.^{94,97} Preclinical data also suggest bidirectional interactions between estrogen therapy and the gut microbiome. In murine models, estrogen combined with bazedoxifene modified gut microbial composition and metabolic function, potentially altering estrogen metabolism.⁹⁷ However, robust high-quality interventional trials are still needed to confirm long-term efficacy and clinical impact.^{94,97}

SYNOPSIS

- A healthy menopause diet should be balanced and nutritious. Daily calorie requirements vary with activity: 2,000 calories for sedentary work, 2,230 calories for moderate work, and 2,800 calories for heavy work.
- The diet should provide approximately 50–60% of total calories from complex carbohydrates, $\leq 30\%$ from total fats with saturated fats contributing $< 10\%$, and 15% from protein. Protein should be obtained from a combination of animal and plant sources if possible, with an adequate intake of ~ 1 g/kg body weight per day. Cooking oils should be limited to ~ 15 g per person per day (~ 0.5 L per month), favouring a combination of oils rich in MUFA and omega3 PUFA.
- Consume at least 300 g of vegetables and 100 g of fruits daily, emphasising whole fruits over juices. Include high fibre, vitamin C-rich produce to support calcium absorption.
- Staple and functional foods include whole grains, legumes (lentils, kidney beans, bengal gram, soy), nuts (almonds, walnuts), seeds (flax, pumpkin, sunflower), and spices (cinnamon, fenugreek, saunf) to enhance nutritional quality and phytoestrogen intake.
- Consume 500–600 mL of low-fat milk or curds daily to support bone health, accompanied by vitamin C-rich fruits and vegetables to facilitate calcium absorption.
- Limit tea and coffee to ≤ 3 cups/day; caffeine intake should not exceed 200 mg/day. Drink at least 8 glasses of water daily.

- Foods to limit are ghee, vanaspati, butter, pickles, papad, chips, sweets, processed, canned, frozen, and packaged foods. Limit sugar intake to reduce empty calories. Use iodised salt and restrict to 3–5 g/day.
- Regular breakfast consumption is recommended. Snacks may include 2–4 nuts (almonds, walnuts), dried fruits (dates, figs, apricots), or seeds (pumpkin, sunflower). Add powdered flaxseed, cinnamon, fenugreek, or saunf to salads or curds for added nutrition.
- Natural remedies marketed as dietary supplements may cause more harm than benefit.
- During menopause, declining estrogen levels alter the composition of the gut and vaginal microbiomes, contributing to genitourinary and metabolic changes; emerging evidence suggests that hormone therapy and dietary interventions can help restore microbial balance and support overall health.

RESEARCH AGENDA

Evaluate culturally appropriate, diet-based interventions to reduce cardiometabolic and bone health risks in peri- and postmenopausal Indian women.

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EXERCISE THERAPY

Keywords: Exercise, benefits, fitness, types, circuit training, yoga, tai chi

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INTRODUCTION

In modern life, we rarely engage our muscles beyond our fingertips and rely solely on our body weight, contributing to sedentary lifestyles and chronic diseases. Non-communicable diseases (NCDs) cause 43 million deaths annually, accounting for 75% of non-pandemic deaths, with cardiovascular disease (CVD), cancer, chronic respiratory disease, and diabetes accounting for 80% of premature mortality.¹ Key behavioural risk factors include tobacco, harmful alcohol, excessive salt, and physical inactivity.²⁻⁴

Menopause increases NCD risk due to estrogen decline, which raises blood sugar and blood pressure and adversely affects lipids.⁵ Combined with poor diet and inactivity, this heightens susceptibility to CVD, diabetes, osteoporosis, and certain cancers. Early menopause (<45 years) further increases these risks. Lifestyle interventions, including regular physical activity, a healthy diet, and targeted healthcare, can reduce NCD risk and improve quality of life in menopausal women.^{3,4} In the Study of Women's Health Across the Nation (SWAN) study, researchers conclude that a healthy lifestyle during the menopausal transition is associated with less subclinical atherosclerosis, highlighting the growing recognition that midlife is a critical window for cardiovascular prevention in women.⁵

INDIAN CONTEXT

India, with a population exceeding 1.4 billion, has a female life expectancy of 73.6 years, projected to rise to 77 years by 2050.⁶ NCDs account for about 66% of all deaths in India, mainly due to CVDs, cancers, chronic respiratory diseases, and diabetes.⁷ Currently, over 120 million Indians are aged 50 or older, reflecting a rapidly ageing population.⁷ The mean age of menopause in Indian women is approximately 46 years, lower than that of Caucasian women, predisposing them to chronic disorders such as osteoporosis, diabetes, and CVD at an earlier age.⁸

Osteoporotic fractures are reported to occur 10–20 years earlier in Indian women than in Western counterparts, and type 2 diabetes and myocardial infarction also manifest about a decade earlier.^{9,10} According to the Indian Council of Medical Research (ICMR), India had an estimated 14 lakh cancer patients in 2016, and this number continues to rise. Breast cancer remains the most common cancer among Indian women, followed by cervical, oral, and lung cancers, together accounting for over 40% of the national cancer burden.^{11,12} The CVD burden has increased steadily, with India now accounting for nearly a quarter of global CVD deaths, projected to rise further with urbanisation and lifestyle transitions.¹²

HISTORY OF THE ROLE OF EXERCISE IN HEALTH

Until the mid-20th century, the health benefits of physical activity were poorly understood in medicine. In 1953, Professor Jeremy N. Morris and colleagues published a landmark epidemiological study in *The Lancet* examining CVD mortality among London double-decker bus drivers and conductors. Conductors, who climbed the bus stairs repeatedly during duty, had significantly lower rates of CVD and cardiovascular mortality than drivers who remained seated at the wheel. This seminal observation provided the first population-level evidence that habitual physical activity protects against CVD, and it is widely regarded as the birth of modern exercise epidemiology and physical activity science.¹³

IMPORTANCE OF EXERCISE AT MENOPAUSE IN INDIA

Meeta et al. conducted a multicentre, cross-sectional survey across hospitals in India to examine exercise habits among postmenopausal women. This study by the Indian Menopause Society included 1,180 participants from different hospitals. Results showed that walking was the most common exercise among older women, followed by yoga. In contrast, strengthening exercises were significantly less popular.¹⁴ This trend aligns with broader observations in India, where traditional exercises such as yoga are culturally ingrained, whereas resistance training is less emphasised. The preference for walking and yoga may be attributed to their accessibility, low cost, and cultural acceptance. However, the underrepresentation of strength training is concerning, given its proven benefits in

mitigating menopause-related health issues such as osteoporosis and sarcopenia. Addressing this gap requires targeted interventions to promote resistance exercise among postmenopausal women, emphasising its importance for maintaining musculoskeletal health and overall well-being.

HEALTH BENEFITS OF REGULAR EXERCISE/ PHYSICAL ACTIVITY

Regular physical activity is a proven strategy for improving health and preventing disease. Moderate to vigorous activity reduces the risk of CVD, type 2 diabetes, certain cancers, and obesity, while enhancing musculoskeletal strength, balance, and flexibility, thereby lowering the risk of falls and disability.¹⁵⁻¹⁷ It also benefits mental health, cognitive function, and sleep.¹⁸ Promoting physical activity across all ages is vital for longevity and quality of life (QoL).¹⁹ Higher cardiorespiratory fitness is associated with lower cardiovascular and all-cause mortality, independent of body mass index, underscoring fitness as a key determinant of survival.²⁰

RISKS OF EXERCISE

The health risks of physical inactivity far outweigh those of appropriately prescribed exercise. Promotion of physical activity should be integrated with basic safety strategies, especially in midlife and in postmenopausal women with chronic disease.²¹ Hyperthermia, hypothermia, and dehydration are potential preventable risks of physical activity. Musculoskeletal injury is the most common risk of exercise.²² More serious but much less common risks include arrhythmia, sudden cardiac arrest, and myocardial infarction.²³ Intense exercise can lead to amenorrhoea and infertility, particularly in women with low body weight. The “female athlete triad” consists of disordered eating, amenorrhoea, and osteoporosis.²⁴

EFFECT OF EXERCISE AND PHYSICAL ACTIVITY ON LONGEVITY

Regular exercise during menopause markedly reduces mortality risk, particularly from CVD. Even minimal levels of physical activity significantly reduce all-cause mortality in postmenopausal women, with a clear dose-response relationship between activity intensity and survival. In a cohort of 40,417 postmenopausal women aged 55-69 in the Iowa Women’s Health Study, followed for seven years, women who exercised once weekly had a 12% lower risk of mortality, while the most physically active women had nearly a 30% lower risk of overall mortality compared with sedentary women. The greatest reductions were observed in CVD and respiratory mortality, establishing physical inactivity as a major modifiable determinant of longevity in midlife women.²⁵ Long-term data from the Nurses’ Health Study and the Health Professionals Follow-Up Study further demonstrate that adopting healthy lifestyle behaviours, such as maintaining a normal body weight, engaging in regular physical activity, following a healthy diet, not smoking, and consuming moderate alcohol, increases disease-free life expectancy at age 50 by more than a decade, from 23.7 years with no low-risk factors to 34.4 years with ≥ 4 low-risk factors. In contrast, obesity markedly shortens healthy life expectancy and increases cardiometabolic and cancer risk.^{26,27} In a study of 2,500 postmenopausal women aged 63-99, 1 hour of daily moderate-to-vigorous activity reduced all-cause mortality by 40% and cardiovascular mortality by 60%, while an additional 2,500 steps per day reduced cardiovascular mortality risk by 34%.²⁸ Every 102-minutes of sitting time per day was associated with a 12% increased risk of all-cause mortality and a 30% higher risk of death from cardiovascular disease. Even light daily walking improved survival, underscoring that consistent physical activity enhances longevity and heart health in postmenopausal women, including cancer survivors.^{29,30}

BODY COMPOSITION AT MENOPAUSE AND EFFECT OF PHYSICAL ACTIVITY AND EXERCISE

The menopausal transition (MT) is associated with significant changes in body composition, including increases in fat mass and declines in muscle and bone mass, reflecting age-related and menopause-specific physiological changes, as well as lifestyle factors such as physical activity, diet, addictions, and sleep. Longitudinal population-based studies show that women experience a predictable, progressive increase in body weight during midlife, gaining on average approximately 0.6-0.7 kg (1.3-1.5 lb) per year between 50 and 60 years of age, largely independent of baseline body size and across racial and ethnic groups.³¹⁻³⁴ Maintaining or increasing participation in regular physical activity helps prevent or attenuate these gains.³¹ However, weight gain is not limited to midlife; numerous studies have documented an average yearly weight gain of 0.5-1 kg (1-2 lb) that may accumulate over years.³⁵

The Framingham Heart Study concluded that although postmenopausal women had higher body mass index (BMI) and increased visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT), the association was

predominantly due to age.³⁶ Beyond weight gain alone, menopause is associated with a preferential redistribution of adipose tissue towards the visceral compartment, even after adjustment for age, physical activity, smoking, and overall adiposity.³⁷⁻³⁹ After age 30, muscle mass declines at a rate of 3–8% per decade, making it more challenging to maintain.⁴⁰ This adverse remodelling of body composition results in a reduced basal metabolic rate and progressive loss of muscular strength and endurance, culminating in sarcopenic obesity and heightened cardiometabolic risk. It is further associated with musculoskeletal complications, increased cancer risk, adverse effects on cognition and mental health, and more severe menopausal symptoms, ultimately predisposing midlife women to functional decline and frailty.⁴¹

Peak bone mass is attained by age 35 years. From age 35 years onward, women lose bone mass at a rate of about 0.75–1.00% per year, or 1–2% per year (range 1–5% per year). This loss is most marked at the lumbar spine.^{42,43} Estrogen decline accelerates bone loss, muscle atrophy, and fat accumulation, increasing the risk of osteoporosis, sarcopenia, and central obesity.⁴⁴ Physical activity and regular exercise are essential in mitigating musculoskeletal and metabolic changes during menopause.⁴⁵ Weight-bearing and resistance exercises improve bone mineral density (BMD) and reduce fracture risk, while progressive resistance and impact training enhance muscle strength and lean mass.^{46,47} Aerobic and combined training decrease adiposity and improve cardiometabolic health.^{48,49}

Structured programmes lasting ≥ 12 weeks have been shown to benefit bone, muscle, and body composition.^{25,27} High-intensity resistance training at $\geq 70\%$ of 1 (RM), three times weekly, effectively increases BMD at the lumbar spine, femoral neck, and hip, making exercise a safe and essential non-pharmacological strategy during menopause.⁵⁰

EXERCISE EFFECT ON SARCOPENIA

Menopause accelerates sarcopenia due to declining estrogen.⁴⁴ Resistance and combined resistance-aerobic training preserve or increase muscle mass, strength, and function in postmenopausal women.⁵¹ High-intensity resistance programmes at $\geq 70\%$ 1RM, 2–3 times/week, for 12–24 weeks improve lower-limb strength, grip strength, and gait, reducing fall risk.⁵² Systematic reviews confirm that structured exercise is a safe, effective strategy to prevent sarcopenia and maintain physical function during menopause.^{49,51,52}

- *Age is no bar:* Resistance training, especially, targets the decrements in muscle mass and function typically seen in sedentary individuals. Evidence now indicates that one is never too old to benefit from exercise; this is true even for frail, institutionalised women as old as 100. Fiatarone and others even noted progressive gains in strength among frail 86–96-year-old men and women participating in a strength-training program.⁵³

EXERCISE EFFECT ON BONE HEALTH

Menopause accelerates bone loss, increases the risk of osteoporosis and spinal complications, and is associated with estrogen deficiency.⁵⁴ Regular exercise during menopause enhances physical function, bone health, and quality of life.^{55,56} Resistance training, particularly high- and moderate-intensity programmes performed 2–3 times weekly, significantly improves BMD at the lumbar spine, femoral neck, and hip, providing a safe, non-pharmacological strategy to prevent osteoporosis.^{50,57} Combined resistance, impact, and balance programmes are most effective for preserving skeletal integrity and functional mobility in postmenopausal women.⁵⁸ Balance and core-strengthening exercises, including yoga and Pilates, enhance postural control and reduce the risk of falling.^{59,60} Low-impact resistance training increases strength, flexibility, and balance, while moderate-to high-intensity activity reduces menopausal symptoms, including hot flushes.⁶¹

Back Exercises for Kyphosis

It is very important to understand that women with spinal bone loss should not do any exercises that involve forward bending, side bending, or rotational movements of the spine.⁶² The thoracic kyphosis of estrogen-deficient women is directly correlated with weakness of the back extensor muscles, and increasing the back extensor strength has been shown to decrease the kyphosis. This was a prospective 10-year trial. In this instance, when the torso is carried flexed forward, the patient will need to retrain the extensor muscles of the spine with isotonic resistance exercises. This is most effective when done in an upright, weight-bearing position. Exercises need to be done under expert guidance.⁶³⁻⁶⁵

Prolonged Exercise Has Diminishing Returns

During resistance exercise, adequate rest between loading bouts is essential to maximise musculoskeletal adaptation. Bone cells become transiently desensitised to continuous or prolonged mechanical loading, resulting in a diminished osteogenic response. Experimental studies demonstrate that approximately 98% of bone mechanosensitivity is restored after 24 hours of rest. Consequently, exercise regimens that incorporate short, high-intensity skeletal loading sessions separated by adequate rest periods elicit a greater boneogenic response than prolonged continuous loading.^{66,67}

EXERCISE EFFECT ON CANCER

Lifestyle modifications are crucial for improving outcomes in breast cancer survivors. Physical activity enhances metabolic health, body composition, and cardiorespiratory fitness, while diet and weight management improve quality of life.^{68,69} Adherence to lifestyle recommendations, including exercise, a healthy diet, smoking cessation, moderate alcohol use, and weight control, reduces cancer recurrence and all-cause mortality, with physical activity and never smoking as the strongest predictors.⁷⁰⁻⁷² The Women's Health Initiative Observational Study provides evidence that weight loss may have a preventive effect on new breast cancer incidence (HR 0.88; 95% CI 0.78-0.98; P 1/4 0.02) and provides mortality benefit (HR 0.65; 95% CI 0.45-0.94); P 1/4 0.02) for women with existing breast cancer. Integrating exercise, nutrition, sleep, stress management, and social support further improves survival and quality of life in cancer.^{73,74}

Weight loss after midlife significantly lowers breast cancer risk, and women who lose excess weight after age 50 achieve risk profiles comparable to those of women who maintain a stable normal weight, emphasising that it is never too late to benefit from lifestyle modification.⁷⁵

Higher levels of total physical activity, including light- and moderate-to-vigorous intensity activity, and greater daily step counts are associated with a lower risk of incident cancer, independent of sedentary behaviour.²⁸ A 3-year structured exercise programme initiated soon after completion of adjuvant chemotherapy for colon cancer was associated with significantly improved disease-free survival and findings consistent with longer overall survival.⁷⁶

EXERCISE EFFECT ON HOT FLUSHES IN MENOPAUSE

Evidence is insufficient to show whether exercise is an effective treatment for vasomotor menopausal symptoms. One small study suggested that Hormone therapy (HT) is more effective than exercise. The evidence was insufficient to demonstrate the relative effectiveness of exercise compared with HT or yoga; the limitation is that data are scarce.^{77,78} A meta-analysis revealed that aerobic exercise improved menopausal symptoms, although studies supporting its effect on vasomotor symptoms are lacking. Resistance muscle training improves postmenopausal symptoms, bone density, and functional capacity, with no difference in quality of life or body mass index.⁷⁹ Both approaches are safe, non-pharmacological strategies that have positive effects on women's health in the climacteric, hence should be prescribed as adjunctive lifestyle therapy rather than as primary treatment for vasomotor symptoms.

EFFECT OF EXERCISE ON MOOD ELEVATION AND COGNITION

Menopause increases the risk of mood disturbances, such as depression and anxiety, due to hormonal and psychosocial changes. Regular aerobic and resistance exercise significantly improves mood, reduces depressive symptoms, and enhances well-being through neurochemical and psychological mechanisms.^{80,81} Randomised trials show that exercising 3–5 times weekly for 12–24 weeks improves mood and quality of life but does not alleviate VMS.^{82,83} Thus, exercise is a safe, effective, and low-cost strategy for maintaining mental health during menopause.⁸⁴ Recent World Health Organisation (WHO) guidelines to reduce cognitive decline recommend regular exercise, maintaining a healthy weight, managing blood sugar levels, keeping cholesterol within recommended limits, and giving up unhealthy habits such as drinking and smoking. A study from the United Kingdom Biobank programme suggested that lifestyle measures could reduce the risk of cognitive decline, even in those at high genetic risk for dementia. In older adults at risk of cognitive decline, a structured, higher-intensity multidomain lifestyle intervention produced greater improvement in global cognitive function than a self-guided approach.⁸¹

PELVIC FLOOR MUSCLE TRAINING (PFMT) IN URINARY INCONTINENCE

The most common types of bladder dysfunction in midlife and older women are stress urinary incontinence (SUI) and urge urinary incontinence (UII), with mixed urinary incontinence (MUI) also frequently encountered. Several

conservative and physical-therapy-based modalities have been evaluated for managing these conditions, including PFMT/Kegel exercises, intravaginal resistance devices, vaginal cones, electrical stimulation, myofeedback, and biofeedback.⁸⁵ Among these, PFMT is the most extensively studied and widely recommended first-line physical therapy intervention, particularly for women with SUI. It is also recommended for women with MUI and, to a lesser extent, for UUI. A well-established Cochrane systematic review demonstrated that PFMT is significantly more effective than no treatment or placebo interventions for women with stress and MUI.⁸⁶ Supervised, intensive, and structured programmes were superior to standard or unsupervised regimens. PFMT was found to be at least as effective as, and in some comparisons superior to, certain forms of electrical stimulation.⁸⁶ Overall, the review provides strong support for the routine inclusion of PFMT as the cornerstone of first-line conservative management for stress, mixed, and UUI. However, the available evidence also indicates that most randomised trials have been conducted in younger, premenopausal populations, underscoring the need for further high-quality studies specifically addressing peri- and postmenopausal women.

OSTEOARTHRITIS AND EXERCISE

Exercise is safe, cost-effective, and disease-modifying in functional terms, and should be prescribed as first-line non-pharmacological therapy for knee, hip, and hand OA.⁸⁷ Exercise is strongly recommended for all patients, regardless of age or disease severity. Regular, structured physical activity reduces pain, improves joint function, enhances muscle strength, and slows disability progression without accelerating joint damage.⁸⁸ Best-evidence modalities include aerobic walking, quadriceps and hip strengthening, neuromuscular/balance training, and flexibility exercises. Weight loss achieved through exercise further reduces knee joint loading and symptom severity. Supervised progressive programmes are superior to unsupervised activity and improve long-term adherence. Low-impact activities (walking, cycling, swimming) are preferred, while high-impact twisting or jumping should be avoided in symptomatic joints.⁸⁹

PHYSICAL ACTIVITY AND EXERCISE: THE DIFFERENCE

Physical fitness comprises health- and skill-related attributes. Physical activity encompasses all movements produced by skeletal muscles that result in energy expenditure above resting levels, including activities performed during work, household chores, transport, and recreation.⁹⁰ Exercise, by contrast, is a structured, planned, and repetitive form of physical activity designed to improve or maintain specific components of physical fitness, such as cardiovascular endurance, muscular strength, flexibility, or balance.⁹¹ While all exercise is physical activity, not all physical activity qualifies as exercise. Both regular physical activity and structured exercise play vital roles in health promotion and disease prevention. Evidence shows that consistent participation reduces the risk of major NCD, including CVD, diabetes, cancer, and osteoporosis, and also improves mental health, cognitive function, and overall quality of life. Encouraging active living through daily movement and organised exercise programmes is therefore essential for maintaining health and longevity across all age groups.

RESISTANCE TRAINING

Resistance training is a cornerstone of adult fitness and healthy ageing. It is essential for developing and maintaining muscular strength, muscular endurance, fat-free mass, and BMD.⁹² The physiological adaptations to resistance exercise are site-specific; therefore, all major muscle groups should be trained through a full range of motion to achieve optimal functional and skeletal benefits. Muscular strength is best developed with higher loads and fewer repetitions, whereas muscular endurance is best developed with lighter loads and more repetitions. Both components are particularly important for midlife and postmenopausal women to maintain functional independence, prevent falls, and reduce fracture risk.⁹³

In women with osteoarthritis and inflammatory joint disorders, strengthening the periarticular muscles reduces joint loading, absorbs shock, improves balance, alleviates pain, and enhances mobility and quality of life. Strengthening exercises may be isometric or isotonic; isometric exercises involve muscle contraction without joint movement and are especially useful during acute pain or joint inflammation, as they strengthen muscles while minimising joint stress. Isotonic exercises involve joint movement and improve dynamic strength and functional capacity, with intensity easily modified by adjusting resistance or repetitions based on tolerance and symptoms.

For healthy midlife and postmenopausal women, dynamic resistance exercises are preferred because they most closely mimic daily activities. They should be performed two to three non-consecutive days per week at a moderate, controlled pace through a full range of motion, with normal breathing, preceded by flexibility exercises, and with

adequate recovery between sessions. Heavy resistance training may cause marked transient increases in systolic and diastolic blood pressure, particularly during breath holding or the Valsalva manoeuvre; therefore, proper breathing techniques must be emphasised, and women with cardiovascular risk factors should undertake high-intensity training under supervision.

YOGA IN MENOPAUSE

Yoga is a traditional Indian mind-body discipline that incorporates asana (postures), pranayama (regulated breathing), and meditation, aimed at restoring neuroendocrine and autonomic balance. Growing evidence supports yoga as an effective adjunctive therapy for managing menopausal symptoms, psychological distress, sleep disturbance, and impaired quality of life. Randomised controlled trials show that 8–12 weeks of integrated yoga therapy significantly reduces climacteric symptom scores, perceived stress, anxiety, and depressive symptoms, and improves overall quality of life compared with usual care or conventional physical activity.⁹⁴ Yogic practices modulate the sympathetic–parasympathetic balance, reduce oxygen consumption, stabilise heart rate and blood pressure, and induce a hypothermic relaxation response that may contribute to the relief of vasomotor symptoms.⁹⁵ Slow-paced breathing and relaxation techniques reduce the intensity of hot flushes, and structured pranayama programmes have demonstrated a 30–40% reduction in vasomotor symptom severity. Regular yoga practice increases central γ-aminobutyric acid (GABA) activity, improves mood and anxiety scores more than metabolically matched walking programmes, and enhances sleep quality.⁹⁶ Meditation has been shown to increase endogenous melatonin levels, thereby improving sleep efficiency and circadian stability.⁹⁷

- *Surya Namaskar*: A dynamic 12-posture yogic sequence performed rhythmically. It combines flexibility, muscular endurance, balance, and controlled breathing, making it a safe, low-impact whole-body conditioning exercise for midlife women.⁹⁸
- *Tai Chi and “Meditation in Motion”*: Tai Chi is a slow, flowing, low-impact mind-body exercise that improves balance, flexibility, muscle strength, joint mobility, and psychological well-being. It is particularly beneficial for women with musculoskeletal pain, osteoarthritis, and impaired balance. Its synchronised breathing and fluid movements promote relaxation, enhance postural control, and reduce the risk of falling.⁹⁹
- *Pilates*: Pilates is a low-impact, mind-body exercise system that emphasises core stabilisation, controlled movement, posture correction, flexibility, and breathing.¹⁰⁰

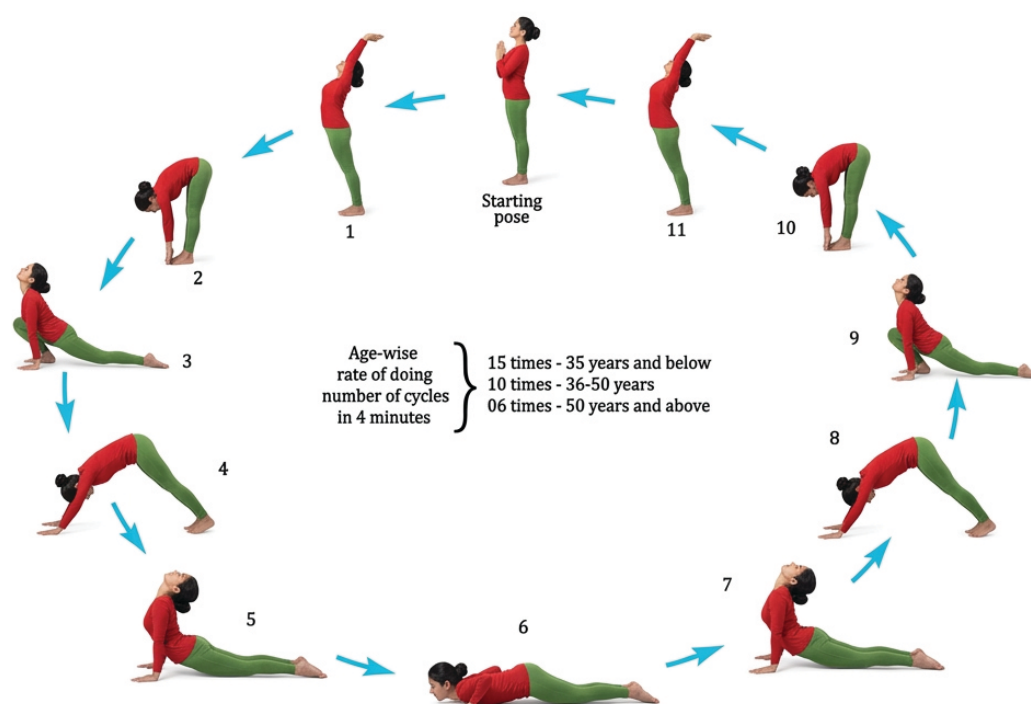


Figure 1: Surya Nmaskar

EXERCISE PRESCRIPTION: TYPES, DOSAGE, AND OUTCOME MEASUREMENT

Exercise may be divided into four major types, although these may overlap in a given activity: aerobic or endurance, resistance or strength, weight-bearing, balance, flexibility and mind–body exercises.

- Aerobic or endurance activities, such as brisk walking, cycling, swimming and dancing, improve heart and lung fitness, lower blood pressure and cholesterol, reduce the risk of diabetes, and enhance mood and longevity.
- Resistance and weight-bearing exercises, including squats, step-ups, dumbbell exercises, resistance band exercises and stair climbing, strengthen muscles and bones, prevent sarcopenia, improve BMD and reduce fracture risk.
- *Balance exercises* such as single-leg standing, heel-toe walking, Tai Chi, and yoga postures help prevent falls and postural instability.
- *Flexibility and stretching exercises* maintain joint mobility, posture and pain control. These gentle exercises should be done every day and are the most important of all exercises. Flexibility exercises can help protect joints by reducing the risk of injury, help us warm up for more strenuous exercise by getting our body moving, and help us relax and release tension from the body. These exercises can be done on land or in water, such as a pool, hot tub or warm bath. They can be particularly useful for easing stiff joints in the morning. A good range of motion exercises includes tai chi and yoga. Work up to 15 minutes of flexibility exercises a day.
- *Mind–body and breathing exercises*, including yoga, pranayama, and meditation. Regular practice for 20–30 minutes daily improves flexibility, muscle strength, balance, and psychological well-being; enhances sleep quality; and contributes to reduced vasomotor symptoms. It is recommended to reduce falls, improve mobility, and reduce perceived stress.
- *High-intensity interval training (HIIT)*, which alternates brief periods of intense activity with slower recovery, further improves insulin sensitivity, waist circumference, and cardiorespiratory fitness.
- *Circuit Training*: Circuit-based combinations of resistance and functional exercises improve strength, endurance, and mobility and have been shown to significantly enhance muscular strength, even in very elderly populations. 6–10 exercises performed sequentially with brief rests can be introduced after basic technique is learned, typically 1–2 sessions/week, with 30–60 s of work and 30–60 s of rest for 2–4 rounds, to improve strength, endurance, mobility, and adherence.⁹⁰
- *Functional fitness training* – This form of exercise prepares the body for daily activities. Functional fitness exercises use multiple muscles in the upper and lower body simultaneously, emphasising core stability.
- *The most effective regimen* for menopausal women combines aerobic, resistance, breathing and balance training to deliver optimal cardiometabolic, skeletal, mental health and functional fitness outcomes.
- *Duration of exercise*: Women should engage in at least 30 minutes of moderate-intensity physical activity on most days of the week (preferably ≥ 5 days/week) and muscle-strengthening exercises on at least 2 days per week. Engaging in 150–300 minutes of moderate or 75–150 minutes of vigorous activity per week significantly reduces all-cause mortality.¹⁰¹
- *The daily duration of activity may be individualised to meet health goals*: 30 minutes/day improves cardiorespiratory fitness and reduces chronic disease risk; 60 minutes/day helps prevent weight gain and maintain metabolic health; and 60–90 minutes/day supports the prevention of weight regain after weight loss.

All sessions should include appropriate warm-up and cool-down periods to reduce the risk of injury.

- *Intensity of aerobic exercise*: Exercise intensity can be assessed using simple, reliable methods such as the Talk Test, target heart-rate monitoring, perceived exertion scales, and metabolic equivalents (METs). With the Talk Test, the ability to sing indicates light-intensity activity, comfortable conversation reflects moderate intensity, and an inability to speak comfortably suggests vigorous intensity. Target heart-rate monitoring defines moderate-intensity exercise as 50–70% of the age-predicted maximum heart rate ($HR_{max} = 220 - \text{age}$). The Borg Rating of Perceived Exertion (RPE) scale (6–20) provides a subjective assessment of effort that integrates sensations of physical stress, fatigue, and breathlessness. METs provide an objective metabolic measure; 1 MET equals resting energy expenditure. Activities of 3–6 METs are considered moderate intensity, and those exceeding 6 METs are classified as vigorous.

- *Intensity of resistance exercise:* Intensities are typically determined as a percentage of the maximum weight a person can lift for a single repetition of a given exercise. That weight is called the one-repetition maximum (1-RM). Before prescribing strength exercise, the clinician or coach should explain how to determine a 1-RM for each exercise. Several online tables and calculators are available to help patients estimate a 1-RM.
- *Volume/Load:* The total mechanical or metabolic workload, calculated as frequency $\times$ duration $\times$ intensity for aerobic exercise and as sets $\times$ repetitions $\times$ external load for resistance training.
- *Accurate measurement* of physical activity is essential for evaluating its effects on health outcomes, guiding individualised prescriptions, and establishing dose–response relationships. Exercise can be quantified across several standardised dimensions.
- *Objective Measures:* Accelerometers, pedometers, wearable activity trackers, and heart-rate monitors provide quantitative data on step count, energy expenditure and activity intensity.
- *Subjective Measures:* Validated self-report tools such as the International Physical Activity Questionnaire (IPAQ) and activity logs are widely used in clinical and epidemiological research. However, they may be affected by recall bias.^{102,103}
- *Standardised measurement* enables reliable comparison across studies, accurate prescription of exercise interventions, and evaluation of dose–response effects on bone health, cardiometabolic risk, sarcopenia, mood, and menopausal symptoms.

PRE EXERCISE MEDICAL EVALUATION

Healthy, asymptomatic midlife women without known chronic disease do not require routine medical clearance before initiating moderate-intensity physical activity; targeted screening should be reserved for women with known disease or suggestive symptoms. In symptomatic midlife women with known chronic disease, exercise should be initiated at low to moderate intensity, with gradual, individualised progression based on tolerance and clinical response. Preferred modes include walking, stationary cycling, aquatic exercise, and chair-based resistance training, which provide cardiovascular and musculoskeletal benefits while minimising joint stress and injury risk. Initial supervision is recommended, particularly for women with cardiovascular, metabolic, or musculoskeletal comorbidities. High-intensity, ballistic movements and Valsalva-type exertion should be avoided, as they may precipitate excessive blood pressure responses or injury. Ongoing monitoring of blood pressure, symptoms, and blood glucose levels in women with diabetes is essential to ensure safety and guide progression.¹⁰⁴

EXERCISE SAFETY AND INJURY PREVENTION

Safe exercise practice is essential for maximising health benefits while minimising injury risk, particularly in midlife and among postmenopausal women. Exercise-related musculoskeletal injuries are common but largely preventable through adherence to basic safety principles. All exercise sessions should include a 5–10-minute warm-up and cool-down, static stretching of major muscle groups, core muscle engagement, appropriate footwear and protective equipment, and gradual progression of exercise intensity. Movements should be performed within a comfortable, pain-free range of motion, using slow, controlled technique, avoiding breath holding, joint locking, and unaccustomed vigorous exertion. These evidence-based strategies substantially reduce the risk of strains, sprains, and overuse injuries while enabling safe participation in physical activity.⁹⁰ Warning symptoms during or after exercise should never be ignored. Medical evaluation is advised if an individual experiences extreme breathlessness persisting for 5–10 minutes after completing exercise, prolonged fatigue or unexplained loss of energy, dizziness, chest discomfort or pain, a persistently rapid heart rate for 5–10 minutes post-exercise, nausea immediately after activity, persistent muscle or joint pain, or new-onset difficulty with sleep. These features may indicate excessive physiological strain, underlying cardiopulmonary disease, metabolic imbalance, or musculoskeletal injury and warrant prompt clinical assessment before further exercise is undertaken.¹⁰⁴

HOME-BASED EXERCISE PRESCRIPTION FOR A HEALTHY WOMAN AT MENOPAUSE

A multicomponent home-based exercise program integrating aerobic, resistance, balance, flexibility, and postural conditioning provides comprehensive protection against cardiometabolic disease, fractures, falls, and functional decline in healthy menopausal women.



Figure 2: Global recommendations: Physical activity in middle-aged and older adults (50+ years of age).

- Aerobic Exercise
 - *Frequency:* 3–5 days per week
 - *Intensity:* Moderate to vigorous (≈ 50 – 70% heart-rate reserve)
 - *Duration:* 30–60 minutes per session (minimum ≥ 150 minutes/week)
 - *Mode:* Brisk walking, cycling, swimming, treadmill walking, elliptical training, or similar rhythmic large-muscle activities
 - *Progression:* Gradual increase in duration and/or intensity based on tolerance to enhance adherence and minimise injury risk
- Resistance Training
 - *Exercises:* Wide-leg squats, step-ups, lunges, seated overhead press, chest press, biceps curls, side-leg raises, calf raises, and back extensions
 - *Frequency:* 2–3 non-consecutive days per week
 - *Intensity:* Moderate to high (60 – 80% 1-RM; 8–12 repetitions/set)
 - *Volume:* 2–3 sets per major muscle group
 - *Mode:* Free weights, resistance bands, machines, or body-weight exercises
 - *Progression:* Gradual increase in resistance or repetitions; reassess 1-RM every 6–8 weeks
- Abdominal & Postural Conditioning
 - *Tummy tucks and reverse curls* strengthen abdominal and spinal stabilisers, improve posture, and enhance spinal protection, particularly in women with vertebral osteoporosis.

- *Flexibility & Stretching* Regular stretching of the neck, shoulders, back, hips, thighs, hamstrings, and ankles maintains joint mobility, reduces stiffness and musculoskeletal pain, and supports optimal posture.
- *Frequency:* ≥2–3 days per week
- *Duration:* 10–15 minutes per session
- *Mode:* Static and dynamic stretching; yoga- and Pilates-based routines
- *Balance Training:* Balance exercises enhance proprioception and postural control and significantly reduce fall risk.
 - *Frequency:* 2–3 days per week
 - *Duration:* 20–30 minutes per session
 - *Mode:* Tai chi, yoga, Pilates, single-leg stance, heel-to-toe (tandem) walking, mountain pose, and dynamic balance drills.
 - *Breathing and Relaxation; Paced/Diaphragmatic Breathing Exercises:* Improve autonomic balance, reduce vasomotor symptoms, enhance sleep quality, and reduce stress and anxiety. Paced/diaphragmatic breathing may be prescribed for 10–20 minutes once or twice daily (target ~6 breaths/min), continued for at least 6–12 weeks, with brief “as-needed” practice during vasomotor episodes.

Some Exercises That Can Be Done at Home

These simple, safe exercises help strengthen bones, improve muscle mass, balance, posture, and overall mobility

Exercise 1: Wide Leg Squat

It strengthens the muscles of your front, back and inner thighs, as well as your buttocks and the hip bones. Stand about 6 inches in front of the chair with your feet a little wider than shoulder-width apart.

- 1-2-3-Down: Take a deep breath, then sit back on your buttocks and slowly lower yourself into the chair. Keep your knees above your ankles; pause, then slowly stand. Then repeat the move 8–16 times.

Exercise 2: Step Up

Strengthens the muscles on the front and back of the thigh, hip bones also improve balance and coordination.

Starting position: Stand close to the bottom step of a sturdy staircase with a handrail and hold it. Step up to the first step with one leg.

- 1-2-3-Up: Lift your body straight up using the muscles of your front leg so that your back foot reaches the level of the first step. Tap the toes of your back foot on the step. Slowly return to the starting position. Repeat the move with the same front leg. Your foot should remain on the first step while you complete all reps in the set.

Exercise 3: Seated Overhead Press

- Strengthen the muscles of the upper spine and shoulders. Improves posture—an important benefit for women with spinal osteoporosis.
- Starting position: Sit upright towards the front of the chair with your feet flat on the floor, about hip-width apart. Hold one dumbbell in each hand, keeping your upper arms at your sides.
- 1-2-3-Up: Slowly press the dumbbells straight up. Extend your arms, but do not lock your elbows. Pause for a breath.
- 1-2-3-Down: Slowly return to the starting position and repeat.

Exercise 4: Forward Fly

Strengthens the muscles of your shoulders and upper back, strengthens your bones, and improves your posture. If you already have some spinal curvature, strengthening your upper back muscles will help you improve your posture as much as possible.

- Caution: If you have crush fractures or spinal curvature, discuss this exercise with your doctor. Starting position: Sit in the chair with your feet flat on the floor, hip-width apart. Your thigh and lower leg should be perpendicular to

each other. Holding a dumbbell in each hand, bend forward from your hips by about 3–5 inches. Keep your back flat and your spine straight. The forward movement comes from your hips. Hold the dumbbells straight up in front of your chest with your palms facing inwards. Bend your elbows slightly.

- 1-2-3-Up: Pull your shoulder blades together, moving your elbows as far back as possible.
- 1-2-3-Down: Slowly return your arms to the starting position and repeat.

Exercise 5: Back Extension

This exercise strengthens the muscles in your buttocks and the back muscles that support your spine. Strengthening these muscles stimulates the bones of your hip and spine.

- *Starting position:* Lie face down on a mat or towel with your legs straight and your toes pointed so that the laces of your trainers face the floor. Place your right arm down along your side and your left arm straight up above your head. Your right palm should face up, while your left palm faces down.
- 1-2-3-Up: Raise your right leg and left arm as high off the floor as you comfortably can. Lift your leg from the hip, keeping it straight. As you lift your arm, your head and neck will rise too; keep them in line with the arm. Move your arm and leg together as smoothly as possible. Pause for a breath in the lifted position.
- 1-2-3-Down: Slowly return to the starting position.
- Take a breath, then repeat the move.

Exercise 6A: Abdominal Exercise 1-Tummy Tuck

Strengthening your abdominal muscles is one of the best things you can do for good posture. The combination of strong back and abdominal muscles helps stabilise your torso and protect your spine. Of course, tighter abs also look better. Use the first version of the exercise until it stops being challenging. Then move on to the second version, which is more difficult.

- *Starting position:* Lie on your back with your knees bent and your feet flat on the floor. Your feet should be hip-width apart and about 12–18 inches from your buttocks. Place one hand on your stomach to feel your abdominal muscles working as you perform the exercise. Your other arm should be extended straight at your side, palm down.
- 1-2-3-Up: Press the small of your back against the floor and contract your abdominal muscles, tilting your pelvis towards your shoulders. Your pelvis and the bottom of your buttocks should come up only a few inches off the floor. Pause for a breath.
- 1-2-3-Down: Slowly return to the starting position.
- Take a breath, then repeat the move.
- *Reps and sets:* Repeat until you have completed eight tummy tuck moves—this is the first set. Rest for a minute or two, then do a second set.

Exercise 6B: Abdominal Exercise 2—Reverse Curl

When the tummy tucks are no longer challenging, and you are easily able to bring your entire buttocks off the floor in a steady movement, substitute the reverse curl. This is a more difficult move that also strengthens your abdominal muscles.

- *Starting position:* Lie on your back with your knees bent, thighs together, and the small of your back pressed against the floor. Lift your feet off the floor by about 5-8 inches so your thighs are perpendicular to your body. Place one hand on your stomach to feel your abdominal muscles working during the exercise. Extend the other arm straight at your side with the palm facing down.
- 1-2-3-Up: Contract your abdominal muscles to lift the bottom of your buttocks up and back towards your shoulders. Your knees will move approximately 1–3 inches as you lift, coming up slightly and towards your chest. Pause for a breath.
- 1-2-3-Down: Slowly move your buttocks and thighs back to the starting position. Pause for a breath, then repeat. The small of your back should remain on the mat throughout the set.
- *Reps and sets:* Repeat until you have done eight reverse curls; this is the first set. Rest for a minute or two, then perform a second set.

Exercise 7: Side Leg Raise

This is one of the best exercises for strengthening the muscles and bones of the hip and thigh. Developing the muscles on the outside of your hip is also important for agility and balance.

- *Starting position:* Strap an ankle weight to each leg. Lie on the floor on your left side with your legs straight and together, one on top of the other. Bend the lower part of your left leg back behind you, keeping your hips and knees aligned. Support your head with your left arm and place your right hand on the floor in front of you for balance. 1-2-3-Up: In a slow, controlled movement, lift your top leg while keeping your trunk straight, then slowly return to the starting position.
- Pause for a breath, and then repeat the move with the same leg.

Exercise 8A: Ankle Exercise 1 - Standing Calf and Toe Raise

This exercise increases lower-leg strength and ankle flexibility, thereby improving balance.

- *Starting position:* Stand facing a counter or wall, about 6–12 inches away, with your feet hip-width apart.
- Place your fingertips lightly on the counter or wall for balance. 1-2-3-Up: Slowly raise yourself as high as possible on the balls of your feet. Hold for three seconds, then lower yourself back to the starting position.

Exercise 8B: Ankle Exercise 2—Push and Pull Toes

You will further strengthen your calves and ankles with this more advanced version of the exercise. Strong lower legs make it easier to climb stairs, walk more easily, and maintain your balance.

- *Starting position:* Sit in a chair with your feet flat on the floor. The seat should be deep enough to support your entire thigh. Strap the ankle weights snugly around your feet so they rest on top of your shoelaces. Position yourself so your back is against the back of the chair. Place your hands on your thighs and extend your legs slightly so your heels are 3–4 inches off the floor.
- *1-2-3-Push:* While keeping your legs raised off the floor, push your toes away from you as far as you can.
- *1-2-3-Pull:* Pull your toes towards you as much as you can.
- Pause for a breath, and then repeat eight to 12 times.

Exercise 9: Chest Press

Strong chest muscles contribute to good posture and a strong back. This exercise strengthens your chest muscles (under your breasts), the front of your shoulders, and the backs of your arms. These muscles help support your breasts and are important for pushing and lifting. *Starting position:* Place your dumbbells on the floor far enough apart to lie between them. Lie on the floor with your knees bent. Carefully pick up the dumbbells. Move your upper arms out to the sides so they rest on the floor. Raise your forearms straight up and parallel to each other, like goalposts. Your palms should face your feet, with your wrists and elbows in a straight line. Position the dumbbells in line with your mid-chest.

- *1-2-3-Up:* Press the dumbbells straight up until your arms are fully extended, with your wrists, elbows and shoulders in a straight line. Your elbows should not be locked. Pause for a breath, then slowly lower the dumbbells back to the starting position and repeat.

Exercise 10: Biceps Curl with Rotation

Strengthening the biceps increases the density of the wrist bone, a common site for osteoporotic fractures, and this exercise will help you carry heavy loads with ease.

- *Starting position:* Sit towards the front of the chair with your feet flat on the floor, about hip-width apart. Hold a dumbbell in each hand so that your elbows and upper arms are snug against your sides. Your forearms should be extended straight down at your sides, with your palms facing your thighs.
- *1-2-3-Up:* Raise the dumbbell in one hand towards your shoulder by bringing your forearm up.
- *1-2-3-Down:* Slowly lower the dumbbell and rotate your forearm to return to the starting position.

Exercise 11: Front Lunge

The lunge is a dynamic exercise that targets the muscles of the thighs, back and buttocks, strengthening the bones in the hip and spine. The wide-leg squat targets the same muscles, but the lunge also engages balance and coordination.

- *Starting position:* Stand next to a table or counter with your feet hip-width apart and knees slightly bent. Lightly hold the counter with one hand.
- *1-2-3-Forward:* Take a large step forward with your right leg. Land on the heel of your right foot, then roll your foot forward until it is flat on the floor. Keep your body erect. Bend both knees so your hips drop straight down. Your front thigh should be almost parallel to the floor, and the knee of your back leg should approach the floor. The knee of your forward leg should be over your ankle, not past your toes. The heel of your back leg will come off the floor. Your weight will be equally distributed between your front foot and the ball of your back foot. Pause for a breath.
- Push back forcefully with the front leg to return to the starting position. Pause for a breath, then repeat the move.
- *Reps and Sets:* Alternate legs as you step forward until you have done eight reps with each leg—this is the first set. Rest for a minute or two and do a second set. Stretching is a vital component of any exercise programme. A brief stretch after your workout is a wonderful way to relax and helps prevent injury and maintain flexibility. Furthermore, stretching helps reduce back pain from osteoporosis and other aches and pains.

FLEXIBILITY/STRETCHING EXERCISES

General Instructions

Stretching is necessary after you strength-train or do aerobic exercise, but you can stretch as often as you please. A stretch is one of my favourite pick-me-ups when I am working at my computer. Take a 2-minute stretch break every hour to relieve tension in your neck, back, and shoulders; it is a real revitalizer that makes you feel good all over.

- *Neck:* sit or stand comfortably, then flex your neck backwards so that your face is looking at the ceiling. Repeat slowly 10 times. Then turn your head from side to side (left to right, so that the ear touches the shoulder). Repeat 10 times.
- *Eyes:* from a sitting position, look straight ahead. Then slowly raise your eyes up and down, then side to side. Repeat 10 times.
- *Shoulders:* with arms bent and fingertips touching the shoulders, make circular motions with the elbows. Repeat 10 times clockwise and 10 times counterclockwise.
- *Elbows:* stretch out the arms at shoulder height with palms facing upwards. Bend the arms at the elbows and touch the shoulders with your fingertips; then straighten the arms again. Repeat 10 times with arms in front, then with arms extended to the sides.
- *Wrists:* flex and extend the wrists 10 times. Rotate your wrists clockwise and counterclockwise ten times each. Now hold the hand in extension and move it from side to side at the wrist. Repeat 10 times.
- *Fingers:* lift your arms to shoulder height. Keeping your arms straight, open your hands wide. Flex your fingers, closing over your thumbs. Repeat 10 times.
- *Shoulders, hands and waist:* keep knees slightly flexed. Raise arms overhead. Hold the elbow with the hand of the opposite arm. Gently pull the elbow behind the head as you slowly lean to the side until a mild stretch is felt. Hold for 10–15 seconds. Repeat on the other side.
- Stand with back straight, legs slightly apart. Keep the hands on the back and hip bone and bend backwards slowly, holding for a few seconds, then return to the starting position. In the same position, rotate the hips slowly clockwise and anticlockwise.
- Stand with your feet together, then slowly bend at the waist to touch your toes. Keep your knees straight. Repeat 10 times. Remain standing, then spread your legs about 2 feet apart. Bend to the left at the waist first, then reach your right arm over your head. Repeat five times. Then repeat, bending to the right with your left arm over your head.
- *Thighs:* Stand a little away from the wall and place your left hand on the wall for support. Standing straight, grasp the top of the left foot with the right hand. Pull heel towards buttock. Hold for 10–20 seconds. Repeat on the other side.
- *Hips:* while sitting, bend the left leg and place your left foot on your right thigh. Hold the left knee with the left hand

and the left ankle with the right hand. Gently move the knee up and down with the left hand; then repeat with the right leg.

- Now rotate the left knee clockwise 10 times, then counterclockwise 10 times. This improves hip flexibility. Repeat with the right knee. For hip flexibility, bring the soles of the feet together and draw the heels toward the body. Using your hands, press your knees to the floor and let them come up again. Repeat 10 times.
- *Knees:* bend the right leg and bring the heel towards your buttock. Then lift the right leg off the floor and straighten the right knee, repeating 10 times. Then do the same with the left leg and knee, 10 times. Next, holding your thigh close to your body, rotate your lower leg as you did your ankle, 10 times clockwise and 10 times counterclockwise.
- *Ankles:* rotate your ankles in each direction 10 times, keeping heels on the floor.
- *Toes:* place your hands at your sides and flex your toes 10 times.

Hamstring stretch

You will need a towel for this stretch, which improves the flexibility of the hamstring muscles in the backs of your thighs and your lower back. It promotes back flexibility, reducing the risk of injury and relieving and preventing lower back pain. These exercises are safe and very beneficial for women with osteoporosis.

- *Starting position:* Lie on your back on the floor, holding the ends of a towel. Bend your knees with your feet flat on the floor, and press the small of your back into the floor. Bend one knee towards you and loop the towel around the bottom of your shoe. Extend this leg straight up so the sole of your shoe is flat and facing the ceiling. Your knee should not be locked. The towel will help you maintain the correct position. The stretch: Slowly pull on both ends of the towel to draw your leg towards your body until you feel a gentle stretch. The leg may move just an inch or several inches, depending on your flexibility. Keep your buttocks on the mat. Also, be sure to keep the foot of the stretched leg flat. If you point your toe towards the ceiling, the stretch will not be as effective. Hold the stretch for 20–30 seconds.
- Breathing normally and relaxing the rest of your body. Then release. Reps: Perform a stretch with each leg. Repeat if desired. You will feel the stretch along the back of your thigh and calf.

Shoulder stretch

This stretch will help improve your posture and back flexibility, plus, it is a great tension reliever. Starting position: Stand with your feet hip-width apart, knees slightly bent, and shoulder blades drawn slightly together at the back. Lace your fingers together and then rotate your wrists so your palms face away from you.

Press your palms out and away from your body until your arms are straight but unlocked. Keeping your shoulders down and back, lift your arms up to chest height.

- *The stretch:* Press your palms away from you until you feel gentle tension across your back and shoulders. Do not bend your spine forward when performing this exercise. Also, be sure not to lock your elbows. Check for tension in your neck. Your entire body, except for the parts you are stretching, should be relaxed. Hold the stretch for 20–30 seconds, breathing normally.
- *Reps:* Perform 1 stretch. Repeat if desired. You will feel the stretch across your back, shoulders and arms.

Upper back pullback

This is a particularly helpful exercise for women with osteoporosis, back pain, or a curved spine. It stretches the muscles of your chest and the middle of your upper back, improving posture and relieving pain. You can perform this stretch whenever you are sitting down. I do it hourly while sitting at my desk.

- *Starting position:* Sit towards the front of your chair with your feet flat on the floor and hip-width apart. Bend your elbows so that your forearms are parallel to your thighs and your upper arms are against the sides of your body.
- *The stretch:* Press your shoulders down and draw your shoulder blades together at the back. Your upper arms will move back slightly. Sit with good posture and hold the stretch for 20–30 seconds, breathing normally and relaxing the rest of your body. Pause for a moment, then repeat if desired.
- *Reps:* Perform 1 stretch. Repeat if desired. You will feel the stretch across your chest and in your biceps.

Breathing exercise

- Inhale-Hold-Exhale can be done while sitting, lying down, standing, or walking. Repeat four times, twice a day.
 - Exhale through your mouth while making an audible sound.
 - Close your mouth and inhale quietly through your nose for a count of four.
 - Hold your breath for seven counts.
 - Exhale audibly through your mouth for a count of eight.
- Inhale-Exhale, do this once a day, increasing the duration of the exercise by 5 seconds until you can do a full minute.

Sit comfortably, keeping your back straight, and eyes closed. Breathe in and out rapidly through your nose. Keep the breaths equal and short, and keep your mouth lightly closed.

- Paced respiration is a technique that uses slow, controlled, diaphragmatic breathing. In three randomised prospective trials, paced respiration reduced the frequency of hot flushes by 50%.

Deep abdominal breathing. Lie flat on your back with your knees pulled up, keeping your feet slightly apart. Inhale deeply through the nose, allowing your stomach to relax. Your stomach should balloon out as you breathe in. Imagine your body filling with energy with each inhalation. As you exhale, imagine the air being pushed from the bottom to the top of your lungs. This breathing technique promotes deep relaxation, increased energy, and stress management.

THE EXERCISES FOR IMPROVING BALANCE

Aim to do the balance exercises at least three times per week after your strength-training workout. They are a great way to cool down, and if you enjoy them, you can do them as often as you like. They do not require a warm-up or cool-down.

Mountain Pose and Sway

- *Position:* Stand with your feet close together, touching if possible, with knees slightly bent. Distribute your body weight evenly between the balls and heels of your feet. Keep your arms straight at your sides, with your hands relaxed. Your shoulders should be down and gently drawn back; your head should be high. Tuck the bones of your pelvis under, moving them slightly forward and up. Working from the soles of your feet, visualise how each part of your body rises from the part below it. See how your shinbones rise from your feet to your knees. Notice how the slight bend of your knees allows your thigh and hip bones to extend upwards in neutral alignment. Feel your rib cage expanding and lifting. Sense how the vertebrae of your spine stack on top of each other. Imagine the spaces between the vertebrae expanding, lengthening your spine. Your head should feel almost weightless, and you should feel slightly taller than before the pose.
- Hold this position for a minimum of 30 seconds up to 2 minutes, breathing evenly.

One-legged stork

This exercise is also adapted from a classic yoga pose. It is designed to improve your posture, balance, and hip flexibility.

- *Position:* Stand to the side of a counter or wall with your feet hip-width apart. Keep your knees slightly bent. Lightly touch the counter or the wall with one hand for support; hold your other arm straight out to the side. Bring one knee up slightly, about 6 inches, keeping your back straight. Point the toes of that foot down and turn your knee out to the side by rotating your hip. Place the bottom of your foot against your opposite shin. Keep your head up and your eyes focused straight ahead.
- Hold this position for a minimum of 30 seconds, up to 2 minutes.
- Release the pose: Lower your knee and return to the starting position.

Tandem walk

Police use the tandem walk to test for drunk driving— it is nearly impossible to perform if your balance and coordination are compromised by alcohol. Though the test is very helpful for those with poor balance, it is not sufficiently challenging for those with good balance.

- *Starting position:* Find a hallway with a clear wall where you can walk at least 10–20 steps while holding on to it. Place one hand on the wall at shoulder height for support. Focus your eyes on a point straight ahead. Keep your head up and do not look at your feet.

The global recommendation for physical activity for mature adults and the elderly is shown in Figure 8

COST-EFFECTIVENESS OF PHYSICAL ACTIVITY AND EXERCISE AT MENOPAUSE

Unsupervised physical activity sessions of at least 50 minutes, four times a week, were cost-effective for cardiorespiratory fitness, lean muscle mass, and QALYs gained among menopausal women.¹⁰³ Another study found that the programme could be considered cost-effective, although the overall difference in health benefits and costs was very modest. Longer-term follow-up is needed.¹⁰⁴

SYNOPSIS

- Exercise plays a vital role in healthy ageing, as the saying goes, “Ageing happens, but good health is planned.”
- Exercise during menopause transition is essential for maintaining physical function, bone health, metabolic health, and psychological well-being.
- Evidence-based guidelines emphasise that programmes should be individualised, progressive, and multimodal, combining aerobic, resistance, flexibility, and balance training.
- Aerobic: ≥150 min/week of moderate-intensity or 75 min/week vigorous activity.
- Resistance: 2–3 days/week, targeting major muscle groups, 8–12 repetitions per set.
- Flexibility/Balance: 2–3 days/week, 15–30 min per session.
- Screen for cardiovascular risk, osteoporosis, and musculoskeletal issues before starting an exercise program.
- Use proper technique and consider supervision initially, especially for resistance exercises. Encourage gradual increases in intensity, volume, or complexity to prevent overuse injuries.
- Combine exercise with a healthy diet, stress management, sleep hygiene, and smoking cessation to optimise health outcomes. Encourage consistency; even home-based or short-duration sessions yield significant benefits.

COST-EFFECTIVENESS OF PHYSICAL ACTIVITY AND EXERCISE AT MENOPAUSE

RESEARCH AGENDA

Effectiveness of online yoga intervention on Menopause-Specific QoL among Indian Women: A Randomized controlled trial

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IMMUNIZATION

Keywords: Immunisation, vaccine-preventable diseases, adult vaccination

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INTRODUCTION

Vaccination in adults is a critical preventive strategy for reducing the burden of infectious diseases, which were previously managed largely through antimicrobial therapy. With the rapid emergence of antimicrobial resistance, vaccines have become increasingly important as a sustainable public-health intervention to prevent infections and their complications, rather than relying solely on treatment.¹ Additionally, vaccination has evolved beyond infection control to become an effective cancer-prevention strategy, with established evidence demonstrating that human papillomavirus (HPV) vaccination prevents cervical cancer and that hepatitis B immunisation prevents hepatocellular carcinoma, marking a paradigm shift in preventive medicine.^{2,3}

In the Indian context, adult vaccination is recognised as a highly cost-effective public-health intervention, with evidence demonstrating substantial reductions in healthcare utilisation, productivity losses, and economic burden from vaccine-preventable diseases (VPDs), yielding a favourable return on investment even in resource-constrained settings.⁴ Despite these advances, adult vaccination has historically received limited attention in India, where public-health priorities have been predominantly focused on achieving universal childhood immunisation. Although India has made substantial progress in paediatric vaccination, complete coverage has not yet been achieved, and this has inadvertently contributed to adult immunisation being accorded lower priority at the national level.^{4,5}

Until recently, adult vaccination practices in India were largely fragmented, opportunistic, and clinician-driven. In 2024, updated expert consensus guidance on adult immunisation was released in India, representing an important step toward standardising adult vaccine recommendations.⁶ However, despite this progress, India does not yet have a centrally mandated, uniformly implemented national adult immunisation programme comparable to the Universal Immunisation Programme for children, and uptake of adult vaccines continues to vary widely across regions and healthcare settings. As a result, implementing structured adult vaccination strategies remains challenging in a resource-constrained environment, where childhood immunisation targets continue to face logistical and coverage barriers.

Nevertheless, increasing awareness of the value of adult vaccination, combined with the identification of practical strategies to overcome barriers such as cost, limited awareness, and the absence of structured delivery mechanisms, can empower clinicians in India to develop context-appropriate adult immunisation practices. Such efforts have the potential to significantly reduce morbidity and mortality associated with VPDs, particularly among high-risk and ageing populations.

The Coronavirus Disease 2019 (COVID-19) pandemic served as a global eye-opener, clearly demonstrating the ability of vaccines to limit severe disease, hospitalisation, and mortality at the population level.⁶ This lesson is especially relevant for midlife and older women, including those in the peri-menopausal and postmenopausal period, in whom immunosenescence, hormonal changes, and age-related physiological decline may increase susceptibility to infections and their complications. Integrating adult vaccination into preventive healthcare for women aged 40 years and above offers a valuable opportunity to preserve health, functional capacity, and quality of life (QoL) during the menopausal transition (MT) and beyond.

AGE AND IMMUNE RESPONSE

The efficacy of vaccination depends on the quality and magnitude of the immune response generated in the vaccinated individual. Ageing is associated with progressive alterations in both innate and adaptive immunity, leading to diminished and sometimes delayed responses to vaccines. This process, termed immunosenescence, is characterised by reduced naive T-cell output, impaired B-cell function, altered cytokine profiles, and a decline in immune memory.^{7,8} Consequently, vaccine-induced immune responses in older adults may be suboptimal compared with those in younger individuals, despite a greater clinical need for protection. Older adults are therefore a key target population for vaccination. Naturally acquired immunity wanes with age, and the high prevalence of comorbid conditions such as cardiovascular disease, chronic respiratory illness, diabetes mellitus, chronic kidney disease, and metabolic disorders

further increases susceptibility to VPDs.^{4,9} Infections in this age group are more likely to be severe and are associated with increased rates of complications, hospitalisation, functional decline, and mortality.¹⁰ Despite reduced immunogenicity, vaccination in older adults remains highly beneficial. Even partial immune responses can significantly reduce disease severity, complications, and mortality. This has been consistently demonstrated for vaccines against influenza, pneumococcal disease, COVID-19, and herpes zoster, which have led to substantial reductions in severe outcomes among older populations.^{11,12} Immunosenescence should therefore be viewed not as a barrier, but as a rationale for timely, targeted, and optimised adult vaccination strategies, particularly in ageing populations such as India.

GENDER AND IMMUNE RESPONSE TO VACCINATION

Biological sex is an important determinant of immune responses to both infections and vaccines. Women generally mount stronger innate and adaptive immune responses than men, resulting in higher antibody titres and more robust cellular immunity following vaccination.¹³ These differences arise from the combined effects of sex hormones, X-linked immune regulatory genes, and sex-specific immune gene expression.¹⁴ Estrogen enhances humoral and cell-mediated immune responses, whereas testosterone has predominantly immunosuppressive effects. As a result, premenopausal women often demonstrate stronger vaccine responses than age-matched men. However, during the MT, declining estrogen levels contribute to immune dysregulation and immunosenescence, reducing the previously observed immune advantage in women.¹⁵ Sex-based differences in vaccine responses have been documented for several vaccines, including influenza, hepatitis B, yellow fever, and COVID-19 vaccines. While women often achieve higher seroconversion rates, they also report higher rates of vaccine-related adverse events, reflecting heightened immune reactivity.^{16,17} Recognition of these sex- and age-related immune differences is particularly important when planning vaccination strategies for peri-menopausal and postmenopausal women, enabling more effective counselling, appropriate vaccine selection, and optimisation of preventive healthcare.

TARGET POPULATION AND TYPES

Adult populations targeted for vaccination may be broadly categorised into healthy adults, high-risk individuals, and those with occupational or travel-related exposure.

Healthy adults are individuals without known chronic medical conditions or immunocompromising states, for whom age-based and booster vaccinations are recommended to maintain immunity.

High-risk adults include those with chronic noncommunicable diseases such as diabetes mellitus, cardiovascular disease, chronic respiratory illness, chronic kidney or liver disease, metabolic disorders, immunocompromising conditions, or advancing age, all of which increase susceptibility to vaccine-preventable diseases and their complications.

Occupational risk groups comprise healthcare workers, laboratory personnel, caregivers, sanitation workers, and others with increased exposure to infectious agents

Travel-related risk groups include individuals travelling to endemic or outbreak-prone regions who may require additional vaccines.

Types of adult vaccines may be classified as routine, risk-based, occupational, travel-related and mass-gathering, with recommendations tailored to age, risk profile, and exposure.⁶

Screening: Before adult vaccination, a brief clinical screen is required, including review of prior vaccination history, allergies, and any prior serious vaccine reactions. Vaccination should be deferred only in cases of moderate or severe acute illness; minor illness is not a contraindication. Pregnancy and immune status must be assessed, as live vaccines are contraindicated during pregnancy and in immunocompromised states, whereas inactivated vaccines are generally safe. Chronic comorbidities, occupational or travel risks, and age should guide vaccine choice. Routine laboratory testing is not required, except in selected situations, such as hepatitis B serology for healthcare workers, and appropriate counselling and documentation should follow.

Adverse effects: Patients should be counselled regarding expected adverse effects, which are usually mild and self-limiting. Common reactions include local pain, redness, or swelling at the injection site, as well as mild fever, fatigue, headache, myalgia, or malaise, lasting 1–3 days. Live vaccines may occasionally cause low-grade fever or mild rash 1–2 weeks after vaccination. Serious adverse events are rare, and the benefits of vaccination far outweigh these risks. Clear

counselling about expected side effects helps reduce anxiety, improves adherence to multidose schedules, and reinforces confidence in adult immunisation programmes.

Co-administration of vaccines is safe and recommended to improve coverage and compliance in adults. In general, live attenuated vaccines such as measles-mumps-rubella (MMR), varicella, live attenuated influenza, and yellow fever may be administered on the same day; if not given simultaneously, they should be spaced by at least 4 weeks to avoid immune interference. Inactivated, recombinant, and subunit vaccines, such as influenza, pneumococcal, hepatitis B, HPV, and the recombinant zoster vaccine, can be administered together or at any interval with other vaccines, including live vaccines, using different injection sites.

SUGGESTED VACCINATIONS FOR 40-PLUS WOMEN

The menopause visit provides a unique, reliable opportunity to assess adult vaccination status. Integrating immunisation review into menopause care enables timely prevention of infections, reduces complications, and supports healthy ageing in women.

ROUTINE VACCINATIONS

Tdap/Td (Tetanus–Diphtheria–Pertussis)

The tetanus–diphtheria–acellular pertussis (Tdap) vaccine provides protection against three serious bacterial infections whose risks and clinical impacts persist into adulthood. Immunity to tetanus and diphtheria declines over time without booster doses, leaving many adults susceptible if boosters are missed.^{18–22} Pertussis immunity also wanes substantially after childhood vaccination or natural infection, and adult pertussis is increasingly recognised as an underdiagnosed cause of prolonged cough illness. Importantly, adults with waning pertussis immunity can act as a reservoir for transmission to infants, pregnant women, and other vulnerable populations, a concept underpinning the strategy of “cocooning.”

In India, tetanus remains endemic due to the ubiquitous presence of *Clostridium tetani* spores in soil and animal waste, and non-neonatal (adult) tetanus continues to be reported, particularly among older adults, agricultural and manual workers, and those sustaining wound injuries. Adult tetanus is associated with significant morbidity and higher case-fatality rates, reflecting delayed presentation and waning immunity. Diphtheria has re-emerged among adolescents and adults in India, with reported outbreaks linked to declining immunity in older age groups and inadequate booster coverage; adult cases often present with severe complications such as myocarditis and neuropathy.

Schedule: A single dose of Tdap is recommended for all adults who have not previously received Tdap, regardless of the interval since the last tetanus- or diphtheria-containing vaccine, followed by Td or Tdap boosters every 10 years. Adults with unknown or incomplete vaccination history should receive a three-dose primary series (Tdap as the first dose, followed by Td/Tdap at 4 weeks and 6–12 months).

In the context of wound management, booster dosing is guided by wound type and time since last vaccination, with Tdap preferred if no prior adult Tdap has been administered. These recommendations are particularly relevant for midlife and older adults, including women in caregiving roles, for whom maintaining immunity to tetanus, diphtheria, and pertussis is essential for both individual protection and community health.^{6,23,24}

Influenza

Seasonal influenza is a major contributor to acute respiratory illness, hospitalisation, and excess mortality in adults, particularly in older age groups and those with chronic conditions such as diabetes, obesity, and cardiovascular disease, which are highly prevalent among midlife women in India. Influenza infection in adults may also precipitate cardiovascular events and metabolic decompensation, increasing overall morbidity. Annual influenza vaccination has been shown to reduce severe disease, hospitalisation, and death, even when vaccine effectiveness against infection is moderate. In India, vaccination should be timed prior to regional peaks, typically before the monsoon season in southern states and before winter in northern regions. The Indian Association of Preventive and Social Medicine (IAPSM) recommends considering routine influenza vaccination for all individuals aged 60 and above and for adults with comorbidities.^{6,25,26}

Trivalent Inactivated Influenza Vaccines vs the Quadrivalent Inactivated Influenza Vaccine: Recent global influenza surveillance continues to show no confirmed circulation of the influenza B/Yamagata lineage since March 2020. Based

on this sustained absence, the World Health Organisation (WHO) has recommended removal of the B/Yamagata component from seasonal influenza vaccines at the earliest feasible opportunity and a transition back to trivalent inactivated influenza vaccines (IIVs) for the 2025–2026 Northern Hemisphere season. Consistent with this, the U.S. Centres for Disease Control and Prevention (CDC) has confirmed that, beginning with the 2024–2025 season, licensed inactivated influenza vaccines in the United States no longer contain a B/Yamagata antigen, reflecting the extremely low current risk of infection from this lineage.

In India, quadrivalent inactivated influenza vaccines have been in routine use, as trivalent formulations were previously unavailable. However, domestic manufacturing of a trivalent inactivated influenza Vaccine by Zydus Lifesciences commenced in September 2025, aligning India with updated WHO recommendations. The shift to trivalent vaccines offers several public-health advantages, including avoiding a non-circulating antigen, improved manufacturing efficiency that allows greater dose availability, and potential cost reductions that may enhance vaccine access and coverage. Until trivalent formulations are widely available across India, quadrivalent vaccines remain appropriate and effective, and annual influenza vaccination should not be delayed, particularly for adults aged ≥ 40 years and those with comorbidities.²⁷

Schedule: The standard adult dose is 0.5 mL administered intramuscularly as a single dose annually with inactivated influenza vaccine (IIV) formulations. Where available, trivalent IIV may be preferred; nevertheless, quadrivalent IIV remains an acceptable alternative, and annual vaccination should not be delayed.

Herpes Zoster (Shingles) Vaccine

Herpes zoster (shingles) is a neurocutaneous disorder resulting from reactivation of the latent varicella-zoster virus (VZV) acquired during childhood chickenpox. Following primary infection, the virus persists in a dormant state within sensory dorsal root ganglia and may reactivate years later as cell-mediated immunity declines. This reactivation leads to herpes zoster, a condition characterised by severe neuropathic pain named post-herpetic neuralgia (PHN) that can persist for weeks or months and markedly impair quality of life. Age-related immune decline is a key factor predisposing older adults to herpes zoster. Historically, two types of vaccines have been developed for zoster prevention: a live-attenuated vaccine (Zostavax) and a recombinant subunit vaccine (Shingrix).^{6,28}

The live-attenuated zoster vaccine (Zostavax) is a single-dose vaccine that has been shown to reduce herpes zoster incidence by approximately 51% in adults aged ≥ 60 years and around 70% in those aged 50–59 years, with additional protection against post-herpetic neuralgia. However, vaccine effectiveness declines over time, with waning protection observed several years after vaccination, and its use is contraindicated in immunocompromised individuals due to its live-attenuated formulation.^{28–30} In contrast, the recombinant zoster vaccine (Shingrix) is a two-dose, non-live, adjuvanted subunit vaccine administered intramuscularly with the second dose given 2–6 months after the first. It demonstrates high efficacy exceeding 90% and sustained protection against herpes zoster and post-herpetic neuralgia in adults aged ≥ 50 years, and, owing to its non-live formulation, is suitable for use in immunocompromised populations.^{31–34} Although effective, the live-attenuated vaccine's waning immunity and contraindication in immunocompromised adults limit its role in routine practice, leading to a preference for the recombinant zoster vaccine where available.

In India, Shingrix has been licensed and launched since 2023 and is indicated for the prevention of herpes zoster and its complications in adults aged 50 years and above. The recombinant vaccine's non-live nature allows its use in individuals who might be unsuitable for live vaccines due to immunocompromise. Given the high prevalence of VZV latency in adult populations and the increasing incidence of herpes zoster with age, especially in women ≥ 50 years, the recombinant zoster vaccine represents a key preventive intervention in menopause and older adult clinics, reducing both acute disease and long-term complications like PHN.³⁵

Schedule: The recombinant zoster vaccine is administered as two 0.5 mL intramuscular doses, given 2–6 months apart.

Pneumococcal Vaccination

Streptococcus pneumoniae remains a major cause of community-acquired pneumonia and invasive pneumococcal disease (bacteraemia/meningitis) in adults, with risk and severity increasing with age, diabetes, chronic cardiopulmonary disease, chronic kidney disease (CKD)/liver disease, and immunocompromise. Pneumococcal vaccines used in adults comprise polysaccharide and conjugate formulations that differ in immunologic mechanism, durability of protection, and serotype coverage. The 23-valent pneumococcal polysaccharide vaccine (PPSV23) provides broad serotype coverage but induces predominantly T-cell-independent immune responses, resulting in

limited immunologic memory. In contrast, the 13-valent pneumococcal conjugate vaccine (PCV13) elicits T-cell-dependant immunity, leading to the development of immune memory and more durable protection, and is therefore recommended as the initial vaccine in sequential adult immunisation strategies.

Newer conjugate vaccines further expand serotype coverage: PCV15 adds serotypes beyond PCV13, while PCV20 provides broader protection and enables a simplified single-dose strategy in many adult immunisation schedules. PCV20 has been introduced for adult use in India, representing an important advancement in pneumococcal disease prevention.

Why is PCV given before PPSV23? Giving a conjugate vaccine (PCV) first “trains” the immune system to respond more effectively. When PPSV23 is given afterwards, the immune response is stronger and more effective. If PPSV23 is given first, this training effect is reduced, and subsequent PCV doses may be less effective. This is why the recommended order is PCV first, followed by PPSV23.³⁶ Active immunisation is recommended for all adults aged ≥ 50 years and for adults aged 19–49 years with high-risk conditions

Cost-effectiveness: The PCV20-alone approach is often more cost-effective and simpler, as it requires only one dose to provide broader protection, saving the cost and time of the second vaccine.^{37,38}

Schedule: Current adult pneumococcal vaccination guidelines recognise two acceptable pathways. For vaccine-naïve adults, a single dose of PCV20 is preferred where available. In adults who have already received PCV13, completion with PPSV23 remains appropriate; alternatively, CDC guidance permits a single dose of PCV20 ≥ 1 year after PCV13, particularly if PPSV23 has not been administered or the series is incomplete.^{6,39}

Human Papillomavirus Vaccination

Human papillomavirus (HPV) infection is a well-established cause of multiple anogenital and oropharyngeal malignancies. Oncogenic HPV types, particularly HPV 16 and 18, are responsible for approximately 70% of cervical cancers, and are also implicated in vulvar, vaginal, anal, penile, and oropharyngeal cancers in women and men. Non-oncogenic types HPV 6 and 11 account for nearly 90% of genital warts and are included in both quadrivalent and nonavalent HPV vaccines.^{40,41}

Three HPV vaccines are currently approved for use in India: the bivalent vaccine (HPV 16, 18), the quadrivalent vaccine (HPV 6, 11, 16, 18), and the nonavalent vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52, 58). All three vaccines provide protection against HPV types 16 and 18, which together account for approximately 70% of cervical cancers, while the nonavalent vaccine extends protection to five additional oncogenic types, increasing coverage to nearly 90% of cervical cancer.^{6,34,42} Importantly, HPV vaccination may confer benefit even in individuals with prior HPV exposure or treatment for HPV-related disease. Evidence suggests that vaccination following treatment for high-grade cervical intraepithelial neoplasia (CIN2+) is associated with a reduced risk of recurrent disease, likely by preventing reinfection or reactivation at the same or different anatomical.^{43,44}

Human Papillomavirus Vaccination Guidance For Adults Aged ≥ 40 Years

In India, HPV vaccination is not routinely recommended for adults aged ≥ 40 years under government schedules. The National Centre for Disease Control (NCDC)/MoHFW adult immunisation schedule limits routine HPV vaccination to younger adults (up to 26 years). However, professional consensus guidelines from the Association of Physicians of India (API) and Federation of Obstetric and Gynaecological Societies of India (FOGSI) (2024) allow individualised consideration of HPV vaccination up to age 45, with shared clinical decision-making. Population-based cancer registry data from India demonstrate that cervical cancer incidence increases from midlife and remains substantial in older and postmenopausal women, including those aged ≥ 50 –60 years. This sustained burden beyond the reproductive years underscores the continued relevance of HPV prevention and cervical cancer screening strategies later in life.⁴⁵⁻⁴⁸ Routine HPV vaccination beyond 45 years is not recommended in the current Indian guidance, and emphasis should instead be placed on regular cervical cancer screening and early detection strategies.

HEPATITIS B VACCINATION

Hepatitis B virus (HBV) infection remains a major public health problem in India, which is classified as a country with intermediate endemicity. An estimated 3–4% of the Indian population is chronically infected with HBV, accounting for nearly 40 million carriers. Chronic HBV infection is a leading cause of cirrhosis and hepatocellular carcinoma, contributing substantially to liver-related morbidity and mortality in adults. Because HBV infection is often asymptomatic until advanced liver disease develops, prevention through vaccination is critical, particularly in adults who may have missed childhood immunisation.⁶

Vaccination Strategy: Universal vs Risk-Based

- Universal infant hepatitis B vaccination is part of India's Universal Immunisation Programme.
- In adults, routine universal vaccination is not yet implemented nationally, but adult vaccination is strongly recommended, particularly for:
 - Unvaccinated adults
 - Individuals at increased risk of exposure
- Given the high background prevalence and the difficulty in identifying exposure risk, API 2024 recommends offering hepatitis B vaccination to all unvaccinated adults, with special emphasis on high-risk groups.
- *We suggest hepatitis B vaccination should be offered to all unvaccinated adults, with particular emphasis on individuals at increased risk of exposure*
- Vaccines available include recombinant monovalent hepatitis B vaccines and combined hepatitis A–hepatitis B (HepA–HepB) vaccines, the latter being useful for selected indications such as travellers.

Schedule: The preferred adult schedule consists of a three-dose series administered at 0, 1, and 6 months, with minimum intervals of ≥ 4 weeks between doses 1 and 2, ≥ 8 weeks between doses 2 and 3, and ≥ 16 weeks between doses 1 and 3. In situations requiring rapid protection, an accelerated schedule using the combined HepA–HepB vaccine (0, 7, and 21–30 days) may be used, followed by a booster dose at 12 months to ensure long-term immunity.⁶

For detailed information on vaccines for the risk-based, occupational, travel-related, and mass gathering events, refer to Table 1.

Table 1: Adult Vaccination Recommendations for Women ≥ 40 Years

Category	Vaccines Recommended
Routine (Offer to all women ≥ 40 years)	Tdap/Td (10-year booster); Influenza (annual); COVID-19 (as per national guidance); Hepatitis B (if unvaccinated); Pneumococcal (≥ 50 years or earlier with comorbidity); Herpes Zoster (≥ 50 years, 2-dose recombinant vaccine)
Risk-Based (Medical conditions / Immunity gaps)	MMR (if no documented immunity); Varicella (if non-immune); HPV (shared decision-making ≤ 45 years); Hepatitis A (chronic liver disease / exposure risk) ; Hib (selected high-risk conditions)
Occupational (especially Healthcare Professionals)	Hepatitis B; Tdap/Td (up to date); Influenza (annual); COVID-19; MMR (if non immune); Varicella (if non-immune); Rabies (laboratory/animal exposure risk)
Travel-Related	Hepatitis A; Hepatitis B; Typhoid; Japanese Encephalitis (endemic rural areas); Polio (inactivated poliovirus vaccine (IPV) booster for endemic regions); Yellow Fever (for travel to endemic countries only); Meningococcal (as indicated)
Mass-Gathering (such as Hajj/ Umrah)	Quadrivalent Meningococcal (MenACWY) – Mandatory; Influenza – Recommended; Polio – As required; Pneumococcal – If high risk or prolonged stay

ENDEMIC INFECTIONS IN INDIA

Japanese Encephalitis virus: is endemic in numerous states across the northeast, north, central, and south, including Assam, Bihar, Uttar Pradesh, West Bengal, Odisha, and Tamil Nadu, with transmission linked to rural agricultural ecologies and seasonal mosquito activity.⁴⁹

Meningococcal disease (primarily serogroup A) occurs as both endemic and epidemic illness in India, with documented outbreaks in regions such as Delhi and other states, indicating a risk in crowded, close-contact settings; however, routine nationwide vaccination is not currently implemented.⁵⁰

Yellow fever is not endemic in India, but travellers arriving from yellow fever-risk countries must be vaccinated under international health regulations.⁵¹

SYNOPSIS

- Adult vaccination can minimise the burden of illness in adults caused by VPDs.
- Immunity wanes after 40, increasing susceptibility to vaccine-preventable diseases.
- Tdap/Td boosters (one-time Tdap, then every 10 years) remain essential.
- Annual influenza and COVID-19 vaccination reduces the risk of severe respiratory illness.
- Hepatitis B vaccination should be offered to all unvaccinated adults in India.
- Pneumococcal vaccination is recommended for people aged ≥ 50 years or earlier with comorbidities (prefer PCV20 where available).
- Recombinant herpes zoster vaccine is recommended for adults aged ≥ 50 years to prevent shingles and PHN.
- HPV vaccination may be considered up to 45 years based on shared decision-making; screening remains critical thereafter.
- Vaccination is especially important for adults with chronic diseases, healthcare workers, travellers, and participants in mass gatherings.
- Most vaccines can be co-administered safely, with only mild, self-limited side effects expected.

RESEARCH AGENDA

Adult vaccination coverage and determinants among women aged ≥ 40 Years in India

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ESTROGENS AND COMBINED THERAPY

37

Keywords: Estrogens, indications, contraindications, potency, route, regimes, woman's profile, risk-benefit stratification, prescription, pre- and post-hormone therapy monitoring, special situations, timing hypothesis

INTRODUCTION

"The real voyage of discovery does not exist in seeking new landscapes but in having new eyes." Marcel Proust

HISTORY OF MENOPAUSE HORMONE THERAPY

Indian: Classical Ayurvedic texts, including the Charaka Samhita (100 BCE–200 CE), Sushruta Samhita (600–800 BCE) and Ashtanga Hridaya (600–700 CE), described Rajonivritti (menopause) as a Vata-dominant, age-related physiological transition marked by the cessation of menstruation around the fifth decade, vasomotor heat sensations, urogenital dryness, psychological changes and tissue depletion (dhatu-kshaya). These treatises recommended Rasayana chikitsa, using botanicals such as Shatavari, Ashwagandha, Yashtimadhu, Bala and Guduchi, to preserve vitality, constituting the earliest form of "proto-menopausal hormone therapy."^{1–3}

Western: Early Western references date back to Aristotle (384–322 BCE), who observed that menstruation typically ceased around the fifth decade of life. The modern concept of menopause hormone therapy (MHT) emerged in the late nineteenth century. In 1886, German physicians F. Mainzer and R. Mond reported symptomatic improvement in ovariectomised and menopausal women treated with injected ovarian tissue, and later prescribed oral bovine ovarian preparations (5–20 g/day), with notable relief of sexual symptoms.⁴ Subsequent use of ovarian extracts proved effective in alleviating menopausal flushing, laying the foundation for contemporary MHT. In 1895, Chrobak further reported benefit with oral ovarian tissue therapy.^{5,6} As early as 1899, the Merck Manual of Diagnosis and Therapy described Ovarin (Ovariin), a coarse, brownish powder derived from dried cow ovaries, recommended for climacteric symptoms at a dose of 8–24 grains three times daily. It's interesting to note that the commercial beginning of hormone therapy (HT) was reported to be marketed by Ben Labs Ltd., Gujarat, India, which represents the earliest documented commercial MHT and remained in use until the early 1930s.⁷ In the early 1930s, oral menopause products, derived from human pregnancy urine, were developed by Schering AG, Berlin, Germany, and Ayerst, Canada. This was replaced in the late 1930s by Premarin conjugated equine estrogens tablets; Wyeth-Ayerst, Canada.⁸

Emergence of Early Hormone Therapy

The FDA approved the use of conjugated estrogens in postmenopausal women for the treatment of symptoms in 1941 in Canada and in 1942 in the United States.⁹ The FDA initially approved hormone replacement therapy (HRT) only for the treatment of hot flushes, not for the prevention of chronic conditions. Later, following the paper by Grady et al.,¹⁰ the American College of Physicians developed the first guidelines for using HRT as a preventative therapy for chronic diseases in postmenopausal women. In late 1980, the prevention of osteoporosis was added to the FDA-approved indications.¹¹

Since then, estrogen has been under scrutiny, and various facets of this fascinating molecule have been explored. The prescription pattern of MHT by professionals and uptake by women during the menopausal transition (MT) have been a roller-coaster ride, with phases of increases and decreases in MHT use depending on the results of various clinical trials. Unopposed use of estrogen in postmenopausal women in their fifties and sixties was associated with an increased incidence of endometrial cancer, and this effect was negated by the appropriate use of progesterone.^{12–17}

An association between menopausal hormone therapy and breast cancer risk was first highlighted in a large collaborative reanalysis by the Collaborative Group on Hormonal Factors in Breast Cancer in 1997.^{18,19} Studies in the 1980s showed a positive link between HT and the prevention of osteoporosis and the treatment of osteoporotic fractures.^{20–23} The incidence rates of cardiovascular events were lower in premenopausal than in postmenopausal women.²⁴ Later observational trials, including the Nurses' Health Study, indicated that women with or at risk of cardiovascular disease (CVD) are likely to benefit from MHT.²⁵

Development of Modern Menopause Hormone Therapy

The Postmenopausal Estrogen/Progestin Interventions (PEPI) trial, conducted before the WHI, demonstrated favourable effects of estrogen-based therapy on lipid profiles, including reductions in low-density lipoprotein

cholesterol (LDL-C) and increases in high-density lipoprotein cholesterol (HDL-C), without adverse effects on blood pressure or glucose metabolism in recently postmenopausal women.²⁶ Importantly, PEPI established the endometrial safety of appropriate progestogen opposition, providing a physiological and safety foundation for subsequent large-scale outcome trials and for modern MHT regimens.²⁶ Given that most observational studies indicated that HRT conferred cardiovascular protection, the U.S. Food and Drug Administration (FDA) required that any such benefit be substantiated through randomised controlled trials. This requirement led to the initiation of cardiovascular outcome studies designed to test the preventive hypothesis under rigorous experimental conditions.

Importantly, earlier observational data had already raised concerns regarding CVD risk. Findings from the Framingham Study indicated that postmenopausal women using HT had approximately a two-fold higher risk of CVD, highlighting the limitations of observational inference and underscoring the need for randomised evidence to clarify the true cardiovascular effects of HRT.²⁷

Randomised Trials and the Women's Health Initiative Era

The first major randomised trial to address this question was the Heart and Estrogen/Progestin Replacement Study (HERS), which enrolled women with established coronary disease and focused on secondary prevention. The results of the HERS revealed that estrogen was not to be used for secondary prevention of CVD.²⁸ In 1998, the Women's Health Initiative (WHI), designed in 1991 with recruitment from 1993, published results primarily to assess the effect of MHT on the primary prevention of CVD in postmenopausal women.²⁹ The hasty release of the improperly analysed results of the landmark WHI study in 2002 created a lasting negative impact on the perception of MHT among healthcare professionals and consumers.³⁰

Consequences of the Women's Health Initiative: Decline in Use and Population Effects

Inferences from epidemiological data suggest that the decline in HRT use is associated with a drop in breast cancer incidence. However, the impact of HRT cessation varied markedly between countries.

Interestingly, the incidence of estrogen receptor-positive breast cancer in the USA peaked in 1999, with a downward trend beginning in 2000, at least two years before the WHI publications. Other factors besides HRT can explain the trend in breast cancer. Some of these data may be explained by changes in national breast cancer screening programmes. The conclusion is that estrogen may have a promotional, noncarcinogenic effect on occult hormone receptor-positive tumour cells, and that this effect is probably greater with estrogen-progesterone therapy.^{31,32} Moreover, two years after the WHI, there is an increasing trend in breast cancer. After the WHI publication and the drop in HRT prescription, endometrial carcinoma rates increased between 2001 and 2012.³³

In the USA, a report comparing male and female mortality between the mid-1990s and 2002-2006 found a reduction in male mortality but an increase in female mortality over the same period.³⁴ A 2011 publication reporting 10.7 years of follow-up in women receiving estrogen-only therapy demonstrated a meaningful reduction in mortality, corresponding to an absolute decrease of approximately 13 deaths per 10,000 women per year among women aged 50-59 years who had undergone hysterectomy.³⁵ Despite the clinical relevance of these findings, the report received limited attention and had little impact on prescribing patterns.³⁶ Use of estrogen therapy (ET) continued to decline following its release, and contemporary data suggest that only about one-third of women who undergo hysterectomy with bilateral salpingo-oophorectomy (BSOP), irrespective of age, are currently treated with ET.³⁷ The risk of fractures in postmenopausal women increased in the three years following the publication of the WHI.³⁸

In contrast, prior to 2002, systemic HT was used by nearly 90% of women in this group.³⁹⁻⁴¹ HRT use has shown two peaks: a first rise in the 1960s and a second, higher increase in 1999-2000, before the publication of the WHI data. Over the years, there has been a precipitous decline in HRT use in many countries, and this decline continues to date.^{42,43}

U.S. Food and Drug Administration Black Box Warning

Regulatory decisions made in 2002 had a profound, global impact on menopausal care. The U.S. FDA's response to the initial release of WHI findings, particularly the introduction of boxed warnings and restrictive labelling, shaped clinical practice, prescribing behaviour, and public perception of MHT worldwide. Although these actions were based mainly on data from a narrowly defined, older trial population, their implications were rapidly and indiscriminately extended to all menopausal women, all hormone formulations, and all stages of menopause, leading to a sustained decline in appropriate MHT use and unintended long-term consequences for women's health.

Reinterpretation of Evidence and Restoration of Menopausal Hormone Therapy

Menopause researchers and specialists quickly recognised that the principal shortcomings of the WHI did not lie in the trial's conduct itself, but in its interpretation and dissemination. Key limitations included enrolling an older, largely asymptomatic population that was unrepresentative of women initiating therapy at the time of menopause; evaluating a single, fixed hormone formulation and dose; and an extrapolation error that implicitly assumed uniform responses to MHT across all postmenopausal women, irrespective of age or time since menopause. The most consequential harm, however, arose from a publication and communication failure: preliminary results were released to the media before adequate analysis was completed. Over the subsequent two decades, continuous re-analysis of WHI data, together with evidence from additional trials and observational studies, has progressively clarified these limitations and ultimately restored MHT to its appropriate, evidence-based role in menopausal medicine.

The Timing Hypothesis and the Window of Opportunity

There was a period of uncertainty that lasted for a couple of years. The reanalysis of WHI data and its correlation with previous observational studies brought new insights. The concepts of the “window of opportunity” and the “timing hypothesis” for HT were first proposed by Thomas B. Clarkson, based on preclinical studies in monkeys that showed that HT was effective in slowing atherosclerosis only when started soon after menopause.⁴⁴ This concept was further developed and championed by Howard N. Hodis, whose research has been central to this paradigm in menopausal medicine.⁴⁵

Evidence from Other Trials

Further randomised clinical trials, such as the Danish Osteoporosis Prevention Study (DOPS),⁴⁶ the Kronos Early Estrogen Prevention Study (KEEPS),⁴⁷ and the Early versus Late Intervention Trial with Estradiol (ELITE),⁴⁸ focusing on the use of MHT in women at the usual age of the MT with more modern types of MHT, showed that there were few risks in this age group. The DOPS, which enrolled women at or near menopause and followed them long-term, showed significant reductions in cardiovascular events and overall mortality among women randomised to MHT, without an increase in breast cancer risk during the intervention period. DOPS uniquely provides long-term randomised evidence that early initiation of MHT confers sustained cardiovascular benefit. The KEEPS, conducted in healthy women within 3 years of menopause, found that low-dose oral conjugated equine estrogen (CEE) or transdermal estradiol (E2) did not accelerate atherosclerosis progression, as measured by carotid intima-media thickness (CIMT) or coronary artery calcium (CAC). KEEPS reinforced the concept that early initiation of MHT is vascularly neutral and symptomatically beneficial in low-risk women. The ELITE provided direct mechanistic support for the timing hypothesis. Estradiol significantly slowed the progression of subclinical atherosclerosis when initiated within six years of menopause, whereas no such benefit was observed when therapy was started more than ten years after menopause.⁴⁹ This trial clearly demonstrated that vascular responsiveness to estrogen is time-dependent.

Publication of new scientific data reporting a more favourable benefit/risk ratio for MHT, the production of national guidance, and increased awareness via social media have led to a significant rise in MHT prescribing and improvements in menopause care in the United Kingdom.⁵⁰ MHT has evolved, clarified some grey areas, and reinforced beneficial effects, as shown by observational trials over the past four decades. Individualisation of therapy and the differential effects of varied estrogen and progesterone formulations are better understood.⁵¹

Regulatory Reappraisal and Food and Drug Administration Label Revisions

Over the subsequent two decades, continuous re-analysis of WHI data, together with evidence from additional randomised trials and high-quality observational studies, progressively clarified the limitations of the original interpretations. This evolving evidence base ultimately prompted regulatory reassessment. In November 2025, the FDA initiated major revisions to the labelling of MHTs, reflecting a more nuanced, evidence-aligned understanding of benefit–risk profiles. The FDA removed the boxed (black box) warning from low-dose vaginal estrogen (LET) products used for genitourinary syndrome of menopause (GSM), acknowledging their minimal systemic absorption and recognising that class-wide warnings had discouraged appropriate care. At the same time, boxed warnings related to CVD, breast cancer, and probable dementia were removed from several systemic MHT labels, while warnings regarding endometrial cancer (EC) risk for systemic ET in women with an intact uterus were retained.⁵²⁻⁵⁴

Clinical implications of regulatory recalibration in menopausal hormone therapy

This regulatory recalibration has important clinical implications. It is expected to improve access to and adherence with LET for GSM, reduce “label-driven fear” among clinicians and patients, and support individualised, risk-stratified counselling for systemic MHT, particularly in symptomatic women initiating therapy near the time of menopause. Equally important, it refocuses attention on correct regimen selection, the need for adequate progestogen protection when the uterus is present, and careful patient selection and follow-up for systemic therapy, thereby aligning regulatory policy more closely with contemporary evidence and best clinical practice.⁵²⁻⁵⁴

ENDOCRINOLOGY OF MENOPAUSE

The woman’s response to endogenous and exogenous estrogens is variable and highly individual, just as her thumbprint is. To understand the nuances of prescribing MHT, a basic understanding of menopausal endocrinology is essential. Here, the relevant clinical aspects of this endocrinology are presented. Additionally, the function of each hormone-responsive tissue is influenced by locally acting paracrine and autocrine signals. The hypothalamus is an autonomous pacemaker with a pulse frequency modulated by ovarian signals.⁵⁵

In the reproductive period, the ovarian cycle results in the development of a mature oocyte every month in a regularly cycling woman. The hypothalamus synthesises gonadotropin-releasing hormone (GnRH), which stimulates the synthesis and secretion of the pituitary gonadotropins, follicle-stimulating hormone (FSH) and luteinising hormone (LH), which act on the gonads.⁵⁶ The hypothalamic-pituitary axis is a portal system connecting the hypothalamus and the anterior pituitary, regulating several hormones. The hypothalamus is connected to the pituitary gland via the infundibulum. Within the infundibulum, capillaries drain into the portal veins, which flow directly to the anterior pituitary. This system ensures that hormones released from the hypothalamus circulate directly to the anterior pituitary gland, never entering the general circulation. The hormones released from the hypothalamus include corticotropin-releasing hormone, thyrotropin-releasing hormone, gonadotropin-releasing hormone, growth hormone-releasing hormone, somatostatin, prolactin-releasing hormone, and dopamine.^{57,58} GnRH has a very short half-life, only 2 to 4 minutes.⁵⁹

The gonads produce the steroid hormones estradiol (E2), progesterone, testosterone, and inhibin A and B, which in turn regulate the hypothalamic-pituitary axis. However, not only do sex hormones affect GnRH, but multiple other molecules have also been found to influence GnRH. These molecules include opiates, kisspeptin, neurokinin B, catecholamines, neuropeptide Y, corticotropin-releasing hormone, galanin, dynorphin, and prolactin.⁶⁰ The perfect coordination along the hypothalamus-pituitary-ovarian axis during the reproductive phase, the MT and post-menopause is clearly depicted in figures 1, 2 and 3.

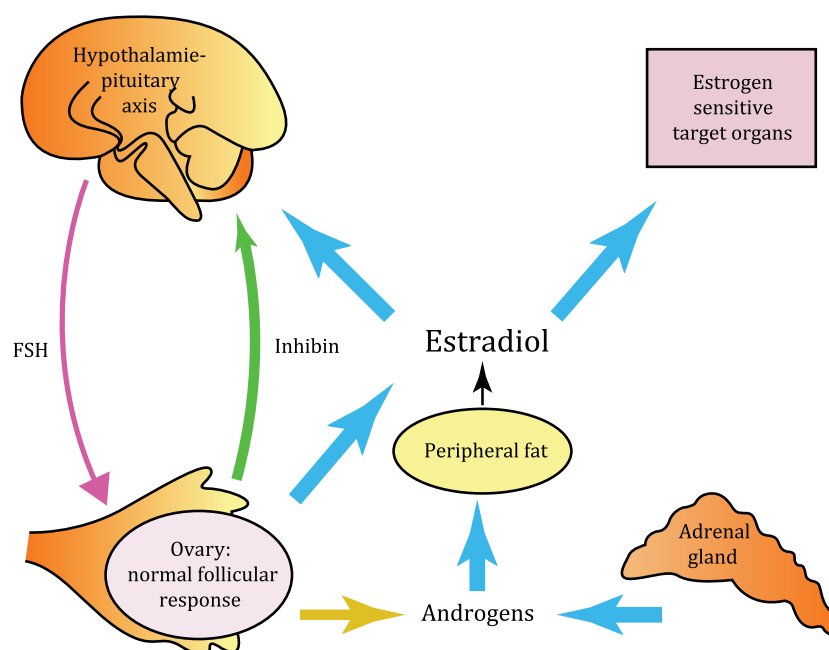


Figure 1. Premenopausal hormone production. The arrow size indicates the levels of hormone secretion. FSH-Follicle stimulating hormone

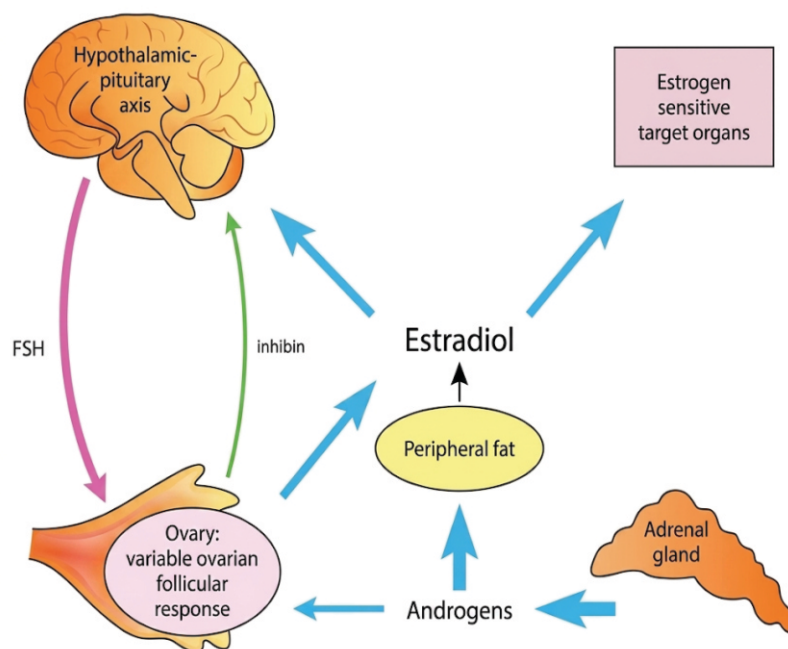


Figure 2. Perimenopausal hormone production. The arrow size indicates the levels of hormone secretion. FSH-Follicle stimulating hormone

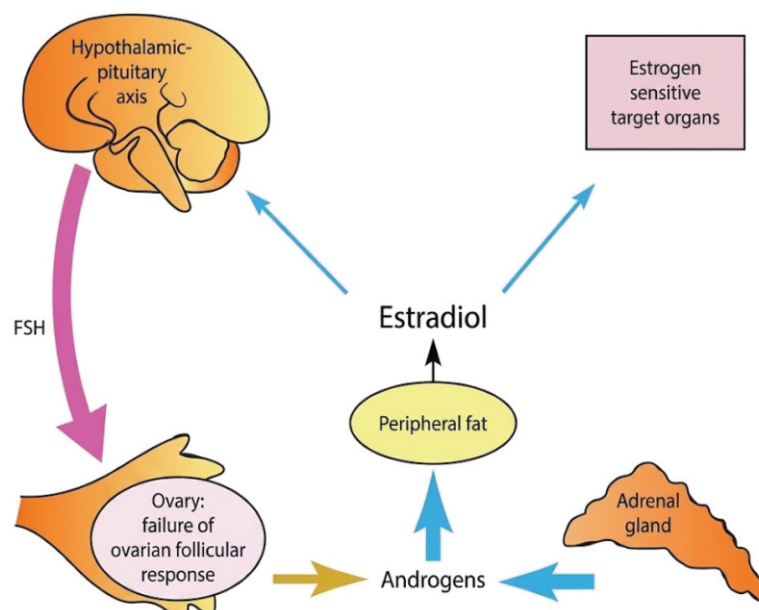


Figure 3. Postmenopausal hormone production. The arrow size indicates the levels of hormone secretion. FSH-Follicle stimulating hormone

Endocrine Changes at Menopause

Menopause is essentially a primary ovarian failure, resulting from the depletion of ovarian follicles secondary to programmed cell death or apoptosis. The number of follicles progressively declines from foetal life onwards. After birth, the number of follicles decreases from several million during the transition phase to a lower number in the post-

menopause. The rate of follicular disappearance increases around age 38 years, the follicular stock reaches a critical number of 25,000, and fecundity starts to decrease.⁶¹ Menopause occurs when the number of remaining follicles falls below the critical threshold of 1,000, regardless of age.⁶¹ A primary event in the ageing of the reproductive system appears to be a decline in the secretion of inhibin B as the follicle pool decreases. Anti-Mullerian hormone (AMH) is produced by small follicles and declines as ovarian reserve declines.⁶²

There is a drastic reduction of E2 and progesterone at menopause. This results in a progressive, fluctuating rise in FSH by 10-20 times and a 2-3-fold rise in LH. These changes are attributable to both the absence of inhibin-B and lower estrogen levels. Levels reach a peak 2-3 years after the final menses. Postmenopausal ET results in a dose-dependent 30% to 40% decrease in plasma FSH relative to pretreatment values. The estradiol-to-estrone ratio of 2:1 during the reproductive phase reverses to 1:2 at menopause, with estrone levels exceeding those of estradiol.⁶³ Although the ovary may still contain some oocytes, the follicles are largely unable to respond to gonadotropins and synthesise E2 because of the lack of inhibin.⁶⁴

Removal of the ovaries in postmenopausal women often fails to change the levels of total circulating estrogen. This is because estrogen produced after the menopause is primarily derived from the peripheral conversion of adrenal and ovarian androgens. This occurs through aromatisation in peripheral adipose tissue, the liver, kidneys, brain, pancreas, bones, muscles, skin, endometrium, and breasts.⁶⁵ Only small quantities of estrone and E2 are secreted by the ovary through aromatisation. The absolute levels of estrogen are influenced by weight, sex, age and stress. Congestive heart failure and liver diseases may increase estrogen levels by decreasing the clearance of androstenedione. Progesterone is not measurable in menopausal women.

The major circulating steroids classified as androgens include dehydroepiandrosterone sulphate (DHEAS), dehydroepiandrosterone (DHEA), androstenedione, testosterone and dihydrotestosterone (DHT), in descending order of serum concentrations. Testosterone and DHT bind to the androgen receptors. DHEAS, DHEA and DHT are considered pro-androgens. The postmenopausal ovary secretes androgens and produces negligible E2. After menopause, the ovary continues to produce androgens. DHEAS is produced almost exclusively by the adrenal gland and declines steadily with ageing.⁶⁶ Levels of testosterone do not change during the MT because the stromal compartment is spared from ageing. The ovaries and adrenals are the main sources of androgens, and the peripheral conversion of androstenedione is the main source of testosterone. There is a steady decline in androgen production with ageing, and the levels of testosterone are not directly influenced by the MT. Ovarian removal results in a further decrease in testosterone (40% to 50%) and, to a lesser extent, in androstenedione. In addition to their direct androgenic effects, testosterone is aromatised to E2, and androstenedione to estrone, in estrogen-responsive organs. The level of testosterone in postmenopausal women with intact ovaries is twice that in oophorectomised younger women.⁶⁷

During the MT, as estrogen levels fall, sex hormone-binding globulin (SHBG) levels drop, raising the free androgen index (FAI) and increasing the amount of free testosterone available. Although total androgen levels fall with menopause, the cumulative effect is an increase in androgenicity, driven by the significant decline in estrogen and reduced SHBG levels. This increase in androgenicity is the cause of increased facial hair growth and scalp hair loss in some postmenopausal women.⁶⁸ The levels of steroid hormones at different stages in a woman's life are given in Table 1.^{69,70}

Table 1: Mean Steroid Level in Women (Values Converted to pg/mL)

Steroid	Reproductive Age	Natural Menopause	Surgical Menopause
Estradiol	100-150	10-15	10
Testosterone	400	290	110
Androstenedione	1900	1000	700
DHEA	5000	2000	1800
DHEAS	3,000,000	1,000,000	1,000,000
Estrone	30-100	10-50	

Source: Adapted from Lobo R. Treatment of Postmenopausal Women. Boston, Mass: Lippincott; 1999; and Judd HL et al. Endocrine function of the postmenopausal ovary: concentration of androgens and estrogens in ovarian and peripheral vein blood. J Clin Endocrinol Metab. 1974;39: 1020-1024.

Thyroid dysfunction is more common in women and increases with age.⁷¹ Although menopause has no definite relationship to thyroid deficiency, it may mimic menopausal symptoms. Hence, it is prudent to screen for thyroid dysfunction at menopause. Menopause, especially ageing, is associated with changes in calcium-regulating hormones. The age-related increase in parathyroid hormone (PTH), often associated with latent vitamin D deficiency, is implicated in senile osteoporosis.⁷² Calcitonin is not significantly affected by menopause. Growth hormone, growth hormone-dependent insulin-like growth factor 1, and growth hormone-independent insulin-like growth factor 1 are associated through complex interrelationships and decrease with menopause and ageing.⁷³

Paradox of Elevated Estrogen Levels at Menopause Transition: Luteal Out-of-Phase (Luteal Out-of-Phase) Event

The hypothesis is that the luteal out-of-phase (LOOP) events are caused by the out-of-phase selection of a dominant follicle during an existing luteal phase. Elevated serum E2 levels during some cycles in the MT reflect a physiological phenomenon termed a LOOP event.⁷⁴ In a LOOP cycle, which occurs in about one in four cycles in women studied during the early menopause transition, elevated FSH levels are sufficient to recruit a second follicle during the luteal phase of an ongoing cycle, resulting in a follicular phase-like rise in E2 secretion superimposed on the mid- to late-luteal phase of the ongoing ovulatory cycle. The raised E2 may result in a low FSH in the next follicular phase. The elevated FSH accelerates follicular maturation and triggers early ovulation, resulting in shorter cycles.^{75,76} During the MT, luteal dysfunction sets in, with a fall in progesterone levels, and many anovulatory cycles may occur.⁷⁷ As described, high and fluctuating FSH levels in the perimenopause may recruit more follicles, leading to overproduction of E2. Moreover, with ageing, aromatase expression increases in regularly cycling women and compensates for the known age-related decrease in granulosa cell number in the dominant follicle, leading to higher E2 levels. The clinical implication is that elevated E2 can suppress FSH, leading to “falsely” normal FSH levels. FSH should therefore be interpreted in conjunction with an E2 level for a diagnosis of menopause. The hyperestrogenic state may lead to menorrhagia, premenstrual dysphoria, growth of fibroids, endometriosis and endometrial hyperplasia(EH). It may also be associated with early and out-of-phase ovulation.

UNDERSTANDING THE BIOLOGY OF ESTROGENS

This section of the chapter is adapted from Morris Notelovitz’s work, with clarifications and a synthesis of key concepts.⁷⁸

Estrogens are largely responsible for the development and maintenance of the female reproductive system and secondary sex characteristics, and they also affect non-reproductive systems. Refer to Table 2.

Table 2: Effect of estrogen on various tissue receptors and clinical implication

Tissue	Effects of estrogen receptor stimulation	Clinical effects of stimulation	Clinical effects of absence of stimulation
Bone	Increased deposits of calcium into bone	Increased bone density	Osteoporosis
Brain	Blocks the release of ovarian estrogen	None	Hot flushes, sleep disorders, mood changes, problems with memory, Alzheimer's disease
Breast	Stimulates growth of breast tissue	Bigger breasts, increased risk of breast cancer, increased sensitivity of the breast	Smaller breasts
Clotting of blood		Increased risk of blood clots	No change in clotting
Blood fats (Lipids) * (increased LDL cholesterol is bad) increased HDL cholesterol is good		Increased HDL, decreased LDL, decreased cholesterol	Decreased HDL, increased LDL, increased cholesterol
Skin	Increased fat deposits in skin	Softer skin	Thinner skin, liver spots, dry skin
Uterus	Increased stimulation of uterine lining and muscle, increased thickening of skin, better blood supply to tissue	Heavier cycles, increased risk of uterine cancer, fibroids, endometriosis	No periods, dryness, vaginal infections, painful sex, incontinence of urine, pelvic weakness

Changes due to the MT can be detected in almost every organ. The hormonal contribution to the clinical and therapeutic variability of endogenous and exogenous estrogens in a woman is influenced by the intracrinologic production of estrogen, which varies from organ to organ. This can be explained by at least 4 factors: (1) the distribution, heterogeneity, and function of subtypes alpha ($ER\alpha$ s) and beta ($ER\beta$ s); (2) the aromatisation of androgens to estrogen in various target organs; (3) the bioavailability of endogenous (and exogenous) estrogen and testosterone; and (4) the biological activity of the sex steroid metabolites.

Estrogen Receptor Distribution and Activation

Estrogens act by regulating the transcription of multiple genes. The biological effects of estrogens are mediated by genomic mechanisms involving interactions with the nuclear $ER\alpha$ and $ER\beta$ to produce a slower genomic response, and by rapid non-genomic actions via membrane receptors.⁷⁹

Ers are widely distributed throughout the body, particularly in organs relevant to HT, such as the brain, heart, breast, bone, and genital tract. $ER\alpha$ is present mainly in the mammary gland, uterus, ovary (thecal cells), bone, male reproductive organs (testes and epididymis), prostate (stroma), liver, and adipose tissue. By contrast, $ER\beta$ is found mainly in the prostate (epithelium), bladder, ovary (granulosa cells), colon, adipose tissue, and immune system. Both subtypes are highly expressed in the cardiovascular and central nervous systems. There are common physiological roles for the two ERs, including the development and function of the ovaries and the protection of the cardiovascular system. These subtypes not only differ in tissue distribution but also in their physiological actions. For instance, $ER\alpha$ promotes cell proliferation in breast and uterine tissue, which is significant when considering the risk of hormone-sensitive cancers. In contrast, $ER\beta$ can have anti-proliferative and possibly protective effects. This knowledge has led to

the development of selective estrogen receptor modulators (SERMs) and tissue-selective estrogen complexes (TSECs), which aim to retain the beneficial effects of estrogen in certain tissues, such as bone, while blocking its adverse effects in others, like the breast or endometrium. Understanding receptor pharmacology has enabled clinicians to choose MHT formulations and routes that optimise benefits while minimising risks, enhancing individualised treatment planning.

The induction of an estrogen response varies by target organ, but in each case it occurs through a multistep molecular process involving either ER- α , ER- β , or both. Each exists as a multiprotein complex that includes a heat-shock protein. Furthermore, although the receptors are usually activated by bioavailable estrogen, non-estrogen ligands such as growth hormone can also initiate the transcriptional response.⁸⁰ Like all steroid hormones, estrogens readily diffuse across the cell membrane and bind to and activate nuclear ER- α or ER- β .^{81,82} This complex then interacts with coregulators (coactivators and corepressors) to bind the hormone response element, initiate transcription, and trigger protein synthesis and biological effects.⁸³ ER- α and ER- β exhibit distinct and overlapping functions in DNA binding.⁸⁴ At the cell membrane, estrogens bind to and activate rapid-signalling membrane estrogen receptors (mERs), which are coupled to the cell membrane G-proteins and can activate intracellular signalling cascades.⁸⁵⁻⁸⁷ The nuclear and membrane ER are biochemically identical and may work in concert. The biologic activity and, with respect to hormone therapy, the potency of the prescribed hormone depend on the retention time in the nucleus; the longer the retention time, the more potent the hormone. E2, the most potent, has the longest retention time, 6-24 hours, while estriol, the least potent, has a retention time of only 1-4 hours.^{88,89} In addition, biological responses to estrogen signalling depend on the cellular concentration and localisation of ERs, the presence of various coregulator proteins, and other signal transduction components.

The progesterone receptor (PR), although structurally very similar to the ER, has little in common functionally. Two forms of PR have been identified: PR-A and PR-B. The PR also has a hormone-binding domain and appears to undergo similar conformational changes to those observed for estrogen.⁹⁰ Progesterone, particularly the androgenic progestins, also binds to androgen receptors and downregulates ERs. Clinically, the relative androgenicity of progestins can be assessed by measuring plasma SHBG levels.^{91,92}

Aromatisation

The main source of estrogen after the cessation of ovarian function is the aromatisation of adrenal androstenedione to estrone(E1).^{93,94} E1 can be converted to the more potent E2 or vice versa, by 17 β -hydroxysteroid dehydrogenase. This rate-limiting step determines the cellular concentration of a particular estrogen. Estriol(E3) is a weak, short-acting estrogen that cannot be reconverted to E2 but undergoes extensive conjugation.^{95,96} The primary site of this conversion is in fat cells; it is now known that significant aromatisation also occurs in tissues such as the breast, brain, bone, coronary artery, and the endometrium. Upregulation of this process could be beneficial in certain tissues (such as bone) but potentially harmful in others (such as breast). Although circulating estrogens are in dynamic equilibrium through metabolic interconversions, E2 is the principal intracellular human estrogen and is substantially more potent than E1 or E3 at the receptor.

Bioavailable Sex Steroids

All estrogens circulate in the blood, either free (biologically active) or bound to protein. Approximately 38% of E2 is bound with high affinity to SHBG, 60% is loosely bound to albumin, and 2% is free to diffuse through or bind to cell membranes. E1 and estrone sulphate bind poorly to SHBG but have a greater affinity for plasma albumin. Alterations in SHBG influence the bioavailability of estrogen. SHBG levels are increased by estrogen (oral more than transdermal) and by thyroid hormone excess. They are lowered by androgens, hypothyroidism, hyperinsulinaemia, glucocorticoids, synthetic progestins (norethindrone, norgestrel, desogestrel, norgestimate) and obesity.⁹⁷ Low levels of endogenous SHBG may explain why untreated older obese women are at greater risk for estrogen-induced cancers, that is, endometrium and breast. Conversely, high levels of endogenous SHBG in older postmenopausal women have been linked to an increased risk of hip and vertebral fractures. Testosterone also has a high affinity for SHBG. Thus, lowering or not raising SHBG will increase the bioavailability of endogenous testosterone. This could influence the choice and route of estrogen therapy. In a recent study, 50 mcg transdermal E2 stimulated less SHBG by 12%, whereas the clinically equivalent doses of oral estrogen: 0.625 mg CEE (100%) or 1 mg of 17-beta E2 (45%), increased it by 100% and 45%, respectively.⁹⁸⁻¹⁰⁰ Adding androgens may also be helpful. Adding 2.5 mg of methyltestosterone to 1.25 mg of esterified estrogen decreased SHBG (from +/- 46 to 24 mcg DHT-bound/dL) and increased bioavailable E2 and testosterone. Androgenic progestins, such as norethindrone acetate (NETA), have similar SHBG-lowering properties.¹⁰¹

Sex-Steroid Metabolite Activity

The metabolites of the various sex steroids have significant biological effects that, in some instances, may influence the efficacy and/or safety of both endogenously produced and exogenously prescribed hormones. Estrogen is metabolised by hydroxylation, mainly in the liver, via 2 dominant pathways, resulting in 2-hydroxy, 4-hydroxy, and 16 α -hydroxy metabolites of estrone and estradiol. Most researchers suggest that 2-hydroxyestrone is benign, whereas 4-hydroxyestrone and 16 α -hydroxylated estradiol derivatives may be carcinogenic.⁹⁷ The 2- and 4-hydroxymetabolites, sometimes referred to as catecholestrogens, have little or no peripheral estrogenic activity. In addition, 2-hydroxyestradiol is further metabolised and methylated to 2-methoxyestradiol, an anti-angiogenic metabolite with mitosis-inhibiting potential.¹⁰² The 16-alpha-hydroxy metabolite has the same estrogenic activity as the parent hormone and, because of its low affinity for SHBG, acts as a potent estrogen.¹⁰³ In summary, the 2-hydroxylation and 16-alpha-hydroxylation of estrogen control the proportions of anticarcinogenic and carcinogenic metabolites. Women who metabolise their endogenous estrogen via the 16-alpha pathway may therefore be at greater risk of breast cancer. The same is true for women with high 17-beta-hydroxysteroid dehydrogenase activity in their breast tissue.^{104,105} This enzyme is responsible for converting E1 into the more potent E2. Thus, there are several variations in estrogen catabolism and metabolism that would either increase or decrease an individual's risk of cancer. This underlying potential is influenced by the individual's lifestyle (such as smoking, which increases 2-hydroxylation of E2) and by factors that affect the enterohepatic recirculation of estrogen.^{106,107}

E2, E1, and their metabolites are conjugated in the liver and excreted via the bile into the gastrointestinal tract. Intestinal bacteria deconjugate the estrogens, and about 80% is reabsorbed for further metabolism in the liver. Intestinal malfunction (for example, diarrhoea), high fibre diets, and bulk laxatives all decrease estrogen reabsorption and can markedly reduce systemic estrogen blood levels.¹⁰⁸⁻¹¹⁰ The type and route of estrogen therapy are also relevant: oral ET is associated with significant enterohepatic circulation and metabolism of estrogens. This is reduced with certain percutaneous products (such as estrogen gel) and is minimal after transdermal ET (patch).

TERMINOLOGY, TYPES, AND CLINICAL PHARMACOLOGY OF ESTROGENS

Definitions

Natural Sex Hormones

Hormones that are endogenously produced by the human body (such as E2, progesterone, and testosterone). The term "natural" is sometimes applied misleadingly to hormones derived from plants (such as soy and yams) or animals (such as conjugated equine estrogens from horse urine), even though they may not be chemically identical to human hormones.

Synthetic Sex Hormones

Hormones that are chemically manufactured and may be structurally different from human hormones, but are designed to mimic or modify their biological activity. Examples: Ethinyl estradiol (EE, commonly used in contraceptives), medroxyprogesterone acetate, norethindrone acetate. These modifications often make the molecules more potent, orally bioavailable, or longer-acting, but sometimes with different side-effect profiles compared with endogenous hormones. The terms "natural" and "synthetic" are often used to distinguish between exogenous hormones; however, they can be confusing or misleading. For some, the term "natural" refers to the source of the preparation (plant or animal), while others use it to refer to the chemical structure (identical to human estrogens).^{111,112}

Bioidentical Sex Hormones

Compounds that are chemically identical in structure to the hormones produced by the human body (such as 17 β -estradiol, micronised progesterone, testosterone). Usually synthesised in a laboratory from plant precursors (such as diosgenin from wild yams, soy phytosterols), and then processed to make them structurally indistinguishable from endogenous human hormones. Used in both FDA-approved preparations and compounded formulations.

Compounded Sex Hormones

Custom-made hormone preparations mixed by a compounding pharmacy according to a prescriber's instructions, often combining bioidentical hormones in non-standard doses, routes, or combinations. These include creams containing E2, E3, and progesterone, or sublingual lozenges containing testosterone. Unlike FDA-approved

bioidentical hormones, compounded hormones are not standardised or strictly regulated, raising concerns about purity, potency, and safety, and hence should not be prescribed or promoted.

ESTROGENS

The term estrogen (endogenous and exogenous) refers to a variety of related chemical compounds with varying affinities for estrogen receptor ER- α and ER- β .⁵¹ The critical determinant of an estrogen preparation's usefulness is not its origin but its potency and biological effectiveness, which are described in the section on potency.

Bioidentical Estrogens

17 β -estradiol, estriol, estetrol (when synthesised to match the natural structure).

Synthetic Bioidentical Prodrugs

Estradiol valerate (becomes bioidentical after metabolism).

Natural, Non-bioidentical

Conjugated equine estrogens (from animal source).

Synthetic, Non-bioidentical

Ethinyl estradiol (structurally modified for pharmacokinetics).

Physiological/Endogenous Estrogens

Estrogen is a steroid hormone derived from the androgenic precursors androstenedione and testosterone via aromatisation. Estrogens are available in various forms, and their concentrations depend on the stage of a woman's life. The four major naturally occurring estrogens in women are estrone (E1), estradiol (E2), estriol (E3), and estetrol (E4). In order of potency, the naturally occurring estrogens are 17 β -estradiol (E2), estrone (E1), estriol (E3), and estetrol (E4). Circulating estrogens exist in a dynamic equilibrium of metabolic interconversions. E2 is the principal intracellular human estrogen and is substantially more potent than E1 or E3 at the receptor level. Estrone sulphate is the most abundant circulating endogenous estrogen in postmenopausal women and serves as a reservoir for estrone.¹¹³

The synthesis and actions of these estrogens are complex. In brief, these forms of estrogen can be summarised as follows:

Estradiol

Primarily produced by theca and granulosa cells of the ovary, it is the predominant form of estrogen found in premenopausal women. The minimum E2 level during the normal menstrual cycle is approximately 30-60 (mean 40) pg/mL, with a peak of 100-400 (mean 250) pg/mL at mid-cycle and 20-150 (mean 100) pg/mL during the luteal phase. During pregnancy, E2 levels rise 100-fold, reaching 20 ng/mL at the end of the third trimester. At menopause, E2 levels drop to 5-20 pg/mL. E2 is bound to SHBG and albumin. It is the most potent estrogen, approximately 10 times more potent than E1 and about 80 times more potent than E3.

Estrone

A product of the peripheral conversion of androstenedione by adipocytes. The greater the number of adipocytes, the higher the serum E1 concentration.^{114,115} It is also formed from E2 via a reversible reaction; it is the predominant circulating estrogen after menopause and is a medium-strength proliferative estrogen.¹¹⁶

Estriol

E3 is not synthesised in or secreted from the ovaries. It is a peripheral metabolite of E2 and E1, and is derived mainly, if not exclusively, from 16 α -hydroxylation of E2 and E1, mainly in the liver.^{117,118} E3 is cleared from the circulation rapidly in non-pregnant women, so circulating levels are very low, almost undetectable (about 10 pg/ml), but concentrations of E3 in the urine are relatively high. The placenta secretes E3, and serum levels during pregnancy increase to 12,000 pg/ml of unconjugated E3 and 210,000 pg/ml of total E3. It is the weakest of the estrogens. The relative binding affinity (RBA) of E3 for ER α and ER β is 14% and 21% of that of E2, respectively, suggesting that, unlike E1 and E2, E3 may have a preferential affinity for ER β .¹¹⁹ Although E3 is an efficacious agonist of the ERs, it is reported to exhibit mixed agonist-antagonist (partial agonist) activity at the ER. On its own, it is weakly estrogenic, but in the presence of E2, it is

antiestrogenic.^{120,121} In addition to acting as an agonist of the nuclear ERs, E3 acts as an antagonist of the G-Protein-Coupled-Estrogen-Receptor (GPER) at high concentrations (1,000-10,000 nM), whereas E2 acts as an agonist at this receptor. E2 increases breast cancer cell growth by activating the GPER (in addition to the ER), and E3 has been found to inhibit E2-induced proliferation of triple-negative breast cancer cells by blocking GPER.^{122,123}

Estetrol

Estetrol is a weak estrogen steroid hormone synthesised only during pregnancy in the foetal liver from E2. Estetrol is a weak estrogen steroid hormone synthesised only during pregnancy in the foetal liver from E2 and E3. Estetrol is closely related to E3. Along with E1, E2 and E3, estetrol is a major estrogen in the body, though only during pregnancy.¹²⁴ So far, the physiological function of estetrol remains unknown.

Xeno-estrogens

A range of synthetic and natural substances that possess estrogenic activity have been identified in the environment and are referred to as xeno-estrogens. These include synthetic chemicals (such as bisphenol A, diethylstilbestrol, pesticides such as DDT (dichlorodiphenyltrichloroethane) and its metabolite o,p'-DDT, plus other organochlorine pesticides, polychlorinated biphenyls from industrial chemicals formerly used in coolants, lubricants, and electrical equipment) and natural compounds (such as phyto-estrogens, myco-estrogens).¹²⁵ Xeno-estrogens can mimic or interfere with normal estrogen activity via genomic and non-genomic mechanisms.¹²⁶ They are considered endocrine-disrupting compounds with possible reproductive, developmental, and carcinogenic risks.^{127,128}

Phyto-estrogens

Plant-based estrogens without a steroid skeleton. Also known as phytoestrogens, plant-based estrogens can exhibit both estrogenic and antiestrogenic properties, depending on the target tissue.¹²⁹ Equol (4',7-isoflavandiol) is a non-steroidal estrogen metabolised from daidzein, a type of isoflavone found in soybeans and other plant sources, by bacterial flora in the intestines.¹³⁰ However, only about 30-50% of people have intestinal bacteria that produce equol. Equol exists in two enantiomeric forms, (S)-equol and (R)-equol.¹³¹ (S)-Equol is more potent than (R)-equol and has about 2% of the affinity for the human ER α compared with E2. (S)-Equol has a stronger affinity for the human ER β , yet this affinity is still only 20% that of E2.¹³²

Exogenous Estrogens for Therapy: Refer to Table 3

17 β -Estradiol

Exogenously administered 17 β -estradiol (17 β E2) (the most physiologically active estrogen) has poor bioavailability and is rapidly metabolised. It therefore needs to be esterified or micronised to become bioavailable to any significant extent. It is metabolised to E1, E2, and estrone sulphate.¹³³

Estradiol Valerate

A slight modification of the natural molecule (esterified form). Metabolised in the liver to 17 β -estradiol and valeric acid, yielding E1, E3 and estrone sulphate.^{133,134}

Estradiol hemihydrate and estradiol valerate (EV) are considered dose equivalents, with comparable pharmacokinetics.

Conjugated Equine Estrogens (CEEs)

A mixture of estrogens (estrone sulphate and equilin sulphate) derived from the urine of pregnant horses. The hepatic potency is 2-3 times higher than that of E2, but the propensity to affect hepatic proteins is much lower than that of EE.^{133,135}

Estriol

Oral and vaginal preparations for use in GSM.¹³³

Estetrol

Estetrol/drospirenone (E4/DRSP) has been available for clinical use since 2021, following regulatory approvals in the United States, Europe, and other regions for oral contraception. To date, post-marketing surveillance, including pharmacovigilance reports and real-world observational data, has not identified any new or unexpected safety signals.

beyond those anticipated for combined oral contraceptives.¹³⁶ In particular, rates of venous thromboembolism, cardiovascular events, and serious adverse outcomes appear consistent with pre-approval trial data, although continued long-term surveillance is warranted given the relatively recent introduction of this formulation.^{137,138}

It is considered a very weak estrogen, with dose-dependent estrogenic effects on endocrine parameters, bone turnover markers, and lipids and lipoproteins. Clinical studies have shown agonist effects in relieving menopausal symptoms and in supporting the health of the bones, vagina, arteries, and uterus (both endometrium and myometrium). Estetrol appears to be highly tissue-selective, with minimal effects on coagulation. However, it is an agonist in the uterus, and as such, would need to be combined with a progestogen to protect the uterus if developed as MHT.

E4 has been evaluated in phase II clinical trials for menopausal hormone therapy, primarily for the treatment of vasomotor symptoms (VMS) in postmenopausal women. These studies assessed oral E4 monotherapy at varying doses and demonstrated significant, dose-dependent reductions in the frequency and severity of hot flushes compared with placebo.¹³⁹

Improvements in sleep disturbance and menopause-related quality-of-life measures were also observed. Endometrial safety with E4 monotherapy was acceptable in short-term studies; however, as with other estrogens, progestogen co-administration is required for long-term use in women with an intact uterus. To date, no phase III outcome trials or regulatory approvals exist for estetrol in MHT, and its use in menopause remains investigational.^{139,140}

Ethinylestradiol

EE is a potent, orally active estrogen, much more active than the natural estrogens, because the 17 α -ethynyl group prevents oxidation of the 17 β -hydroxy group. EE may inhibit its own hydroxylation, and the reduced inactivation rate results in a more pronounced hepatic effect of EE than of estradiol.¹³³

Table 3. Classification and Clinical Implications of Common Estrogens

Hormone	Classification	Clinical Uses	SHBG Effect	Safety & Cancer Risk Notes
17 β -estradiol (E2)	Bioidentical (natural if endogenous)	MHT, contraception (patches, rings, pills), osteoporosis prevention	Raises SHBG moderately (oral), minimal with transdermal	Transdermal route has lower VTE risk.
Estradiol valerate (E2V)	Synthetic bioidentical (prodrug of E2)	Oral MHT, contraceptive pills (with dienogest)	Oral increases SHBG like E2	Converted to E2; oral carries more VTE risk vs transdermal.
equine estrogens (CEEs)	Natural (animal-derived), non-bioidentical	Oral MHT (Premarin)	Strongly raises SHBG	Higher VTE, stroke and breast cancer risk in WHI; $\uparrow$ CRP vs transdermal.
Estriol (E3)	Bioidentical (natural metabolite)	Local vaginal therapy for GSM/VVA	Minimal SHBG effect when local	Weak estrogen; lower breast/endometrium stimulation; considered safe in local low-dose use.
Estetrol (E4)	Natural & bioidentical (foetal origin, synthetically produced)	New contraceptives, potential MHT	Mild SHBG increase, far less than EE	Lower impact on coagulation and liver proteins than EE; emerging evidence of reduced VTE risk.
Ethinylestradiol (EE)	Synthetic, non-bioidentical	Standard COCs	Strong SHBG increase	Higher VTE risk vs E2/E4; avoided in MHT.

PHARMACOKINETICS

Oral Administration

E1 and E2 are poorly absorbed from the gastrointestinal tract. Rapid conversion of E2 to E1 occurs in the intestinal mucosa. To enhance oral bioavailability and prevent degradation, estrogens can be conjugated to form sodium sulfates or stabilised by adding a piperazine or an ester group. Estrogens may also be micronised, creating very small particles that increase surface area and promote rapid absorption.¹³³

All orally administered, naturally occurring estrogens and their esters are rapidly metabolised in both the gut and the liver before reaching the general circulation, a process known as the first-pass effect. This results in higher E1 than E3 levels, because E2 is metabolised by the intestinal mucosa during first-pass metabolism to E1. In addition, the first pass through the liver affects other liver functions and is presumed to be one reason various routes of administration affect lipid profiles differently. Synthetic estrogens (specifically EE) are degraded very slowly in the liver and other tissues, which accounts for their high potency.

The hepatic effect of oral ET results in greater stimulation of certain proteins, including renin substrate and angiotensin, compared with transdermal therapy. Oral estrogen increases HDL-C and SHBG. Oral estrogen is also associated with about a 25% increase in triglycerides (TG), increasing the risk of pancreatitis in women who already have hypertriglyceridaemia. Oral ET stimulates hepatic globulins, coagulation factors, and some inflammatory markers, such as C-reactive protein and matrix metalloproteinase 9, with implications for CVD.¹⁴¹

The half-lives of the different estrogens vary. For CEE, the range is 10 to 25 hours. The half-life of E2 is approximately 16 hours (oral) and 4 to 8 hours (transdermal). After oral administration, the pharmacokinetics of E2 differ from those of most other sex steroids. While the serum concentrations of EE, E3, and the progestogens rise rapidly to a maximum within 1-3 h and then decline, E2 levels remain elevated for up to 12 hours and decrease slowly thereafter. During oral treatment with 2 mg micronised E2 or EV, the average peak levels of estradiol are 40 pg/ml on day 1 and 80 pg/ml on day 21.¹⁴²

The conversion of E2 to E1 and the formation and hydrolysis of estradiol conjugates, catalysed by intestinal and hepatic enzymes, are important factors in the regulation of E2's pharmacokinetics and pharmacodynamics. There are large inter-individual differences in absorption and metabolism, leading to considerable variation in the course and peak levels of serum sex steroid concentrations in women treated with the same preparation. The coefficients of variation are usually in the range of 30-60%.¹⁴³ The inter-individual variations are mainly due to genetic or acquired differences in intestinal and hepatic metabolism.^{144,145} While intraindividual day-to-day variations may be caused by external factors such as diet, alcohol or drug consumption, smoking, physical activity, stress and other factors, these factors can lead to rapid, transient changes in peripheral or splanchnic blood flow, absorption, or metabolism.¹⁴⁶

Non-Oral Administration

Estrogens are also well absorbed through the skin, mucous membranes, and subcutaneous fat. Transdermal ET is associated with relatively stable serum levels, unlike the fluctuating levels seen with oral estrogen. However, there may be substantial patient-to-patient variability in blood levels because of differences in absorption. Transdermal and topical administration achieve therapeutic plasma levels of E2, with lower circulating levels of E1 and estrane conjugates, and require lower total doses than oral therapy. In contrast to oral ET, transdermal and topical administration of estrogen has the advantage of not increasing TG but the disadvantage of not increasing HDL-C.¹⁴⁷ Because of less liver exposure, transdermal and topical ET may have less effect on gallbladder disease, C-reactive protein (CRP), and coagulation factors.¹⁴¹

Transdermal estrogen has minimal effects on SHBG and thus has a less negative effect on sexual functioning. Transdermal estrogen may be the clinical choice because its controlled-release formulation may reduce migraines and have little effect on blood pressure.¹⁴⁸

Estradiol: E2 is rapidly absorbed by the vaginal mucosa. Because local metabolism is low, serum E2 concentrations after vaginal administration are 10-20-fold higher than after oral administration of the same dose.¹⁴⁹ Using very low estrogen doses, 10 or 25 micrograms E2, a local effect on vaginal tissue is achieved, and systemic effects are avoided.^{150,151}

Conjugated Equine Estrogens: Topical CEE is rapidly absorbed by an atrophic vaginal mucosa.^{152,153} Owing to poor metabolism in the vaginal mucosa, serum concentrations of unconjugated estrogens and, hence, systemic effects are

relatively low. After vaginal treatment of postmenopausal women with 0.3 mg, 0.625 mg, 1.25 mg or 2.5 mg CEE daily for 4 weeks, the mean serum levels of E2 measured after 4 weeks were 13, 23, 38 and 63 pg/ml, while those of E1 were three times higher.¹⁵⁴

Estriol: In most tissues, such as the endometrium or liver, E3 acts as a weak estrogen, but produces full estrogenic responses in the vaginal epithelium. 1 mg/day of vaginal E3 produced plasma levels comparable to those with 10 mg of oral E3, confirming a 10-fold higher bioavailability via the vaginal route.¹⁵⁵ If oral E3 is administered at high doses or if the dose is divided and taken twice or three times a day, E3 will be present within the endometrial cell for a prolonged period and, hence, may cause endometrial proliferation. When 8 mg of estriol succinate was given once daily, the endometrial effect was mild, but dividing the same dose into 2 daily doses produced clear proliferative changes.¹⁵⁶ The same holds true for the effect of a meal on the pharmacokinetics of orally administered E3, with levels increasing after a meal.¹⁵⁵ Oral E3 absorption and serum concentrations were significantly influenced by food intake, showing increased exposure after a meal. A meal may stimulate the enterohepatic circulation of E3, causing a second peak in serum E3 concentration, thereby prolonging its presence in target cells and, specifically, leading to endometrial proliferation. Owing to rapid absorption and low metabolism in an atrophic vaginal mucosa, topical administration of E3 results in serum concentrations 10-20 times higher than those achieved with the same dose by oral administration. As about 20% of vaginally administered E3 reaches the circulation unchanged, the peak level after topical application of 0.5 mg E3 is 130 pg/ml, which is in the range of that found after oral administration of 8 mg E3.¹⁵⁷

The standard dose of E3 is 1-2 mg, preferably as a single evening dose. When administered at the recommended dose and regimen (0.5 mg daily for the first 2-3 weeks, followed by 0.5 mg twice a week), vaginal E3 therapy does not cause endometrial proliferation. As with oral E3, vaginal E3 did not alter serum concentrations of hepatic proteins.

Ethinyl Estradiol: A single dose of oral or vaginal administration of EE produced similar effects on hepatic proteins, indicating a potent first-pass effect with both modes of administration. This may be due to the chemical properties of ethinyl estradiol rather than the route alone. Ethinyl estradiol's 17 α -ethinyl group makes it resistant to metabolism and intrinsically more potent at the liver.^{158,159}

POTENCY

Although there is a significant correlation between serum E2 concentrations and clinical effects, such as hot flushes or bone mass, an individual woman's serum level does not predict therapeutic effect. Determining a so-called 'estrogenicity', which reflects the effects of various estrogens on hepatic production of, specifically, SHBG, cannot be extrapolated to the effect on, such as hot flushes. Refer to Table 4 for potencies and Table 5 for dose equivalents of estrogens.

Table 4: Relative Potency of Various Estrogens^{160,161,162}

Estrogen	Hot flushes	FSH	HDL cholesterol	SHBG	CBG	Angiotensinogen
17 β -estradiol (E2)	100	100	100	100	100	100
Estriol	30	30	20			
Estrone sulphate		90	50	90	70	150
CEE	120	110	150	300	150	500
Equilin sulphate			600	750	600	750
Diethylstilbestrol		340		2560	2450	1950
Ethinylestradiol	12,000	12,000	40,000	50,000	60,000	35,000

CEE: conjugated equine estrogens; Source:¹³³

Table 5. An approximate equivalence of doses and routes of different formulations of estrogens

Route / Formulation	Dose equivalent (mg)
Oral	
Conjugated equine estrogens	0.625
17beta-estradiol	1
ethinyl estradiol	0.005
Transdermal	
17beta-estradiol Patch	0.05
17beta-estradiol gel	1.5 mg / 2 metered doses
Vaginal	
Conjugated equine estrogens	0.3125
17beta-estradiol	0.5

Source:¹⁵²

Measuring estrogen potency is challenging because estrogens vary in dose equivalence and in their effects across different target tissues. Oral micronised estrogen 1.0 mg is equivalent to CEE 0.625 mg in terms of effects on liver function; whereas oral micronised estradiol 0.5 mg produces changes in bone density equivalent to CEE 0.625 mg.

Very few head-to-head trials have compared different estrogens. Clinicians tend to view estrogen products as equivalent on a dose-for-dose basis, although data do not support this assumption; metabolic pathways and adverse effects can vary in general and from woman to woman.

Comparing the pharmacokinetics and pharmacodynamics of transdermal 0.025, 0.05, or 0.1 mg/day and oral dosages of 2 mg of micronised 17 β -E2 or 1.25 mg of CEE, it was found that continuous application of transdermal E2 over 3 weeks did not result in any accumulation of E2 or E2 conjugates. After only three doses of oral estrogens, signs of retention were observed. Suppression of gonadotropins by oral and transdermal administration of estrogens was in a similar range. The increases in both serum and urinary E2 were dose-proportional. Serum levels of E2 obtained 24 hours after oral administration of estrogens were in a range similar to the steady-state levels obtained with transdermal E2 delivery. This observation supports the conclusions that circulating E2 levels are relevant to efficacy and that excessively high E1 levels after oral administration of estrogens merely reflect a non-physiological precursor or metabolite pattern.

As with most medications, the type, dose, formulation, and route of administration of MHT must be tailored to provide symptom relief for the individual woman. Refer to Table 5. The hormonal potency of the various estrogens is not only determined by their interactions with ERs and estrogen response elements (EREs) on the DNA, but also by the intracellular concentration of the estrogen. The latter depends on the bioavailable ('free') fraction of the circulating steroid, intracellular production, and the inactivation rate. As discussed above, serum E2 levels may not reflect the differential effects of different estrogen therapies at the tissue level. Moreover, commercially available tests are not very sensitive, and serum estradiol levels vary among individuals; they are not used to titrate the MHT response. Refer to Table 6.

Table 6. The serum levels of estradiol and estrone with different doses and routes of estrogen

Formulation (oral in mg)	Estradiol level (pg/ml) range	Estrone level (pg/ml) median value
Conjugated equine estrogens 0.625	30-50	153
17beta-estradiol	30-50	160
Formulation(transdermal in mg)		
17beta-estradiol patch 0.05	30-40	45
17beta-estradiol gel 1.5	60-90	90
Formulation (Vaginal mg)	After 4 Weeks	
Conjugated equine estrogens 0.625	13	40
17beta-estradiol 0.01	5	

Source:^{157, 158}

TERMINOLOGY IN HORMONE THERAPY

HT in menopause medicine is an umbrella term that covers various treatment approaches. The term HT covers therapies including estrogens, progestogens, combined therapies, androgens and tibolone. HT involves different routes of administration, different potencies, potentially different effects for each molecule, and risks and benefits that vary across individuals and within the same individual over time. Hence, there is no surprise that discrepancies exist across studies that use fixed combinations and fixed doses.

Standard abbreviations used are in Table 7

Table 7 Abbreviations for terminology in menopause hormone therapy

Abbreviation	Meaning
MHT	Menopausal Hormone Therapy
HT	Hormone Therapy (MHT and HT are interchangeable and mean the same)
HRT	Hormone replacement therapy, when used as replacement therapy for premature ovarian insufficiency
ET	Estrogen therapy
EPT	Estrogen-progestogen therapy
LET	Local estrogen therapy
AT	Androgen therapy
SERM	Selective Estrogen Receptor Modulator (such as raloxifene, bazedoxifene)
Gonadomimetics	Tibolone, which has estrogenic, progestogenic, and androgenic activity
OCP	Oral contraceptive pills ; CC: Combined contraceptive: COC : : Combined oral contraceptive
POP	Progestogen-only pill

Based on ET's pharmacokinetics and the individual's age and health profile, the following terminology is suggested.

Estrogen Replacement Therapy/Hormone Replacement Therapy: replicate the estrogen environment of premenopausal women as in POI and EM. It has no contraceptive effect.

Estrogen Additive Therapy: complements and replenishes endogenous postmenopausal estrogen with exogenous estrogen, tailored to meet the indication for HT as in the management of menopause within 10 years of menopause.

Estrogen Maintenance Therapy: Continued use of previously prescribed MHT beyond 10 years after menopause in appropriately selected women, aimed at maintaining the long-term benefits of estrogen where the benefit-risk profile remains favourable.¹⁶³

SUMMARY OF MAJOR MENOPAUSAL HORMONE THERAPY TRIALS

Table 8 A and B. Major Randomised Controlled Trials of Menopausal Hormone Therapy

Table 8 A. Primary Prevention and Surrogate-Endpoint Trials							
Trial	Year	N	Population	Intervention	Comparator	Primary Outcome	Duration
WHI (CEE+MPA) ^{29,30}	2002	16,608	PM women with uterus, 50-79 y (mean 63.3y)	Oral CEE 0.625 mg/d + MPA 2.5 mg/d	Placebo	Global index (CHD, stroke, PE, breast Ca, colorectal Ca, hip fracture, death)	5.6 y (stopped early)
WHI(CEE-alone) ^{29,35,164}	2004	10,739	Hysterectomised PM women, 50-79 y	Oral CEE 0.625 mg/d	Placebo	Same global index	7.2 y (stopped early)
PEPI ^{23,26,161}	1995	875	Healthy PM women, 45-64 y	4 arms: CEE alone; CEE + cyclic MPA; CEE + continuous MPA; CEE + cyclic micronised progesterone	Placebo	HDL-C, SBP, fibrinogen, 2-h insulin	3 y
DOPS ⁴⁶	2012	2,016	Early PM women, 45-58 y (mean 7mo post-menopause)	Triphasic 17β-E2 ± NETA 1 mg (Trisekvens); E2 2 mg/d in hysterectomised	No treatment (open-label)	Composite: death, MI, heart failure	10 y Rx; 16y FU
KEEPS ^{47,165}	2014	727	Healthy women, 42-58 y (mean 52.7 y), 0.5-3 y since LMP	Oral CEE 0.45 mg/d or transdermal 17β-E2 50µg/d + oral micronised progesterone 200 mg/d × 12 d/mo	Placebo	CIMT progression; CAC	4 y
ELITE ^{48,49,166}	2016	642	Healthy PM women in 2 strata: <6 y or ≥10 y since menopause	Oral 17β-E2 1 mg/d + vaginal progesterone gel 45 mg (if uterus)	Placebo	Rate of change in CIMT	5 y (median)

EPAT ¹⁶⁷	2001	222	Healthy PM women without CVD, 46-80y	Oral micronised 17 β -E2 1 mg/d	Placebo	CIMT progression rate	2 y
HOPE ¹⁶⁸	2001	2,673	PM women, 40-65 y	Various low-dose CEE (0.3, 0.45, 0.625 mg) $\pm$ MPA (1.5, 2.5 mg)	Placebo	VMS, vaginal atrophy, BMD, endometrial safety	2 y
WISDOM ¹⁶⁹	2002	5,692 (of planned 22,300)	PM women $\geq$ 50 y (mean $\sim$ 63 y, $\geq$ 10 y past menopause)	Oral CEE 0.625 mg/d + MPA 2.5-5 mg/d; or CEE alone	Placebo	Major CVD, fractures, breast Ca, dementia	11.9 mo (stopped early)

Table 8 B. Secondary Prevention Trials

Trial	Year	N	Population	Intervention	Comparator	Primary Outcome	Duration
HERS / HERS II ^{170,171}	1998 / 2002	2,763	PM women with established CHD (mean 66.7 y)	Oral CEE 0.625 mg/d + MPA 2.5 mg/d	Placebo	Nonfatal MI + CHD death	4.1 y (HERS); 6.8 y total
ERA ¹⁷²	2000	309	PM women with $\geq$ 1 coronary lesion (mean 63.5y)	Oral CEE 0.625 mg/d $\pm$ MPA 2.5 mg/d	Placebo	Coronary angiographic progression	3.2 y
ESPRIT ¹⁷³	2002	1,017	PM women 50-69 y surviving first MI	Oral estradiol valerate 2 mg/d	Placebo	Reinfarction or cardiac death	2 y
WEST ¹⁷⁴	2001	664	PM women (mean 71 y) with recent ischaemic stroke/TIA	Oral 17 β -E2 1 mg/d	Placebo	Recurrent stroke or death	2.8 y
WELL-HART ¹⁷⁵	2003	226	PM women with $\geq$ 1 coronary lesion (mean 63.5y, $\sim$ 18 y post-menopause)	Oral micronised 17 β -E2 1 mg/d $\pm$ sequential MPA	Usual care	Coronary angiographic progression (% stenosis)	3.3 y
RUTH ¹⁷⁶	2006	10,101	PM women (mean 67.5 y) with CHD or CHD risk factors	Oral raloxifene 60 mg/d	Placebo	Coronary events; invasive breast cancer	5.6 y (median)

PM = postmenopausal; CEE = conjugated equine estrogens; MPA = medroxyprogesterone acetate; E2 = estradiol; NETA = norethisterone acetate; CHD = coronary heart disease; MI = myocardial infarction; CIMT = carotid intima-media thickness; CAC = coronary artery calcium; BMD = bone mineral density; VMS = vasomotor symptoms; LMP = last menstrual period; FU = follow-up; Rx = treatment; Ca = cancer; PE = pulmonary embolism

PARADIGM SHIFT IN USE OF MENOPAUSAL HORMONE THERAPY

There has been a shift in the indication for use of MHT from 1994 to 2026, as shown by studies. Prevention is out (for now); symptom relief is in (if necessary); generalisation is out; and individualisation is the keyword.

Earlier: MHT should be considered for all postmenopausal women.

Current thought: Selective use for symptom relief within 10 years of menopause. MHT solely for the prevention of chronic disorders is a debatable issue.^{177,178}

Earlier: MHT may offer CVD protection at all ages.

Current thought: 10 years post-WHI, MHT does not increase the risk of CVD events and may even benefit when used within 10 years of menopause in healthy postmenopausal women. Risks are more and not to be used solely for primary or secondary prevention of CVD.^{179,180}

Earlier: Standard combination, fixed dose and continuous combined regimes were used.

Current thought: Natural and progesterone formulations, tailoring the dose to the woman's needs, low-dose therapy, and minimum effective therapy are being evaluated.^{181,182}

Earlier: Oral route was preferentially used.

Current thought: The expanded role, risks, and benefits of the transdermal route are under consideration.^{177,178}

Earlier: All types of progesterone can cause an increased incidence of breast cancer.

Current thought: With estrogen alone, there is no increase in breast cancer. Use of micronised progesterone and dydrogesterone may not increase the risk of breast cancer.^{183,184}

Earlier: All types of vaginal estrogen, like systemic therapy, may cause adverse effects. *Current thought:* No absolute contraindications for use of vaginal estrogen.

AUTO-REGULATION OF THE POTENCY OF ENDOGENOUS ESTROGEN

Depending on the reproductive phase, nature auto-regulates and provides the body with the needed potency of estrogen. The most potent E2 is the predominant circulating hormone in the reproductive phase; E3 is the predominant circulating hormone during pregnancy, and E1 is less potent during menopause.

INDIVIDUALISATION OF MENOPAUSAL HORMONE THERAPY: THE RATIONALE

Biological Variability

The response and intensity of symptom presentation during the MT vary and are as individualised as her thumbprint. Women respond differently to declining estrogen levels, indicating biological variability. The plasma, tissue, and cellular levels of estradiol depend on endogenous production, the aromatisation of adrenal androgens, the levels of the carrier protein, SHBG, and, finally, on interactions with estrogen receptor availability and response, which may be further modified by various endogenous and extraneous factors.

Therapeutic Variability

Estrogen endocrinology is complex, with intricate feedback mechanisms, numerous metabolic pathways, SHBG and free hormone issues, intracrinology specific to humans, and various variability among women. The time interval and route of administration, whether dermal or oral, are important, as oral estrogen is influenced by hepatic catabolism and the metabolism of various catechol estrogens with different estrogenic potencies. The drug and its metabolism must be considered. The distribution, type, and number of estrogen receptors also depend on the progestin, which downregulates estrogen receptors. The transcriptional process underlying a response to a given estrogen is extremely complex and may be induced genomically or nongenomically. The bioavailability of free hormones depends on their binding to plasma proteins. Various studies on MHT have clearly demonstrated that clinical response depends on the

indication, age, comorbidities, MHT type, dose, and route.¹⁸⁷⁻¹⁸⁹ The response may vary in the same individual over time. We need to tailor therapy to the woman's needs and remove the misconception that all MHT is the same.¹⁹⁰

Low-Dose Adjustive Hormone Therapy

VMS typically begin during the MT and tend to decline gradually in prevalence and intensity over time, whereas GSM usually emerges after menopause and worsens with advancing age. Both conditions are primarily driven by estrogen deficiency, although individual susceptibility and local tissue sensitivity influence symptom expression. In contrast, major NCDs such as osteoporosis, CVD, and breast cancer are multifactorial in origin. Estrogen is not the sole determinant but may act as a modifying factor, exerting either protective or adverse effects depending on the timing of initiation, dose, route of administration, baseline risk profile, and individual biology.

In November 2025, the US FDA removed the black box warning from MHT products and is already approved for the following indications:^{52, 53}

- VMS in menopause. HT is considered first-line therapy for these symptoms unless contraindicated.
- Prevention of bone loss and reduction of fractures in postmenopausal women.
- Prevention of bone loss and provision of health benefits for the treatment of menopausal symptoms, cognition and mood, and heart disease in women with premature ovarian failure, hypogonadism, or early surgical menopause who have no other contraindications to HT.
- Treatment of GSM and vulvovaginal atrophy.

MENOPAUSE HORMONE THERAPY

Most long-term, randomised data on MHT come from international studies. Hence, when interpreting this data in India, one should account for local epidemiological differences, such as an earlier age at menopause (ANM) and distinctive patterns of breast cancer, CVD, metabolic risk, and osteoporosis in Indian women.

MHT should be prescribed for accepted indications in appropriately selected women, with the understanding that secondary benefits alone do not constitute a sufficient indication. Individualising therapy based on each woman's health profile is essential. A documented informed consent form must be obtained.

Refer to Chapter 59. An annual benefit–risk review is recommended for all women receiving MHT.¹⁹³⁻²⁰⁰

The concept of precision medicine in prescribing systemic MHT emphasises individualised therapy, tailoring treatment to each woman and allowing it to change over time as her age, risk profile, symptoms, and health status evolve.

Checklist Before Prescribing Menopausal Hormone Therapy

Before starting MHT, every woman should undergo a comprehensive clinical evaluation and a personalised general and menopause-related risk assessment in a menopause proforma. Refer to Chapter 4 and Chapter 59.

The information obtained from the MRS scale and the risk screening results defines the stage of lifespan and health status. Based on the symptom profile, women can generally be categorised as either symptomatic or asymptomatic. Document the final diagnosis under the following headings.

- *The life stage:* Reproductive/Early MT; Late MT/Menopause: Early postmenopause < 8 years/Late postmenopause > 8 years
- *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 final diagnosis will include all five parameters. For example, Early MT, natural, asymptomatic, overweight, healthy

Table 9. Comprehensive chart for documenting the risk score for NCDs over 5/10 years & lifetime results

Tool	5/10 years risk score	Lifetime risk score	Risk status
Gail model			
WHO/ISH Globorisk-India			
OSTA/SCORE/FRAX			
SARC-calf			

Risk/Benefit Analysis

Local vaginal therapy: Record the presence of GSM by noting the most bothersome symptoms, the vaginal pH using narrow-range litmus paper, and the signs noted on examination. Vaginal estrogen is not associated with an increased risk of cardiovascular events, and assessment of CVD and breast cancer risk is generally not needed when low-dose vaginal estrogen is prescribed.

Systemic therapy: Benefit Stratification -Quality of life, severity of VMSs and other symptoms at menopausal transition, urogenital symptoms, bone health, cardiovascular health, mood and cognition.

A comprehensive chart for grading the health status and risk for diseases based on tools for invasive breast cancer, CVD and musculoskeletal health. Refer to Table 9.

Table 10. Management plan for women with menopausal symptoms (Vasomotor Symptoms/Genitourinary Syndrome of Menopause/Bone health)

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

Individualised management should place strong emphasis on symptom presentation, single or clustered symptoms and comorbidities, and target interventions to inform decisions more effectively. Refer to Table 10. Based on the health profile, women are further classified as low-, moderate-, or high-risk to personalise care and treatment decisions. Evaluate women's individual benefits and risks to help them understand the indication for therapy and support shared decision-making. Evaluate women's needs and preferences through counselling.

COUNSELLING REGARDING MENOPAUSE HORMONE THERAPY

Counselling: The physician should discuss with the woman about (a) the indications, benefits, risks and side effects of MHT, (b) Pre MHT tests, the types of MHT available, and the options suitable for her, (c) the way treatment will be monitored, (d) how long MHT might be used, (d) economic consideration and (e) other available options. This will improve compliance with treatment. It is preferred to have informed consent and document it. This will improve treatment compliance.

CONCEPT OF ABSOLUTE NUMBERS IN COUNSELLING THE ADVERSE REACTIONS

Adverse reactions are ranked under headings of absolute numbers. The number of adverse effects is expressed as a proportion of the number of subjects exposed for one year. It is easier to counsel a woman in simple terms rather than in numbers, using the Council for International Organisations of Medical Sciences (CIOMS), which has classified the frequency of drug reactions, including the impact of MHT or estrogen therapy. Refer to Table 11. Rare findings in large RCTs and observational studies may be statistically significant, as seen in WHI, because of the large sample size, but may be of minor clinical importance when applied to a particular patient in the clinical setting.

Table 11. Risk counselling

TERM	NUMBER	COLLOQUIAL
Very common	1/1 to 1/10	A person in family
Common	1/10 to 1/100	A person in street
Uncommon	1/100 to 1/1,000	A person in village
Rare	1/1,000 to 1/10,000	A person in a small town
Very rare	Less than 1/10,000	A person in a large town

Source: RCOG Clinical Governance Advice

THE SIX RIGHT PRINCIPLES FOR PRESCRIBING SYSTEMIC MHT ARE TO SELECT THE RIGHT ELIGIBLE WOMAN, THE RIGHT AGE, THE RIGHT HORMONE, THE RIGHT REGIMEN, THE RIGHT ROUTE, AND THE RIGHT DOSE.

Right Eligible Women

Indications

The classical indications for MHT that have consistently withstood the test of time, supported by evidence from multiple randomised clinical trials and meta-analyses, are the beneficial effects of estrogens on moderate-to-severe VMS and associated symptoms, such as mood, sleep, and GSM.^{30,201-206}

In eligible women at risk for fracture, MHT may be considered after a full risk assessment.^{205,207}

HRT is strongly recommended for women with and should be offered to women with EM until they reach ANM.²⁰⁸

Absolute Contraindications To Systemic Hormone Therapy

Undiagnosed abnormal vaginal bleeding; known, current, suspected, or past breast hormone receptor-positive cancer; estrogen-dependent cancers (endometrial, ovarian, and others); active or recent venous thromboembolism (VTE); recent history of stroke or myocardial infarction (MI); severe active liver disease with impaired or abnormal liver function; porphyria cutanea tarda; dementia; hypersensitivity; and known or suspected pregnancy.²⁰⁹

Relative Contraindications

The presence of latent or established comorbidities requires personalised assessment, shared decision-making, and coordination within a multidisciplinary care team to ensure safe initiation and monitoring of therapy.²¹⁰

Right Age

MHT has the most favourable benefit-to-risk profile when started within roughly 10 years of menopause. (Refer to the section on timing hypothesis) For starting later than 10 years after menopause or in women over 60, the benefit-to-risk ratio becomes less favourable, and shared decision-making is crucial. It is not recommended for women > 20 years post-menopause.²¹⁰⁻²¹⁶

Continuing Menopausal Hormone Therapy Beyond 10 Years After Menopause Or After Age 60

MHT may be continued in healthy women who are already using low-dose transdermal estradiol with micronised progesterone (MP) or dydrogesterone (DYD), provided the benefits outweigh the risks. An annual review of symptoms, breast and cardiovascular health, and any emerging contraindications is essential.^{48,217-219} When risks related to cardiovascular, thrombotic, or cognitive issues emerge, nonhormonal options are preferred. Vasomotor and sexual symptoms may continue into the seventh and eighth decades, and residual GSM symptoms often need ongoing treatment. Symptom-driven, personalised continuation is appropriate when the benefits outweigh the risks.²¹⁷⁻²¹⁹ Refer to the section on long-term therapy.

Restarting Or Initiating Systemic Menopausal Hormone Therapy More Than 10 Years After Menopause Or After Age 60

Restarting or initiating systemic MHT more than 10 years after menopause or after age 60 places the early hazard window for VTE and stroke. Accordingly, routine initiation of systemic MHT in this setting is not recommended based on contemporary evidence. If treatment is nevertheless deemed clinically necessary for severe, bothersome symptoms after careful individualised risk-benefit assessment and shared decision-making, a safer approach is to prefer transdermal 17 β -estradiol at low or ultra-low doses (25 μ g or 12.5 μ g/24 h), combined with MP or DYD in women with an intact uterus. This regimen is associated with a more favourable thrombotic and cerebrovascular safety profile than oral estrogen-progestin therapy (EPT).^{48,210,211,220-224}

Starting Systemic Menopausal Hormone Therapy De Novo More Than 20 Years After Menopause

Starting systemic MHT de novo more than 20 years after menopause, usually at age 70 or older, is not recommended, owing to increased risks of coronary events, stroke, VTE, and dementia as shown in WHI and other studies.²²¹

In this age group, non-hormonal therapies should be preferred as first-line treatment for vasomotor symptoms. However, evidence specifically guiding optimal non-hormonal dosing in women ≥ 70 years is limited, and symptom patterns, frailty, comorbidities, and polypharmacy may necessitate individualised dosing strategies that differ from those used in younger postmenopausal women. In particular, doses of SSRIs, SNRIs, gabapentinoids, and other alternatives may need to be lower and titrated more cautiously in older women.²²¹ For bone health after 10 years postmenopause, nonhormonal pharmacological options, such as bisphosphonates, denosumab, or SERMs, are preferred when MHT is generally not recommended for primary osteoporosis prevention at this age.

Right Hormone

Estrogen

Both CEE and 17 β -estradiol effectively relieve vasomotor symptoms.²⁰¹ Oral CEE favourably alters HDL and Lp(a) but raises triglycerides, CRP, and clotting factors due to hepatic first-pass effects.²²⁵ EE 5 μ g increased triglycerides by approximately 39% relative to baseline.²²⁶ The comparable mean triglyceride elevations for CEE 0.625 mg and E2 1 mg were 35% and 10%, respectively.^{226,227} Oral CEE is the most extensively studied estrogen formulation (WHI), with well-characterised benefits and risks, and remains an acceptable option in appropriately selected women.^{47,48,210,222} When cardiovascular or thrombotic risk is a concern, transdermal 17 β -estradiol at low doses is preferred over oral estrogen formulations.²²⁸ EV is a synthetic ester of 17 β -estradiol that is quickly hydrolysed to E2 following oral or parenteral administration. Its clinical efficacy and safety are comparable to those of other oral estrogens for symptom relief and bone protection, although large RCTs are lacking.²²⁹

Progesterone

The choice of a progestogen to accompany systemic estrogen therapy should be based on endometrial safety, systemic risk profile, tolerability, route preference, and cost-effectiveness.²³⁰⁻²³³ All approved progestones effectively prevent estrogen-induced EH when used at the correct dose and duration, tailored to individual needs based on estrogen potency and route. MP and DYD maintain a neutral metabolic and vascular profile and are considered VTE neutral when combined with transdermal ET.²³³⁻²³⁶ Evidence from large cohort studies indicates that estrogen combined with MP or DYD does not seem to increase breast cancer risk during typical usage durations of < 5 years and may pose a lower risk than regimens using synthetic progestins such as medroxyprogesterone acetate (MPA). Long-

term use exceeding 5-7 years requires individualised reassessment, as data beyond this period remain limited. However, the National Institute for Health and Care Excellence (NICE) evidence review states that “it is unclear whether different progestogen types alter breast cancer risk.” It therefore does not currently recommend choosing progestogen solely based on breast cancer risk.²³⁷⁻²⁴⁰

A large Norwegian cohort study involving over 1.3 million women found that combined oral EPT was linked to a twofold increase in breast cancer risk, with variation according to formulation and duration, whereas vaginal estradiol has not been associated with increased risk. These studies largely reflect the effects of synthetic progestins, as MP and DYD were not evaluated. Collectively, these data highlight that breast cancer risk with menopausal hormone therapy is regimen-specific and support an individualised approach with regular review.²⁴¹ MP helps improve sleep in women with insomnia, but it can cause daytime drowsiness in some.^{242,243} The combination with the DYD formula offers oral bioavailability, minimal sedation, and fixed-dose components, all of which improve patient adherence. Given sequentially at 300 mg/day, vaginal MP induced a full secretory endometrium in premenopausal women, while at a dose of 100 mg per day, along with 25 µg E2 patches, there was no EH, and some patients developed vaginal atrophy.²⁴²²⁴⁴ LNG-IUS 20 µg/day offers effective endometrial protection for 5 years with minimal systemic effects. It has a higher initial cost and necessitates procedural insertion.²⁴⁵

Oral Contraceptive Pills

Hormonal preparations containing either combined estrogen-progestin (usually including EE, and in some cases, 17β-estradiol, EV, or estetrol) or progestin alone are used primarily for contraception and for the regulation of menstrual and hormonal disorders. OCPs were developed to suppress ovulation in normally cycling women and, as such, supply supraphysiologic levels that are needed to suppress FSH.²⁴⁶

At menopause, they provide no additional benefit beyond that of MHT, with much added risk, namely increased risk of VTE, stroke, increased blood pressure, unfavourable lipid profiles, and general increased cardiometabolic risk. MHT at physiological doses does not suppress serum FSH or ovulation; therefore, it is not a contraceptive. In healthy women aged 50 to 64 years, HT exposure did not appear to adversely influence other risk factors, and exposure generally played a minor role in VTE risk. Contraceptives, however, were a strong risk factor for VTE in this age group.²⁴⁷ During MT, low-dose COCs can ease vasomotor and mood symptoms and may support bone health.

Long-term use of COC reduces endometrial cancer risk by more than 50%, with protection lasting decades after cessation.²⁴⁸ COCs are associated with a modest reduction in colorectal cancer risk.²⁴⁹ COCs offer effective contraception, help regulate irregular bleeding, lower the risk of endometrial and ovarian cancers, reduce the incidence of functional ovarian cysts, and reduce the risk of pelvic inflammatory disease.^{248,249} Newer COCs contain E2 or estetrol in addition to progestins and may have a better metabolic profile than those containing EE.²⁵⁰ Although no definitive randomised trials to date compare continuous versus cyclic OCP use specifically in women, expert guidance and reviews support shortened or eliminated hormone-free intervals with continuous or extended use to reduce VMS and abnormal bleeding, as learned from continuous combined hormone therapy users. The other indication for use is premature ovarian insufficiency (POI) and early menopause (EM), where higher doses of MHT are required, offering psychological benefits and cost-effectiveness in these younger women.²⁵¹

Tibolone, SERMS, and Androgens-Refer to Chapters 38,39, and 40.

Right Regimen

The clinical goal of these ET/EPT regimens is to provide uterine protection, maintain estrogen benefits, and minimise side effects. Commonly prescribed treatment options include estrogen alone, sequential combined hormone therapy (scMHT), continuous cyclic MHT, and continuous combined hormone therapy (ccMHT) regimens. The choice of an appropriate regimen should be guided by factors such as menopausal stage, uterine status, symptomatology, and patient preferences. Earlier, various regimens were available. Refer to Table 12.

Table 12. Terminology defining types of Estrogen-Progestin Therapy regimens

Regimen	Estrogen	Progestogen
Cyclic	Days 1–25	Last 10–14 days of the month
Cyclic-combined	Days 1–25	Days 1–25
Continuous-cyclic (sequential)	Daily	10–14 days every month
Continuous long-cycle	Daily	14 days every 3–6 months
Continuous-combined	Daily	Daily
Intermittent-combined (pulsed-progestogen; Continuous-pulsed)	Daily	Repeated cycles of 3 days on, 3 days off

Estrogen alone regime: An estrogen-only regimen is recommended for women who have undergone surgical menopause. Estrogen is administered daily without interruption. In certain circumstances, a combined estrogen-progestogen regimen is indicated in women after hysterectomy. In patients with endometriosis, unopposed estrogen may stimulate residual pathology, and adenocarcinoma has been reported in patients with pelvic endometriosis treated with unopposed estrogen. Hence, progestogens have a place in the management of residual endometriosis following radical surgery or subtotal hysterectomy. Reactivation of residual endometriosis is very low in hormone-treated postmenopausal women compared with those who did not receive HT. MP and DYD are both highly effective in reducing endometriosis-related symptoms. Patients who have had stage I or II adenocarcinoma of the endometrium can take estrogen without fear of recurrence, but the estrogen-progestogen combination is recommended in view of the potential protective effect of the progestational agent. Treatment can be initiated immediately postoperatively. The combined estrogen-progestogen approach may be given to patients previously treated for endometrioid tumours of the ovary. Patients who have had procedures that may leave residual endometrium, such as supracervical hysterectomy, and who have undergone endometrial ablation should be treated with an estrogen-progestogen combination. Firm evidence is lacking; we recommend adding progestogen to estrogen in hysterectomised women who have residual endometrial tissue after endometrial ablation or supracervical hysterectomy, a history of endometriosis, and stage I endometrial carcinoma.²⁵²⁻²⁵⁴ Tibolone 2.5 mg/day may also be considered for women without a uterus.^{255,256} A significantly increased risk of EC among estrogen-only MHT users in women with a uterus, RR of 4.4.²⁵⁷

scMHT Regimen: In women with an intact uterus, adding a progestogen is crucial to counter the proliferative effects of estrogen on the endometrium and prevent hyperplasia or carcinoma. Estrogen daily with progestogen added for 12–14 days each month is indicated for women in late MT or within 1–2 years of the FMP. Predictable withdrawal bleeding occurs at the end of each progestogen cycle. Shorter progestogen phases (< 10 days) or use beyond 5 years are linked to an increased risk of endometrial cancer.²⁵⁸⁻²⁵⁹ Starting on the first day of the month may facilitate tracking uterine bleeding episodes, as the cycle day corresponds with the day of the month. In a typical continuous-cyclic regimen, progestogen is started on day 1 or day 15 each month.²⁶⁰ Low-dose combined OCPs may be used in early or late MT for both symptom relief and contraceptive protection.²⁶⁰⁻²⁶²

ccMHT regimens: should not be used at MT/perimenopause, because of the high risk of irregular bleeding. Involves daily administration of estrogen and progestogen without interruption. This approach maintains consistent hormonal levels and aims to induce endometrial atrophy over time.²⁶³ EPT preparations have a low rate of endometrial cancer, based on short-term studies of up to 1 year. A 2020 review suggests that scMHT with synthetic progestins, as well as either scMHT or ccMHT with MP, may be associated with a modest increase in endometrial cancer risk when progestogen exposure is insufficient.²⁵⁹ This risk appears especially relevant with shorter progestogen phases, lower doses, or duration exceeding 5 years. Adequate endometrial protection requires administering progestogen for 12–14 days per 28-day cycle or providing continuous exposure, depending on the type of progestin, dose, and duration of MHT use.^{210,259,264,265}

ccMHT is generally the preferred regimen for amenorrhoeic postmenopausal women with an intact uterus and, through continuous progestogen exposure, suppresses endometrial proliferation and promotes atrophy. In the WHI randomised trial, ccMHT was associated with lower endometrial cancer incidence than placebo,²⁶⁶ and in the Million Women Study, ccMHT was associated with lower endometrial cancer risk than in never-users.²⁶⁷ Irregular bleeding or spotting is common during the first 4–6 months after starting ccMHT and usually does not require investigation initially; however, assessment is warranted if bleeding becomes heavier rather than lighter, persists beyond 6 months, or recurs after a substantial period of amenorrhoea.²¹⁰ The incidence of irregular bleeding may be reduced by ensuring that the progestogen dose is proportionate to the estrogen dose.²⁶³

Switching From scMHT To ccMHT

It may be difficult to decide when women can switch from sequential to continuous combined therapy. Pragmatically, postmenopausal status can be estimated from age. It has been estimated that the majority of women in India will be postmenopausal by the age of 50 years in India.^{268–270} Biochemical markers such as FSH are not routinely required to confirm menopausal status in women using hormone therapy, as levels may fluctuate and are not reliably predictive during the menopausal transition. Clinical assessment, including age, menstrual history, and symptom profile, remains the cornerstone of decision-making.²¹⁰

Switching From Oral Contraceptive Pill To Menopausal Hormone Therapy

In women aged 45–50 years using CCP, the presence of menopausal symptoms should prompt consideration of transition to MHT for symptom relief, keeping in mind the need for contraception. This strategy is further supported by the increased risk of VTE and arterial events associated with EE-containing contraceptives.^{271,272} An age-based clinical approach is preferred over biochemical testing, as CCPs suppress gonadotropin and estradiol secretion, rendering FSH and estradiol measurements unreliable.^{271,272} For women who require ongoing contraception, switching to progestogen-only methods such as the levonorgestrel-releasing intrauterine system, or E2-based pill is recommended in accordance with eligibility criteria.²⁷³

In women aged ≥ 50 years using progestogen-only contraception who are amenorrhoeic, menopausal status may be supported by two FSH measurements ≥ 30 IU/L taken at least 6 weeks apart.²⁷⁴ However, in women using combined oral contraceptives, hormonal testing is not recommended for diagnosing menopause due to suppression of the hypothalamic–pituitary–ovarian axis; if required, assessment should be performed after discontinuation of CHCs.

In the absence of robust evidence supporting the superiority of biochemical markers over clinical assessment, management is individualised. The changeover from OCP to MHT is performed if estradiol is less than 20 pg/mL,²⁷⁴ and a serum FSH is greater than 20 IU/L, or on the 7th day of the pill-free interval, with tests done twice at least 4 weeks apart.²⁷⁵

Right Route

Oral versus transdermal should be personalised based on the cardiovascular/metabolic risk profile, clinical indications, and patient preference.^{211,234,276–279} Transdermal estrogen is the preferred route of administration for postmenopausal women with metabolic or vascular risk factors such as obesity, metabolic syndrome, diabetes mellitus, hypertriglyceridaemia, elevated CRP, and controlled hypertension.^{234, 235, 280} It is also recommended for women with migraine with aura, gallbladder disease, bowel disorders (such as irritable bowel syndrome or inflammatory bowel disease), or those who smoke, or have a history of VTE or varicose veins, including women using hepatic enzyme-inducing medications such as phenytoin or carbamazepine.^{235,281} Oral but not transdermal estrogen is associated with an increased risk of VTE.^{278,282} Additionally, data suggest that norpregnane derivatives may be thrombogenic, whereas MP and pregnane derivatives appear safe with respect to thrombotic risk.^{235,279,280} Transdermal estradiol may be beneficial for women experiencing sexual dysfunction, as it avoids first-pass hepatic metabolism and has a lesser effect on SHBG, thereby preserving circulating free testosterone levels. In contrast, oral ET may increase SHBG and reduce free testosterone, potentially adversely affecting libido in some women. Evidence from randomised studies, including ancillary analyses of the KEEPS, suggests possible differences in sexual function outcomes between oral and transdermal preparations, supporting biological plausibility.²⁸³ However, overall clinical data remain limited, and systematic reviews have not specifically evaluated differences by route of administration.²⁸⁴

Transdermal E2 generally produces steadier circulating E2 levels than oral administration, avoiding large peaks and troughs and first-pass hepatic metabolism.²⁸⁵

In a randomised crossover study comparing oral and transdermal 17 β -estradiol, mean serum E2 concentrations were 40-70% lower in smokers than in non-smokers among women using oral therapy, whereas this smoking-related reduction was not observed with transdermal E2, suggesting that the transdermal route is less influenced by hepatic induction from cigarette smoking.²⁸⁶

Despite this theoretical advantage, substantial pharmacokinetic variability exists with both routes. Among women compliant with oral E2 in the ELITE trial, mean serum E2 levels ranged from 9 to 360 pg/mL, reflecting marked interindividual differences in absorption, metabolism, and clearance.²⁸⁷ Similar variability has also been documented with transdermal therapy; real-world data show up to 10-fold differences in serum E2 concentrations at equivalent transdermal doses, indicating that steady delivery does not eliminate biological variability in systemic exposure.²⁸⁸ Overall, while transdermal E2 offers more stable pharmacokinetics and avoids first-pass hepatic effects, clinically meaningful variability in achieved serum levels persists regardless of route, underscoring the importance of individualised dosing guided primarily by clinical response rather than routine hormone monitoring. Limitations of transdermal preparations include the fact that serum E2 levels are influenced not only by the prescribed dose and adherence, but also by differences in skin characteristics and application practices, lifestyle and metabolic factors, biological variability over time, and formulation-specific properties, which can lead to considerable variation in systemic exposure and the predictability of achieved estradiol levels in individual women.

Oral Estrogen

Oral estrogen therapy exerts pronounced hepatic effects due to first-pass metabolism, resulting in favourable changes in lipid parameters. In women with low HDL-C, oral estrogen is more effective than transdermal therapy in increasing HDL levels and is also associated with reductions in lipoprotein (a).^{114,289-291} Eleven randomised trials have compared the lipid effects of oral vs transdermal HT. Consistently, these trials have found that, unlike oral HT, which increases triglycerides by 5-15%, transdermal HT decreases triglyceride levels by 5-30%. In this context, the transdermal route of ET is used for symptomatic menopausal women with dyslipidaemia, particularly those with a tendency towards hypertriglyceridaemia.²⁹²

In pooled analyses of the WHI clinical trials, an increased risk of coronary heart disease was observed in women with adverse baseline lipid profiles receiving CEE with or without MPA.³⁰ However, age-stratified and timing-based analyses of WHI data have demonstrated that in younger, recently postmenopausal women (aged 50-59 years or within 10 years of menopause), MHT is associated with a low absolute cardiovascular risk and may even confer neutral or favourable effects on coronary outcomes, supporting the “timing hypothesis”.^{186,211}

A 2023 systematic review found that transdermal HT has a more favourable safety profile than oral therapy, particularly regarding thrombotic risk, while demonstrating comparable efficacy.²⁹³ There is a lack of evidence comparing the incidence of CVD between oral and transdermal administration routes, and it is recommended that further investigation be conducted.

Regarding VTE, all identified studies consistently report that the transdermal route is safer than oral HT.^{279,280,294} The effect of HT on blood pressure depends on the formulation used, especially the type of estrogen, rather than the route. The combined formulations of CEE plus progestogen increased systolic blood pressure and the risk of hypertension, which was not observed among E2 plus progestogen, E2 alone, and tibolone users.²⁹⁵

MHT improves glucose metabolism and insulin sensitivity, with evidence suggesting a reduced risk of developing type 2 diabetes in women without pre-existing disease; these metabolic benefits appear to be more pronounced with oral therapy, although they are observed with hormone therapy overall.²⁹⁶

Circulating E2 levels achieved with therapy vary depending on formulation and route, but a physiological E2 concentration of approximately 40-60 pg/mL, sufficient to maintain vascular and skeletal health, can be achieved with both oral and transdermal preparations, provided adequate bioavailability is ensured. Higher levels up to 100 pg/mL may be needed to restore bone density. Both routes have demonstrated beneficial effects on BMD, with greater improvements observed when therapy is initiated early after menopause and at higher doses, irrespective of the route of administration.²⁹⁷⁻³⁰¹

Six cohort studies and one case-control study compared the effects of oral and transdermal HT on breast cancer risk and found no significant differences between oral and transdermal estrogen administration.³⁰² Evidence from the WHI further showed a reduced incidence of breast cancer with estrogen-alone therapy using oral CEE.¹⁸³ Current data suggest that breast cancer risk is influenced more by the type of progestogen and duration of therapy rather than the

Table 13. Advantages and disadvantages of oral and transdermal estrogen therapy

Oral estrogen therapy: Advantages	Oral estrogen therapy: Disadvantages	Transdermal therapy: Advantages	Transdermal therapy: Disadvantages
Easy to take, convenient	High-dose required	Low dose	Patches can detach or leave a residue. Gels can be messy.
Cheap	Variation in absorption	Generally better than oral; steady serum levels	Absorption can be limited by skin permeability and poor patch adhesion.
Good control	Alters liver protein synthesis	No effect on hepatic enzymes and proteins	Gels can be transferred to other persons
Short half-life	Minor side effects	–	Skin reactions can occur.
Wide choice	Daily dosage	–	patches and depot preparations
–	All tablets contain lactose	–	Gel takes 2-3 minutes to dry and 2 hours to be kept dry
	Has the potential to interact with other medications.	Unlikely to interact with other medications.	Marked interindividual variability

Right Dose

Use the appropriate, minimum, effective, and adjustable dose for symptom relief or bone protection, tapering the dose as age advances.^{303,304}

The minimum effective dose is the principle to follow when prescribing HT. The potency a woman needs may change over time. Oral micronised 1 mg 17 β -E₂, equivalent to 0.625 mg of CEE, is the most useful starting dose for treating moderate and severe vasomotor symptoms in menopausal women. Lower doses (0.5 mg) take longer to relieve symptoms, and 0.25 mg is ineffective in women with moderate-to-severe hot flashes. A higher dose of 2 mg is effective for symptom relief but is associated with increased estrogen-related adverse events and higher discontinuation rates, and should be used only in women who do not have adequate symptom relief with lower doses.³⁰⁵ At comparable estrogenic exposures, equivalent doses of other formulations or routes transdermal may be selected based on individual risk profile, patient preference, and clinical context.

After starting standard-dose therapy, the dose can be reduced and maintained as needed. Low-dose and ultralow-dose therapy may be effective in maintaining symptoms and increasing bone mass. Refer to Tables 14 and 15. Standard-dose HT may be preferred in women with POI, EM, or younger postmenopausal women requiring optimal skeletal protection. (A transdermal E₂ dose of at least 100 μ g/day, oral micronised E₂ 2 mg/day or CEE 1.25 mg/day) is recommended for skeletal protection in women with premature ovarian insufficiency, women with significant psychological or depressive climacteric symptoms, and women who do not achieve adequate symptom control with low-dose HT.²⁰⁸

Table 14. Approximate Doses of estrogen therapy in milligrammes based on pharmacokinetics & clinical trials, & the dose equivalents are subject to individual variation

Estrogens	Ultra low	Low	Standard	High
Conjugated equine estrogens (mg, CEE)-oral	0.15	0.3, 0.45	0.625	1.25
17 β -estradiol (mg) oral	0.5	1	2	2
17 β -estradiol (mg) Transdermal patch (not available in India)	0.014	0.025	0.05	0.1
17 β -estradiol (mg) Transdermal patch (not available in India)	0.014	0.025	0.05	0.1
17 β -estradiol (mg) Transdermal pump / Gel-1.25 g of gel is equal to 0.75 mg	$\frac{1}{2}$ pump 0.375	One Pump 0.75	Two Pump /1.5	3-4 Pump / 3
Estradiol valerate (mg)-oral	–	1	2	4

Table 15. Types of progestogens and the required dose for preventing Endometrial Hyperplasia from the available information

Progestosterone (mg)	Sequential combined regimen	Continuous combined regimen
Micronised progesterone (MP; oral preferable vaginal)	Oral E2 1 mg/ CEE-0.3 mg/ TDE $\leq$ 0.025 mg patch or 0.75 mg gel or pump — 200 mg of MP for 12-14 days	Oral E2 -1 mg / CEE-0.3 mg/ TDE - 0.025 mg — 100 mg of MP Daily
	Oral E2 -1-2 mg / CEE-0.625 mg/ TDE -0.05 patch or 1.5 mg gel — 200 mg MP for 14 days	Oral E2 -2 mg / CEE 0.625/ TD-0.05 — 200 mg
Dydrogesterone (Dyd)	Oral E2 1 mg/ CEE-0.3 mg / TDE $\leq$ 0.025 mg; 10 mg of Dyd for 12-14 days	E2 1 mg; 5 mg of Dyd
	Oral E2 1 mg/ CEE-0.3 mg / TDE $\leq$ 0.025 mg; 10 mg of Dyd for 12-14 days	Ultra low dose: E2 0.5 mg; 2.5 mg of Dyd
LNG (intrauterine)	52 mg (releases 20 μ g/day)	52 mg (releases 20 μ g/day)

Norethisterone acetate (NA): Oral E2 1 mg/CEE 0.3 mg: 0.5 mg NA. Oral E2 2 mg/CEE 0.625 mg: 1 mg NA. (0.5/1 mg of norethisterone is not available in India)

Low-dose and ultra-low-dose therapies effectively alleviate symptoms and help sustain bone mass. Refer to the section on low-dose therapy. It is important to note that the precise optimal dose for each patient remains personalised, and the evidence is continually evolving. The progestogen dose should be proportional to the estrogen dose. Evidence comparing oral and transdermal MHT in terms of dose equivalence is limited.^{230,238,306-309}

Enhanced monitoring and clinical vigilance are recommended for women with persistent endometrial thickening (> 5 mm), obesity (associated with higher endogenous estrogen levels), or those who have been receiving MHT for more than 5 years.

Flow chart to Prescribe MHT: Refer to Chapter 59

DRUG INTERACTIONS OF MENOPAUSAL HORMONE THERAPY

Most available MHT products undergo liver metabolism mediated by the CYP450 system. Specifically, estrogen products are partially metabolised by CYP3A4; therefore, strong inducers of CYP3A4 can reduce the efficacy of estrogen, and strong inhibitors can increase serum concentrations. Additionally, other drug substrates of these enzymes can interfere with MHT metabolism. Drugs such as rifampicin and barbiturates increase the metabolism of MHT. Hormone therapy enhances the effects of imipramine, phenytoin, and carbamazepine, and reduces the effects of anticoagulants and hypoglycaemic agents. MHT increases thyroid-binding globulin levels and may increase T4 requirements.

Duration Of Use

At present, no studies indicate a time limit for the administration of properly monitored MHT/ET.³¹⁰ Short-term use may be defined as use for up to 1, 2, or 5 years.³¹¹

Premature Ovarian Insufficiency

In POI, HRT should be maintained until the average ANM.³¹²⁻³¹⁹ Continuation beyond the ANM should be a jointly reviewed decision that considers ongoing indications, patient preferences, and an evolving risk profile.^{206,208,204,320,321}

Early Menopause

Consider continuation beyond 48-50 years on an individual basis through shared decision-making when symptomatic or for bone protection.³²²⁻³²⁴

Natural Menopause

After nearly 20 years of follow-up, WHI trials showed that neither EPT nor ET were associated with increased all-cause, cardiovascular, or overall cancer mortality when initiated around the MT.²⁹⁶⁻²⁹⁸

Extended therapy beyond these durations may be justified through shared decision-making, particularly for women with recurrent vasomotor symptoms or for osteoporosis prevention when other therapies are unsuitable. Management should remain personalised, with an annually documented benefit-risk review and careful attention to the hormone regimen, duration, and route of administration. The prescription should be adjusted according to the woman's annual health profile.^{240,325,326} Refer to the section on long-term therapy.

LET remains the first-line treatment for GSM across all ages, because of its well-established efficacy in relieving vaginal dryness, dyspareunia, irritation, and urinary symptoms, while producing minimal systemic absorption at approved doses.

Although long-term randomised safety data beyond one year are limited, extensive real-world clinical experience and the consensus of major international menopause societies support continued use for as long as symptoms persist, provided therapy is individualised and supervised, rather than imposing a fixed upper time limit.^{210,327}

Follow-up

Review at 1-2 months after initiation to assess compliance, tolerance, and side effects; at 3 months to address unscheduled bleeding or intolerance; and annually thereafter for a comprehensive evaluation, including risk re-evaluation for NCDs and an updated benefit-risk analysis. Modify the dose or route of therapy as appropriate to the changing clinical profile of the ageing woman.

Situations Requiring Immediate Discontinuation Of Hormone Therapy

New or worsening migraine and headache pattern.

Visual disturbances such as blurring or symptoms indicating vascular occlusion, like retinal thrombosis.

Jaundice or indications of liver dysfunction.

Persistent or significant elevation in blood pressure.

Furthermore, HT should be stopped 4-6 weeks prior to elective major surgery involving prolonged immobilisation to reduce the risk of VTE.

If new breast symptoms (lump, nipple change) or unexpected bleeding occur during therapy, the appropriate evaluation should be undertaken while the decision to continue or pause MHT is made on a case-by-case basis.

Unscheduled bleeding until a diagnosis is reached.

Therapy may be reviewed and resumed once the patient has fully recovered and a comprehensive clinical reassessment of the patient's risk profile has been completed.

Problems Due To Menopausal Hormone Therapy And Management

Common Adverse Effects

Fluid retention

May occur in the short term. Recommend reducing dietary salt intake, maintaining adequate hydration, encouraging regular physical activity, and reviewing the estrogen dose. Persistent or troublesome oedema should prompt dose reduction or a change in route.

Bloating

Consider switching to a low-dose transdermal estrogen; reduce the progestogen dose to the level that still protects the uterus; switch to an alternative progesterone.

Breast tenderness

Common during the first few months. Consider reducing the estrogen dose, switching to a different form of estrogen, or trying a different progestin.

Headaches

Switching to transdermal estrogen and using the lowest effective dose often improves tolerance; some women benefit from a continuous-combined regimen.

Mood changes

Lower the progestogen dose; switch progestogen; or change from systemic progestin to the progestin IUS.²⁵⁸

Nausea

Advise taking the tablet with food or at bedtime; if it persists, reduce the estrogen dose or switch to a transdermal preparation.

Chloasma

Recommend broad-spectrum sunscreen for women prone to it.

Hormone Therapy and Weight Gain

It is a common myth that MHT causes weight gain. A Cochrane systematic review of 28 randomised controlled trials found no difference in weight gain between women receiving MHT and those not using hormones, and in some studies, MHT was associated with less central fat accumulation.³²⁸

Persistent Menopausal Symptoms

Despite seemingly adequate MHT, reassess the diagnosis, adherence, and drug-drug interactions, specifically enzyme-inducing antiepileptics and TB drugs. Identify coexisting medical, social, psychological or sexual problems. Then adjust the estrogen type or dose, or change the route, and optimise the progestogen formulation or regimen.^{258,329}

Bleeding While On Menopausal Hormone Therapy

Women need to be counselled before starting HT that bleeding is a common problem during HT, particularly during the first few months. Sequential regimens should result in regular, predictable withdrawal bleeds. However, bleeding patterns vary considerably between individuals. While most women experience cyclical bleeding, a proportion may have absent or irregular withdrawal bleeding, which may reflect reduced endometrial responsiveness and is not necessarily pathological in the absence of other risk factors.³³⁰

In contrast, unscheduled bleeding is common with continuous combined hormone therapy, particularly during the

initial months of treatment. The incidence of irregular bleeding varies widely in the literature, reflecting differences in regimens and populations, but is most frequent during the first 6–12 months and declines progressively with continued use.^{331,332} After approximately 6–12 months, most women achieve amenorrhoea, and only a small proportion continue to experience persistent bleeding.²⁶³

Measured median blood loss with two different HRT preparations was 16–26 ml; some may have experienced a genuine objective menorrhagia with HT, with a measured blood loss of more than 80 ml per bleeding episode.^{330,331}

During both sequential and continuous combined therapy, abnormal bleeding is usually due to persistent ovarian activity, which often can be overcome by altering the dose of estrogen and/or type of progestogen. Unscheduled bleeding, such as spotting, heavy, or persistent bleeding outside the normal phase, or any new bleeding after 6 months on a continuous-combined regimen, requires investigation.^{332,306}

EVALUATION OF BLEEDING IN A PATIENT TAKING MENOPAUSAL HORMONE THERAPY

Bleeding Problems

The prevalence of abnormal bleeding in HT users will depend on myometrial integrity, endometrium thickness, whether the woman is in the premenopause or postmenopause period at the start of replacement therapy, the time that has elapsed since menopause, the pattern of bleeding before menopause, the dose and type of sex steroids, the regimen used, and the treatment duration.

Bleeding

Any scheduled or unscheduled bleeding requiring more than one sanitary napkin/day, during the use of any oral or non-oral HT regimen.

Spotting

Any scheduled or unscheduled bleeding not requiring any sanitary towel, or not more than one per day, during the use of any oral or non-oral HT regimen.

Two patterns of bleeding occur in women on HT: scheduled “withdrawal” bleeding, or unscheduled “breakthrough bleeding”.

Scheduled, programmed bleeding/spotting

Any bleeding or spotting occurring after the end of the progestogen sequence, in the scMHT regimen

Early scheduled bleeding/spotting

Any bleeding or spotting with onset before the end of the progestogen sequence, in the scMHT

Unscheduled or irregular bleeding

Irregular bleeding which occurs after initiating, or changing, a HRT preparation, which should be “bleed-free”, ccHRT, or which occurs, in addition to the scheduled monthly withdrawal bleed in persons taking scMHT. Unscheduled bleeding within the first 6 months of initiating HRT or, within 3 months of a change in dose or preparation in those already established on HRT, is common. It can affect up to 38% of people using sHRT and 41% using ccHRT.³³³ The cause of unscheduled or irregular bleeding is poor compliance, intrauterine pathology, obesity, or at perimenopause, there may be an asynchrony of endogenous and exogenous hormones in scMHT regimens.³³⁴

When To Investigate?

Routine endometrial surveillance is not needed. With cyclical regimens, if bleeding starts at the onset of progesterone therapy, or there is a change in the duration or intensity of bleeding, which is normal for that woman. With continuous combined regimens, if bleeding is heavy or continuous and persists after 6–12 months of use. In women with a high risk of uterine cancer. For the majority of women with postmenopausal bleeding, the cause is inadequate MHT. However, because of the risk of EH and EC, abnormal bleeding must be evaluated. While transvaginal sonography (TVS) of the endometrium is the standard first-line investigation, it may not exclude pathology in women on MHT, and endometrial sampling remains the definitive method to exclude hyperplasia or carcinoma.³³²

Thick Endometrium On Transvaginal Ultrasound In Women Without Bleeding

After 6 months of amenorrhoea, with an ET of < 10 mm, and no significant risk factors for endometrial cancer, they can be offered adjustments in their progestogen therapy and follow-up instead of immediate biopsy.³³² Individuals with one major or two minor risk factors for endometrial carcinoma, and with ET > 4 mm on ccMHT or > 7 mm on sc/ccMHT, or endometrium is not adequately visualised, should be offered EB. If the endometrium appears inhomogeneous, cystic, or irregular, or if bleeding recurs, EB is recommended regardless of ET measurement.³³² Hysteroscopy is the gold standard for evaluating bleeding and for ruling out polyps, myomas, or other anatomic causes, or when a pipelle biopsy result is inconclusive. It has been shown that women who experience bleeding with MHT have the same incidence of uterine pathology as women who do not bleed. It is not necessary to biopsy women every time they bleed, unless there has been a period of amenorrhoea or a change in the bleeding pattern. Frequently, if the TVS and/or biopsy are normal, it may be wise to try to change the estrogen or progestin before proceeding to more invasive testing.

Comparative analyses of endometrial biopsies obtained from women with and without bleeding while on the same hormone therapy regimens have not demonstrated consistent histological differences, indicating that unscheduled bleeding is not necessarily associated with underlying pathology.^{331,335} In women receiving sequential combined therapy, most endometrial samples show partial or complete secretory transformation, although a spectrum of findings may be observed, including weakly secretory, proliferative, inactive, atrophic, and, less commonly, hyperplastic patterns.^{336,337} In contrast, continuous combined regimens are associated predominantly with endometrial atrophy, although proliferative, dysfunctional, or occasional hyperplastic changes may still occur. When atrophic and insufficient samples are considered together, the majority of biopsies approaching 90% reflect an inactive or suppressed endometrium.

Structural abnormalities such as endometrial polyps or other focal lesions are identified in a minority of cases, typically in the range of 7–8%, and occur irrespective of the hormone therapy regimen used. These findings underscore that most bleeding episodes during hormone therapy are benign and related to endometrial adaptation rather than significant pathology.³³⁴

Management³³²

Reassess the patient's understanding of the therapy. Check the absorption and distribution of the administered hormones. Consider the regimen in use. Assess the timing and characteristics of the bleeding. Exclude intercurrent or unidentified organic causes in the first assessment. Common causes include poor compliance, incorrect use of steroids, concomitant use of broad-spectrum antibiotics, anticoagulants, and anticonvulsants, forgetting to take the HT tablets, alterations in hormone absorption, metabolism, and excretion, and uterine abnormalities.

Continuous Sequential Menopausal Hormone Therapy

Increasing the dose or changing the progestogen type. Spotting before the withdrawal bleed may indicate inadequate endometrial stromal development, and a higher estrogen dose could be considered. If bleeding problems persist, further investigation is required.

Continuous Combined Menopausal Hormone Therapy

Bleeding between 3 and 6 months is usually considered to be acceptable, but persistent bleeding after 6 months or bleeding commencing after a spell of amenorrhoea. Increasing the dose or switching to a different progestogen may help. A small estrogen supplement may help some women to revert to sequential MHT and a regular bleed. There is uncertainty about whether MHT should be stopped prior to investigation for bleeding; it is unlikely to cause any problems with histological interpretation if the patient remains on MHT, provided the pathologist is given details of the hormonal treatment.

Management Based On The Histopathology Report And Menopausal Status

Atrophic adjusted Menopausal Hormone Therapy

Atrophic-adjusted MHT dose and follow-up as scheduled. In case of recurrent episodes with normal TVS and biopsy report, no risk factors for endometrial cancer, a follow-up with a TVS after 3 months is done. Inadequate sample with no risk factors for endometrial cancer, follow up and re-evaluate with hysteroscopy if another episode occurs. If there are risk factors for endometrial cancer, a repeat hysteroscopy-guided biopsy is the standard of care.

At MT

Proliferative endometrium, increase or opt for a haemostatic progesterone like norethisterone, LNG-IUD, or COC with estradiol in a long cycle or continuous regimen.

Women one year or more after menopause

The management protocols are similar to those for postmenopausal bleeding.

Stopping Menopausal Hormone Therapy

When considering discontinuation of MHT, clinicians should discuss both abrupt cessation and gradual tapering, and tailor the approach to the woman's prior VMS burden, osteoporosis indication, age, duration of use, and individual tolerance. The evidence does not show a clear advantage of tapering over abrupt stopping in preventing the recurrence or worsening of vasomotor symptoms. In a large randomised trial, Ockene and colleagues found that symptom recurrence after stopping EPT was common regardless of whether women discontinued therapy abruptly or tapered gradually.³³⁸ Subsequent observational data suggest that some women are more likely to struggle with stopping MHT. Women who had undergone hysterectomy, those who had used MHT for ≥ 10 years, and those who initiated therapy primarily for symptom relief were significantly more likely to be unable to discontinue therapy successfully.^{339,340} Clinicians should actively plan follow-up after stopping MHT, as symptoms recur in up to 50% of women, typically within the first few months.³³⁸ For women who experience intolerable symptom recurrence, it is reasonable to resume MHT and attempt discontinuation later, either by initiating a slow taper or by waiting approximately six months before trying again. Tapering may be achieved either by reducing the daily dose or, more practically for many women, by gradually reducing the number of days per week that MHT is used. This process may take many months and occasionally years, depending on symptom burden and individual sensitivity. When tapering systemic estrogen in women with an intact uterus, the dose should remain appropriately opposed by a progestin to protect the endometrium.³⁴¹ For women who cannot tolerate even a slow taper, the benefit of symptom relief may outweigh the potential risks of continued therapy when used at the lowest effective dose and with regular review. In women at higher baseline risk of adverse outcomes prior to VTE, stroke, or high breast cancer risk, it is reasonable to consider non-hormonal alternatives such as SSRIs/SNRIs, gabapentin, or clonidine during tapering or after discontinuation, recognising that these agents have not been specifically tested for symptoms triggered by stopping MHT. Discuss both abrupt and gradual taper options, taking into account the woman's previous VMS burden, age, and tolerance.³³⁸ There is no high-quality evidence that tapering the dose reduces recurrence or severity of vasomotor or other menopausal symptoms compared with abrupt cessation. Women who had undergone a hysterectomy, who had used HT for ≥ 10 years, and who started mainly for reasons other than health promotion were more likely to be unsuccessful in quitting.³³⁹

COST-EFFECTIVENESS

Robust health-economic modelling consistently demonstrates that MHT is a cost-effective and often cost-saving intervention when appropriately targeted. A landmark patient-specific Markov state-transition model concluded that, for nearly all women in whom therapy might be considered, the cardiovascular benefit of MHT outweighs the breast cancer risk, with only women at simultaneously the highest breast cancer risk and the lowest coronary risk failing to derive net benefit. From the Markov model, it was found that women with multiple risk factors for CHD would benefit most from HRT, with gains in life expectancy exceeding 3 years. Gains in life expectancy from mammography are estimated at less than 1 month, gains from faecal occult blood testing are 2 months, and gains from Papanicolaou smears are approximately 3 months.³⁴²

Women at high risk for breast cancer but not CHD would benefit most from raloxifene therapy. Most importantly, women at low risk for any disease would not benefit substantially from any of these treatments and need conservative management.³⁴³ Subsequent cost-utility analyses confirmed that in younger symptomatic postmenopausal women, MHT administered for 5-30 years increases quality-adjusted life-years (QALYs) and remains cost-effective, whereas initiation in later years is associated with a transient loss of QALYs before a delayed net gain is realised.^{344,345} An economic evaluation based on prospective cohort data further demonstrated that targeted estrogen use in women with low bone mineral density resulted in a 50% reduction in appendicular fractures, at a cost per fracture averted of approximately ₹11 lakh in low-risk women and ₹2 lakh in high-risk women, supporting the cost-effectiveness of

unopposed estrogen in hysterectomised women even in the absence of vasomotor symptoms.³⁴⁶ A systematic review of international economic evaluations confirmed that for women aged 50-60 years, MHT is consistently below national willingness-to-pay thresholds across the USA, UK, Finland and Sweden.³⁴⁷ More recently, modelling from China demonstrated that estradiol plus dydrogesterone may be cost-saving for symptomatic women aged 45 years or older.³⁴⁸

In special clinical situations, newer non-hormonal options also show emerging economic value; fezolinetant, by significantly reducing vasomotor symptom burden, improves work productivity and reduces indirect societal costs, highlighting a potential cost-utility advantage in women with moderate to severe vasomotor symptoms. A NICE technology appraisal Markov model evaluating fezolinetant for moderate-severe vasomotor symptoms demonstrated that treatment over a 10-year horizon resulted in a mean gain of 0.116 quality-adjusted life-years (QALYs) at an incremental cost of £1,199 (Rs 1.2 lakh) per woman, yielding an incremental cost-effectiveness ratio (ICER) of £10,³⁶⁴ (Rs 10-10.5 lakh) per QALY gained, which is well below the UK willingness-to-pay threshold of £20,000 per QALY.³⁴⁹

Low-dose vaginal estrogen, when not contraindicated, remains the most effective and economical option and has the fewest side effects.³⁵⁰

SPECIAL CLINICAL SITUATIONS

Comorbid conditions require judicious use of MHT, with shared decision-making that weighs the benefits and risks.

Menopausal Hormone Therapy And Comorbidities : Refer to each individual chapter for details.

Asthma : Small increased risk; no worsening of pre-existing disease.

Breast Cancer/Previous Abnormal Smears : Refer to Chapter 29

Cervical Cancer/Previous Abnormal Smears : Not contraindicated.

Coronary Heart Disease : Contraindicated.

Crohn's/Coeliac Disease : Transdermal route preferred to enhance absorption.

Diabetes Mellitus Type 2 : Not contraindicated. Not advised in diabetics with end-organ damage.

Diabetics Type 1 : Data on MHT in type 1 diabetes are insufficient and should be cautiously prescribed while monitoring relevant diabetes parameters.

Endometriosis : Not contraindicated; small increased risk of disease reactivation with ET in hysterectomised women; EPT even in the absence of the uterus.

Epilepsy : MHT only after risk-benefit analysis and close monitoring. CEE/MPA is associated with a dose-related increase in seizure frequency in postmenopausal women with epilepsy. Consider concomitant liver enzyme inducers and osteoporosis risk in phenytoin and carbamazepine users.

Fibroids : Tibolone. MHT with caution

Gallbladder Disease : Increased risk with oral use. Transdermal may be given.

Hyperlipidaemia : Not contraindicated: Triglycerides > 400 mg/dL - use transdermal

Varicose Veins : Transdermal

Morbid Obesity : Transdermal

Migraine Headaches : Transdermal estrogen with progesterone, prefer continuous therapy

Otosclerosis : Insufficient to contraindicate

Prolactinoma : A history of microprolactinoma does not preclude the use of menopausal hormone therapy when

clinically indicated. In women with macroprolactinomas, estrogen therapy should be considered only after careful individual assessment and with close monitoring, as cyclic hormone regimens may mask symptoms suggestive of tumour activity.³⁵¹

Parkinson's Disease : May reduce the risk of Parkinson's disease; it is not contraindicated

Post-Transplant : Should be considered, increased risk of osteoporosis

Renal Failure : Should be considered, increased risk of early menopause. Rheumatoid arthritis, past history of benign breast disease, contact lens wearers, sickle cell anaemia

Thyroid Disease : Not contraindicated.

Hyperandrogenism In Menopause : Oral estrogens to increase SHBG; progesterone choice: dydrogesterone or natural progesterone. Can add spironolactone.

Cancer And Hormone Therapy : For women with an increased risk or genetic predisposition to develop breast, ovarian and/or endometrial cancer. Refer to Chapters 31 and 32

CANCER SURVIVORS AND MENOPAUSE

Advances in cancer diagnosis and treatment have led to substantial improvements in survival, resulting in a growing population of women living long enough to experience either natural menopause or treatment-induced ovarian failure. Many women develop POI as a direct consequence of chemotherapy, radiotherapy, or surgical oophorectomy, while others transition into menopause during survivorship. Consequently, menopausal symptoms, particularly VMS, are increasingly prevalent among cancer survivors and often more severe than in women undergoing natural menopause. Breast cancer survivors receiving adjuvant endocrine therapy experience a higher burden of menopausal symptoms, including hot flushes, night sweats, sleep disturbance, mood changes, and sexual dysfunction, compared with age-matched menopausal women without cancer.³⁵²

Menopause at a younger age has important long-term health implications, including fertility. Observational data show that early menopause is associated with increased cardiovascular and osteoporotic morbidity, contributing to reduced life expectancy. A large Dutch cohort study reported an average loss of approximately 2 years of life expectancy over a 17-year follow-up in women with earlier menopause, largely attributable to CVD and fractures.³⁵³ Furthermore, epidemiological evidence indicates that each year of delay in menopause onset is associated with approximately a 2% reduction in cardiovascular mortality, underscoring the biological importance of endogenous estrogen exposure in midlife health.³⁵⁴ Following a cancer diagnosis, women are at increased risk of affective disorders such as depression and anxiety. Menopausal symptoms, particularly sleep disruption, vasomotor instability, and sexual dysfunction, can further exacerbate psychological distress and impair overall quality of life. Addressing menopausal symptoms is therefore a critical component of survivorship care, not merely a quality-of-life adjunct.

Clinical Challenges In Cancer Survivors

Management of menopausal symptoms in cancer survivors is inherently complex and must be individualised. Clinical decision-making is influenced by several interrelated factors, including the type of malignancy and its biological behaviour, hormone receptor status, the interval since cancer diagnosis, and the woman's anticipated survival. In addition, the potential risks of MHT must be weighed against existing comorbidities, such as CVD, osteoporosis, and metabolic risk factors. These overlapping considerations require a cautious yet patient-centred approach, in which oncologic safety is carefully balanced with the need for effective symptom relief and the preservation of long-term health and quality of life.

Management

Cancer treatment in women should be holistic and extend beyond disease eradication. In premenopausal women, survivorship care must include counselling on fertility preservation, menopausal symptoms, sexual health, and the long-term consequences of estrogen deprivation. Referral to specialised menopause or survivorship clinics should be considered whenever available. Every effort should be made to preserve ovarian function during cancer treatment without compromising oncological outcomes. When ovarian failure occurs, early identification and proactive

management of menopausal sequelae, including VMS, are essential to optimise quality of life and long-term health.

Hormone Therapy: Benefit-Risk In Cancer Survivors

MHT may be clinically indicated for symptom relief and long-term health protection in women with POI or early menopause, even when asymptomatic, provided there are no contraindications. However, in cancer survivors, particularly those with estrogen-dependent tumours, systemic MHT is contraindicated.

Importantly, the reflexive denial of MHT “just to be on the safe side,” without individualised risk assessment, may itself be harmful, as untreated estrogen deficiency adversely affects quality of life, bone health, cardiovascular risk, and mental well-being. Hence, a prudent approach to care during the MT and postmenopause integrates the best available evidence with individualised risk assessment and shared decision-making. While this approach may be challenging in clinical practice, it remains essential to ensure safe, effective, and patient-centred care.

Biological Complexity Of Estrogen Receptors And Cancer Risk

The biological effects of estrogen are highly context-dependent and cannot be reduced to uniformly proliferative or carcinogenic actions. Estrogen exerts its effects through multiple pathways involving classical nuclear ER α and ER β , membrane-associated receptors, and G-protein-coupled estrogen receptors (GPER/GPR30). These receptors may be activated through ligand-dependent or ligand-independent mechanisms, including phosphorylation cascades triggered by growth factor signalling (HER2, IGF-1R).

While ER α is generally associated with estrogen-mediated cellular proliferation, ER β often counteracts proliferative signalling. The net biological effect of estrogenic compounds depends on a complex interplay of receptor subtype expression, receptor isoforms, heterodimerisation, transcriptional co-activators and co-repressors, and cross-talk with non-estrogen signalling pathways. Such mechanistic complexity explains why estrogen cannot be uniformly classified as harmful or beneficial across tissues and tumour types, and why rigid, absolute risk classifications in cancer survivors are scientifically challenging.³⁵⁵

Menopausal Hormone Therapy And Nongenital Cancers

Menopausal Hormone Therapy Is Not Contraindicated

Haematological malignancies

Gonadotoxic cancer therapies, including intensive chemotherapy and haematopoietic stem-cell transplantation, frequently result in POI in survivors of haematological malignancies. Experimental and clinical observations indicate that estrogen supports haemopoiesis, and the currently available evidence does not suggest an adverse effect of menopausal hormone therapy on disease recurrence or progression. On the contrary, estrogen replacement in this context appears biologically neutral and may improve systemic recovery and long-term health outcomes. In the absence of disease-specific contraindications, MHT may therefore be considered appropriate in this group.^{356,357}

Non-Hodgkin lymphoma

Epidemiological analyses have shown no increased risk of non-Hodgkin lymphoma associated with MHT. Large pooled datasets suggest that hormone use, particularly when initiated near the time of menopause, is associated with a lower incidence of lymphoma. These findings support the view that MHT does not exert lymphoproliferative effects and can be prescribed to symptomatic survivors following individualised assessment.³⁵⁸

Colorectal cancer

The relationship between estrogen exposure and colorectal carcinogenesis differs fundamentally from that observed in hormone-dependent tumours. Observational data indicate a reduced incidence of colorectal cancer among hormone therapy users, and limited survivorship studies suggest a possible benefit with respect to overall and disease-specific mortality. In women with a history of colorectal cancer who develop clinically significant menopausal symptoms or premature ovarian insufficiency, MHT may be offered after careful evaluation.³⁵⁹⁻³⁶¹

Renal cell carcinoma

There is no convincing biological or clinical evidence linking menopausal hormone therapy to recurrence or progression of renal malignancies. Accordingly, a history of kidney cancer should not, in itself, preclude the use of MHT when clinically warranted.³⁵⁶

Thyroid cancer

Suppressive thyroxine therapy is commonly used after differentiated thyroid cancer, resulting in subclinical hyperthyroidism that accelerates bone loss and increases cardiovascular risk. Estrogen replacement counterbalances these effects in menopausal women. From a survivorship perspective, a past diagnosis of thyroid cancer should not be regarded as a contraindication to MHT.³⁵⁶

Pancreatic cancer

Reproductive history and exogenous hormone exposure do not appear to influence pancreatic cancer risk. Current evidence does not suggest harm from menopausal hormone therapy in pancreatic cancer survivors, and treatment decisions should be guided by symptom burden and general health considerations rather than cancer history alone.³⁵⁶

Hepatocellular carcinoma

Estrogen exerts multiple hepatoprotective effects, including modulation of oxidative stress, inflammatory pathways, and hepatic fibrosis. Experimental and clinical data also suggest that estrogen may interfere with hepatitis B virus-mediated carcinogenic processes.³⁶² Observational studies in women with hepatocellular carcinoma have reported reduced incidence and improved survival associated with estrogen exposure. While causality cannot be assumed, these findings support consideration of MHT in carefully selected survivors under specialist supervision.³⁶³

Use Menopausal Hormone Therapy With Caution

Estrogen exerts multiple hepatoprotective effects, including modulation of oxidative stress, inflammatory pathways, and hepatic fibrosis. Experimental and clinical data also suggest that estrogen may interfere with hepatitis B virus-mediated carcinogenic processes.³⁶² Observational studies in women with hepatocellular carcinoma have reported reduced incidence and improved survival associated with estrogen exposure. While causality cannot be assumed, these findings support consideration of MHT in carefully selected survivors under specialist supervision.³⁶³

Use Menopausal Hormone Therapy With Caution

Gastric cancer

Data regarding the safety of menopausal hormone therapy after gastric cancer remain sparse. Given the occasional expression of sex-steroid receptors in gastric tumours, hormone therapy should generally be avoided. Exceptionally, in receptor-negative disease with severe menopausal morbidity, cautious use may be contemplated after multidisciplinary discussion.³⁵⁶

Menopausal Hormone Therapy Should Be Avoided

Hormone-sensitive brain tumours

Certain intracranial tumours, particularly meningiomas, show clear sensitivity to sex steroids, with evidence of accelerated growth during periods of high endogenous or exogenous hormone exposure. Progesterone appears to play a particularly important role in tumour proliferation. In women with a history of meningioma or other hormone-responsive brain tumours, systemic MHT should be avoided because of the risk of tumour growth or recurrence.³⁵⁶

Bladder cancer

Bladder cancer is increasingly recognised as a hormonally responsive malignancy. In the absence of reassuring clinical data, menopausal hormone therapy should not be prescribed to survivors of bladder cancer.³⁵⁶

Menopausal Hormone Therapy Prescription In Cancer Survivors: Type, Route And Duration

Malignancy itself confers an increased risk of venous thromboembolism. When systemic MHT is used in cancer survivors, transdermal estrogen is preferred to minimise thrombotic risk. If progestogen therapy is required, micronised progesterone or dydrogesterone appears to offer a more favourable vascular risk profile than older synthetic progestins.^{279,280}

The levonorgestrel-releasing intrauterine system(LNG-IU) provides effective endometrial protection but should be avoided in women at elevated risk of breast cancer. In women with treatment-induced premature menopause, HRT should generally be continued until at least the average age of natural menopause. Decisions regarding ongoing therapy beyond this point should be individualised, taking into account symptom persistence, therapeutic response, comorbidities, and evolving risk–benefit considerations. Monitoring and follow-up are essential, with more frequent visits and vigilance.

A detailed description of genital cancer survivors and MHT is in section 8.

Summary Of Menopausal Hormone Therapy Use In Cancers

Menopausal Hormone Therapy Is Neutral

Low-grade, early-stage endometrial cancer type I, cervical, vaginal and vulvar squamous cell carcinoma, most types of ovarian cancer, germ cell tumours, BRCA 1/2 mutation carriers without cancer, haematological malignancies, local cutaneous malignant melanoma, colorectal cancer, hepatocellular cancer, BRCA 1/2 mutation carriers without cancer, prolactinoma, kidney cancer, pancreatic cancer, thyroid cancer.

Menopausal Hormone Therapy Is Relatively Contraindicated

Leiomyosarcoma, endometrial cancer type II, advanced metastatic malignant melanoma, lung cancer, gastric cancer, bladder cancer, clear cell and mucinous ovarian cancer, borderline ovarian tumour, cervical adenocarcinoma. Note: the risk of serous, endometrioid and clear cell ovarian cancers is increased by the use of estrogens alone, but it is decreased by the use of combined estrogen–progestin MHT.

Menopausal Hormone Therapy Is Contraindicated

Basically, in all estrogen-dependent cancers (breast cancer, endometrial stromal sarcoma, uterine carcinosarcoma, ovarian cancer [estrogen-dependent granulosa cell, low-grade serous, and Sertoli-Leydig, endometrioid types of ovarian tumours]), meningioma, glioma, hormone receptor-positive gastric, lung and bladder cancer.

Low-Dose, Local Vaginal Estrogen Therapy

May be an option for the treatment of vaginal dryness related to hormone deficiency after certain types of cancers, even if systemic MHT is not recommended.

Non-Hormonal Therapy

Options, including pharmacological agents and non-pharmacological interventions, can significantly reduce symptom burden while avoiding estrogen exposure. Refer to Chapter 9.

Preexisting Cancers And Genitourinary Syndrome of Menopause And Low-Dose Vaginal Therapy

Refer to Chapter 10. Low-dose LET is generally not contraindicated in genital and nongenital cancers except in cancers with estrogen-positive tumours.

LOW-DOSE HORMONE THERAPY

Following the WHI, it became clear that no single type, dose, or regimen of MHT can be universally applied to all postmenopausal women. MHT must be individualised based on age, time since menopause, symptom burden, metabolic and genetic profile, and comorbidities. Consequently, the type, dose, route, and regimen of MHT may change for the same woman over her lifespan.

This understanding has led to the guiding principle of “Right Woman, Right Age, Right Therapy, Right Dose, Right Route, and Right Regimen,” with particular emphasis on using the minimum effective dose.

Clinical evidence, albeit short-term, indicates that many therapeutic benefits of ET or EPT, including relief of VMS, treatment of GSM, preservation of bone mass, and endometrial protection, can be achieved with lower doses than traditional regimens, while improving tolerability and long-term adherence. However, the minimally effective dose is individual-specific; the lowest dose does not adequately control symptoms in all women. In addition, large, long-term randomised trials specifically evaluating the safety of low-dose HT remain limited. The shift toward lower ET/EPT doses parallels the historical reduction in COC, estrogen doses from 100-150 µg to ≤35 µg after early studies demonstrated higher risks of coronary, venous, and arterial thrombosis with high-dose formulations. Reducing estrogen content substantially lowered cardiovascular risk without compromising contraceptive efficacy.^{364,365}

This experience supports the broader medical principle that lower effective doses can maintain benefit while reducing harm. Although definitive long-term RCT data on low-dose ET/EPT are lacking, observational and comparative evidence suggest that lower doses, like those of low-dose OCs, likely retain clinical efficacy and offer a more favourable safety profile than standard doses.³⁶⁶ Historically, much higher estrogen doses were used in postmenopausal therapy; until the mid-1970s, daily CEE doses of 1.25-2.5 mg were common. By contrast, contemporary practice includes doses as low as 0.3 mg/day. Moreover, in the 1980s–1990s, ET/EPT was widely recommended for long-term use in most women, an approach that has since been replaced by a more cautious, individualised strategy.³⁶⁷

Vasomotor Symptoms And Effects Of Low-Dose Therapy

Robust clinical evidence demonstrates that low-dose and ultra-low-dose MHT are effective for the treatment of VMS across diverse populations. The Pan-Asia Menopause (PAM) study, a prospective, randomised, double-blind trial conducted across 22 centres in Asia, enrolled 1,028 healthy postmenopausal women, with a mean age of 53.5 years and an intact uterus. Participants received one of three continuous combined regimens of CEE/MPA: 0.625/2.5 mg, 0.45/1.5 mg, or 0.3/1.5 mg for 6 months. The study aimed to characterise menopausal symptoms in Asian women and evaluate the efficacy and safety of HT on quality of life, lipid profile, bleeding patterns, and adverse effects. Approximately 75% of women reported meaningful improvement in VMS, confirming the effectiveness of lower-dose CEE/MPA in real-world Asian populations.

Complementing this, several randomised studies by Utian, Speroff, Notelovitz, Bachmann, Panay, and Stevenson, using different low-dose estrogens (17β-estradiol or CEE) combined with various progestogens (norethindrone acetate 0.1 mg/day, MPA 1.5 mg/day, or dydrogesterone 2.5 mg/day), consistently demonstrated that low-dose ET/EPT, on average, achieves about an 80% reduction in VMS compared with placebo after 8-12 weeks of therapy.^{168,225,305,368-373} The large, multicentre Health, Osteoporosis, Progestin, and Estrogen (HOPE) trial in the United States further strengthened this evidence.^{168,374} In this randomised, double-blind, placebo-controlled study of 2,673 women aged 40-65 years, varying low doses of CEE/MPA significantly improved hot flushes and vaginal atrophy, produced favourable lipid changes, and protected the endometrium. Women receiving ET/HT also reported better sleep quality, longer REM sleep, shorter sleep latency, and less weight gain than those on placebo. Importantly, adding MPA to low-dose estrogen provided an additive benefit for symptom control rather than diminishing efficacy.

European evidence from the CHOICE study, a 24-week randomised trial in 577 postmenopausal women with a mean age of 55.5 years, showed that ultra-low-dose continuous combined therapy (0.5 mg E2 with either 0.1 mg or 0.25 mg norethisterone acetate) significantly reduced VMS, had a neutral effect on mammographic breast density, was associated with high rates of amenorrhoea, did not increase endometrial thickness, and improved treatment adherence.³⁷⁵

Very low transdermal dosing has also proven effective. In a stepwise trial, daily application of 14 µg of transdermal E2 cream reduced moderate-to-severe hot flushes by 2 weeks in 50% of women, by 4 weeks in 70%, and by 12 weeks in 95% ($P < 0.001$), demonstrating that even minimal systemic estrogen exposure can provide substantial symptomatic relief. A growing body of global data supports the use of ultra-low-dose continuous combined therapy with 0.5 mg 17β-E2 plus 2.5 mg DYD. European subgroup analyses confirmed a consistent reduction in VMS with a favourable safety profile across different patient characteristics. A phase III trial in China demonstrated significant reductions in hot flushes, validating this regimen for Asian women. Earlier double-blind studies also showed superiority over

placebo for symptom control. Most recently, a pooled analysis of three multinational trials including women of diverse ethnicities found that this ultra-low-dose combination was well tolerated, with no increase in treatment-emergent serious adverse events, reinforcing its suitability for broader clinical use.³⁷⁶⁻³⁷⁸ In a 24-week randomised, placebo-controlled trial in Brazilian postmenopausal women, continuous ultra-low-dose oral 17β -E2 0.5 mg plus norethisterone acetate 0.1 mg produced a significantly greater reduction in vasomotor symptoms than placebo ($\approx 77\%$ vs 50%), with high rates of amenorrhoea and a generally acceptable short-term safety profile.³⁷⁹

Taken together, these studies indicate that low-dose and ultra-low-dose MHT can achieve substantial relief of VMS (often 70-95% improvement within 8-12 weeks), maintain endometrial safety when combined with appropriate progestogens, and offer improved tolerability and adherence compared with standard doses, making them a rational first-line approach for many symptomatic postmenopausal women.

Bone And The Effects Of Low-Dose Therapy

The dose of estrogen required for skeletal protection is now recognised to be substantially lower than previously prescribed, supporting the use of low-dose hormone therapy for bone preservation in many postmenopausal women. E2 1 mg, CEE 0.45 mg, and 25 μ g transdermal estradiol patches are consistently protective for bone health, and evidence indicates that even lower doses can be effective. Multiple randomised controlled trials demonstrate that low-dose hormone therapy reduces bone turnover by approximately 30% while producing significant gains in bone mineral density (BMD) at the spine and hip.³⁸⁰⁻³⁸⁶ These benefits are observed not only in older women but also in younger postmenopausal women (mean age 50-53 years) within 3-5 years of menopause, a group at risk of rapid bone loss.³⁸⁰ Findings from smaller mechanistic trials are supported by the bone substudy of the HOPE trial, which showed that lower doses of CEE (0.45 mg and 0.3 mg/day), with or without low-dose medroxyprogesterone acetate (1.5 mg/day), effectively prevented loss of spine and hip BMD and suppressed biochemical markers of bone resorption in early postmenopause.³⁸⁰ Similar skeletal efficacy has been demonstrated with 0.3 mg oral CEE, 0.5 mg oral 17β -E2, and 14 μ g transdermal E2, in both early (mean age 51-52 years) and late postmenopausal women (mean age 67-74 years), indicating that clinically meaningful BMD gains can be achieved across the age spectrum.^{381,384} Interestingly, older women may achieve comparable skeletal responses with lower estrogen doses than younger women; for example, 1 mg oral E2 in women over 58 years produced BMD gains similar to those with 2 mg in women under 51 years. Nevertheless, in younger postmenopausal women, the response remains dose-related, with higher doses yielding greater increases in BMD.^{385,387} Beyond standard estrogen therapy, the LIFT trial demonstrated that tibolone 1.25 mg significantly reduced both vertebral and non-vertebral fractures in women with established osteoporosis (mean age 68 years), reinforcing the principle that estrogenic therapies can reduce fracture risk in later life.³⁸⁸ Additional trials of ultra-low-dose estrogen, including 14 μ g transdermal E2 for two years, showed modest but significant increases in lumbar spine ($\approx 2.6\%$) and hip BMD ($\approx 0.4\%$), without excess EH when accompanied by adequate calcium and vitamin D supplementation.³⁸³ Overall, low-dose oral estrogens (CEE 0.3 mg; estradiol ≤ 0.5 mg) and low- or ultra-low-dose transdermal E2 (25 μ g or 14 μ g patches) consistently preserve BMD and suppress bone turnover.

In a 24-week randomised, double-blind, placebo-controlled trial in postmenopausal women aged 45-60, ultra-low-dose continuous combined E2 0.5 mg plus norethisterone acetate 0.1 mg significantly suppressed biochemical markers of bone resorption and favourably modulated overall bone turnover in postmenopausal women, supporting the biological plausibility of ultra-low-dose MHT for early bone preservation.³⁸⁹ However, current evidence has not conclusively shown fracture reduction at the very lowest doses. Importantly, estrogen's skeletal benefits are maintained only while therapy is continued; BMD declines after discontinuation.^{380,381} Collectively, these data confirm that low-dose ET/EPT is effective for preventing postmenopausal bone loss and reducing the risk of osteoporosis, while highlighting the need for further fracture-outcome trials with low-dose regimens.^{380,386,390}

Cardiovascular System And Effects Of Low-Dose Hormone Therapy

In the WHI Observational Study, Shufelt et al. found that lower-dose oral estrogen, particularly when combined with progestin, was associated with significantly lower risks of coronary heart disease and venous thromboembolism compared with standard or higher doses, while no clear dose-response relationship was observed for estrogen-alone therapy.³⁰³ Observational data from the Nurses' Health Study suggest that lower oral estrogen doses, such as CEE 0.3

mg/day are associated with a nonsignificant trend toward reduced coronary heart disease risk compared with higher doses, and that the absolute risk of stroke increases with higher estrogen doses, with low-dose use showing little or no increased risk.³⁹² With respect to VTE, Jick et al. in a nested case-control study reported a clear dose-response increase in VTE risk with oral estrogen use; however, the absolute risk is low for both groups and accounts for only a modest increase in morbidity.³⁹³ Despite ongoing debate regarding HT and CHD, the favourable effects of both standard- and low-dose estrogen on lipid profiles are well established; estrogen therapy typically lowers total cholesterol and LDL cholesterol, and may reduce lipoprotein(a), while raising HDL cholesterol, and secondary analyses from the PAM study demonstrated that continuous combined conjugated estrogen/medroxyprogesterone acetate regimens, including lower-dose formulations, significantly reduced total cholesterol and LDL-C with minimal adverse effects on HDL, triglycerides, and other lipoprotein fractions.³⁹⁴

Breast Effects Of Low-Dose Hormone Therapy

With regard to the breast, women using lower doses of ET/EPT consistently report less breast pain and tenderness than those on higher doses. In the Women's Health, Osteoporosis, Progestin, Estrogen (WHOP) study, breast pain was reported by 26% of women receiving CEE 0.625 mg + MPA 2.5 mg compared with 13% among those receiving CEE 0.3 mg + MPA 1.5 mg, supporting a clear dose-related effect on breast symptoms.^{395,396} The relationship between estrogen dose and breast cancer risk, however, remains uncertain. The Collaborative Group on Hormonal Factors in Breast Cancer, in a meta-analysis of 51 epidemiological studies, found no consistent association between estrogen dose and breast cancer risk. Similarly, the WHI prospective observational study reported no increase in breast cancer risk with CEE alone at doses of 0.3, 0.625, or 0.9 mg/day over five years; in fact, there was a non-significant inverse trend across doses ($P = 0.06$). In contrast, the WHI of 17,835 postmenopausal women suggested a dose-related increase in breast cancer risk with estrogen, although low-dose estrogen (≤ 0.3 mg/day) was not associated with increased risk (RR 0.87; 95% CI 0.44-1.73), similar to a study from Mayo Clinic.³⁹⁷ Evidence for breast cancer risk with low-dose EPT remains largely limited to observational data; reassuringly, no increased risk has been observed with oral contraceptive use or with pregnancy before age 35, two exposures that also involve combined estrogen-progestin environments earlier in life.^{398,399}

Endometrium Effects Of Low-Dose Hormone Therapy

There is a clear dose-response relationship between systemic estrogen exposure and adverse endometrial effects, which underpins the fundamental clinical principle that women with an intact uterus must receive adequate progestin whenever systemic estrogen is prescribed. Extensive randomised trials and systematic reviews show that when lower estrogen doses are combined with appropriate (and sometimes lower) progestin doses, endometrial safety is excellent and uterine bleeding patterns are improved. Compared with standard-dose therapy, low-dose sequential or continuous EPT is consistently associated with higher rates of amenorrhoea and fewer episodes of unscheduled vaginal bleeding, particularly in the early cycles of treatment, thereby enhancing tolerability and persistence with therapy. Because the frequency and unpredictability of bleeding are major determinants of adherence to HT, this more favourable bleeding profile is clinically important for long-term continuation.⁴⁰⁰ In contrast, use of unopposed estrogen in women with a uterus is no longer standard of care, even at low doses, because it carries a measurable risk of endometrial proliferation and carcinoma. Seminal epidemiological studies demonstrated a clear association between unopposed CEE and EC, establishing a dose- and duration-dependent increase in risk.^{401,402} Subsequent clinical observations further confirmed the link between unopposed estrogen and EH.⁴⁰³ This risk was clearly quantified in a two-year randomised substudy of the HOPE trial. Among women receiving unopposed CEE, the incidence of EH increased in a dose-dependent manner from 3.17% with 0.3 mg/day to 27.27% with 0.625 mg/day. When estrogen is combined with progestin, endometrial outcomes are markedly different. Trials using low-dose CEE (0.3-0.45 mg/day) with MPA 1.5 mg/day effectively prevented EH, and similarly low doses of norethindrone acetate (NETA 0.1-0.5 mg/day) were associated with significantly lower hyperplasia risk compared with the more commonly used 1 mg dose. Overall, the incidence of EH with sequential or continuous low-dose EPT is comparable to that in untreated postmenopausal women, supporting its endometrial safety. In the HOPE study with different doses, no hyperplasia occurred in any combined estrogen-progestin arms, confirming the protective role of progestogens and reinforcing that unopposed ET is inappropriate for women with an intact uterus.⁴⁰⁴ With respect to tolerability, lower-dose ET/EPT is consistently associated with reduced rates of irregular bleeding and breast tenderness, two of the most common reasons for treatment discontinuation. Using lower estrogen doses also permits the use of lower

progestin doses, which may reduce potential adverse metabolic and breast-related effects of progestogens. Multiple randomised trials demonstrate less breakthrough bleeding with low-dose regimens compared with standard doses, further improving acceptability, adherence, and real-world persistence with HT.⁴⁰⁰

Genitourinary Syndrome of Menopause And The Effects Of Low-Dose Therapy

In the context of LET, systemic absorption is dose-dependent but generally minimal at ultra-low doses. Intravaginal 50 µg estradiol cream produced only a small, non-significant rise in serum E2 after 8 weeks (from 7.7 to 9.7 pg/mL). With 25 µg E2, transient early increases in serum levels were observed, whereas with 10 µg E2, only a brief, minimal elevation was observed, with no difference from placebo by 14 days. Consistent with this, the 10 µg vaginal E2 formulation has been shown to have negligible to very low systemic absorption, supporting its safety for long-term local use.⁴⁰⁵ Ultra-low-dose vaginal E3 0.03 mg effectively improves GSM, and when combined with *Lactobacillus acidophilus* (100,000 CFU), reduces recurrent urinary tract infections. Importantly, in a small study of postmenopausal women with breast cancer receiving aromatase inhibitors, daily E3 0.03 mg for 4 weeks, followed by thrice-weekly maintenance, caused only a slight increase in serum E3 without raising E1 or E2, suggesting a favourable safety profile even in this high-risk group.⁴⁰⁶ A large multicentre German randomised trial (2008-2011) further evaluated low-dose E3 pessaries (0.2 mg vs 0.03 mg) versus placebo over 12 weeks (daily for 20 days, then twice weekly for 9 weeks). Vaginal dryness was the most common presenting symptom. Both E3 doses were superior to placebo in improving clinical signs and symptoms of vaginal atrophy. Notably, the 0.03 mg dose produced clinically meaningful improvements in the vaginal maturation index and reduced vaginal pH to approximately 5, indicating restoration of a healthier acidic vaginal environment.⁴⁰⁷ Together, these studies demonstrate that ultra-low-dose LET provides effective local treatment for GSM with minimal systemic exposure, making it a rational and generally safe option for many postmenopausal women, including selected breast cancer survivors on endocrine therapy.

RISKS AND BENEFITS OF SYSTEMIC HORMONE THERAPY

Integrated conclusions on the risks and benefits of systemic hormone therapy within 10 years of menopause, based on evidence from WHI. Refer to Tables 16,17. DOPS PEPI, KEEPS and ELITE Trials.

Table 16. Absolute Benefits and Risks: HT Women Aged 50-59 over 5 yrs

Absolute Change in cases / 1000 women Aged 50-59 over 5 yrs		
	EPT	ET
HOT FLUSHES	-825	-900
VULVOVAGINAL ATROPHY	-875	-800
FRACTURES	-5	-6
HEART DISEASE	-1	-4
OVERALL MORTALITY	-6	-5
COLORECTAL CANCER	-1	??
BREAST CANCER	+4	-7
STROKE	+<1	+1
VTE	+6	+2

Table 17: Based on WHI, the Number of Excess Events on HT vs Placebo per 10,000 Women per Year of HT. Use Between the Age Groups of 50–59 Years; NA-Not applicable

Disease	E	WHO/CIOMS definition of risk	E + P
VTE	4	Rare/1/1,000 to 1/10,000	11
Stroke	1	Rare/1/1,000 to 1/10,000	4
Breast cancer	NA	Rare/1/1,000 to 1/10,000	5
CVD	NA	Rare/1/1,000 to 1/10,000	5

The risk–benefit balance of MHT varies depending on several factors, including the woman’s age, time since menopause, baseline health status, family history of noncommunicable diseases and cancers, route of administration, and the specific regimen used. Risks are reduced when therapy starts before age 60 or within 10 years of menopause, following a thorough individual risk assessment, with annual reviews to reassess the indication, dose, and duration. As with other long-term therapeutic interventions, careful patient selection, judicious use, and regular monitoring are essential to maximise benefits and minimise potential risks.

Risks of Systemic Therapy

The magnitude and type of MHT-related risks in the 50–59-year age group, including breast cancer and stroke, are rare, with fewer than 10 cases per 10,000 women with VTE showing 11 events. These risks are lower with CEE than with CEE plus MPA and are equal to or lower than those linked to obesity, a much more common and modifiable risk factor.^{408–413}

Cardiovascular disease: Systemic therapy should not be used for primary or secondary prevention of CVD. At any age, women at high risk of CVD or with established CVD should avoid MHT.⁴¹⁴ Venous thromboembolism: MHT increases the absolute risk by 4 in 10,000 women for ERT users and 11 in 10,000 for EPT users, while in OCP users, it ranges from 3 to 15 per 10,000 woman-years. The risk peaks during the first 1–2 years of treatment and is influenced by the oral route, obesity, smoking, thrombophilia, and age.^{278, 415–417} The absolute risk of VTE is significantly higher during physiological states such as pregnancy, with 5–20 VTE cases per 10,000 deliveries, and reaches its peak in the postpartum period at 40–65 per 10,000 woman-years. [242] Transdermal ET and natural progestones may not cause VTE. Population screening for thrombophilia is not recommended before using MHT.^{418,419}

Stroke: Unlike CVD, the timing hypothesis does not apply to stroke, as the risk appears predominantly thrombotic rather than atherosclerotic.²⁴⁵ Standard-dose oral estrogen or combined EPT is linked to an absolute increase of 2 additional strokes per 10,000 woman-years among those aged <60 years.^{420,421} For women aged 50–54 years, the excess absolute risk is 1.5 per 10,000 woman-years, rising to 2.2 at age 59 and 2.8 at ages 60–64.^{416,418,420–422} The risk increases with estrogen dose, age, and route of administration, reaching its highest during the first 1–2 years of treatment. In contrast, low-dose (≤ 50 µg/day) transdermal E2 and nonoral routes do not seem to raise stroke risk compared to nonusers. [198] The event rate, therefore, stays very low, particularly in younger, healthy postmenopausal women using low-dose or transdermal formulations.⁴²³

MHT and breast cancer: The impact of MHT on breast cancer risk is complex, influenced by background risk, type of MHT, dose, duration of use, regimen, route of administration, and prior exposure. The incremental risk associated with MHT is minimal, with an estimated increase of fewer than 1 additional case per 1000 women aged 50–59 years annually.^{320,424–426}

This level of risk is comparable to or lower than that related to common preventable lifestyle factors such as obesity, alcohol consumption, and physical inactivity.^{320, 424–426}

The increased breast cancer risk associated with CEE + MPA diminishes after discontinuation, usually returning to nonuser levels within about 3 years, particularly following short-term use. However, some elevated risk may persist

after more than 5 years of use or with certain synthetic progestins.^{320,424-426} Tumours in women using MHT are usually ER-positive and of the lobular type.^{424,426} The Collaborative Group Lancet 2019 meta-analysis synthesised only observational data. These findings suggest a slight absolute increase in breast cancer risk, mainly with combined estrogen–progestin therapy, and a lower risk with estrogen-only therapy.²³⁸

According to this analysis, adopted by NICE Guidance 2020 (NG23) as a patient discussion aid for women starting MHT at around age 50 and assessed for risk between ages 50–69 years, the estimated excess breast cancer cases after 5 years of use are:²³⁷

Continuous combined MHT: one additional case per 50 users. *Sequential combined MHT:* one additional case for every 70 users. *Estrogen-only MHT:* one additional case per 200 users. All estimates are based on observational data, primarily using oral 17β-E2 and synthetic progestins in older women aged 50–69 years.²³⁷ The findings generally align with the Norwegian EBBA-Life cohort, and both studies found no increased risk with vaginal estrogen.²⁴¹

In contrast, DOPS, a randomised trial in younger postmenopausal women using 17 β-estradiol ± norethisterone acetate, found no increase in breast cancer incidence or mortality and reported an overall reduction in mortality after 16 years.⁴²⁷ Similarly, in the WHI trial, women receiving CEE 0.625 mg experienced a statistically lower incidence of breast cancer compared with placebo, and this benefit persisted for over 20 years of extended follow-up.³²⁰ The combined estrogen plus progestin arm showed a modest increase in incidence, mainly limited to the duration of treatment, but no significant difference in breast cancer-specific mortality was observed. When counselling women, focus should be on absolute risks quantified in RCTs, as observational data are susceptible to residual confounding and selection bias.^{428,429}

Therefore, counselling should primarily depend on RCT-derived absolute risk estimates from WHI and DOPS, while recognising supportive observational trends. This approach encourages shared decisionmaking and personalised risk stratification based on age, time since menopause, comorbidities, and treatment goals.

MHT and Ovarian cancer: In absolute terms, ovarian cancer risk is a rare event with estrogen alone (CEE), the increase is by approximately 0.2 per 1000 women, 0.1 in CEE plus MPA regime, and about 1 per 1000 women with estradiol alone.^{237,322}

MHT and Endometrial cancer: Unopposed systemic estrogen (CEE or E2 alone) in women with an intact uterus carries an absolute risk of 1–3 cases per 1,000 women.^{430,431}

COC provide significant and lasting protection against both ovarian and endometrial cancers and should be recognised as a protective factor in women’s lifetime risk assessments.^{430,432}

MHT and Gall Bladder: The use of oral estrogen-alone or combined MHT is linked to a higher risk of gallstones, cholecystitis, and cholecystectomy.⁹² Observational evidence suggests that transdermal estrogen has a lower risk of gallbladder disease than oral preparations, and that oral E2 may pose a lower risk than CEE. However, these differences have not been confirmed in randomised controlled trials.^{433,444}

Benefits of Systemic Therapy Refer to Table 18

Table 18: Based on WHI: fewer events on estrogen versus placebo per 10,000 women per year of HT use between the age group of 50 years and 59 years

Disease	Number of less events with ET
Heart Disease	12
Breast cancer	8
Overall Mortality	10
Fractures	5
Colorectal cancer	6

When initiated near menopause, systemic HT offers significant benefits beyond vasomotor relief and maintenance of bone and urogenital health. MHT improves mood and sleep, and may also lower the risk of colorectal cancer.⁴³⁵⁻⁴³⁷

There are reports of improved joint health, retention of skin thickness and elasticity, and collagen.⁴³⁸ A meta-analysis of 9 randomised clinical trials showed HT was associated with increased lean body mass and reduced visceral fat.⁴³⁹ Another recognised benefit for which more research from the Nurses' Health Study, the HERS, WHI and others is showing promise is the decrease in new-onset diabetes by 30%.⁴³⁹⁻⁴⁴²

MHT has been shown to decrease coronary heart disease by 30%-48% when initiated in women below 60 years and/or within 10 years of menopause.^{414,443}

Estrogen benefits verbal memory over the short period when initiated soon after surgical menopause.⁴⁴⁴ Hormone therapy reduces the neovascular macular lesions, decreases the risk of cataracts and open-angle glaucoma.^{445,446}

MHT enhances QOL by providing consistent relief from vasomotor and urogenital symptoms and by improving sleep quality, mood, and cognitive well-being. Over the past 5 decades, 40-50 postmenopausal observational studies in younger women have shown that MHT is consistently associated with a 30-50% decrease in CVD risk and total mortality with low absolute risks of serious adverse events.^{447,448} Evidence also suggests a potential reduction in the incidence of colorectal and endometrial cancers, and may be protective for lung cancers in selected populations.⁴⁴⁹

MHT remains effective for the treatment of VMS and GSM and for the prevention of osteoporosis-related bone loss in appropriately selected women.

THE TIMING/THE WINDOW OF OPPORTUNITY HYPOTHESIS

The MT is characterised by progressive ovarian failure, declining estrogen levels, and relative androgen predominance. Although this is a normal physiological phase of ageing, in genetically or metabolically predisposed women, it may accelerate the onset and progression of non-communicable diseases (NCDs), particularly cardiometabolic, musculoskeletal, and neurocognitive disorders. Importantly, NCDs are multifactorial in origin: alterations in endogenous or exogenous estrogen exposure are neither primary causes of disease nor definitive cures. Rather, estrogen acts as a system-specific, context-dependent modulator that interacts with underlying biological, metabolic, and environmental risk factors to influence disease trajectory and therapeutic responsiveness.

Against this background, the timing or window-of-opportunity hypothesis proposes that MHT has its most favourable benefit-risk profile when initiated during the late menopause transition, within approximately 10 years of the final menstrual period or before age 60. Beyond this window, delayed initiation may confer attenuated cardiovascular benefit or early harm in women with established atherosclerosis or metabolic dysfunction.⁴⁰⁸ The hypothesis holds that the vascular effects of MHT are determined primarily by time since menopause and stage of atherosclerotic disease, rather than by whether menopause was natural or surgical. Evidence from women after oophorectomy indicates that the duration of postmenopausal vascular ageing, rather than the type of menopause, best predicts excess subclinical atherosclerosis, supporting a stage-of-disease model of estrogen responsiveness.^{450,451} Outcomes are further modified by estrogen formulation (CEE vs 17 β -estradiol), route (oral vs transdermal), dose, and progestogen type.

Cardiovascular Disease (CVD)

Experimental Foundation: Primate Models

Clarkson first provided experimental evidence for the "timing" hypothesis in the 1990s, based on studies in cynomolgus monkeys, demonstrating the protective vascular effects of hormone therapy when initiated soon after menopause for CVD prevention. He investigated the effects of postmenopausal estrogen on cynomolgus monkeys, dividing them into three groups, including a placebo group. All were oophorectomised. Group 1 had little or no atherosclerosis before oophorectomy, received CEE for 30 months, and was fed a moderately atherogenic diet. This group showed a 70% reduction in coronary artery atherosclerosis compared with placebo. Group 2 had moderate atherosclerosis before menopause; early use of CEE was associated with 50-70% less atherosclerosis than in controls. In group 3, monkeys with little or no atherosclerosis underwent oophorectomy and were fed an atherogenic diet for 2 years prior to estrogen treatment. In this group, with a delayed start to HT (equivalent to 6 human years), no difference from placebo was observed in the amount of atherosclerosis. Estrogen given soon after oophorectomy markedly

inhibited coronary atherosclerosis, but when initiation was delayed after prolonged exposure to an atherogenic milieu, the benefit disappeared, and a healthy-user benefit was also observed. These experiments demonstrated that estrogen powerfully modifies early lesion biology, but has little effect once plaque is advanced, independent of “healthy user” bias.⁴⁵²⁻⁴⁵⁴

Parallel work by Adams and colleagues showed that 17 β -estradiol inhibited coronary atherosclerosis in ovariectomised monkeys, whereas the addition of progesterone provided no further vascular benefit. Moreover, medroxyprogesterone acetate antagonised the protective effects of CEE, an observation that later became highly relevant when interpreting clinical trials using different progestogens.⁴⁵⁵⁻⁴⁵⁷ Mechanistic studies support the biological plausibility of this stage-dependent model. In relatively healthy arteries or early lesions, estrogen enhances endothelial function, reduces vascular inflammation, and slows plaque progression. In contrast, in older vessels with advanced plaque, estrogen receptor signalling is blunted by receptor downregulation, endothelial dysfunction, and a procoagulant milieu, particularly with oral therapy, due to hepatic first-pass effects, potentially increasing early thrombotic risk.⁴⁵⁸

Brinton’s “healthy cell bias” theory proposes that estrogen exerts protective and reparative effects only in metabolically healthy and functionally competent cells, whereas in aged or metabolically compromised tissues, estrogen signalling may become ineffective or even detrimental. In healthy vessels, during early atherosclerotic disease, and during the menopausal transition, the beneficial effects of estrogen are observed due to the number and responsiveness of estrogen receptors. Estrogen is blocked by atheroma, either through age-related downregulation of endothelial estrogen receptors or through estrogen receptor blockade in the plaques themselves. Hence, diseased arteries with advanced atheroma appear to respond less well to estrogen, where estrogen receptors are less functional; instead of slowing atherosclerosis, there may be an increased risk of rupture of a vulnerable atherosclerotic plaque and of thrombosis within a narrowed, stenotic blood vessel, leading to thrombotic occlusion of the blood vessel.⁴⁵⁹

Together, the animal and bench research suggest that estrogen is protective in early lesions but largely ineffective once plaque is advanced and that arteries are more sensitive to estrogen in early menopause than in later menopause.⁴⁶⁰ Hence, the timing hypothesis and Brinton’s healthy cell bias theory explain the variability in MHT outcomes across cardiovascular, neurological, musculoskeletal, and metabolic domains. These models emphasise that both the timing of initiation and the metabolic health of target tissues determine estrogen’s benefit-risk profile, refining the understanding of its context-dependent actions and guiding individualised therapeutic decisions.

From a clinical standpoint, early initiation of MHT is associated with reductions in all-cause mortality and cardiovascular events, whereas late initiation does not confer similar cardiovascular benefit. In contrast, for bone and genitourinary health, MHT is clearly protective and restorative, with maximal benefit when initiated early and continued efficacy without evidence of harm when initiated later. Emerging data suggest potential neurocognitive benefits of early initiation, although further high-quality evidence is required before definitive recommendations can be made. Preclinical, epidemiological, and clinical data, as well as meta-analyses, support a favourable benefit-risk profile for HT use in early menopausal women. The following studies support the window-of-opportunity hypothesis.

Epidemiological Studies

The Nurses’ Health Study, which followed 120,000 female nurses between 1976 and 2000, provided foundational observational evidence: in the 1991 NEJM analysis (Stampfer et al.), current estrogen use was associated with reduced incidence of coronary heart disease and lower cardiovascular mortality, setting the stage for the long era in which MHT was widely considered cardioprotective.¹⁰ However, as later analyses and methodological critiques emphasised, the NHS and similar cohorts largely reflected women who tended to start therapy at/near menopause (mean initiation around the early 50s), contrasting sharply with the WHI trial population (mean age more than 63; and more than 12 years since menopause), implying that “timing of initiation” and underlying plaque burden could plausibly explain divergent outcomes.¹⁶⁵

In the Rancho Bernardo cohort, women who had used HT for at least 10 years had significantly lower plaque burden than those who had used HT for shorter durations. This suggests that if MHT modifies atherosclerosis, it may do so over years rather than months. Later, atherosclerosis-modifying effects may emerge only with longer exposure in appropriate candidates.⁴⁶¹

In the California Teachers Study (CTS), which followed 71,237 postmenopausal women (mean age 63 years) prospectively from 1995-1996 to 2004, current HT use at baseline was associated with reduced all-cause mortality in younger postmenopausal women, but not in older women. This suggests that estrogen may confer cardiovascular or survival benefit primarily when initiated closer to menopause, whereas continued use in older women who started HT late is unlikely to provide similar advantages. The CTS, which followed 71,237 postmenopausal women (mean age 63 years) prospectively from 1995-1996 to 2004, demonstrated that the association between HT and lower all-cause and ischaemic heart disease mortality was largely confined to younger current users at baseline, with progressive attenuation in older age groups. Importantly, the study recorded whether women used ET or EPT, but did not capture detailed information on estrogen dose or route of administration in a manner suitable for outcome analyses, and therefore could not evaluate whether lower doses or transdermal routes might have altered risk-benefit profiles, particularly in older women. Because systemic HT use in the United States during the CTS enrolment period was predominantly oral and fixed-dose, the observed lack of mortality benefit in older women may partly reflect exposure to relatively higher biologic oral doses in a more atherosclerotic vascular milieu, rather than an intrinsic absence of estrogen benefit per se. Consequently, while the CTS strongly supports age at current use as a key modifier of HT-mortality associations, its inability to analyse dose or route constitutes an important limitation when extrapolating its findings to contemporary practice, where lower-dose and transdermal regimens are increasingly used.⁴⁶²

Mack et al. support the centrality of time since menopause by showing that elevated subclinical atherosclerosis after oophorectomy was more closely associated with time since menopause than with whether menopause was surgical or natural, consistent with the concept that the postmenopausal interval is a proxy for plaque evolution and arterial ageing, which in turn governs estrogen responsiveness.⁴⁶³

Puget Sound Group Health Cooperative (PSGHC) analyses, the relative risk of MI was reported to be > 2-fold higher in new users compared with women using HRT for 1-2 years, suggesting an early hazard after initiation, particularly relevant to older starters with higher baseline plaque burden.⁴⁶⁴

In a large nationwide Finnish registry study of ^{489,105} women with about 3.3 million MHT exposure-years from 1994-2009, systemic estradiol-based MHT was associated with significantly lower risks of CHD death (18-54% reduction) and all-cause mortality (12-38% reduction) compared with an age-matched background population, with greater reductions observed with longer MHT exposure; stroke death was also reduced by 18-39%.⁴⁶⁵

In contrast, long-term follow-up of 29,243 women aged 50-64 years in the Danish Diet, Cancer and Health Cohort demonstrated no significant association between baseline use of MHT and overall mortality over approximately 20 years of observation after adjustment for lifestyle and other confounders, although transient differences in cause-specific mortality were observed early after initiation.⁴⁶⁶

In the WHI Observational Study (WHI-OS), postmenopausal women who reported current use of systemic hormone therapy at baseline had substantially lower rates of CVD compared with never-users, with risk reductions in the order of 40-50% overall. However, this apparent cardioprotection was strongly age- and timing-dependent: the greatest reductions were seen in women who initiated HT closer to menopause, whereas little or no benefit was observed in older women or those starting therapy many years after menopause.⁴⁶⁷

Observational data from the Group Health Cooperative of Puget Sound suggested differential cardiovascular associations with HT according to duration of use, with relatively short use (< 2 years) among combined hormone users and variable MI odds between users and non-users supporting an early initiation hazard, a pattern particularly relevant to older women with more advanced atherosclerotic plaque, and consistent with temporal modifications in cardiovascular risk discussed under the timing hypothesis.⁴⁶⁸

Primary Prevention Trials Of CVD

WHI, EPAT, WISDOM, DOPS, ELITE, KEEPS

Women's Health Initiative

The WHI was a large, multicentre, double-blind, randomised, placebo-controlled primary prevention trial designed to assess the long-term effects of MHT on a global health index, including CVD, stroke, fractures, cancers, and mortality in generally healthy postmenopausal women aged 50-79 years, the mean age being 63.3 years, and an average of 12 years

since menopause.³⁰ WHI comprised two hormone therapy arms: CEE+MPA in women with intact uteri, and oral CEE alone in hysterectomised women, with clinical CVD, MI, revascularisation, cardiovascular death and all-cause mortality reported in both intervention and post-intervention follow-up.²⁹ The intervention phase was stopped early for both regimens due to an unfavourable balance of risks and benefits, CEE+MPA after a median of 5.6 years and CEE alone after 7.2 years, primarily driven by increased stroke risk without significant CVD benefit in the overall cohort.

In the total WHI population, CVD risk was neutral to slightly elevated for CEE+MPA (HR 1.23; 95% CI 0.99-1.53) and neutral for CEE alone (HR 0.95; 95% CI 0.78-1.16).

Subsequent extended follow-up through long-term post-intervention analyses showed no significant reduction in CHD or all-cause mortality across all ages combined, but age-stratified analyses revealed reduced CHD and mortality in women aged 50-59 years at randomisation, consistent with the timing hypothesis, whereas older women showed trends towards null or adverse cardiovascular outcomes.⁴⁶⁹ Evidence from cumulative randomised and observational data supports that MHT initiated < 60 years of age or within 10 years of menopause is associated with lower CHD and all-cause mortality, whereas initiation many years post-menopause confers less benefit or potential risk, underscoring the importance of timing, as well as considerations of type, dose, and route of administration.^{165,470-472}

In an ancillary substudy of the WHI Estrogen-Alone Trial, coronary artery calcium (CAC) was measured by cardiac CT after a mean of 7.4 years of estrogen use and 1.3 years after trial completion in women aged 50-59 years at entry. Women randomised to CEE had significantly lower mean CAC scores (83.1) compared with those randomised to placebo (123.1), and this difference was statistically significant ($P=0.02$). After adjustment for risk factors, odds ratios for higher CAC categories (>100 Agatston units) were lower in the estrogen group, supporting the conclusion that estrogen initiated in this younger age group was associated with a lower calcified plaque burden.⁴⁷³

The Estrogen in the Prevention of Atherosclerosis Trial (EPAT)

The EPAT was a prospective, randomised, double-blind, placebo-controlled study in healthy postmenopausal women without clinical cardiovascular disease that evaluated the effect of unopposed micronised 17 β -estradiol 1 mg/d versus placebo on progression of subclinical atherosclerosis measured by CIMT. EPAT demonstrated that, compared with placebo, estradiol significantly slowed the progression of subclinical atherosclerosis, with the average rate of CIMT change lower in the estradiol group over a 2-year period, supporting atheroprotection in healthy vascular beds.

The Danish osteoporosis prevention study

The DOPS was a large, prospective, partially randomised cohort trial initiated in 1990, with inclusion completed between 1990 and 1993. The study enrolled 2,016 early postmenopausal women, the majority of whom were enrolled within 24 months of their final menstrual period, to evaluate the effects of early HRT on bone health, fracture risk, and long-term clinical outcomes.⁴⁷⁴ The criteria for inclusion in the study were healthy, recently postmenopausal white women aged 45-58, with last menstrual bleeding 3-24 months before study entry or perimenopausal symptoms (including irregular menstruation), and women who had had a hysterectomy (age 45-52). The women in the treated group with an intact uterus were on 2 mg 17 β -estradiol for 12 days, 2 mg 17 β -estradiol plus 1 mg NETA for 10 days, and 1 mg 17 β -estradiol for 6 days and in the hysterectomised group 2 mg 17 β -estradiol a day was given. Safety endpoints included death or a diagnosis of breast cancer or other cancer grouped together and admission to the hospital for pulmonary embolism or VTE. The planned duration of the study was 20 years. However, as the WHI data, which came out in 2002 around the time of the 10-year visit, indicated that use of HT might result in more harm than benefit, the participants were advised to stop treatment. But they were followed for death, CVD, and cancer for up to 16 years. After 10 years of randomised treatment, women receiving hormone replacement therapy early after menopause had a significantly reduced risk of mortality, heart failure, or myocardial infarction, without any apparent increase in risk of cancer, VTE, or stroke. The participants, who used HT for more than 10 years, were not at significantly increased risk of breast cancer or stroke. After 16 years, the reduction in the primary composite outcome persisted and was not associated with an increase in any cancer. These findings confirm the “timing hypothesis”. Compared with the women in the WHI study, those in the Danish study were 13 years younger. DOPS has been criticised for the small number of participants, but no other randomised trial has enrolled as many women in close proximity to menopause (mean 7 months postmenopausal), with as long a trial time (mean 10.8 years randomised) and follow-up. Results after 10 years of intervention in DOPS are seen in Table 19.

Table 19. Results after 10 years of intervention in Danish osteoporosis prevention study

End point	HT group (n = 502), n	Control group (n = 504), n	Hazard ratio	95% CI	P
Primary ^a	16	33	0.48	0.26–0.87	0.015
Mortality	15	26	0.57	0.30–1.08	0.084
Cancer	36	39	0.92	0.58–1.45	0.71
Breast cancer	10	17	0.58	0.27–1.27	0.17
DVT	2	1	2.01	0.18–22.16	— ^b
Stroke	11	14	0.77	0.35–1.70	0.70

Notes: ^a 50% reduction in cardiovascular end points—significantly reduced risk of the combined end point of death, MI, or heart failure. No significant increased risk of breast cancer, stroke, VTE or PE. ^b Numbers too low to calculate p

The Kronos Early Estrogen Prevention Study

A 4-year, 9-centre randomised placebo-controlled trial enrolled 727 healthy women aged 42–58 years (mean, 52.7 years) who were at low risk for CVD and within 0.5–3.0 years of their last menses. The primary aim was to assess, via non-invasive vascular imaging, the effect on atherosclerosis progression of early initiation of a 4-year regimen of low-dose HT with oral 0.45 mg/day CEE or transdermal 17 β -estradiol, 50 μ g/day, plus oral MP, versus placebo. Secondary endpoints included changes in markers of CVD risk. A subset was observed for cognitive function, mood symptoms of menopausal hormone deficiency, and sexual function over the 4 years of the KEEPS trial. The study showed that HT has no effect on the progression of atherosclerosis. No changes in blood pressure were observed. Insulin resistance decreased with transdermal estrogen, whereas oral estrogen improved both LDL and HDL levels. Oral therapy also increased levels of CVD markers, such as CRP and SHBG, but not interleukin-6. A weakness of the KEEPS study was that it was a marker study rather than an outcomes study. A substantial reduction in menopausal symptoms (hot flushes, night sweats) and some improvement in BMD were observed in the active treatment groups compared with placebo. In terms of mood and sexual function, evidence for benefits (for both outcomes) and also quality of life was seen with both forms of HT. Adverse events such as rashes, fractures, headaches, and genitourinary problems were similar in all three groups, whereas vaginal bleeding was significantly more common in the treated groups.

The early versus late intervention trial with Estradiol

The ELITE study is a randomised, placebo-controlled trial investigating the effect of oral 1 mg of 17 β -estradiol plus vaginal MP in two age groups: those less than 6 years postmenopausal and those more than 10 years. The primary outcome was the rate of change in coronary artery IMT, measured by ultrasound. Women in early menopause, overall, had a slower progression of atherosclerosis, measured by carotid IMT, than those randomised to placebo. However, older women did not show these differences. This finding is in line with the timing hypothesis.

The estrogen for the prevention of reinfarction trial

The ESPRIT trial randomly assigned 1,017 women who had survived a first MI to receive either a placebo EV. ESPRIT ran for 2 years and showed no significant difference in reinfarction or cardiac death.

Women's estrogen–progestin lipid-lowering hormone atherosclerosis regression trial

The WELL-HART trial investigated the impact of 17 β -estradiol alone or combined with sequential medroxyprogesterone acetate on progression of coronary artery atherosclerosis in older postmenopausal women with established coronary artery disease (mean age ~63.5 years, mean ~18.2 years post-menopause), using

quantitative coronary angiography over 3.3 years. WELL-HART found no significant difference in change in per cent stenosis or minimal lumen diameter between estrogen, estrogen–progestin, or control groups, indicating that hormone therapy did not slow progression of advanced atherosclerosis in this higher-risk population. The divergent outcomes of EPAT and WELL-HART likely reflect differences in the vascular health of the study populations and disease stage: EPAT enrolled healthy women without clinical cardiovascular disease, in whom estrogen may modulate early atherogenic processes, whereas WELL-HART enrolled women with pre-existing coronary atherosclerosis, where late-stage disease may be less responsive to hormonal modulation. These trials collectively suggest that estrogen's effects on atherosclerosis may depend on vascular disease stage, with beneficial effects on early, subclinical atherosclerosis in healthy postmenopausal women (EPAT) but minimal impact on progression of established coronary lesions in older women (WELL-HART).

Raloxifene use for the heart

In the RUTH trial (10,101 postmenopausal women), raloxifene, a selective estrogen receptor modulator, had no effect on CHD incidence across all ages after a median treatment of 5.6 years. However, among women younger than 60 years of age, when randomised to raloxifene, CHD was statistically significantly reduced 41% relative to placebo.⁴⁷⁵

Secondary Prevention Trials Of CVD

Across a series of secondary-prevention trials in postmenopausal women with established cardiovascular disease, initiation of systemic MHT consistently failed to demonstrate cardiovascular benefit. In the HERS, combined estrogen–progestin therapy did not reduce overall coronary events and was associated with an early increase in CHD risk during the first year, a finding that persisted as neutral with longer follow-up in HERS II. The Estrogen Replacement and Atherosclerosis (ERA) trial showed no slowing of angiographic progression of coronary disease, while the Women's Estrogen for Stroke Trial (WEST) found no reduction in recurrent stroke or death after ischaemic stroke or TIA. Similarly, the PHOREA trial demonstrated no meaningful effect on the progression of carotid or femoral intima–media thickness. In contrast, the EPAT showed modest slowing of carotid IMT only in healthy women without clinical disease, highlighting the importance of vascular stage, and the Estrogen Angiographic Graft Evaluation Trial (EAGER) revealed mixed effects, with possible benefit in vein grafts but adverse changes in native coronary arteries, with no clear clinical advantage. Similarly, in the WELL-HART, a trial of older women with established coronary atherosclerosis, 17 β -estradiol alone or with sequential medroxyprogesterone acetate had no significant effect on angiographic disease progression, reinforcing that MHT does not reverse advanced coronary plaque.

Collectively, these trials indicate that initiating MHT in women with established atherosclerotic disease does not confer cardioprotection and may carry early risk, reinforcing the timing and arterial-stage hypothesis.^{170-172,174,175,476-479} A meta-analysis of 23 MHT trials, including 39,049 participants followed for 191,340 patient-years, showed that HT appeared to significantly reduce CHD events in younger women (mean time postmenopause < 10 years or age < 60 years) but not in older women. In older women, hormone therapy increased CHD events in the first year, then reduced events after 2 years.

The 2015 Cochrane review concluded that, overall, MHT provides little or no benefit for the primary or secondary prevention of cardiovascular disease in postmenopausal women, while increasing the risk of stroke and VTE. The 2025 Cochrane review found that long-term risk profiles differ between estrogen-only and combined hormone therapy. ET probably has little or no effect on coronary events, likely increases the risk of stroke and gallbladder disease, probably does not increase breast cancer risk, and likely reduces fracture risk. EPT may increase the risk of thromboembolism and probably increases breast cancer risk. These findings should be interpreted cautiously because they are largely based on one study using oral therapy, which may not reflect current clinical practice regimens.^{414-447,480}

Possible Causes Of Discrepancies Between Observational Studies And RCTs: The Timing Hypothesis

Early observational studies suggested a cardiovascular benefit with MHT, whereas large RCTs, notably the WHI, did not confirm this effect. These discrepancies are largely explained by differences in timing of initiation, baseline cardiovascular risk, and healthy-user bias inherent to observational designs. The timing hypothesis proposes that MHT initiated in younger women or within 10 years of menopause, when the vasculature is relatively free of advanced atherosclerosis, may exert neutral or potentially favourable vascular effects, while initiation in older women or those

with established atherosclerosis may be harmful. This concept is supported by mechanistic studies and imaging-based RCTs demonstrating slower progression of subclinical atherosclerosis when estrogen is started early after menopause, but not when initiated later. Refer to Chapter 12, Figure 1

In conclusion, the net cardiovascular impact of hormone therapy is not uniform and is critically shaped by the timing of initiation and the woman's underlying cardiovascular health. Additionally, pharmacogenomic variability is emerging as an important modifier of risk and benefit.⁴⁸¹ Finally, emerging evidence indicates that genetic variability, single-nucleotide polymorphisms (SNPs), and pharmacogenomic differences may influence individual responses to MHT through altered estrogen signalling, metabolism, and coagulation pathways. In the future, clinically validated SNP screening may enable more personalised selection of MHT, optimising efficacy while minimising harm.

Venous Thromboembolism

Later age at menopause onset, as well as both early and late extremes of age at menopause, has been associated with an increased risk of VTE in analyses of the WHI cohort, with women experiencing menopause at < 40 years or > 55 years showing higher VTE risk compared with those aged 40-49 years at menopause. In these analyses, traditional reproductive and menopause-related variables did not materially modify the effect of hormone therapy on VTE risk, suggesting that the association with VTE is independent of timing relative to menopause.⁴⁸²

Stroke

The risk of ischaemic stroke with HT is influenced by when treatment is started, as well as by the route and dose of estrogen. Evidence from meta-analyses of randomised controlled trials suggests that when HT is initiated in women younger than 60 years or within 10 years of menopause, there is no significant increase in stroke risk, supporting a timing-dependent effect.^{414,483} Oral estrogen is associated with a higher risk of ischaemic stroke, whereas transdermal E2 does not appear to carry the same excess risk, due to avoidance of first-pass hepatic effects.⁴²⁰ Additionally, stroke risk with oral estrogen appears to be dose-dependent, with higher doses such as CEE > 0.625 mg/day or oral E2 > 2 mg/day being associated with the greatest increase in risk.^{223,302,484}

Central Nervous System

A substantial body of evidence indicates that the association between MHT and cognitive outcomes is influenced by the timing of initiation relative to the final menstrual period, supporting the "critical window" or "timing" hypothesis. Few observational cohorts, including the Cache County Study and the Nurses' Health Study, have reported lower risks or null effects of Alzheimer's disease or all-cause dementia when MHT was initiated in midlife or close to menopause, whereas initiation in later life has generally shown no benefit and, in some analyses, potential harm.^{485,486} However, not all observational data are concordant; more recent large population-based studies from Finland and Denmark, as well as a Taiwanese nationwide cohort, have reported an association between systemic MHT and a modestly increased risk of dementia or Alzheimer's disease, including in some women who initiated therapy at or before age 55 years, although the absolute risk increase was small and findings varied by route of administration, with vaginal estradiol not showing this association.⁴⁸⁷⁻⁴⁸⁹ Randomised evidence from the Women's Health Initiative Memory Study (WHIMS) provides the clearest data on late initiation: starting estrogen-progestin or estrogen alone approximately 10-20 years after menopause (mean age ≥65 years) significantly increased the risk of probable dementia and mild cognitive impairment, establishing that late initiation is unsafe for cognitive prevention.^{490,491}

In ELITE-Cog, oral E2 started within 6 years of menopause did not improve global cognition compared with placebo and performed similarly to late initiation, although some memory trajectories differed by timing. In KEEPS-Cog, MHT started within 3 years of menopause was cognitively neutral over 4 years, showing neither clear benefit nor harm on global cognition compared with placebo.^{492,493} Synthesising all evidence, the 2023 systematic review and meta-analysis by Nerattini et al. concluded that associations between MHT and dementia risk are inconsistent and influenced by age at initiation, formulation, and study design, with possible signals of benefit near menopause but neutral or adverse associations with late use.⁴⁹⁴ Consistent with this, the Cochrane Review found no reliable evidence that systemic MHT improves cognitive function in postmenopausal women and did not support its use for cognitive prevention.⁴⁹⁵ Collectively, these data support a biologically plausible window in which estrogen may be more favourable to the brain than when started late, but they do not provide sufficient randomised evidence to recommend MHT for the prevention of dementia or Alzheimer's disease; therefore, MHT should not be prescribed solely for cognitive protection.

Diabetes

Across the experimental and observational literature, the “timing/window of opportunity” concept for diabetes proposes that estrogen’s metabolic effects are most favourable when therapy is initiated near menopause and may attenuate or even reverse when initiated long after menopause.

A landmark meta-analysis of 107 trials reported reductions in HOMA-IR and fewer new-onset diabetes (RR 0.7), reduced insulin resistance and fasting glucose in women with diabetes, with oral regimens producing larger metabolic benefits than transdermal, but increased CRP and decreased protein S.⁴³⁹ More recent syntheses of RCTs continue to support improved insulin resistance in non-diabetic postmenopausal women (HOMA-IR reduction).⁴⁹⁶ Trial data also demonstrate reduced incidence of diabetes in major RCT cohorts: in HERS and WHI, combined oral CEE+MPA reduced incident diabetes (RH 0.65),^{497,498} while CEE alone showed a smaller, borderline benefit (HR 0.88) with early improvements in insulin resistance.⁴⁹⁹ A systematic review/meta-analysis spanning 1997-2011 likewise found a lower diabetes incidence with combined estrogen-progestogen therapy (OR 0.61) and improvements in fasting glucose/HbA1c. Mechanistic “timing” evidence using gold-standard clamps comes from a randomised crossover study showing 1 week of transdermal estradiol improved glucose disposal in women ≤ 6 years since menopause but worsened it in women ≥ 10 years since menopause, supporting time-since-menopause as a biological modifier of estrogen action on insulin sensitivity.⁵⁰⁰ Concordant observational data suggest a greater benefit with midlife/earlier use and may vary by route: in the French E3N cohort, ever-use of MHT was associated with lower risk of new-onset diabetes (HR ≈ 0.82), with a stronger association for oral versus transdermal estrogen.⁵⁰¹ These data support a plausible early “metabolic window” for more favourable insulin action, while reinforcing that despite consistent improvements in glycaemic indices, MHT should be prescribed for menopausal indications rather than diabetes prevention (risk-benefit must remain individualised).

Bone

Bone loss accelerates sharply in the early postmenopausal period, with the greatest rate of resorption occurring within the first 3-5 years after the final menstrual period, driven by abrupt estrogen deficiency and expansion of the remodelling space.⁵⁰² During this phase, initiation of MHT is most effective because suppression of osteoclast-mediated resorption rapidly reduces the remodelling space, allows secondary mineralisation to catch up, and shifts bone balance toward formation, resulting in larger early gains in BMD than when therapy is started later.^{503,504} Randomised trials consistently show that MHT initiated early in menopause prevents rapid trabecular and cortical bone loss at the spine, hip, and forearm, whereas delayed initiation produces smaller BMD gains and less impact on fracture risk.^{205,164,505} Observational data and fracture trials, including WHI, further suggest that the greatest antifracture benefit of estrogen is observed when therapy is initiated near menopause and continued for several years, supporting the existence of a time-sensitive skeletal window.⁵⁰⁶ Collectively, these findings justify early consideration of MHT for bone protection in symptomatic women or those at high fracture risk, while recognising that therapy should be individualised and balanced against non-skeletal risks.^{507,508}

Breast

Unlike cardiovascular outcomes, breast cancer does not have a clearly protective “window of opportunity” for MHT. Instead, available evidence indicates that the time since menopause at initiation modifies breast cancer risk primarily for combined EPT. In the WHI, EPT increased breast cancer incidence, and secondary analyses suggested that women who began therapy closer to menopause experienced a greater increase in breast cancer risk, with the magnitude of excess risk diminishing as the interval between menopause and initiation increased.⁵⁰⁹ In contrast, in women with prior hysterectomy, randomised use of CEE in WHI was associated with lower breast cancer incidence and mortality on long-term follow-up, underscoring the importance of regimen type and implicating the progestogen component as a major contributor to breast risk in many settings.³²² Large pooled observational evidence further demonstrates that breast cancer risk rises with longer duration of systemic MHT, varies by formulation (with higher risks for several combined regimens), and is minimal with vaginal estrogen, reinforcing that duration and regimen are more clinically actionable modifiers than timing alone.²³⁸ Accordingly, contemporary guidance emphasises individualised counselling based on baseline breast cancer risk, the need for progestogen, dose and duration, rather than assuming early initiation confers breast safety.²¹⁰

Genitourinary Syndrome of Menopause

The GSM, a collection of vaginal and urinary symptoms arising from estrogen deficiency, unlike vasomotor symptoms,

typically persists or worsens over time if untreated, creating a practical “window of opportunity” for early recognition and therapy to prevent escalation to severe atrophy, introital narrowing, dyspareunia, and recurrent urinary symptoms.^{210,510} Longitudinal community data show that vaginal symptoms frequently persist over years in women not using estrogen therapy, supporting the concept that delay allows symptom chronicity and tissue deterioration.⁵¹¹ Early estrogen deficiency leads to thinning of the epithelium, loss of rugae, reduced elasticity and lubrication, rising vaginal pH with loss of lactobacilli, and inflammation changes that become more clinically entrenched with time since menopause. Although direct RCT evidence comparing “early versus late” initiation is limited, high-quality syntheses consistently demonstrate that local vaginal estrogen (creams, tablets, rings) is effective for GSM, and that timely initiation is clinically sensible because symptoms are progressive and treatment response is often faster and more complete before advanced stenosis and severe atrophy develop.⁵¹² Contemporary systematic reviews (including the 2024 AHRQ comparative effectiveness review) conclude that GSM therapies improve key outcomes but emphasise heterogeneity, limited long-term safety data for some modalities, and insufficient evidence to recommend energy-based devices.⁵¹³ The “timing” concept in GSM is best viewed as a prevention-of-progression clinical principle rather than a formally established differential-efficacy hypothesis; robust longitudinal studies are needed to better quantify the long-term sequelae of delayed treatment.

SERUM ESTRADIOL AROUND MENOPAUSE: WHAT TO MEASURE, WHEN, AND HOW

Common Clinical Indications For Serum Estradiol Testing

Serum estradiol is most useful when it will change diagnosis or management, particularly in reproductive endocrinology and in conditions where estradiol is expected to be very low or unexpectedly high. In premenopausal women, estradiol measurement is commonly used to assess ovarian function and to guide assisted reproduction (such as monitoring follicular response during ovulation induction/IVF) and to evaluate amenorrhoea/oligomenorrhoea and suspected hypogonadism.⁵¹⁴ Estradiol measurement is also indicated when evaluating estrogen-secreting tumours (such as granulosa cell tumour; adrenal/ovarian/testicular sources) in either sex, and in selected paediatric evaluations (delayed puberty, hypogonadism, disorders of sex development).⁵¹⁴ At menopause, the test is done to diagnose POI and EM, to monitor estrogen therapy, if there is an inadequate response, and to confirm that the therapeutic dose is achieved in select cases.

Assay Implication

In most of the above situations (IVF monitoring; typical female hypogonadism work-up), standard clinical assays are usually sufficient because concentrations are not at the very lowest range where immunoassays perform poorly.⁵¹⁵

Indications For Extra-Sensitive Estradiol Assays: Liquid Chromatography–Tandem Mass Spectrometry (LC–MS/MS)

Ultra-low estradiol concentrations occur in settings where routine automated immunoassays are prone to poor specificity and overestimation, so high-sensitivity LC-MS/MS is preferred. Aromatase inhibitor or anti-estrogen therapy monitoring (such as breast cancer; ovarian suppression), where estradiol targets are often in the single-digit pg/mL range, and immunoassays can be misleading.⁵¹⁶ Estradiol assessment in men (male hypogonadism, gynaecomastia evaluation, suspected aromatisation excess), where concentrations may be low and assay interference matters. Selected puberty/Disorders of sex development evaluations and inborn errors of steroidogenesis, where precise low-level quantification may be needed. Bone health research / selected fracture-risk work-ups when using proposed low-estradiol thresholds and where method accuracy is essential (LC-MS/MS).¹⁹⁴

Therapeutic Drug Monitoring In Menopausal Hormone Therapy

In routine menopause care, estradiol levels are infrequently required to manage VMS, but may be considered in selected situations such as unexpected lack of response, suspected malabsorption/non-adherence, drug interactions, or safety concerns, recognising the limitations of assays at low levels.⁵¹⁴

Situations Associated With Increased Estrone And/Or Estradiol

Circulating estrone and estradiol may be elevated in several clinical and physiological contexts, most commonly through enhanced peripheral estrogen production or reduced clearance. Increased aromatisation of androgens in adipose tissue, seen in obesity, androgen-producing tumours, or during exogenous androgen therapy, leads to higher circulating estrone and estradiol concentrations, with estrone typically predominating after menopause. Similarly,

obesity itself is associated with increased peripheral tissue conversion of androgens to estrone via aromatase, making adiposity a major determinant of postmenopausal estrogen exposure. Reduced hepatic clearance, particularly in chronic liver disease, can further elevate circulating estrogen levels by impairing metabolism and conjugation. Estrogen-secreting tumours, such as ovarian granulosa cell tumours and rare adrenal or testicular neoplasms, represent another important cause of elevated estradiol or estrone in both women and men. Finally, exogenous estrogen exposure through oral, transdermal, or systemically absorbed vaginal preparations, as well as supplements or inadvertent contamination, can substantially increase measured estrogen levels.

Methods For Measuring Estradiol: Strengths And Limitations

Direct (non-extraction) automated immunoassays frequently overestimate estradiol at low concentrations typical of postmenopausal women and men due to antibody cross-reactivity with estradiol metabolites and other structurally related steroids. This limitation has been consistently demonstrated in epidemiologic and clinical studies and has contributed to historically inflated “normal” postmenopausal estradiol values.^{194,517,518} In contrast, liquid chromatography–tandem mass spectrometry (LC–MS/MS) with appropriate sample preparation and chromatographic separation provides markedly superior specificity and sensitivity for low estradiol concentrations. Contemporary reference procedures increasingly rely on isotope-dilution LC–MS/MS, which corrects for matrix effects and analytical variability and is considered the most accurate approach for measuring estradiol at very low levels.^{517,519} Classic comparative studies in postmenopausal women have shown substantial method-dependent differences between immunoassays and mass spectrometry techniques, underscoring that LC–MS/MS should be preferred whenever precise low-level measurements are required. Although estradiol can be measured in urine or saliva using spectrophotometric, RIA, or immunoenzymatic methods, these approaches remain primarily research tools. They are not reliable substitutes for validated serum LC–MS/MS when clinical decisions depend on accurate quantification of low estradiol levels.

Postmenopausal Reference Range For Estradiol

There is no universally accepted reference range for postmenopausal estradiol, largely because many automated immunoassays lack adequate sensitivity, specificity, and standardisation at low concentrations, and because study populations differ with respect to age, BMI, and other determinants of estrogen levels. Using more accurate LC–MS/MS methods, a commonly cited estimate of basal systemic estradiol in untreated postmenopausal women ranges from undetectable to 10.7 pg/mL. Consequently, it is reasonable to state that with contemporary high-sensitivity assays, typical untreated postmenopausal estradiol concentrations are generally below 10 pg/mL, often lying near the assay’s lower limit of detection.⁵²⁰

Target estradiol concentrations vary among individuals and depend on biological tissue responsiveness, the analytical method used to measure estradiol, the clinical outcome of interest (such as VMS control or bone health), and the therapeutic goals agreed upon with the patient. Available evidence suggests that circulating estradiol levels achieved with MHT that approximate early follicular-phase concentrations of approximately a therapeutic estradiol range of 60–150 pg/mL are generally sufficient for relief of VMS and prevention of bone loss.^{114,521,522,523} No single standardised dose reliably achieves optimal clinical response in all women.⁴⁷⁸ In asymptomatic women treated primarily for bone protection, circulating estradiol levels may provide supportive physiological information, although routine dose titration based on serum measurements is not recommended in clinical practice. When measured using direct immunoassay, levels above approximately 55 pg/mL (≥ 200 pmol/L) are likely to maintain bone density in most women, whereas higher levels may be more appropriate for younger women or those with established osteopenia or osteoporosis. The achieved mean serum E2 levels among oral E2-compliant postmenopausal women in ELITE varied widely, from 9 to 360 pg/mL.⁵²¹ Hence, it is seen that considerable inter-individual variability exists, and treatment decisions should be guided primarily by clinical response and bone health outcomes rather than target hormone levels.^{523,524}

Serum Estradiol And Its Relation To Different Systems

Lifestyle Factors

Higher serum E2 levels were associated with higher body mass index (BMI), higher weight, surgical menopause, alcohol use, and antihypertensive medication use. Current and past smoking and antifungal medication use were associated with lower serum E2 levels.⁵²⁵ In a randomised crossover study of oral and transdermal E2 therapy, E2

levels were 40-70% lower among smokers than among non-smokers; a statistically significant difference in E2 levels was seen among postmenopausal women taking oral, but not transdermal, E2 therapy.^{526,527}

Endometrium

Endometrial cancer is strongly influenced by hormonal exposure, with endogenous estrogen exposure recognised as a key aetiological factor. Prospective serum hormone measurements show that higher circulating levels of endogenous estrogens are associated with increased endometrial cancer risk in postmenopausal women, particularly for estrogen-dependent (Type I) tumours. In the largest prospective study of serum estrogens and endometrial cancer risk among postmenopausal women not using exogenous hormones, unconjugated estradiol showed the strongest positive association with risk (highest versus lowest quintile, adjusted OR ~6.19, 95% CI 2.95-13.03). This association was stronger for Type I than Type II endometrial cancers and was independent of BMI effects, underscoring the importance of estradiol in estrogen-driven carcinogenesis.⁵²⁸

Breast Cancer

Epidemiological evidence consistently links higher concentrations of endogenous estradiol with increased risk of breast cancer in postmenopausal women. Plasma estradiol levels measured before diagnosis predict future hormone-receptor-positive breast cancer, and women in the upper quartiles of estradiol have significantly elevated relative risks compared with those in the lowest quartiles. Studies adding endogenous estrone, estradiol, or estrone sulphate measurements to breast cancer risk prediction models (such as Gail, Rosner-Colditz models) demonstrate improvements in risk discrimination, with increases in the area under the receiver-operating characteristic curve (AUC), indicating that serum sex hormone levels can improve individual risk stratification when incorporated into existing models.⁵²⁹

Skeletal System And Fracture Risk

Estradiol plays a fundamental role in bone metabolism. In postmenopausal women, lower endogenous estradiol levels are associated with increased rates of bone loss, reduced BMD, and higher fracture incidence. Estradiol strongly inhibits bone resorption and promotes osteoblast activity; its deficiency is a central contributor to postmenopausal osteoporosis.⁴⁸² Cauley reviewed the literature on the relationship between plasma estradiol and fracture risk. Low estradiol concentration (< 5 pg/mL) was associated with a relative risk of fracture of 2.51 (95% CI, 1.4-4.6) in one study, and several others support the concept that low estradiol levels may be used as one component in the assessment of fracture risk.⁴⁸³ In postmenopausal women not using MHT, estradiol levels > 25 pg/mL (92 pmol/L) are associated with a significant decrease in BMD and a significant increase in the Fracture Risk Assessment Tool (FRAX) score, as measured by LC-MS/MS. Aiming for a serum estradiol concentration of > 25 pg/mL (> 92 pmol/L), therefore, seems reasonable.⁵³⁰

Other Systems

Evaluation of estrogen levels and CV risk in postmenopausal women should be interpreted in the context of obesity, other comorbidities, degree of inflammation, insulin levels and resistance, and other factors. It was suggested that low levels of estradiol in postmenopausal women reduced quality of life and parameters of sexuality. These hypotheses need to be confirmed in future studies.⁵³¹ Existing data on the relationship between estradiol and cognitive dysfunction are conflicting, and no conclusions can be drawn.

To conclude, while awaiting easy, readily available, and cost-effective methods to measure low levels of estradiol, estrone, and estrogen metabolites, it is prudent in clinical practice to restrict serum estradiol measurement to indications that require moderately sensitive tests.

LONG-TERM MENOPAUSAL HORMONE THERAPY: EVIDENCE REVIEW

Long-term MHT, which refers to continuation of therapy initiated in early menopause, is distinct from initiating MHT for the first time more than 10 years after menopause. While extended use may be appropriate in selected women with ongoing indications, late initiation is associated with a less favourable risk-benefit profile. Long-term MHT, arbitrarily defined as use beyond five years and, in selected women, beyond ten years, is appropriate when there is a persistent symptom burden or an ongoing preventive benefit that clearly outweighs individualised risks. The decision should be personalised, reassessed periodically, and made through shared decision-making. The indications for continuing MHT include persistent moderate-to-severe VMS that significantly impair sleep, mood, daily functioning, and GSM when

symptoms are moderate–severe, recurrent, or progressive despite initial treatment, particularly recurrent urinary symptoms, vaginal atrophy, or dyspareunia due to GSM. Long-term MHT is also justified for osteoporosis prevention or treatment in women who are intolerant of, unsuitable for, or prefer not to use non-hormonal bone-active agents. Additionally, women with POI or early menopause may wish to continue systemic MHT unless contraindicated. Together, VMS and GSM can adversely affect quality of life, relationships, work productivity and functional health in later life, reinforcing the need for individualised, long-term symptom management as part of a healthy-ageing strategy. Moreover, emerging evidence indicates a link between frequent, persistent, severe, or late-onset VMS as a potential clinical signal of increased cardiometabolic and vascular risk.^{532,533}

While direct evidence that GSM predicts osteoporosis is limited, GSM-associated urinary urgency/incontinence is linked to increased falls and fracture risk; therefore, women with troublesome GSM, especially urinary urgency/nocturia, should be assessed for falls risk and bone health as clinically indicated.^{534,535}

In all cases, the need for continuation of MHT should be reviewed at regular intervals, balancing evolving benefits against age-related and treatment-related risks. VMS are among the most prevalent and persistent manifestations of the MT and often persist well into later life, with important implications for quality of life, sleep, mental health, sexual function, and healthy ageing. Contrary to earlier beliefs that hot flushes are short-lived, contemporary cohort studies consistently show that a substantial proportion of women experience VMS for a decade or more after the FMP. Refer to Table 20

Table 20. Persistence of VMS beyond 10 years of menopause

Evidence source	Key finding
Meta-analysis	VMS often persist > 12 years 10% ⁵³⁷
Penn Ovarian Aging Study	One-third symptomatic ≥ 10 years ²¹⁷
SWAN	Median duration 10 yrs in African Americans ^{538, 539}
MORE trial	11.8% symptomatic at mean age 62.7 ⁵³⁹
UK cohort	54% symptomatic at 54-65 years ⁵⁴⁰
Mayo Clinic (DREAMS)	41% symptomatic of the 18% who were > 60 years ⁵⁴¹
Australia	6.5% (60-65 y); 542 33% (65-79 y) ⁵⁴³
Sweden	16% symptomatic at age 85 ⁵⁴⁴

For the prevalence of osteoporosis and GSM, refer to Chapters 10 and 17.

Efficacy Of Long-Term Menopausal Hormone Therapy

Swedish national registry data show that among women aged ≥ 80 years, a small but meaningful proportion remained current users of systemic MHT, and a much larger proportion regularly used local vaginal estrogen. This suggests that menopausal symptoms, including GSM and possibly VMS, remain clinically relevant even in very elderly women, underscoring the need for informed, individualised counselling rather than automatic discontinuation.⁵⁴⁵ Long-term prospective observational data now demonstrate that carefully selected hysterectomised women can safely continue systemic MHT well beyond conventional time limits. In a 20-year follow-up study of hysterectomised women, Lorite et al. reported sustained benefits in cardiovascular parameters, BMD, and quality of life when transdermal E2 was continued long-term, with a planned dose reduction from 0.050 mg/day to 0.025 mg/day at age 60. Importantly, this regimen exceeded the traditional 5-year duration threshold yet was associated with favourable clinical outcomes rather than harm.⁵⁴⁶ Qualitative and survey-based data from Canada provide further insight into real-world practice. In women aged ≥ 65 years who continued MHT, the mean age of initiation was 52, and the average duration of use was 18 years; notably, 42% had used MHT regularly for more than 20 years. The vast majority (88%) used transdermal E2, with very few using synthetic progestins. The primary motivation for continuing was persistent hot flushes (55%), followed by improvements in overall quality of life (29%) and relief from chronic pain or arthritic symptoms (7%). These findings highlight that long-term use is often symptom-driven rather than preventive alone.⁵⁴⁷ Large-scale US Medicare analyses involving over 10 million women who continued MHT beyond age 65 further suggest that outcomes vary by type, route, and dose. Baik et al. reported that lower doses, vaginal or transdermal routes, and estradiol-based

therapy were associated with greater risk reductions in all-cause mortality, breast cancer, lung cancer, colorectal cancer, heart failure, VTE, atrial fibrillation, myocardial infarction, and dementia compared with higher-dose or oral conjugated estrogen. Although reasons for continuation were not documented, the overall pattern favoured low-dose transdermal E2.⁵⁴⁸

A 2025 Cochrane review of long-term hormone therapy concluded that risk profiles likely differ between ET and EPT. ET probably has little effect on coronary events, may increase stroke and gallbladder disease, has little effect on breast cancer risk, and likely reduces fracture risk. EPT may increase VTE and probably increases breast cancer risk, though these conclusions were largely based on older oral formulations and may not fully reflect modern transdermal regimens.⁵⁴⁹

These findings align with a broader conceptual shift that views MHT not merely as symptom relief but as a means of mitigating accelerated biological ageing, which begins earlier in women who lose ovarian function. In this context, several guidelines state that there is no compelling reason to impose a strict upper age limit for MHT, provided the lowest effective dose is used, and a non-oral route is employed. Despite these encouraging data, continued vigilance is warranted with long-term therapy, and ongoing individualised reassessment of risks and benefits is essential. Follow-up should be more risk-stratified and focused on age-related comorbidities rather than solely on symptom control. Compared with routine early-menopause monitoring, clinicians should place greater emphasis on cardiovascular risk assessment (blood pressure trends, lipids, glucose/diabetes risk, and body composition), VTE risk profile, and medication interactions. Preference for lower and ultra-low doses, as well as non-oral estradiol, becomes increasingly important with advancing age. Bone health surveillance should be individualised based on fracture risk rather than performed uniformly. Breast surveillance with heightened clinical vigilance for any interval breast changes. In women with a uterus, even minimal or atypical bleeding warrants prompt evaluation.

Special warning signals in long-term users include: new or worsening hypertension, unexplained weight gain or oedema, rising triglycerides, new cognitive symptoms, reduced mobility or unexplained leg pain/swelling, and any change in breast or vaginal bleeding patterns, each of which should trigger early review and possible regimen modification.

MENOPAUSAL HORMONE THERAPY AS PRIMARY PREVENTION:

WHAT IS THE EVIDENCE?

In the early 1990s, before large cardiovascular outcome trials were available, the prevailing view, supported largely by observational data, was that postmenopausal estrogen could be used as a preventive strategy. In 1992, Grady and colleagues published a major evidence review explicitly addressing long-term hormone therapy in asymptomatic postmenopausal women for disease prevention and life prolongation.⁵⁵⁰ Following this paper in 1992, the American College of Physicians (ACP) issued a statement stating that “all women, regardless of race, should consider preventive hormone therapy” and that “women who have coronary heart disease or who are at increased risk for CHD are likely to benefit from hormone therapy.”¹¹

This prevention-oriented paradigm shifted sharply after RCT evidence became available. The HERS trial found that combined CEE plus MPA did not reduce recurrent CHD events in women with established coronary disease and showed an early excess of events.¹⁷⁰ The WHI then demonstrated that, in generally older postmenopausal women, combined EPT was associated with an overall unfavourable risk-benefit profile for chronic disease prevention, and specifically was not consistent with use for primary prevention of CHD.³⁰ These landmark data led to the well-known “lowest effective dose for the shortest duration” messaging and reinforced that systemic MHT should be used primarily for menopausal symptom control, not for chronic disease prevention.

Has The Thinking Changed By 2026?

Yes, but not as a return to “preventive hormone therapy for all.”¹¹ The modern approach is balanced, risk-stratified, timing-aware, and individualised, informed by reanalyses of the WHI and DOPS, and by additional trials, KEEPSS, and ELITE focused on early postmenopause. Contemporary major society statements emphasise that MHT is the most effective therapy for VMS and GSM, prevents bone loss, and reduces fracture risk, but it is neither approved nor recommended as primary cardioprotection.

Osteoporosis

Randomised trial evidence from the WHI shows that systemic MHT reduces fracture risk (including hip and total fractures) in generally healthy postmenopausal women. In the WHI trials, both EPT and ET were associated with fewer fractures versus placebo, establishing MHT as an effective anti-fracture intervention in primary prevention settings.⁵⁵¹ A later WHI combined analysis also supports fracture reduction across baseline FRAX strata and falls history, reinforcing that MHT has clinically meaningful anti-fracture efficacy.⁵⁵² Two perspectives coexist in contemporary practice for primary prevention of fractures. One prioritises MHT as a symptom-directed therapy and discourages its use in asymptomatic women for fracture prevention alone.⁵⁵³ The other considers MHT a physiologic replacement in early menopause that may be appropriate for bone protection irrespective of symptoms, provided the woman is within 10 years of menopause, under 60 years of age, and has a favourable individualised benefit-risk profile.⁵⁵⁴⁻⁵⁵⁷

Genitourinary Syndrome of Menopause

For the GSM, the evidence base is strongest for treatment, not “primary prevention in asymptomatic women.” Local therapy can be used long-term once GSM begins, and many experts frame early recognition and treatment as a means of preventing progression, worsening dyspareunia, recurrent symptoms, and tissue fragility. Asymptomatic women with GSM may also benefit from treatment to reduce the risk of urinary tract infections and of future symptoms.⁵⁵⁸ However, formal RCT evidence for initiating therapy solely to prevent future GSM in asymptomatic women is limited.

Cardiovascular Disease

WHI was explicitly designed to test major chronic disease outcomes in older postmenopausal women (mean age 63 at entry). In the combined estrogen–progestin trial, overall health risks exceeded benefits, and the findings did not support MHT for primary prevention of CHD in that older population.³⁰

Systematic reviews of trial data (including the Cochrane reviews) likewise conclude that HT should not be used to prevent cardiovascular events in unselected postmenopausal women. AHA scientific statements similarly emphasise that MHT is not indicated for the primary prevention of CVD and that cardiovascular risk assessment and timing matter.^{48, 414} Evidence from clinical trials, imaging studies, and long-term follow-up cohorts underpins the timing (or window-of-opportunity) hypothesis, which suggests that the vascular effects of MHT are influenced by age and time since menopause (see Section on Timing Hypothesis). When initiated in younger women or within approximately 10 years of the final menstrual period, MHT, particularly transdermal estradiol, appears to have more favourable effects on surrogate markers of atherosclerosis, endothelial function, and arterial ageing.^{30, 44, 186, 281, 302, 414, 422} However, despite these biologically plausible and imaging-based benefits, robust evidence that MHT prevents hard cardiovascular outcomes, such as myocardial infarction or stroke, is lacking. For this reason, major professional bodies and preventive medicine organisations advise against using MHT solely for the primary prevention of CVD. In clinical practice, the role of MHT is selective and individualised, with prescribing for primary indications while considering secondary benefits and risks. In symptomatic women who are early postmenopausal and at low-to-moderate cardiovascular risk, appropriately chosen MHT may be cardiovascularly neutral or potentially favourable, while effectively treating menopausal symptoms. In this context, cardiovascular risk should be formally assessed, modifiable risk factors optimised, and safer regimens, such as low-dose transdermal estradiol with micronised progesterone, where indicated, are preferred.

FUTURE OF MENOPAUSAL HORMONE THERAPY

Personalised And Precision Medicine Approaches In Menopausal Hormone Therapy

Future developments in MHT are increasingly oriented toward precision pharmacology, moving beyond uniform prescribing to individualised strategies tailored to a woman’s biological, metabolic, and clinical profile. Interindividual variability in symptom burden, cardiometabolic risk, and genetic polymorphisms affecting estrogen metabolism, transport, and receptor sensitivity contributes to heterogeneous responses to MHT and supports personalised selection of hormone type, dose, route, and duration.⁵⁵⁹

Pharmacogenomics and biomarker-based approaches are central to this paradigm. Genetic variation in estrogen receptors and metabolising enzymes may influence therapeutic response and adverse effects, offering the potential to

guide safer and more effective hormone prescribing.⁵⁵⁹ Integration of circulating biomarkers, metabolic profiling, and real-world data is expected to refine risk stratification and treatment optimisation, although clinical validation remains limited.⁵⁶⁰

Innovations in hormone formulations and delivery systems aim to improve physiological hormone exposure and safety. These include bioidentical hormones, ultra-low-dose and transdermal estrogen preparations, MP and DYD, and emerging delivery platforms such as micro-pellet implants, gels, patches, and wearable technologies for sustained release. Experimental injectable hydrogel microspheres and core-shell spherification techniques encapsulating estradiol and progesterone have demonstrated stable plasma hormone levels and symptom improvement in early-phase studies, though long-term safety data are lacking.⁵⁶¹ Therapeutic innovation beyond estrogen includes neurokinin-3 receptor antagonists for VMS, providing effective non-hormonal options for women with contraindications to MHT, as well as tissue-selective estrogen complexes and novel selective estrogen receptor modulators to optimise symptom control while minimising breast and endometrial risks.⁵⁶²

Machine-learning and artificial intelligence-based models are being explored to optimise MHT regimens by analysing large datasets of treatment response. In post hoc analyses of long-term estrogen trials, genetically and clinically informed E2 dosing models have been associated with improved bone outcomes compared with standard dosing, supporting the concept of adaptive, data-driven therapy.⁵⁵⁹ Emerging research is also exploring personalised MHT, incorporating genetic, metabolic, and cardiovascular risk profiling to guide choice of hormone type, dose, route, and duration.⁵⁶⁰⁻⁵⁶² Digital health tools and real-world data registries are expected to play an increasing role in refining long-term safety and effectiveness of MHT across diverse populations.⁵⁶³

Regenerative Medicine

Regenerative medicine, including stem-cell-based therapies and ovarian transplant to restore ovarian endocrine function, remains experimental and is not currently applicable to routine menopause care. Cryopreservation of ovarian tissue at a young age followed by autologous transplantation has been explored as a strategy to restore ovarian endocrine function and potentially delay menopausal changes. Case series and small observational studies report resumption of ovarian hormonal activity within weeks to months after transplantation, with normalisation of gonadotropins and predominantly estrogenic function lasting several years in some women. Heterotopic transplantation has been shown to restore endocrine activity and relieve menopausal symptoms, with outcomes comparable to orthotopic techniques in terms of endocrine recovery and graft longevity.⁵⁶⁴⁻⁵⁶⁷ Fertility-preservation cohorts have also reported spontaneous pregnancies and live births following ovarian tissue transplantation.⁵⁶⁸

However, this approach has important limitations: it requires surgical procedures, the durability and consistency of symptom relief are unpredictable, costs and technical complexity are high, and graft activity cannot be readily discontinued once transplanted. Consequently, ovarian tissue cryopreservation and transplantation remain investigational for menopausal management and cannot currently be recommended as an alternative to menopausal hormone therapy.

SYNOPSIS

- Evidence from major randomised trials WHI, DOPS, PEPI, KEEPS, ELITE demonstrates the benefits and risks of menopausal hormone therapy in women aged 50-59.
- Hormone therapy effectively relieves vasomotor symptoms, vulvovaginal atrophy, and prevents bone loss and fractures.
- Risks include venous thromboembolism, stroke, and modest increases in breast cancer risk, particularly with combined estrogen-progestin therapy.
- Risk-benefit balance is favorable when therapy initiates before age 60 or within 10 years of menopause with careful patient selection and regular monitoring.
- Low-dose transdermal estrogen has lower cardiovascular and thromboembolic risks compared to oral formulations.
- Benefits and risks vary based on age, time since menopause, baseline health status, route of administration, and specific regimen used.

RESEARCH AGENDA

The effects of sequential 17 β -estradiol and dydrogesterone on symptoms, biochemical markers in healthy women and in women with CVD risk factors at MT.

The effect of transdermal 17E-estradiol on biochemical markers of CVD in women with more than two clinical risk factors of CVD at MT.

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PROGESTERONES AND ANDROGENS

Keywords: Types, receptor activity, indications, effects

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INTRODUCTION

Progesterone (P4) is a steroid hormone produced by the adrenal cortex, ovaries, and testes. In women, it is primarily secreted by the corpus luteum (CL) during the second half of the menstrual cycle in non-pregnant women. During pregnancy, the corpus luteum is the main source of P4 for the first 10 weeks, after which the placenta becomes the principal site of production. P4 plays a fundamental role in coordinating female reproductive physiology, including ovulation, endometrial transformation, implantation, and maintenance of pregnancy.^{1,2}

P4 is derived from cholesterol and is a 21-carbon steroid hormone belonging to the cyclopentane-perhydrophenanthrene family of steroids. Its synthesis begins with the mitochondrial cholesterol side-chain cleavage enzyme (cytochrome P450_{scc}), converting cholesterol to pregnenolone. Pregnenolone is then converted to progesterone by 3 β -hydroxysteroid dehydrogenase (3 β -HSD).³

Progestogens are broadly classified into two main types: natural progesterone and synthetic progestins. Synthetic progestogens, commonly referred to as progestins, represent a diverse group of compounds characterised by their synthetic origin and varied pharmacological properties. The term progestogen (also referred to as progestagen, gestagen, or gestogen) describes any natural or synthetic steroid hormone that produces progestational effects, such as P4. In contrast, the term progestin refers specifically to synthetic agents developed to mimic the biological actions of endogenous progesterone.⁴ The North American Menopause Society recommends that the term progesterone should be reserved for natural progesterone, while progestin should be used for synthetic progestational agents.⁵

Progestogens, including natural progesterone and synthetic progestins, are defined by their ability to convert estrogen-primed proliferative endometrium into secretory endometrium. This transformation is essential for preventing endometrial hyperplasia (EH) and reducing the risk of endometrial carcinoma. They exert this effect partly by decreasing the number of estrogen receptors in target tissues and by suppressing luteinizing hormone (LH) secretion through negative feedback, thereby reducing ovarian estrogen production.⁶ In the absence of progesterone supplementation, the incidence of endometrial atypia may range from 18% to 32%. The addition of progesterone for 7 days per month reduces the incidence of atypical hyperplasia to approximately 3%, whereas administration for 12–14 days lowers it further to nearly 1%.⁷

PROGESTERONE

In adult non-pregnant women, the CL is the principal source of progesterone production. Progesterone is also synthesised in the adrenal glands as an intermediate product in the steroidogenesis pathway leading to testosterone and cortisol synthesis. Smaller amounts are additionally produced by the ovaries and testes. P4 secretion from the ovaries varies significantly throughout the menstrual cycle. During the follicular phase, secretion is minimal, with approximately 2 mg/day produced by the preovulatory follicle. Following ovulation, P4 production rises markedly during the luteal phase, reaching approximately 25 mg/day due to secretion by the corpus luteum.

P4 is often referred to as the “pregnancy hormone” because of its essential role in implantation, maintenance of early pregnancy, and support of fetal development. During pregnancy, the corpus luteum remains the primary source of P4 during the first 8–10 weeks, after which the placenta takes over as the major site of synthesis. Placental progesterone production progressively increases throughout gestation and may reach approximately 250 mg/day in the later stages of pregnancy.⁸

DEFINITION AND CLASSIFICATION

P4, a naturally occurring steroid hormone, transforms the estrogen-primed proliferative endometrium into a secretory endometrium, thereby preparing the uterus for implantation and supporting early pregnancy. In addition, progesterone helps maintain pregnancy by reducing uterine contractility and supporting placental function.

The pharmacological characteristics of progestogens used in contraception and menopausal hormone therapy (MHT) vary according to their molecular origin, whether derived from progesterone or testosterone. Studies have shown that even minor structural modifications in these compounds can lead to significant differences in their biological activity, receptor affinity, and clinical effects. Progestogens are broadly classified into two main categories: natural progesterone and synthetic progestins. Refer to Table 1.⁸

Table 1: Classification of progesterones

Progesterones	Example
1. Progesterone	Natural Progesterone
2. Retroprogesterones	Dydrogesterone
3. Progesterone derivative	Medrogestone
4. 17a-Hydroxyprogesterone derivatives (Pregnanes)	Medroxyprogesterone acetate, Megestrol acetate, chlormadinone acetate, cyproterone acetate
5. 17a-Hydroxynorprogesterone derivatives (norpregnanes)	Gestonorone caproate, norgestrol acetate
6. 19-Norprogesterone derivatives (norpregnanes)	Demegestone, promegestone, nestorone, trimegestone
7. 19-Norprogesterone derivatives (estranes)	Norethisterone, norethindrone, norethisterone acetate (NETA), lynestrenol, Ethynodiol acetate, norethynodrel
8. 19-Notestosterone derivatives (gonanes)	Norgestrel, levonorgestrel, desogestrel, etonogestrel, gestodene, norgestimate, dienogest
9. Spironolactone derivative	Drospirenone

NATURAL PROGESTERONE

Natural progesterone includes micronised progesterone (MP) and dydrogesterone (DYD). These compounds have a molecular structure that closely resembles endogenous human progesterone and are primarily derived from plant sterols. Because of their similarity to natural progesterone, they generally exhibit better metabolic and cardiovascular safety profiles. Natural progesterone preparations are currently available in oral, injectable, and intravaginal formulations. Micronisation improves oral bioavailability by enhancing gastrointestinal absorption, making oral MP a commonly used option in hormone replacement therapy.

SYNTHETIC PROGESTINS

Synthetic progestogens, commonly referred to as progestins, comprise a broad group of compounds developed to mimic the biological effects of natural progesterone. They are chemically synthesised by modifying the steroid nucleus or side chains, resulting in variations in potency, receptor selectivity, and additional hormonal effects. Synthetic progestins are widely used in contraception and menopausal hormone therapy because of their strong progestational activity and good oral bioavailability. Although all progestins exhibit progestogenic effects, many also demonstrate antiestrogenic, androgenic, antiandrogenic, glucocorticoid, or antimineralocorticoid properties depending on their chemical structure.

STRUCTURAL CLASSIFICATION OF SYNTHETIC PROGESTINS

Orally active progestins structurally related to progesterone include 17 α -hydroxyprogesterone derivatives

(pregnanes) and 19-norprogesterone derivatives (norpregnanes). Progestins structurally related to testosterone include 19-nortestosterone derivatives, such as the estranes and gonanes. Additionally, drospirenone (DRSP) is classified as a spironolactone derivative and is notable for its antiandrogenic and antimineralocorticoid properties. Because of structural similarities between steroid hormone receptors, progestins may interact with androgen, glucocorticoid, and mineralocorticoid receptors. This explains why some progestins behave as weak androgens, while others function as antiandrogens, glucocorticoids, or antimineralocorticoids. These differences are clinically important when selecting the most appropriate progestogen for contraception or MHT.⁸

Generational Classification Of Progesterones

Progestins are divided into first, second, third, and fourth generation progestins. The first three generations are testosterone (T) derivatives. They have an affinity for androgen receptors (AR) and may cause undesirable androgenic effects. The fourth generation has activity similar to P4 and therefore does not exhibit androgenic effects like the first three generations. Fourth-generation progestins are newer preparations and have some antiandrogenic properties. Of particular importance is drospirenone, a fourth-generation progestin structurally related to spironolactone.

First generation: norethynodrel, nortestosterone derivatives (that become active after conversion to norethisterone), medroxyprogesterone acetate (MPA), cyproterone acetate (CPA), chlormadinone acetate and megestrol acetate.

Second generation: norgestrel and levonorgestrel (LNG).

Third generation: levonorgestrel derivatives such as desogestrel, gestodene and norgestimate.

Fourth generation: dienogest, DRSP, nestorone, nomegestrol acetate and trimegestone. The fourth generation, which has been synthesised in the past 2 decades, may be defined as “new progestins”. The property of the fourth-generation progestins is that they have no androgenic or estrogenic actions and are closer in physiological activity to the hormone progesterone.¹⁰

Mechanism of Action

Non-contraceptive action: Progesterone exerts its biological effects primarily by binding to the two nuclear progesterone receptor isoforms, PR-A and PR-B. Being a lipophilic steroid hormone, progesterone enters the target cell by passive diffusion through the cell membrane. In its unbound state, the progesterone receptor exists as a monomer associated with heat shock proteins. Upon binding progesterone, the receptor undergoes a conformational change, dissociates from these proteins, and forms a dimer, which then binds to specific progesterone response elements on DNA to regulate gene transcription. In addition to nuclear receptors, progesterone also interacts with membrane progesterone receptors (mPRs), which are believed to mediate rapid, non-genomic responses in various target tissues. Serum concentrations of progesterone are influenced by its pharmacokinetic properties and by levels of sex hormone-binding globulin (SHBG). Only the unbound or free fraction of progesterone is biologically active and capable of entering target cells to initiate its physiological effects.⁸ The biological response to progesterone depends on several factors, including the number and distribution of progesterone receptors, receptor affinity, the degree of conformational change induced in the steroid–receptor complex, and the duration of intracellular receptor retention.³ The clinical effects of synthetic progestins are determined not only by their interaction with progesterone receptors but also by their affinity for other steroid hormone receptors, including AR, estrogen receptor (ER), glucocorticoid receptor (GR), and mineralocorticoid receptor (MR). Refer to Table 2 These receptor interactions may either activate (transactivation) or inhibit receptor signalling, leading to both therapeutic benefits and adverse effects. For example, many progestins used in contraception and MHT are derived from testosterone and may exhibit androgenic activity. Common side effects such as acne, weight gain, fluid retention, and unfavourable changes in lipid profiles are often related to androgenic or glucocorticoid actions.

Therefore, differences in receptor-binding affinity among various progestins result in distinct pharmacological profiles, clinical applications, and side-effect patterns, which are important considerations when selecting an appropriate progestogen for therapy. Refer to Table 3.^{8,11,12}

Table 2: Progestogens: Receptor-bindingactivity
All Progestogens Hhave a protective effects on the endometrium, but not all Progestogens have the same receptor-binding effect

Receptor	A-E	EST	AND	A-A	GLU	A-M
Dydrogesterone ¹	+	-	-	±	-	±
Progesterone ¹	+	-	-	±	+	+
MPA ¹	+	-	±	-	+	-
Norethisterone ¹	+	+	+	-	-	-
Drospirenone ¹	+	-	-	+	-	+
CPA ¹	+	-	-	++	+	-
Dienogest ¹	+	±	-	+	-	-
Levonorgestrel ¹	+	-	+		-	-
Norgestrel ¹	+	-	+	-	-	-
Tibolone ¹	+	±	+	-	-	-

+ Effective; A-E: antiestrogenic; EST: estrogenic; AND: androgenic; A-A: antiandrogenic; GLU: glucocorticoid; A-M: antimineralocorticoid activity; ± Weakly effective; -Not effective. 1Schindler AE, Campagnoli C Druckman R, Huber J, Pasqualini JR, Schweppe KW, et al. Classification and pharmacology of progestin. Maturitas. 2003;46 (Suppl 1):S7-16.2de Gooyer ME, Deckers GH, Schoonen WG, Verheul HA, Kloosterboer HJ. Receptor profiling & endocrine interactions of tibolone. Steroids. 2003;68(1):21-30

Table 3: Binding of proiestins with human steroid receptors in vitro.
Sitruk-Ware R. Pharmacological profile of progestins. Maturitas 2004;47:277-83

Relative binding affinity (%)						
Receptor	TMG	MPA	NET	GES	LNG	DRSP
Progesterone	588	298	134	864	323	19
Androgen	2.4	36	55	71	58	2
Glucocorticoid	13	58	1.4	38	7.5	3
Mineralocorticoid	42	3.1	2.7	97	17	500
Estrogen	<0.02	<0.02	0.15	<0.02	<0.02	<0.05

TMG, trimegestone; MPA, medroxyprogesterone acetate; NET, norethisterone; GES, gestodene; LNG, levonorgestrel; DRSP, drospirenone

Contraceptive action: Progestins inhibit the secretion of gonadotropin-releasing hormone (GnRH), LH, and follicle-stimulating hormone (FSH) by the pituitary gland. This suppresses ovulation in most of the cases. This suppression prevents the mid-cycle LH surge required for ovulation, thereby inhibiting ovulation in most women. However, ovulation suppression is not always complete with all progestin preparations. For example, women using norethindrone-containing contraceptives may still ovulate in some cycles, particularly with lower-dose formulations.¹³

TESTING THE POTENCY OF PROGESTERONE

The activity and potency of synthetic progestins are primarily evaluated by assessing parameters related to their effects on the endometrium. The most important indicator of progestational activity is a compound's ability to transform the estrogen-primed proliferative endometrium into a secretory endometrium capable of supporting implantation and pregnancy.¹⁴ Refer to Table 4.

Table 4: In vivo bioassays for testing. Source: Kumar N, Koide SS, Tsong YY, et al. Nestorone: a progestin with a unique pharmacological profile. Dteroids 2000;65:629-36

Bioactivity	Test	Species	End points
Progestational	McPhail Index	Immature femal rabbits	endometrial transformation
Progestational	Pregnancy maintenance	Female rats	dose able to maintain pregnancy after ovariectomy
Antiovolutory	Ovulation inhibition test	4-days cyclic rats	dose able to suppress spontaneous ovulation
Androgenic	Hershberger assay	Hershberger assay	growth of prostate & seminal vesicles
Antiandrogenic	Hershberger assay	Immature or castrated male rats	inhibition of testosterone-induced prostate & seminal vesicle growth
Estrogenic/ antiestrogenic	Iterotopic	Immature or castrated male rats treated with testosterone	Immature or castrated male rats treated with testosterone
Glucocorticoid/ antoglucocorticoid	Thymolytic assay	ovariectomized male rats	growth of thymus
Antimineralocorticoid	renal function	rats	Na/K and water excretion

Progestins may exhibit several pharmacological actions that help determine their clinical potency:

- *Progestational activity:* conversion of the proliferative endometrium into the secretory phase and maintenance of pregnancy support.
- *Antiestrogenic activity:* downregulation of ER, reduction in estrogen-stimulated endometrial proliferation, and prevention of EH.
- *Antiandrogenic activity:* inhibition of testosterone binding to AR and antagonism of 5 α -reductase, thereby reducing the conversion of testosterone to dihydrotestosterone (DHT) and decreasing androgenic effects.¹¹

The biological action of progestogens in many tissues depends on the presence of estrogen, as estrogen is necessary for PR expression.¹⁵ Therefore, adequate estrogen priming is required for optimal progesterone responsiveness. When combined with estrogen, non-androgenic progestins do not inhibit the estrogen- induced increase in SHBG. As a result, circulating free androgens are reduced, which may provide beneficial effects such as improvement in acne and hirsutism.¹¹

In general, testosterone-derived progestins are more potent than progesterone and pregnane derivatives. Among testosterone derivatives, LNG is approximately 10–20 times more potent, while norgestrel is 5–10 times more potent than norethindrone (NET) in producing progestational effects such as delaying menstruation, inducing subnuclear vacuolization, and promoting glycogen accumulation within the endometrium. MPA exhibits greater potency than DYD, which in turn is more potent than natural progesterone.

Studies evaluating the biochemical and histological effects of orally administered progestogens on estrogen-primed endometrium, rather than universal receptor potency comparisons, have shown marked differences in relative potency at the endometrium. If the potency of NET is assigned a value of 1, LNG is approximately 8 times more potent. NETA is approximately 2 times more potent. MPA is about 10 times less potent. DYD is about 50 times less potent. P4 is approximately 500 times less potent than NET¹⁶. These differences in potency are clinically important when selecting appropriate progestins for contraception, menopausal hormone therapy, and endometrial protection.

Receptor Activities Of Progesterones In Order Of Potency¹⁶

- High progestational activity: 19-norpregnanes: trimegestone > Nestorone > nomegestrol acetate
- Antiestrogenic: 19-norpregnanes > gonanes
- Androgenic: gonanes > estranes
- Antiandrogenic: CPA > dienogest > drospirenone > trimegestone
- Antimineralocorticoid: DRSP > trimegestone
- Glucocorticoid: MPA acetate > gestodene

CLINICAL IMPLICATIONS

The potencies of progestogens shown in studies align with the dosages required for endometrial protection: 1 mg for NET, 2.5-10 mg for MPA, 5-10 mg for dydrogesterone, and 100-300 mg for micronised progesterone. The required doses and duration of progesterone to transform the estrogen-primed proliferative endometrium into a secretory state are indicated in Table 5.

The clinical effects of progestogens vary with dosage and route of administration. Different progestogens have unique pharmacokinetics, hormonal profiles, potencies, metabolic pathways, and, as a result, their specific effects on tissues. Refer to Table 6.

Table 5: Progesterone dose for transformation of the endometrium depending on sequential or continuous therapy

Progestin oral	Daily dose	
	Sequential	Continuous
Progesterone micronized	200-300	100
Dydrogesterone	10-20	5-10
Medrogestone	10	/
Chlormadinone acetate	10	/
Cyproterone acetate	1	/
Medroxyprogesterone acetate	5-10	2.5
Nomegestrol acetate	5	2.5
Promegestone	0.5	0.25
Trimegestone	0.25-0.5	/

Norethisterone	1	0.5
Transdermal		
Levonorgestrel	-	0.02 mg
Norethisterone	0.25 mg	0.125 mg
Vaginal		
Progesterone	200 mg	100 mg
Intrauterine		
Levonorgestrel		0.02 mg

Table 6: Pharmacological properties of progestogens

Effect	Studies	Dydrogesterone	Testosterone and 19-nortestosterone derivatives	Progestogen	Natural Progestogen
Blocking of ovulation	Human	-	+	+	+
Estrogenic	Human/animal	-	+	-	±
Androgenic	Animal	-	+	+	-
Masculinization of fetus	Animal/ Human	-	+	+	-
Relaxation of uterine tissue	Animal/ Human	+	-	±	+
Adrenal atrophy	Animal	-	+	+	-
Thermogenicity	Human	-	+	+	+
Blood clotting	Human	-	+	+	-
Blood lipids Human - + - -, +, effects; -, no effect; ±, equivocal					

ROUTE OF ADMINISTRATION

Progesterone can be taken through various methods, including orally, vaginally, rectally, intrauterine, transdermally, intramuscularly, and via subcutaneous implants. There are significant differences in the performance of progestogens when given via oral, transdermal, parenteral, or vaginal routes. All oral progestogens undergo the hepatic first-pass metabolism. After ingestion and intestinal absorption, progestogens are transported via the portal vein directly to the liver, where they undergo enzymatic conversion into metabolites before entering the systemic circulation.

Some of these metabolites are known to cause side effects, such as drowsiness. The effectiveness of progesterone in oral form is considerably lower, requiring larger doses to achieve the desired effects. To enhance oral bioavailability and provide more potent, longer-lasting uterine effects than natural progesterone, synthetic analogues have been developed.⁷

Oral crystalline P4 is poorly absorbed, but when dispersed into finer particles, as in MP, bioavailability increases to 5%. MP undergoes rapid clearance from the circulation, so a daily or twice-daily dose is necessary. With the injection of 50

mg P4, serum luteal phase levels of P4 are achieved, whereas in transvaginal MP 200 mg achieves lower serum levels, and endometrial tissue P4 concentrations are higher. In the Early Versus Late Intervention Trial With Estradiol (ELITE), however, P4 gel at a 45 mg per day dose given for 10 days each month with daily oral estradiol 1 mg was inadequate for prevention of endometrial hyperplasia. Higher doses, such as P4 gel 90 mg per day or longer duration of therapy, may be needed.¹⁷ Intravaginal P4 capsules, when given with oral estrogens, do not demonstrate endometrial safety. Similarly, transdermal P4 cream is poorly absorbed, with serum levels 4 times lower than those in the luteal phase, and is inadequate to protect the endometrium.¹⁸ MPA and other progestogens, such as NETA and DRSP, are well absorbed orally, with half-lives ranging from 8 to 32 hours.

Advantages and Disadvantages of Different Routes⁷

Oral: Convenience, drowsiness, flushing, nausea, sedative and hypnotic effects, fluid retention after oral ingestion, influenced by food uptake

Vaginal: Discharge, irritation or local warmth. Progesterone absorption from the vaginal epithelium is enhanced after vaginal estrogenization. Progesterone absorption is affected by the formulation used, such as tablets, suppositories, creams, oil-based solutions, or the recently released polycarbophil gel.

Intramuscular Injection: Progesterone injection is uncomfortable. Main concern for patients with ovarian failure in oocyte donation programs, who are in need of a long-term treatment for pregnancy support, may lead to marked inflammation at the injection site, resulting in redness, pain and even sterile abscess.

INDICATIONS FOR PROGESTERONE USE IN HORMONE THERAPY

Endometrial protection: Progestins, along with estrogen, can be used in postmenopausal women with an intact uterus to relieve the symptoms associated with menopause (vasomotor symptoms or genitourinary symptoms) and to prevent osteoporosis. 19-norpregnane derivatives have the greatest potency, followed by MPA, DYD, and MP, in preventing estrogen-induced endometrial hyperplasia. Earlier, MHT was given sequentially, but due to breakthrough bleeding, continuous combined treatment was prescribed to women who did not wish to bleed. Continuous combined treatment has been shown to provide superior endometrial protection compared with sequential treatment.¹⁹ P4 and progestins with or without estrogen are often used to correct irregular bleeding & have also been used for the treatment of gynaecological conditions, including abnormal uterine bleeding, oligomenorrhea, polymenorrhea, hypermenorrhea, dysmenorrhea, secondary amenorrhea, and endometriosis, as well as in MHT, mainly due to its endometrial effects.

Regular progestin supplementation is mandatory to reduce the risk of estrogen-induced hyperplasia.^{20,21} However, the effect depends primarily on the treatment duration; at least 10–14 days per cycle is necessary to achieve sufficient protection.^{19,22} The appropriate dose for either sequential or continuous combined therapy depends on the estrogen dose, the route of administration, the progestin potency, and the duration of the progestin addition.²³ In continuous combined preparations, a lower dose of progestin might be sufficient for endometrial protection compared with sequential formulations.^{20,24} Progestogens with higher androgenic and glucocorticoid activity may interfere with lipid profile and glucose tolerance. If P4 use is required, MP is considered the safer option. When compared with MPA, it has better outcomes in cardiovascular effects, blood pressure, venous thromboembolism (VTE), stroke, and breast cancer.^{25,26,27} A proper clinical evaluation, choosing an adequate dose, and selecting an estrogen/progestin combination are important to maximise the beneficial effects of MHT, especially if given within a reasonable time after menopause to women who need the therapy for relief of menopausal symptoms.²⁸

Hot Flashes: High-dose progesterone derivatives, such as MPA or megestrol acetate, can effectively reduce hot flashes. A 12-week randomised trial involving postmenopausal women demonstrated that the occurrence of daily vasomotor symptoms showed a significantly greater improvement with 300 mg/day of oral progesterone compared to a placebo.

Bone: Progestins such as NETA and tibolone have been shown to improve bone mineral density and offer protection against osteoporosis.²⁹ Progesterone also plays a role in bone formation. The processes of resorption and bone formation require hormones such as estradiol and progesterone, as well as bone-forming cells, such as osteoblasts. Progesterone increases the process of bone formation by stimulating P-4-receptor-mediated osteoblastic growth during the initiation of bone modelling.³⁰

Skin and hair: Progestins with antiandrogenic properties, such as CPA, dienogest, and DRSP, can bind to the AR, reducing its interaction with endogenous androgens. This may help alleviate the signs of relative hyperandrogenism

observed during menopause. This could account for the positive effects of NET-containing ointments on acne. Topical applications of CPA have been noted to improve acne, similarly to oral treatment with a combination of EE and CPA.²⁹

Central nervous system and mood: Natural progesterone, aside from its antagonistic effects on estrogen, has a unique influence on the central nervous system, producing sedative effects. These effects are primarily mediated by progesterone metabolites that may interact with Gamma-Aminobutyric Acid (GABA) receptors. Research indicates that MPA may diminish the beneficial impact of conjugated equine estrogen (CEE) on mood and other psychological symptoms in postmenopausal women.

Although progesterone is primarily associated with the reproductive system, it also plays a functional role in the neuroendocrine axis. Progesterone may exhibit neuroprotective effects in both the central and peripheral nervous systems, affecting myelination processes and regulating astroglial plasticity. Additionally, progesterone promotes neuronal survival in neurodegenerative diseases, such as amyotrophic lateral sclerosis. These effects are due to the expression of progesterone receptors located throughout the nervous system.³¹

*Contraception:*³² The first generation of 19-nortestosterone derivatives had androgenic side effects. Later, potent anti-androgenic progestins became available. The most potent antiandrogenic progestins are cyproterone acetate, dienogest, drospirenone, and chlormadinone acetate. These molecules are antagonists of 5 α -reductase, and they also block T from binding to AR, decreasing the androgen's effect. DRSP, an analogue of spironolactone, has anti-mineralocorticoid and anti-androgenic effects and has the potential to reduce blood pressure and low-density lipoprotein (LDL) levels, while enhancing high-density lipoprotein (HDL) levels.²⁶ Progestins are used for the start of contraception in the postpartum period, since women can restart their sexual life in the first weeks postpartum, and with the use of these contraceptives, an increased risk of stroke, myocardial infarction, or deep vein thrombosis has not been identified. In addition, their administration during lactation has not been reported to affect milk volume or composition or to have any adverse effects on the infant. These contraceptives should be started within the first three weeks postpartum to maximise their effectiveness.^{33,34}

Progesterones in endometriosis: The effectiveness of progestins in treating endometriosis is due to their growth-inhibiting actions, induction of anovulation, inhibition of blood vessel growth, and anti-inflammatory actions.³⁵ As was mentioned above, progestins are effective at resolving pain caused by endometriosis; the suggested mechanisms are reducing the estrogen synthesis, inhibiting the enzyme aromatase, decreasing inflammation and neoangiogenesis and causing endometrial atrophy.³² Currently, only some progestogens are recommended for the treatment of endometriosis: MPA, dienogest, DYD, and NETA.

Endometriosis in a young woman with uterus: The current recommendations are to use combined contraceptives as the first choice, preferably with the lowest possible amount of ethinylestradiol (EE) 10–20 mcg, to choose cyclic combinations over continuous regimens,³⁷ and to use progestins alone as a second line when the combination of estrogens and progestins is not effective or not tolerated. Progestins in intrauterine devices should be considered a second or third line treatment.³⁵ Treatment must be individualised depending on the formulations available in each country.

Progesterone in Hysterectomized Women in MHT: Typically, women who have undergone a hysterectomy should receive estrogen only, without the need for progesterone. Is there ever a reason to provide progesterone to women post-hysterectomy? Certain specific circumstances do justify using a combination of estrogen and progestin for women following a hysterectomy.³⁶ In cases of endometriosis, unopposed estrogen can exacerbate any remaining disease, and there have been instances of adenocarcinoma developing in patients with pelvic endometriosis. Therefore, progestogens have a role in treating residual endometriosis after surgery, with the likelihood of reactivating residual endometriosis being significantly lower in hormone-treated postmenopausal women compared to those who do not undergo hormone therapy. Both MP and DYD have been proven effective in alleviating symptoms of endometriosis. Tibolone serves as a viable alternative.

For those who have been treated for stage I or II endometrial adenocarcinoma, a combined estrogen and progestin approach can be utilised. This is advised due to the potential protective effects of the progestational agent. Treatment may commence in the immediate postoperative period.³⁶ The combined approach using estrogen and progestin may be utilised for individuals who have previously been treated for endometrioid ovarian tumours. Given the various progesterone classes, it is prudent to adhere to prescribing guidelines for each specific molecule. In choosing a progestin and treatment regimen, the ideal progestin for hormone therapy should promote endometrial atrophy while preserving the estrogen-driven advantages for bone health, vascular system, and central nervous system.³⁸

SELECTION OF PROGESTERONE AND REGIMENS

There is no agreement on the ideal type of progesterone or treatment regimen. By personalising the type of progestin, method, or regimen, healthcare providers can help preserve the benefits of estrogen and progesterone while minimising side effects. Currently, there is a growing preference for using MP and DYD.

Typically, for sequential-combined hormone therapy, the progestogen phase should last a minimum of 10 days, ideally between 12 and 14 days each cycle to ensure adequate endometrial protection. Continuous combined regimens should only be administered to postmenopausal women. There is limited observational data regarding the combination of progesterone with transdermal estrogen. When using transdermal estrogen, any progestogen in sufficient dosage and duration needs to be added separately as either an oral preparation, vaginal application, or the LNG-IUD.

The progestogen dose in MHT required to avoid the risk of EH depends on its potency; some authors have concluded that 19-norpregnane derivatives are the most potent, followed by MPA, DYD, & MP. Molecular differences among progestogens account for their distinct clinical effects. Common side effects include fluid retention, bloating, breast tenderness, headaches, mood changes, and nausea.³⁹ Furthermore, all synthetic progestins used for MHT attenuate some or all of the beneficial estrogen-related increases in HDL as a result of androgen-mediated increases in hepatic lipase activity and increased degradation of HDL. To prevent HDL reduction, lowering the dose or the androgenicity of the progestin component of MHT has been proposed.²⁴

Impact of Progesterone on Organ Systems

Cardiovascular System: Menopause is associated with hormonal, psychosocial, and physiologic changes that manifest as vasomotor symptoms, sleep disturbances, mood changes, and metabolic alterations. These negatively impact quality of life and are a risk for future cardiovascular disease (CVD).^{40,41} Worsening cardiovascular (CV) risk factors during the menopausal transition (MT) accelerate atherosclerosis.⁴⁰ Menopausal women may present with elevated blood pressure, central adiposity, insulin resistance, deranged lipid profiles, and subclinical atherosclerosis, as measured by coronary artery calcification (CAC) score and carotid intima-media thickness (CIMT).

MHT demonstrates variable effects depending on formulation and timing, with oral estrogen often improving lipid profiles and lipoprotein a [Lp(a)] levels, but without a clear reduction in cardiovascular events. Transdermal formulations tend to have more favourable effects on blood pressure and metabolic risk, though stroke and thrombotic risks remain formulation- and dose-dependent. The increase in risk for atherosclerotic cardiovascular disease (myocardial infarction and stroke) is age-related; there is an accelerated increase in the incidence of CVD after menopause.^{42,43}

Systemic estrogen and progesterone: Combined MHT carries a higher CVD risk than estrogen-only MHT.⁴⁴ Indicating that progesterone plays a role in adverse outcomes, including elevated stroke and venous thromboembolism risk with elevation of very low density lipoprotein (VLDL) and C-reactive protein (CRP).⁴⁵ MPA has been shown to negate the beneficial LDL-lowering effects of estrogen.⁴⁶

Natural vs synthetic progesterone: Older synthetic progesterone formulations, such as MPA, MNET, LNG and DRSP, as used in the Women's Health Initiative (WHI) and Heart and Estrogen/Progestin Replacement Study (HERS), can lower HDL by 8–18%. MP and DYD, in contrast, have no effect on HDL. Natural progestin also had a lower VTE risk compared with synthetic progestin.^{46,47,48}

Randomised clinical trials (RCT), particularly the WHI⁴⁹ and the HERS,⁵⁰ indicated a significantly elevated risk associated with estrogen combined with a progestogen (EPT). Observational studies have demonstrated that estrogen therapy (ET) has positive effects on various aspects of CVD⁵¹. In MHT that includes combination treatment, the androgenic progestogens diminished the positive effects of estrogens. It is advisable to choose a metabolically neutral progestogen for EPT, such as micronised progesterone or dydrogesterone, to preserve higher plasma HDL cholesterol levels. Research involving animals showed that progestins with greater androgenic activity reduce the beneficial effects of estrogens on vasodilation; however, progesterone and 19-norpregnane derivatives have milder negative effects.⁵² A longitudinal retrospective study involving 313 women divided into three groups was conducted: group 1 not using MHT, group 2 receiving only 1 mg of 17%-estradiol continuously, and group 3 administered 1 mg of 17%-estradiol with 10 mg of DYD. The Framingham score was assessed at baseline and again after 1 and 2 years. Both hormone therapy groups demonstrated an improvement in the Framingham score after just one year, with the

reduction being greater in the combination treatment group. This indicates the additional beneficial effect of dydrogesterone on markers of CVD. Likewise, a 12-week RCT with micronised progesterone showed no alterations in any of these variables or the Framingham General Cardiovascular Risk Profile.⁵²

It's worth noting that in the subgroup analysis of women aged 50–59 years in the WHI, CEE alone was associated with a reduced risk of CHD, whereas CEE plus MPA showed a trend toward increased CHD risk. The ELITE investigated the use of oral estradiol in combination with vaginal progesterone in women who were either less than 6 years or more than 10 years post-menopause. MHT was associated with reduced progression of subclinical atherosclerosis, as measured by CIMT, when initiated within 6 years of menopause. However, this benefit was not observed when MHT was initiated 10 years or more after menopause.⁵³ Currently, most clinical guidelines do not recommend MHT for primary or secondary prevention of CVD. However, the International Menopause Society has proposed that in women under the age of 60 years old, who are recently menopausal and without a history of CVD, the initiation of estrogen-alone therapy can reduce the risk of CHD and all-cause mortality.⁵⁴

Effect on Lipids: Menopause heralds a decline in HDL-C and an increase in total cholesterol (TC), LDL-C, VLDL-C, triglycerides (TG), and Lp (a), all of which are strongly predictive of an increased risk of CVD.⁵⁵ The type of steroids chosen and how they are administered can lead to various effects on lipids and lipoproteins in MHT. The effects on lipids and lipoproteins vary more based on the androgenic properties of progestins. Androgenic progestins, like norgestrel, enhance hepatic lipase activity and negate the HDL-raising benefits of estrogen. However, androgenic compounds also reduce Lp(a), which may have a favourable impact.⁵⁶

Venous thromboembolism: risk in postmenopausal women undergoing MHT is influenced by the method of estrogen administration and the specific type of progestin utilised. Different progestins carry varying risks for VTE. Treatment with progestogens that possess glucocorticoid effects, such as MPA and gestodene, may therefore promote thrombin-induced activation of tissue factor, thereby enhancing procoagulatory and vasoconstrictive responses in damaged arterial walls.⁵⁷

In a French cohort study, researchers found that oral estrogens, unlike transdermal ones, were linked to a heightened risk of thrombosis, with a hazard ratio (HR) of 1.7; 95% CI 1.1–2.8, compared to HR 1.1; 95% CI 0.8–1.8 for transdermal. There was no notable association found for progesterone, with an HR of 0.9 (95% CI 0.6–1.5), and for pregnane, an HR of 1.3; 95% (CI 0.9–2.0), or for nortestosterone derivatives, which had an HR of 1.4; 95% CI 0.7–2.4). Nevertheless, it appears that using transdermal estradiol, alone or in combination with natural progesterone, does not increase thrombotic risk.⁵⁸ A systematic review from 2016 examined nine studies involving 52-mg LNG-IUS in women with high-risk factors such as SLE, hypertension, smoking, thrombophilia, and a history of VTE, concluding that there was no statistically significant increased risk of VTE.⁵⁹ A large observational study, based on the UK general female population aged 40–79, provides information on VTE risk in women taking different types of MHT. This study showed increased VTE risks for all oral HMT formulations, including combined and estrogen-only preparations. Overall, preparations containing conjugated equine oestrogen were associated with a higher risk than preparations containing estradiol. Conjugated equine oestrogen with medroxyprogesterone acetate had the highest risk, and estradiol with dydrogesterone had the lowest risk. Higher doses of oestrogen were associated with higher VTE risks. Transdermal HRT was not associated with increased VTE risk, and this finding was consistent across regimens.⁶⁰ MP and DYD might have a better risk profile than other progestogens. Major surgery under general anaesthesia, including orthopaedic and vascular leg surgery, is a predisposing factor for VTE, and it may be prudent to stop MHT 4–6 weeks before surgery and restart it only after full mobilisation. If MHT is continued or if discontinuation is not possible, VTE prophylaxis is advised.⁶¹

Stroke: Hypertension poses a significant risk for coronary heart disease and stroke. MP appears to have either a neutral or a positive impact on blood pressure in postmenopausal women. Unlike other progestogens, progesterone has been demonstrated to counteract the effects of aldosterone, promoting natriuresis and lowering blood pressure.⁶² In the more extensive randomised, double-blind, placebo-controlled postmenopausal estrogen/progestin interventions (PEPI) study, the combination of micronised progesterone with CEE did not alter blood pressure (n = 178).⁶³ A one-year randomised controlled trial examined the effects of a low dose of 1 mg 17 β -estradiol and 10 mg dydrogesterone on 24-hour ambulatory blood pressure in hypertensive postmenopausal women, revealing a significant decrease in blood pressure during both the day and the night. Van Ittersum used sequential low doses of 1 mg 17 beta-estradiol and 5 mg DYD and reported a similar reduction in blood pressure.⁶⁴

Breast: PR is present in several tissues, including the breast, blood vessels, brain, and bone, resulting in effects beyond

the uterus. The Ki-67 marker signifies that breast cell division peaks in women during the midluteal phase, coinciding with the highest progesterone levels. These findings are consistent with clinical data showing an increased risk of breast cancer in women who take daily progestogens compared to those who receive them intermittently or sequentially.⁶⁵

In the WHI trial, the relative risk (RR) of breast cancer associated with CEE and MPA was found to be 1.26. The Million Women Study reported an increase in RR for breast cancer associated with the use of MHT in both continuous and combined regimens, though no differences were observed among various types of progestin. According to the French E3N cohort study, the link between MHT and breast cancer risk differed significantly based on the specific progestin used: the RR was 1.00 (95% CI 0.83–1.22) for estrogen–progesterone, 1.16 (95% CI 0.94–1.43) for estrogen–DYG, and 1.69 (95% CI 1.50–1.91) for estrogen combined with other progestins. Nonetheless, the overall risk, which is approximately a 30% increase, does not appear to affect mortality. The use of progestogens increases mammographic density, though this change will revert after discontinuation. Additionally, breast discomfort and pain may be heightened with progestogen use.⁶⁶ MHT risk for breast cancer was directly proportional to the duration of use, and in some studies, the risk increased from the first 3 years of use. Depending on progesterone or progestogen, several studies have agreed that MP and DYG were associated with a lower to zero risk for breast cancer, compared to other progestogens, while the risk increased significantly for testosterone-related progestogens, rather than progesterone-related progestogens.

Both progesterone and synthetic progestins, as well as the dosing regimen, may impact breast cancer risk. As regards the method of administration, the continued use of MHT increased the risk of breast cancer, compared to sequential use. The route of administration of hormone therapy, oral, vaginal, or transdermal, did not differentiate the risk of breast cancer.^{67,68} In the E3N cohort study, MHT regimens containing estrogen and MP and DYG were not associated with a statistically significant increase in breast cancer risk. All other progestins were associated with an increased risk, with no difference between them.⁶⁹ The results of this meta-analysis (which includes the E3N study) are consistent with these findings and show a decreased risk of breast cancer associated with the use of progesterone compared with a progestin (RR = 0.67 (95% CI 0.76–0.81)).⁷⁰

Uterus: EH serves as a surrogate indicator for the progression to endometrial cancer, transitioning from benign EH to atypical forms and eventually cancer. Even at high doses of progestogens, a complete secretory transformation is not achieved in all women receiving estrogen treatment. It is important to understand that, in MHT, the purpose of adding progestogens to estrogen replacement therapy is not to induce secretory transformation, but to prevent EH. The formulations approved for oral or injectable MHT ensure that the EH incidence remains below 2% for 1 to 2 years of treatment. Thus, the formulations of the preparations used in hormone therapy vary depending on the route, type, and dosage of both estrogen and progestogen. Generally, in sequential regimens, the number of days with added progestogen is more critical than the progestogen dose, and the dose required for endometrial protection is typically lower in continuous combined therapies than in sequential or cyclic treatments. MHT can be a risk factor or a protective factor, depending on the regimen used.^{71,72} Unopposed oral ET has an annual EH incidence of 85–53%, depending on type, dose, and duration. Furthermore, adding progestin in an adequate suppressive dose and for a sufficient duration, whether combined cyclically or continuously with estrogen, can reduce the risk of endometrial cancer to the expected level of women who do not take MHT. In some studies, it may even lower the risk to levels below expectations.⁹ In the same research, for those using EPT for less than 5 years, the odds ratio for sequential EPT was 0.67 (95% confidence interval 0.52–0.86), for continuous EPT it was 0.45 (0.27–0.73), and for the estradiol plus levonorgestrel-releasing intrauterine device system (LNG-IUS) it was 0.39 (0.17–0.88). A lower risk was observed with continuous EPT and with estradiol plus LNG-IUS use, even after up to 10 years.⁷³

PROGESTERONES IN MHT

Progesterone: Progesterone shows progestogenic and antiestrogenic activity in the endometrium and has no androgenic effects. Therefore, it has a neutral effect on lipid metabolism. The attenuation of the favourable effect of estrogens on the lipid profile is associated with the androgenic activity of progestogens.

Micronised Progesterone: MP demonstrates a lower risk of breast cancer and CVD risk as compared to synthetic progestins. Observational studies of the French E3N cohort of 78,353 menopausal women reported no significant increase in breast cancer in those using estrogen plus MP for fewer than 5 years (hazard ratio [HR], 1.13; 95% confidence interval [CI], 0.99–1.29).⁷⁴ For women using HT for more than 5 years, the associated risk was significantly increased (HR, 1.31; 95% CI, 1.15–1.48). The Postmenopausal Estrogen/Progestin Intervention Trial (PEPI) examined

the effects of MPA 10 mg versus MP4 200 mg, given cyclically with CEE 0.625 mg, over 3 years. MP had the most favourable HDL cholesterol profile compared with the MPA groups. With the hepatic first-pass effect, oral MP is partially converted to 20 α -dihydroxyprogesterone (ie, allopregnanolone), a neuroactive steroid that binds to the GABA-A receptor, inducing sedation.⁷⁵ This can be advantageous because oral MP at 200-300 mg per day can help with sleep when taken at night.⁷⁶

In continuously combined MHT, oral MP at 50–200 mg/day has been shown to protect the endometrium for up to 1 year. In sequentially combined MHT, oral MP at 100–400 mg/day has been shown to protect the endometrium for up to 3 years. Vaginal MP at 45 mg/day has been shown to be not protective for the endometrium if applied in a sequentially combined MHT regimen. There is insufficient data to support the use of intramuscular or transdermal MP for endometrial protection in combined MHT.

Dydrogesterone: DYD is an orally active progestogen that is chemically and biologically very similar to natural progesterone.⁷⁸ As a consequence, DYD has potent progestogenic and antiestrogenic activity, but without any estrogenic, androgenic, antiandrogenic, or glucocorticoid activity.⁷⁹ The data suggested that continuously applied DYD in MHT did not diminish the beneficial effects on lipid metabolism induced by estrogens. Overall, when given in combination with estrogen, DYD does not have a large impact on estrogen effects. This is especially true for the increase in HDL-C and reduction in LDL-C caused by estrogen, which persisted when combined with DYD.⁸⁰ DYD and oral E2, four studies of 1–2 years' duration (n = 27, 151, 188 and 579) showed that sequential combinations of E2 2 mg/day plus DYD 10 or 20 mg/day for 14 days per cycle or E2 1 mg/day plus DYD 5 or 10 mg/day for 14 days provided endometrial progestational success rates of at least 97% (comprising atrophic, inactive or secretory endometrium or insufficient sample for analysis).⁷⁷ In continuously combined MHT, oral DYD at 2.5–20 mg/day has been shown to protect the endometrium for up to 1 year. In sequentially combined MHT, oral DYD at 2.5–20 mg/day has been shown to protect the endometrium for up to 2 years.⁷⁸

Medroxyprogesterone acetate was the most commonly used progestin in the US until the results of the WHI trial indicated that CEE + MPA increased the risk of cardiovascular disease and thromboembolism compared with CEE alone.⁴⁴ In the PEPI trial, the most favourable effect on HDL-C concentrations was observed in women taking unopposed estrogen. Adding MPA diminished many of the benefits of estrogen.⁸¹ Consistent with the PEPI trial results, many other studies have also reported attenuating effects of MPA on blood lipids, especially HDL-C.^{82,83}

Newer Progesterones For Menopause Hormone Therapy

Dienogest: a 19-nortestosterone derivative, is the only progestogen that combines properties of both 17-hydroxyprogesterone and 19-nortestosterone. The strong progestational effect of DNG on the endometrium has been demonstrated in clinical studies that control for endometrial safety by endometrial biopsy in postmenopausal women treated with estrogen in combination with DNG, comparing estradiol valerate/DNG with estradiol/norethisterone acetate over 12 cycles. DNG itself or in combination with estradiol valerate has no negative effect on lipid or carbohydrate metabolism. DNG does not interfere with the vascular system (arterial and venous). Therefore, DNG is suitable for clinical application in perimenopausal and postmenopausal women.

Drospirenone: A derivative of 17-spirolactone, a potent aldosterone antagonist, acts on mineralocorticoid receptors to prevent sodium retention and thus reduces estrogen-related sodium and water retention (viarenin-angiotensin-aldosterone system). Drospirenone is two to four times more potent as a progestin compared with progesterone itself. This guarantees a non-bleeding condition and endometrial protection for users of a drospironone and estradiol combination for the treatment of menopause. The antiandrogenic effect of DRSP counteracts the negative effects on lipid changes, insulin, and body composition, lowers total and very-low-density lipoprotein cholesterol, maintains HDL and triglyceride levels, lowers BP in hypertensive women, and reduces body weight, waist circumference, and waist-to-hip ratio.⁸⁴⁻⁸⁶ For low-dose continuously combined MHT containing E2/DRSP, endometrial safety has been proven in postmenopausal women for up to one year.⁷²

A retrospective analysis revealed that continuous, long-term treatment with DRSP 2 mg/E2 1 mg notably reduced 24-hour systolic BP and diastolic BP, consequently lowering the risk of CVD in early menopausal women with stage 1 hypertension.⁵⁷ This underscores the potential cardiovascular benefits of timely MHT in postmenopausal women.⁸⁷ It is available as an oral estrogen progestogen combination for menopause therapy (1 mg estradiol plus 0.5 mg DRSP, and 0.5 mg estradiol plus 0.25 mg DRSP). For low-dose continuously combined MHT containing E2/DRSP, endometrial safety has been proven in postmenopausal women for up to one year.⁷²

Norethisterone acetate: After oral ingestion, NETA is rapidly hydrolysed into norethisterone (NET) by esterases during intestinal and first-pass hepatic metabolism.^{88, 89} Both NETA and NET compounds are structurally related to testosterone. NETA exhibits strong tissue-specific progestogenic, estrogenic, antiestrogenic and androgenic effects.¹⁶ Kwok et al.⁹⁰ examined the effect of MPA and two other progestogens, the less androgenic desogestrel and the more androgenic NET, on CV risk factors when combined with estrogen therapy. They found that all the progestogens tested in the study significantly reduced HDL-C levels. NET was associated with the greatest reduction in HDL-C and in TG. The evidence from these studies indicated that NETA is a unique progestin that exerts both estrogenic and androgenic properties. It reverses the beneficial effect on HDL but also favourably influences the TG, VLDL, LDL subfractions, and Lp(a).

Nomegestrol acetate: Nomegestrol acetate is considered to be a “new” progestin. It acts as a selective, high-affinity full agonist of the progesterone receptor, conferring greater progestational potency than MPA.⁹¹ Consistent with this, nomegestrol acetate is a potent antigonadotropin but is completely devoid of androgenic effects on male accessory sex organs.⁹² In a double-blind, randomised, prospective, three-cycle study of 57 non-hysterectomized women with natural menopause, the effects of estradiol plus nomegestrol acetate (1.5 mg or 3.75 mg) or placebo on CV risk factors were evaluated. Both the high- and low-dose estradiol plus nomegestrol acetate combinations had favourable effects on plasma lipids and lipoproteins, including significant reductions in LDL-C and Lp(a). The increase in HDL-C was not statistically significant.⁹³ These results are in agreement with other studies, which showed no clinically relevant changes in TC, HDL-C, LDL-C, or TG⁹⁴; additionally, LDL levels were significantly decreased, and the LDL: HDL ratio was reduced by 10%.⁹⁵ Altogether, these results suggest that nomegestrol acetate, a 19-norprogesterone derivative with potent progestational activity and no androgenicity, does not counteract the effect of estrogen on lipoprotein concentration.

Intrauterine LNG: provides endometrial protection in combined MHT for up to 2 years. Compared with NETA and intrauterine LNG, fewer studies assess endometrial safety for oral/transdermal LNG, DNG, GSD, DSG, and NGM.

ANDROGENS

The major circulating androgens in females are dehydroepiandrosterone (DHEA), its metabolite DHEA sulphate (DHEAS), androstenedione, testosterone, and dihydrotestosterone (DHT). DHEA, DHEAS and androstenedione are considered pro-hormones as they require conversion to testosterone to exert an androgenic effect. DHEAS is produced almost exclusively by the adrenal glands and is peripherally converted to DHEA. Around half of DHEA production comes from the adrenal glands, 20% from the ovaries, and the remaining from the conversion of DHEAS.

The primary sources of circulating androgens, including testosterone and 5-dihydrotestosterone (DHT), in women are the adrenal glands and ovaries. The adrenal gland predominantly produces dehydroepiandrosterone (DHEA), which serves as the precursor hormone in human circulation, along with its sulfated form, dehydroepiandrosterone sulfate (DHEAS). Unconjugated DHEA acts as a precursor for sex steroids, amounting to 50% testosterone production, the rest coming from the ovaries and adrenals.

In the adrenal glands, ovaries, & peripheral target cells, DHEA can be converted to androstenedione and testosterone; both can further be converted to estrogens, with estrone (E1) being the most commonly secreted estrogen. Consequently, an increase in testosterone levels will also raise estrogen levels. Testosterone is further converted into the more potent androgen DHT. Testosterone has direct action via androgen receptors (AR). It also acts through its conversion to DHT via 5 α -reductases 1 and 2 present in target cells, including skin, sweat glands, hair follicles and genital skin, and by aromatisation to estradiol. Aromatase is present throughout the body, including the brain, bone, adipose tissue, skin, vasculature, vagina, breast and ovary.⁹⁶

The relative androgenic potency of DHEA, androstenedione, testosterone, and DHT are roughly 5:10:100:300, respectively.⁹⁷ Along with being the most potent, DHT has the highest affinity for the AR.

In women, only around 1% of testosterone is free or unbound. 66% is bound to sex hormone binding globulin (SHBG) and 33% weakly bound to albumin.⁹⁸ It has long been thought that the androgenic effects of testosterone relate mainly to the amount of free testosterone. The relatively small proportion of testosterone available to bind to the androgen receptor is a complex combination of free (unbound) testosterone, a portion weakly bound to albumin, and testosterone produced locally at the cellular level from its precursors.⁹⁹ The free fraction of testosterone is determined by the level of SHBG and the balance between production and clearance.¹⁰⁰

Androgen Levels

During a woman's reproductive years, testosterone and estradiol are primarily produced by the ovary, with some contribution from the adrenal gland. After menopause, the postmenopausal ovary continues to produce a significant amount of androgens. This occurs due to an increase in luteinizing hormone secretion following menopause, which stimulates steroid production in ovarian hilar and stromal cells.

Endogenous Androgens In Women Beyond Menopause

After menopause, the principal steroid secreted by the ovary is androstenedione. Total androstenedione levels decline after menopause, and most androstenedione is produced by the adrenal glands. Similarly, circulating levels of DHEA and DHEAS are lower than those seen in young adulthood.¹⁰¹⁻¹⁰³ In the early post-menopausal period, the ovary secretes more testosterone than in the premenopausal years.¹⁰⁴ Despite the increase in ovarian testosterone production, overall production is lower as there is less androstenedione available for peripheral conversion to testosterone. The peak levels of DHEAS and androstenedione occur during the early reproductive years and decline with age. By the age of 70-80 years, serum DHEAS concentrations can decrease to 10–20% of those in young adults.

Measuring female testosterone levels is challenging due to low plasma concentrations and cross-reactivity with the concurrent presence of steroids. In women, only approximately 1–3% of unbound testosterone circulates freely in the blood; the remainder is bound to SHBG (65–75%) and albumin (25–35%). The bioavailable testosterone is the free testosterone and the weakly bound albumin fraction. Different methods are available to measure or calculate free testosterone or its surrogate. However, these measured levels depend on the quality of the total testosterone assay. Testosterone and SHBG levels can be used to calculate the free androgen index: $(\text{testosterone nmol/L} \times 100) / \text{SHBG nmol/L}$.

Role of Androgens in Women

Androgens are essential precursors of estrogen synthesis. Testosterone is an important factor for female sexuality, enhancing interest in initiating sexual activity and response to sexual stimulation. They also have an anabolic effect on the bone and muscle. Androgen receptors in women have been found in the ovary, breast, brain, muscle, fat, bone, liver and skin. AR activation in the brain is associated with greater well-being and with reduced anxiety and depression. DHEA also has neurosteroidal properties; it has anti- γ -aminobutyric acidergic action, and, hence, may have antidepressant potential. Androgens are thought to affect sexual motivation and desire, and low testosterone levels have been correlated with sexual infrequency.¹⁰⁵

Androgen Insufficiency

Testosterone therapy presents itself as a focused supplementary treatment for addressing hypoactive sexual desire disorder (HSDD) and associated symptoms in women experiencing menopause. The natural decline of testosterone occurs gradually with ageing, which leads to diminished libido, energy levels, and muscle mass by influencing androgen receptors (AR) in the brain, genital areas, and skeletal muscle. Using transdermal testosterone (off-label, at doses of 150–300 μg daily) improves sexual function by boosting arousal and the frequency of orgasms through dopaminergic & nitric oxide pathways, without significantly elevating serum testosterone levels beyond what is typically seen in premenopausal women.

A review conducted between 2019 and 2024 involving nearly 8,500 women indicated a notable enhancement in HSDD, with randomised controlled trials from 2024 verifying improvements in mood and cognitive function, including lower fatigue and better vulvovaginal health. The guidelines from the British Menopause Society (BMS) and International Menopause Society (IMS) recommend testosterone for postmenopausal women with HSDD who do not respond to other treatments, while suggesting monitoring for potential androgenic side effects such as acne or unwanted hair growth, which occur in less than 5% of cases. Some challenges include the lack of FDA-approved formulations for women, necessitating compounded products, as well as concerns about long-term cardiovascular risks; however, data collected from 2023 to 2025 indicate no harmful effects when doses are within physiological ranges. The free androgen index, calculated as total plasma testosterone divided by SHBG, is below the normal quartile in premenopausal women and is confirmatory of female androgen insufficiency.

Route of Administration

Transdermal patches: A recently launched female androgen patch in the USA for treatment of HSDD, and is indicated for use in hysterectomized women using estrogen who are distressed by low libido (European license in July 2006),

and topical gels or creams may be preferred over oral products based on their avoidance of first-pass hepatic effects documented with oral formulations. However, only oral and intramuscular testosterone products for women are currently government-approved, but they have a risk of overdosing

Relative contraindications: Androgenic alopecia, acne, hirsutism, hyperlipidemia and liver dysfunction.

Absolute contraindications: Presence or increased risk of breast cancer, endometrial cancer, venous thrombotic episodes and manifest CVD.

Caution: Testosterone preparations formulated for use in men should not be prescribed for women. Testosterone preparations for use in postmenopausal women are not available in India.

Androgen therapy in women

The principal androgen treatment used in women is testosterone. The only evidence-based indication for testosterone therapy in women is to treat hypoactive sexual desire disorder (HSDD) after menopause. The 2019 Global Consensus Position Statement on the use of testosterone therapy for women reported that available data support a moderate therapeutic effect of systemic testosterone for this indication only, and it is recommended only in doses that approximate physiological testosterone concentrations.¹⁰⁶ Treatment with testosterone should be considered a trial, as there is no way to predict who will benefit. If no improvement is seen after the first six months, therapy should be ceased. Recommendations are that baseline serum total testosterone and SHBG levels are measured prior to commencing therapy and repeated at 3–6 weeks. Concentrations should be monitored 6-monthly throughout use, to ensure supraphysiological levels are not reached.¹⁰⁶ A recent review of trials evaluating the effectiveness of testosterone in women with HSDD reported that transdermal therapy improved the frequency of satisfying sexual events, arousal, orgasm frequency, pleasure, responsiveness, and self-image, and reduced sexual concerns.¹⁰⁷ These studies reported few and were reassuring regarding short-term safety.¹⁰⁸ Vaginal testosterone cream, although not approved for use for any indication in women, has limited data supporting treatment of GSM symptoms.¹⁰⁹

VAGINAL DHEA

The 2019 Global Consensus Position Statement on the Use of Testosterone Therapy for Women advises that vaginal DHEA is an effective treatment for women with dyspareunia associated with GSM, but should not be used for women without this symptom.¹⁰⁶ The only approved androgen therapy for use in women is a vaginal DHEA cream (Prasterone) approved for use in the USA and Canada.¹⁰⁹ Use of Prasterone is associated with slight increases in circulating levels of DHEA, testosterone and which, nevertheless, remain within normal postmenopausal values. Serum steroid concentrations remain within normal postmenopausal values in women receiving daily 6.5mg intravaginal prasterone for 12 weeks.^{110,111}

SYNOPSIS

- Progestogen refers to any synthetic progestin or natural P4 with progestational effects. The preference for its use depends on the desired effect, whether as a contraceptive, for MHT, or for the treatment of endometriosis.
- The proper choice of progestins must be individualised according to the desired effects, as well as a patient's current diseases and CV risk
- Progesterone is mainly used to protect the endometrium in non-hysterectomized women. It is not routinely prescribed for hysterectomized women.
- Progestogens are effective for managing residual endometriosis after surgery and for early-stage endometrial adenocarcinoma. MHT in postmenopausal women shows negligible reactivation of endometriosis.
- MP and DYD are effective in reducing symptoms and are preferred in obese postmenopausal women due to their favourable metabolic profiles. Androgenic progestins like MPA and NETA may increase risks for breast cancer and coronary heart disease.
- The broad interpretation of female androgen deficiency syndrome has been criticised. Physiological menopause does not require routine androgen replacement, and DHEA is only recommended for adrenal insufficiency.
- Current guidelines advise against the widespread use of androgen therapy due to safety concerns. Transdermal testosterone use is approved in Europe but not by the FDA for women in the U.S., and such preparations are unavailable in India.

RESEARCH AGENDA

Association of micronised progesterone and drospirenone on lipid profile and DVT.

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TIBOLONE

Keywords: Mechanism of action, indications, contraindications, effect on various systems

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INTRODUCTION

Tibolone is a synthetic steroid used for the management of menopausal symptoms in postmenopausal women. It is rapidly metabolised into active metabolites with tissue-selective estrogenic, progestogenic, and androgenic effects, which underlie its ability to alleviate vasomotor symptoms (VMS), improve urogenital atrophy, and favourably influence mood and sexual function without the need for added progestogen in women with an intact uterus. Randomised controlled trials (RCTs) and systematic reviews demonstrate that tibolone reduces hot flushes and sweating, preserves bone mineral density (BMD), and improves overall quality of life (QoL) compared with placebo, though it tends to be less effective than conventional estrogen-progesterone therapy (EPT) for vasomotor relief.¹ The “selective tissue estrogenic activity” profile also yields low rates of vaginal bleeding and breast pain, and may enhance libido more than standard EPT regimens.² Safety considerations include evidence linking tibolone to higher risks of recurrent breast cancer in women with previous breast cancer and increased stroke risk in older women, findings that warrant careful patient selection and individualised risk-benefit assessment.² This chapter reviews the mechanism of action, clinical efficacy, and safety profile of tibolone, positioning it as a distinct and evidence-based therapeutic option in contemporary menopausal care.

MECHANISM OF ACTION

Tibolone is a synthetic steroid derived from 19-nortestosterone and is characterised by a unique selective tissue estrogenic activity regulator (STEAR). It exerts tissue-specific estrogenic effects by selectively modulating estrogen activity, thereby producing targeted clinical outcomes. Tibolone is often described as a “designer steroid” because its effects vary based on local metabolism and receptor expression in individual tissues.²

Unlike conventional menopause hormone therapies (MHT) that deliver exogenous estrogens and progestogens directly, tibolone primarily functions as a prodrug, undergoing rapid metabolic conversion into biologically active compounds with estrogenic, progestogenic, and androgenic properties. This selectivity underpins its therapeutic utility in postmenopausal women and distinguishes it pharmacodynamically from traditional EPT regimens.^{3, 4}

Following oral administration, tibolone is rapidly absorbed and extensively metabolised during first-pass hepatic processing and within peripheral tissues. It is converted into three principal active metabolites: 3 α -hydroxytibolone, 3 β -hydroxytibolone, and the Δ 4-isomer. The 3 α - and 3 β -hydroxy metabolites exhibit predominantly estrogenic activity through preferential binding to estrogen receptors (ERs), particularly ER- α and ER- β , and exert their effects mainly in bone, vaginal epithelium, and central thermoregulatory centres. Refer to flowchart 1. In contrast, the Δ 4-isomer demonstrates affinity for progesterone and androgen receptors (PR and AR), thereby mediating progestogenic effects in the endometrium and androgenic effects in the brain & other target tissues involved in sexual function and mood regulation.⁴⁻⁶

The tissue-selective mechanism of tibolone is largely determined by local enzymatic activity and receptor modulation. Differential expression of 3 α - and 3 β -hydroxysteroid dehydrogenases within tissues governs the relative formation of estrogenic metabolites, while sulfatase and sulfotransferase enzymes further regulate the local availability of active hormones.⁸ These enzymatic pathways ensure that estrogenic activity predominates in bone and the vaginal epithelium, whereas progestogenic activity is favoured within the endometrium due to local conversion to the Δ 4-isomer. Receptor distribution further refines this selectivity: ERs mediate skeletal preservation and vasomotor stability; progesterone receptors confer antiproliferative effects in the endometrium; and androgen receptors contribute to central nervous system effects such as enhanced libido and energy.⁶⁻⁸

At the tissue level, tibolone exerts clinically relevant estrogenic effects on bone by suppressing osteoclastic bone resorption and promoting maintenance or modest increases in BMD.⁹ These effects are predominantly mediated by the 3 α - and 3 β -hydroxy metabolites and are comparable to those observed with conventional estrogen therapy (ET).^{6,10} In the hypothalamus, estrogenic activation of thermoregulatory centres reduces VMS, including hot flushes

and night sweats. Similarly, in the vagina and lower urogenital tract, ER activation improves epithelial maturation, vascularisation, and lubrication, thereby alleviating symptoms of urogenital atrophy.^{2,11}

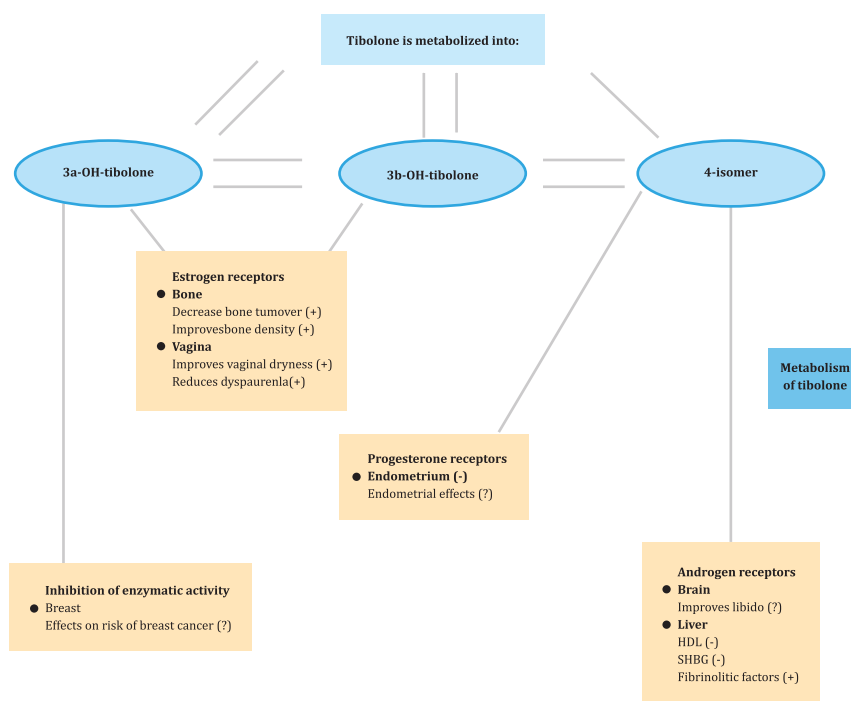
In the endometrium, tibolone demonstrates a distinctive protective mechanism. Local conversion to the $\Delta 4$ -isomer activates the progesterone receptor, which suppresses endometrial proliferation and generally prevents hyperplastic changes when the drug is used appropriately. This contrasts with unopposed estrogen therapy and explains why tibolone does not usually require the addition of a separate progestogen.³ In breast tissue, tibolone exhibits less estrogenic stimulation than conventional estrogen therapy. This effect is attributed to the inhibition of sulfatase activity and the stimulation of sulfotransferase enzymes, thereby limiting the conversion of estrone sulfate to the more potent estradiol (E2) in breast tissue and reducing local estrogen exposure.^{6,11,12}

Within the central nervous system, the combined estrogenic and androgenic actions of tibolone metabolites contribute to improvements in mood, sexual desire, and overall sense of well-being reported by many postmenopausal women. Emerging evidence also suggests that tibolone may exert neurosteroid-like effects by modulating Gamma-Aminobutyric Acid (GABA-A) receptors, which could partially explain its anxiolytic and mood-stabilising properties.^{2,3} In addition, experimental studies have demonstrated suppression of pro-inflammatory cytokine signalling within the vascular endothelium, although the clinical relevance of these anti-inflammatory effects, particularly with respect to cardiovascular outcomes, remains a subject of ongoing debate.^{13,14}

At the molecular level, tibolone and its metabolites modulate gene transcription by regulating tissue-specific expression of estrogen-, progesterone-, and androgen-responsive genes. This selective gene expression underlies the dissociation between its beneficial skeletal and vasomotor effects and the relatively limited proliferative stimulation observed in breast and endometrial tissues, supporting its classification as a tissue-selective menopausal therapy rather than a conventional systemic estrogen.^{3,6}

From a pharmacokinetic perspective, tibolone undergoes extensive hepatic metabolism, and circulating levels of the parent compound are minimal. The drug is excreted predominantly as conjugated metabolites, mainly in the sulfated form. Elimination occurs primarily via the faecal route, with a smaller proportion excreted in urine. Importantly, tibolone pharmacokinetics are largely independent of renal function, and dose adjustment is generally unnecessary in patients with renal impairment.³

In summary, tibolone acts as a prodrug that is converted into estrogenic, progestogenic, and androgenic metabolites in a tissue-dependent manner. This unique metabolic and receptormediated selectivity explains its ability to exert estrogen-like effects in bone and the urogenital tract, progestogenic effects in the endometrium, and androgenic effects in the brain within the same individual, thereby offering a distinct therapeutic profile among menopausal hormone therapies.^{6,12}



Flowchart 1: Tissue-specific effects of tibolone's metabolites

Indications For Use Of Tibolone

Postmenopausal women with vasomotor symptoms in whom tibolone might have added value:-

- with low sex drive, female sexual dysfunction (FSD)
- mood disorders or those receiving psychoactive treatments
- at risk of accelerated bone loss
- premenopausal breast tenderness or mastalgia
- with high breast density
- with fibroids, adenomyosis
- Women with urogenital complaints.

Women who might benefit from a switch to tibolone from hormone therapy (HT) include those who experience:

- An increase in breast pain despite HT dose adjustment
- Increased breast density that resulted in an unreadable mammogram
- Low libido, mood disorders and generalised body aches
- Women with premature ovarian insufficiency
- Women receiving long-term add-back gonadotropin-releasing hormone (GnRH) agonists for endometriosis, tibolone may be beneficial in relieving estrogen deficiency symptoms and preventing
- bone loss in these women.

Dosage and Administration

Tibolone is administered orally at 1.25–2.5 mg once daily, preferably at the same time each day, and should be swallowed with water or another beverage. Clinical improvement in menopausal symptoms generally begins within a few weeks, with optimal benefit typically achieved after at least 3 months of continuous therapy. Tibolone may be used uninterrupted for longer durations, provided that regular clinical reassessment is undertaken.

Tibolone at 1.25 mg or 2.5 mg/day, administered for 24 weeks to postmenopausal women, has demonstrated similar efficacy and safety profiles, with both doses being significantly more effective than placebo. The 1.25 mg dose is associated with a more gradual improvement in climacteric symptoms and a more rapid improvement in sexual function.^{15,16}

When to Start?

Women who experience natural menopause should start tibolone at least 12 months after their final spontaneous menstrual period. Initiating treatment earlier may result in irregular bleeding or menorrhagia.¹⁶ In cases of induced menopause, such as following bilateral oophorectomy, tibolone may be started immediately, as there is no risk of residual endometrial stimulation from ovarian hormone activity.

Initiation of tibolone after the age of 60–65 years or more than 10 years after menopause is generally discouraged because of an increased risk of stroke, and its use in older women should be individualised following careful risk–benefit assessment.^{3,4,9}

Switching from Conventional HT

When switching from another HT preparation in a woman with a uterus, the endometrium may already be stimulated, so inducing a withdrawal bleed with a progestogen is advisable.

Contraindications For Prescribing Tibolone

Undiagnosed genital bleeding in women over 60 years, women with risk factors for stroke, such as hypertension, smoking, diabetes and atrial fibrillation, pregnancy and lactation, known past or suspected breast cancer,¹¹ known or suspected estrogen-dependent malignant tumour, endometrial hyperplasia, previous or current venous thromboembolism (VTE) known thrombophilic disorders such as protein C, protein S or antithrombin deficiency,¹⁷

history of arterial thromboembolic disease, angina, myocardial infarction (MI), stroke or transient ischaemic attack (TIA), acute liver disease or abnormal liver function tests (LFT), porphyria.^{3,9}

Side Effects

As with most drugs, nausea is a common side effect on initiation of therapy, but it resolves within a few weeks. Breakthrough bleeding may also occur. It is best to initiate therapy after a minimum of 12 months of amenorrhoea.¹⁸ Patients should be counselled, and no investigations are required if spotting or slight bleeding occurs in the first 3 months of treatment. Breast tenderness may occur, but it is transient. Some patients experience excessive weight gain. Rarely, androgenic effects, such as increased hair growth, may occur.^{3,19}

Drug Interactions

Since tibolone may increase fibrinolytic activity, it may enhance the effect of anticoagulants. This effect has been reported with warfarin. Medicines that may reduce the blood level of tibolone, making it less effective, include rifampicin and antiepileptic medicines, such as carbamazepine, phenytoin, phenobarbital, primidone, and barbiturates, such as amobarbital (amylobarbitone). Women with diabetes may need a higher dose of their antidiabetic medicine (insulin or an oral antidiabetic medicine). Reference: DrugBank Release Version 5.1,17.

When to Discontinue Treatment

Treatment should be discontinued if signs of thromboembolic complications occur, if results of LFT become abnormal, or if cholestatic jaundice appears. Vaginal bleeding or spotting soon after starting treatment with tibolone may be due to residual effects of endogenous or exogenous estrogens. Bleeding that commences after 3 months of treatment or persists should be appropriately investigated. In most cases, no apparent cause of bleeding is found. As with all steroids with hormonal activity, a yearly medical examination is advisable.¹⁸

EFFECT OF TIBOLONE ON VASOMOTOR SYMPTOMS

A number of randomised trials compared tibolone predominantly with placebo and, in some cases, with conventional HT, finding that tibolone significantly reduced the mean hot flush score and was comparable to conventional HT. The Tolerability Trial (TOTAL study) showed a reduction in menopausal symptoms to a level similar to HT, with significantly less bleeding in the first 3 months of treatment.¹¹ Tibolone is effective and well-tolerated for the treatment of moderate to severe VMS and the effects of vaginal atrophy associated with menopause.²⁰

EFFECT OF TIBOLONE ON NEUROPSYCHIATRIC SYMPTOMS

Tibolone, like estrogens, influences opioid and serotonergic receptors and improves mood. Tibolone helps relieve insomnia and increases beta-endorphin and beta-lipoprotein levels, thereby improving mood. Somunkiran A et al. compared the effectiveness of 17beta-E2 with tibolone in surgical menopause for the management of climacteric symptoms and suggested that tibolone improved mood, somatic symptoms and libido to a greater extent than estrogen therapy alone.²¹ Similar improvements in psychological symptoms, comparable to those with E2, were observed in a study by Baksu A et al.

Regarding cognition, tibolone appears to improve semantic memory but does not significantly enhance recognition memory.²²

EFFECT OF TIBOLONE ON QUALITY OF LIFE AND SLEEP

It significantly increases allopregnanolone, a steroid with sedative and anxiolytic properties. In a placebo-controlled randomised study, Meeuwssen et al. examined the effect of tibolone on QoL in post-menopausal women and concluded that tibolone significantly improved VMS and that there was a statistically significant improvement in the sleep domain (on the QoL measurement scale).²³ An Indian study on the effectiveness of tibolone in 100 women with surgical menopause was conducted by Bhattacharya SM et al. There was a significant improvement in QoL and somato vegetative symptoms, and a moderate improvement in psychological and urogenital symptoms.²⁴

EFFECT OF TIBOLONE ON SEXUALITY

Tibolone increases libido and improves sexual response, comparable to androgen treatment. The overall effect includes increased sexual interest, specifically in fantasies, arousal and orgasm. The clinical effects are due to the mild androgenic action of the Δ4-isomer, which reduces sex hormone-binding globulin (SHBG) and thus increases

bioavailable testosterone, E2, and dehydroepiandrosterone sulphate (DHEA-S).²⁵ The androgen side effects of acne, alopecia and hirsutism have not been reported with tibolone treatment. Tibolone's androgenic effect helps to improve libido. In the LISA study, tibolone significantly relieves climacteric symptoms and improves mood and sexual well-being. A careful exploration of potential confounders for the LISA trial efficacy outcomes confirmed the initial conclusion that tibolone consistently improves sexual function beyond its effect on climacteric symptoms, compared with transdermal E2/NETA (norethisterone acetate) in women with female sexual dysfunction (FSD).²⁶ In a double-blind, randomised study conducted in osteopenic but otherwise healthy older subjects (mean age 66 years) over 2 years, tibolone at a dose of 1.25 mg/day showed a trend towards improvement in QoL and sexuality compared with raloxifene (RLX, 60 mg/day).²⁷ The estrogenic effects on the vagina decrease vaginal dryness and dyspareunia. The TOTAL study showed improvement in vaginal atrophy and in the karyopyknotic and maturation index, comparable to HT. The combined effects cause an overall improvement in mood, libido and sexual enjoyment.²⁸

EFFECT OF TIBOLONE ON THE CARDIOVASCULAR SYSTEM

Action on Lipids

Tibolone reduces triglycerides, total cholesterol, low-density lipoprotein (LDL) and lipoprotein (a) levels. However, it also lowers high-density lipoprotein (HDL) cholesterol, which has been a cause for concern. The reduction in HDL cholesterol was not associated with changes in cholesterol efflux capacity or paraoxonase activity, indicating that the antiatherogenic effects of HDL remained unchanged. Thus, despite the complex effects on the lipid profile, tibolone appears to exert antiatherogenic properties.²⁹

Endothelial

Data suggest that, by activating nitrous oxide (NO) production via its estrogenic effects, tibolone may have a lipid-independent, cardioprotective effect in endothelial cells and reduce leukocyte adhesion molecules.³⁰ Data on the effects of tibolone on C-reactive protein and other inflammatory markers are conflicting. In the Osteoporosis Prevention and Arterial Effects of Tibolone (OPAL) study, both tibolone and estrogen-progesterone increased atherosclerosis compared with placebo. The study group consisted of older women, so the results may not be generalizable to younger postmenopausal women.¹⁴

Venous Thromboembolism

Studies have also found decreases in fibrinogen and factor VII activity, increases in antithrombin III and plasminogen, and an overall trend towards increased fibrinolytic activity with tibolone. A neutral effect on coagulation was observed in recent randomised controlled trials, including the long-term intervention on fractures with tibolone (LIFT) study.^{9,16} The tibolone histology of the endometrium and breast endpoints study (THEBES), which did not show an increased risk of VTE.³¹ Tibolone is contraindicated in women with a recent or past history of thromboembolic complications. Tibolone has a neutral effect on hypertension. It does not adversely affect blood pressure in women with established hypertension.^{14,32}

Stroke

The THEBES study considered cardiovascular events (MI, stroke, VTE and pulmonary embolism) as secondary endpoints. No VTE, pulmonary thromboembolism or stroke events were recorded in this study.³¹ No thromboembolism cases were reported with tibolone, whereas three cases were reported with the conjugated equine estrogen and medroxyprogesterone regimen, supporting differences in the effects of these compounds on the haemostatic system. The LIFT study was planned to assess the risks of breast cancer, cardiovascular disease (CVD) and endometrial cancer after 5 years of treatment with 1.25 mg/day of tibolone.^{9,33}

In the LIFT trial results, there has been a twofold increase in stroke in older women (over the age of 70 years) compared with placebo, similar to that observed with estrogen. It is best to avoid the use of tibolone in elderly women and in women who are at risk of stroke, hypertension, smoking, diabetes and atrial fibrillation.⁹

Effect on Diabetes

Tibolone treatment is associated with increased insulin sensitivity in women with insulin resistance. Therefore, tibolone is an attractive option for postmenopausal women¹⁶ with type 2 diabetes mellitus.¹³

EFFECT OF TIBOLONE ON THE UTERUS

Tibolone does not stimulate endometrial proliferation because the $\Delta 4$ -isomer binds to the progesterone receptor and protects the endometrium from the estrogenic agonist effects of the two estrogenic metabolites. If persistent bleeding occurs, the standard clinical principle is to investigate any postmenopausal persistent vaginal bleeding. The reported breakthrough bleeding rates with tibolone have been comparable to those with combined, continuous EPT.³ 90% of tibolone-treated women are amenorrhoeic by 6 months. Bleeding is less in older women and can be greater with the 2.5 mg dose than with the 1.25 mg dose. Importantly, no correlation has been observed between bleeding and endometrial hyperplasia (EH). This again emphasises the need to biopsy tibolone-treated women with persistent hyperplasia.¹⁸ The THEBES study enrolled 3,240 PMW, who were assessed by biopsy and transvaginal ultrasonography (TVUS) at baseline and after 2 years of treatment with tibolone or EPT to evaluate the endometrium. EH was observed in two women receiving EPT, and did not occur in those given tibolone. No cases of endometrial cancer were reported in either group; one woman assigned to the EPT group developed an endometrial stromal sarcoma during treatment. Tibolone users did not show a significant increase in double-wall endometrial thickness, and tibolone's better tolerability compared with EPT was confirmed. These findings were consistent with the results of another randomised, placebo-controlled clinical trial (OPAL study), which had a secondary objective to assess the effects of tibolone, continuous combined EPT, and PL on the endometrium.³⁴ The incidence of endometrial proliferation was 1.4%, 4.8%, and 0% for the tibolone, EPT, and placebo groups, respectively, while cancer was assessed in one case in the tibolone group and one in the placebo group.³³

There is no evidence that tibolone promotes myoma growth in women with uterine fibroids. As add-back therapy, tibolone effectively prevents vasomotor symptoms and bone loss, without impairing the reduction in fibroid size achieved with GnRH analogue treatment.

EFFECT OF TIBOLONE ON THE BREAST

The breast is a complex estrogen factory. Breast tissue, both normal and abnormal, contains all the enzymes necessary for the formation of estrogens. Estrone sulphate concentrations are higher in the breast than in plasma and even higher in cancer tissue.³⁵ This state is observed in postmenopausal women despite very low systemic estrogen levels, indicating that a local mechanism is at work. In breast tissue, tibolone metabolites inhibit the enzyme sulphatase, thereby blocking the conversion of estrone sulphate to estrone. Tibolone and its metabolites inhibit the conversion of estrone sulfate to E2. Thus, tibolone acts like progestins and weak androgens in the breast. Hence, tibolone increases cellular differentiation and stimulates apoptosis.³⁵ These data support a potential lower risk of breast cancer with tibolone compared with conventional EPT. It also has a positive effect on markers of breast cancer. The incidence of breast tenderness and mastalgia with tibolone is significantly lower than in EPT users and has little effect on mammographic density, probably due to lower plasma estrogen levels.³¹ Postmenopausal HT increases breast density on mammography in about 10–20% of estrogen users and 20–35% of estrogen-progestin users, an effect that occurs within the first month of treatment.¹¹

However, data on breast cancer risk in PMW treated with tibolone are inconclusive. The LIBERATE trial concluded that the risk of recurrent breast cancer is higher in patients treated for breast cancer than in the placebo group. The increase occurred only in women with ERs-positive tumours. It is well documented that the breast responds to tibolone with less stimulation than to estrogen.³⁵ Until new data are available, the use of tibolone in women with a history of breast cancer remains relatively contraindicated. The Million Women Study concluded that current use of HT is associated with an increased risk of incident and fatal breast cancer; the effect is substantially greater for estrogen-progestogen combinations than for other types of HT.³⁶ This was the first study to show an increased risk of breast cancer in tibolone users, and the study has its limitations. As a large observational study, the Million Women Study provides important association data but is limited by confounding, detection bias, and lack of applicability to contemporary, early-initiated, lower-dose menopausal hormone therapy. The preferential prescription of tibolone in women at greater risk for breast cancer may explain the unexpected increase in breast cancer risk for tibolone users in the Million Women Study. In the LIFT trial, secondary endpoints were to determine the risks of breast cancer, CVD and endometrial cancer after 5 years of therapy. The tibolone group had a decreased risk of invasive breast cancer and colon cancer.³⁴

EFFECT OF TIBOLONE ON BONE

Tibolone prevents bone loss in postmenopausal women as effectively as estrogen or estrogen-progestin therapy.

Tibolone (1.25 mg/day) compared with placebo reduced the relative hazard of osteoporosis -related vertebral and nonvertebral fractures in older women with a median follow-up of ³⁴ months (LIFT study).⁹ In particular, the reduction in the relative risk of vertebral fractures was similar to that observed with estrogens, bisphosphonate and raloxifene therapy, while the magnitude of the reduction in the relative risk of nonvertebral fractures was similar to that reported with estrogen therapy. The LIFT trial found that the treated group had 25% fewer falls. However, in the LIFT trial, there was a twofold increase in stroke in older women (over age 70 years) compared with placebo, similar to that observed with estrogen.³⁷ It is best to avoid the use of tibolone in elderly women and in women who are at risk of stroke, hypertension, smoking, diabetes and atrial fibrillation. The Cochrane review cautions against the long-term safety of tibolone compared to ³² combined HT, and there is uncertainty about its risk profile in elderly women. The THEBES study enrolled younger women (mean age 54.5 + 4.4 years), with cardiovascular events (MI, stroke, VTE and pulmonary embolism) as secondary endpoints. No VTE, pulmonary thromboembolism or stroke events were recorded in this study. These results align with the window-of-opportunity concept.³¹

A systematic review and meta-analysis of clinical trials shows that tibolone 2.5 mg/day increases lumbar spine and femoral neck BMD at 24 months compared with inactive controls, with no significant difference compared with estrogen therapy, supporting tibolone as an alternative for menopausal symptom control and bone protection.³⁸

TIBOLONE IN THE INDIAN CONTEXT

Indian women frequently express concern regarding irregular bleeding and spotting associated with menopausal hormone therapy. Tibolone has a low incidence of unscheduled bleeding, making it a particularly acceptable option in this population. Tibolone is currently the only systemic hormonal formulation available in India with evidence-based benefit for improving sexual desire, addressing a common but under-reported concern among postmenopausal women. Hypertriglyceridaemia is the most prevalent lipid abnormality among Indian women, and tibolone has been shown to reduce serum triglyceride levels, offering a potential metabolic advantage in this setting. Evidence from Indian studies demonstrates a significant improvement in quality of life among postmenopausal women treated with tibolone.²⁴

SYNOPSIS

- Tibolone is a STEAR. It is a synthetic steroid compound that has estrogenic, progestogenic, and androgenic properties. It has an estrogenic effect on bone, inhibiting bone resorption by reducing osteoclastic activity.
- Tibolone is approved in multiple countries worldwide for the treatment of menopausal symptoms and, in several regions, for the prevention of osteoporosis.
- Tibolone remains a valuable option for postmenopausal women, especially those younger than 60 or within 10 years of menopause, who are seeking relief from menopausal symptoms, improved bone health, and enhanced quality of life.
- Tibolone is effective in treating VMS and improves urogenital atrophy. It improves mood and libido.
- Tibolone is prescribed in a single daily dose of 2.5 mg orally. A lower dose of 1.25 mg has been found to be equally effective for most indications, including osteoporosis. It should be prescribed at least 12 months after the last menstrual period.
- Tibolone reduces the risk of vertebral and nonvertebral fractures in older osteoporotic women. Tibolone prevents bone loss and is as effective as standard doses of conventional postmenopausal HT. Tibolone increases lumbar spine and total hip BMD to a statistically significantly greater extent than raloxifene.
- Tibolone is associated with a low risk of VTE and has a neutral effect on cardiovascular outcomes when used in appropriately selected women.
- Tibolone does not stimulate the endometrium and is not associated with an increased risk of endometrial hyperplasia or carcinoma in postmenopausal women.
- Tibolone may be preferable to HT in symptomatic menopausal women with mammographically dense breast tissue.
- Tibolone may be used as add-back therapy with GnRH analogues for VMS and to maintain BMD.

- Tibolone may be used in women with myomas and endometriosis
- Tibolone should not be used in breast cancer survivors as it increases the recurrence risk
- Observational data suggest that tibolone does not increase and may reduce the incidence of breast cancer in postmenopausal women, although this finding should be interpreted with caution.
- Tibolone should be used with caution in women over 60 years of age and avoided in those with significant risk factors for stroke, as an increased risk of stroke has been reported in older women.

RESEARCH AGENDA

Efficacy of tibolone in FSD, mood and sleep.

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SELECTIVE ESTROGEN RECEPTOR MODULATORS

Keywords: Tamoxifen, raloxifene, bazedoxifene, ospemifene

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INTRODUCTION

Women entering menopause are often highly motivated to consult healthcare providers to optimise their health and manage emerging menopausal symptoms. Without appropriate attention, menopausal symptoms can impair quality of life (QoL), reduce work productivity, increase vulnerability to cardiovascular and cerebrovascular diseases, musculoskeletal morbidities, and increase the risk of age-related cancers. As specialists, we should assess women's lifestyle factors and associated morbidities to make evidence-based recommendations that improve QoL through appropriate medication and lifestyle changes. Menopausal hormone therapy (MHT) has been associated with an increased risk of venous thromboembolism (VTE) and, in women receiving unopposed estrogen, endometrial carcinoma. Concerns regarding these risks have led to ongoing debate about the role of conventional MHT. Consequently, selective estrogen receptor modulators (SERMs) have emerged as important therapeutic options for specific indications, offering tissue-selective estrogenic effects rather than serving as direct alternatives to MHT.

MECHANISM OF ACTION

Estrogen, besides being the key regulatory hormone of the female reproductive system, also plays a critical role in many complex physiological events related to musculoskeletal, cardiovascular, and neurological wellbeing through estrogen receptors (ERs), ER α and ER β , as nuclear transcription factors.

SERMs are non-steroidal compounds that bind to ERs with high affinity and exert agonist or antagonist effects depending on the target tissue.¹⁻³ The advantage of using SERMs in menopausal women lies in their ability to confer estrogen-like benefits on the skeletal, cardiovascular, and central nervous systems, while eliminating the need for progesterone due to their antagonist or neutral activity in estrogen-sensitive tissues such as the breast and endometrium. An ideal SERM would prevent bone loss and fractures; reduce the risk of breast and endometrial cancer and limit endometrial proliferation; relieve vasomotor and other menopausal symptoms; and not increase the risk of coronary heart disease, stroke, or VTE. Although no single compound meets all these criteria, newer SERMs, such as raloxifene, and others in clinical development demonstrate improved benefit-risk profiles, with selective agonist effects on bone and antagonist effects on the breast and endometrium.

The precise mechanism by which SERMs exert their specific actions is not fully understood. Available evidence suggests that the balance between ER coregulators and the cellular microenvironment determines SERMs' action in a given cell type.¹ Microarray gene expression analysis has shown that distinct sets of genes are regulated by ER α versus ER β in response to estradiol and SERMs.⁴ As a result, SERMs must be evaluated individually, as each has unique pharmacologic properties that determine its clinical potential.³ Refer to Table 1 for the different types of SERMs, their uses and tissue-specific actions.

Table 1: Different SERMs, their uses and action

NAME	USES	EFFECTS/LOCATION
Clomiphene	Anovulation	Antagonist at hypothalamus
Femarelle	Menopausal symptoms, osteoporosis	Agonist breast and bone
Ormeloxifene	Contraceptive	Agonist bone, antagonist breast and uterus
Raloxifene	Osteoporosis, breast cancer prevention	Agonist bone, antagonist breast and uterus
Tamoxifen	Breast cancer	Agonist bone, antagonist breast and uterus
Toremiphene	Breast cancer	Agonist bone, antagonist breast and uterus
Lasofloxifene	Osteoporosis, breast cancer, vaginal atrophy	Agonist bone, antagonist breast and uterus
Bazedoxifene	Osteoporosis	Agonist bone, antagonist breast and uterus
Ospemifene	Genitourinary syndrome	Estrogenic effects on vaginal epithelium

TAMOXIFEN: FIRST GENERATION SERM

Tamoxifen is a SERM and a non-steroidal anti-estrogen that competes for binding to ERs. The complex is then transported to the cell nucleus, where it binds to DNA and inhibits cellular growth and proliferation. The toxicity associated with tamoxifen is minimal, but menopausal symptoms such as hot flushes are common; fluid retention occurs in a third of patients using it. It is used as an adjunct for the treatment of ER-positive breast cancer.⁵ The United States Food and Drug Administration (US FDA) has approved tamoxifen for breast cancer chemoprevention in pre- or postmenopausal women 35 years or older with a 5-year Gail Model risk of more than 1.7%.⁶

Tamoxifen in the Management of Breast Cancer

Five years of tamoxifen therapy is recommended for women with ER-positive ductal carcinoma in situ treated with breast-conserving surgery. Its use is not associated with a statistically significant improvement in overall survival. However, it significantly reduces the incidence of ipsilateral invasive cancer and lowers the risk of contralateral breast cancer.⁷ The introduction of aromatase inhibitors and selective estrogen receptor degraders (SERDs), such as fulvestrant, has reduced the role of tamoxifen. It is now used mainly as adjuvant therapy in selected lower-risk postmenopausal women and for breast cancer risk reduction, while it remains an important option in premenopausal women.⁸

Tamoxifen is used in premenopausal women with ER-positive breast cancer. It is used in approximately 70–80% of such women, either alone or in combination with ovarian function suppression, depending on recurrence risk.^{9–11} Standard treatment duration is 5 years, with extension to 10 years in selected patients.^{10,11}

In postmenopausal women, aromatase inhibitors are preferred first-line therapy. However, tamoxifen continues to be used in 20–40% of women with ER-positive disease, particularly when aromatase inhibitors are contraindicated, poorly tolerated, or used sequentially.^{9,10} Use of tamoxifen in this population has declined over time but remains clinically relevant, especially in resource-limited settings.¹⁰

Tamoxifen Use in Chemoprevention

Large Randomised Controlled Trials (RCTs) have shown that tamoxifen reduces the risk of invasive breast cancer by approximately 40–50%, with benefits persisting for 10–20 years after cessation of therapy.^{5,12,13} The protective effect is limited to ER-positive tumours and is not observed in ER-negative disease. Importantly, tamoxifen remains the only pharmacological agent approved for chemoprevention in premenopausal women.⁶

Tamoxifen is particularly beneficial in women at increased breast cancer risk, including those with a strong family 181

history, prior atypical ductal or lobular hyperplasia, lobular carcinoma in situ (LCIS), or an elevated estimated lifetime risk ($\geq 20\%$) based on validated risk-prediction models. In such women, the absolute reduction in breast cancer incidence generally outweighs the potential risks.^{14,15}

The standard chemopreventive regimen is tamoxifen 20 mg daily for 5 years. A lower dose of tamoxifen, 5 mg per day, may achieve meaningful risk reduction with fewer adverse effects; however, this strategy has not yet been universally incorporated into clinical guidelines for postmenopausal women. Reductions in mammographic density and endometrial proliferation, increased bone density, and reduced markers of cardiovascular disease (CVD) confer additional potential benefits of low-dose tamoxifen.¹⁶

Adverse effects

Tamoxifen is associated with an increased risk of endometrial cancer and thromboembolism, including deep vein thrombosis (DVT), pulmonary embolism and stroke. Women treated with tamoxifen for breast cancer, whether pre- or postmenopausal, have an increased risk of ovarian cyst formation. Most studies report rates of 15-30%, compared with 7% in the general postmenopausal population. Most of these cysts are functional, but the exact mechanism by which tamoxifen stimulates their formation remains unknown.^{17,18} Fortunately, most of these cysts resolve over time, whether tamoxifen is continued or not. Small, simple cysts can be managed with sonographic surveillance. If malignancy is suspected, surgical exploration is indicated, along with discontinuation of tamoxifen.

Tamoxifen stimulates endometrial proliferation, and its use has been linked to endometrial hyperplasia, polyps, carcinoma and uterine sarcoma.⁶ Tamoxifen use is associated with a two- to threefold higher risk of developing endometrial carcinoma, attributable to its partial estrogen agonist effect on the endometrium. The risk level also increases linearly with the duration of therapy and the cumulative dose. Available data suggest that endometrial cancers that develop in women receiving tamoxifen have the same stage, grade, and prognosis as those in non-users.¹⁹ Tamoxifen upregulates progesterone receptor expression and is postulated to enhance progestin efficacy in endometrial cancers. Clinically, high response rates have been observed with tamoxifen as an adjunct to progestin therapy. Toxicity is generally low, and this combination is most commonly used for recurrent disease.²⁰

Routine endometrial screening in tamoxifen users who do not have abnormal bleeding has not proved effective.²¹ Protocols using transvaginal sonography (TVS) or endometrial biopsy (EB) failed to identify endometrial cancer in asymptomatic tamoxifen users effectively.²² However, a baseline TVS is recommended at the start of therapy and at annual examinations.

Women using tamoxifen should undergo evaluation for endometrial cancer only when bleeding develops. The increased risk of endometrial cancer occurs almost exclusively in postmenopausal women. The first line of investigation requires evaluation with a hysteroscopic-guided biopsy. If hysteroscopy is unavailable, saline infusion sonography (SIS) and a guided EB should be performed. In asymptomatic postmenopausal women on tamoxifen, endometrial thickness alone is an unreliable predictor of malignancy and must always be interpreted in conjunction with clinical presentation, including additional risk factors such as obesity and prolonged tamoxifen use and detailed sonographic features, such as irregular or cystic morphology and increased vascularity on Doppler. An observational study has suggested an endometrial thickness threshold of 9–10 mm to guide individualised decision-making in asymptomatic tamoxifen users; however, these thresholds are not validated for screening and should not be used in isolation.²³

(SIS) can be used to evaluate the uterine cavity and distinguish true epithelial thickening from combined endometrial changes. This is particularly useful in tamoxifen users, in whom ultrasonography characteristically demonstrates subepithelial cystic (sonolucent) changes beneath an atrophic endometrial epithelium, resulting in an apparent increase in endometrial thickness.²⁴

The levonorgestrel-releasing intrauterine system (LNG-IUS) probably slightly reduces the incidence of benign endometrial polyps and endometrial hyperplasia in women with breast cancer receiving tamoxifen. There is no clear evidence from the available RCTs, that the LNG-IUS prevents endometrial cancer in these women.^{25,26} LNG-IUS may be used for endometrial protection in women receiving tamoxifen who develop abnormal uterine bleeding or endometrial hyperplasia, and for whom tamoxifen must be continued, particularly when oral progestogens are ineffective or contraindicated. The LNG-IUS provides continuous local progestogenic activity, leading to endometrial decidualisation and atrophy; however, breakthrough bleeding, particularly during the first 3–6 months, is common. It may be used in both premenopausal and carefully selected postmenopausal women. If regression of endometrial hyperplasia does not occur within six months of LNG-IUS use, further regression is unlikely, and alternative

management, including surgical options, should be considered.²⁷ Premenopausal women treated with tamoxifen do not have an increased risk of endometrial cancer and do not require additional monitoring beyond routine gynaecological care; however, any abnormal uterine bleeding warrants evaluation.²¹

RALOXIFENE

Raloxifene is a second-generation SERM. It is a benzothiophene derivative indicated for the treatment and prevention of osteoporosis and for reducing the incidence of breast cancer in high-risk postmenopausal women. It activates ERs in bone but does not appear to activate those in the breast or uterus. Raloxifene exerts estrogen-like effects on bone remodelling, reducing bone turnover and fracture risk. Evidence from large clinical trials suggests neutral to modest tissue-specific effects beyond bone, particularly on CVD outcomes, without consistent benefit across non-skeletal systems.

In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, which enrolled postmenopausal women (N=7705) with osteoporosis, raloxifene 60 mg/day significantly reduced new vertebral fractures, with a rapid 68–70% risk reduction within the first year and a sustained 36–40% reduction at 4 years. However, no significant decrease in non-vertebral fractures was observed after four years.²⁸

In addition to its bone effects, raloxifene reduces the risk of ER-positive breast cancer. In the MORE trial, it was associated with approximately a 76% relative risk reduction of ER-positive breast cancers among postmenopausal women with osteoporosis at four years.²⁸ The Continuing Outcomes Relevant to Evista (CORE) trial, for a further four years, showed a continued reduction in ER-positive breast cancer by 66%.²⁹

In the Study of Tamoxifen And Raloxifene (STAR) trial, postmenopausal women (N=19747) at increased risk of breast cancer were enrolled and given 60 mg/day raloxifene or 20 mg/day tamoxifen.³⁰ Both decreased the risk of breast cancer by 50%. However, raloxifene had a better overall safety profile than tamoxifen, with fewer cases of uterine cancer and fewer thromboembolic events. In the MORE trial, tamoxifen was found to reduce ductal carcinoma in situ of the breast to a greater extent than raloxifene.^{30,31}

Raloxifene is not associated with increased CVD risk seen with estrogen therapy. In women with increased CVD risk, it had no significant effect on the incidence of primary coronary events.³¹

Carneiro and colleagues conducted a semi-systematic review of six clinical trials assessing the endometrial safety, menopausal symptoms, and vaginal complaints associated with raloxifene and estrogen use in healthy postmenopausal women. Raloxifene demonstrated a highly favourable endometrial safety profile; only two cases of simple endometrial hyperplasia were reported in the pooled population, both occurring after approximately 24 weeks of therapy, with no cases of atypical hyperplasia or endometrial carcinoma. Overall rates were comparable to those seen in untreated postmenopausal women.³² Raloxifene was associated with a higher prevalence of vasomotor symptoms and vaginal dryness compared with estrogen therapy.

Furthermore, its use for 4 years has been associated with an increased risk of thromboembolic events; there is a slightly increased risk of fatal stroke when raloxifene is compared with placebo over 5.6 years of follow-up.³³ They concluded that raloxifene conferred a more favourable endometrial safety profile, supporting its role as a SERM suitable for women requiring breast and bone protection where endometrial stimulation is undesirable.

LASOFOXIFENE

A third-generation SERM binds to both ER-alpha and -beta with high affinity and has markedly improved bioavailability. Clinical studies have shown that lasofoxifene significantly increases bone mineral density (BMD) and reduces bone turnover markers compared with placebo. It has also been shown to lower the incidence of vertebral and non-vertebral fractures in postmenopausal women with osteoporosis and is associated with a lower risk of developing ER-positive breast cancer. It is also associated with improved lipid profile and reduced incidence of vaginal atrophy.³⁴

BAZEDOXIFENE

An ideal SERM for osteoporosis prevention and treatment should exert estrogen-agonistic effects on bone while remaining neutral or antagonistic on breast and uterine tissues. Bazedoxifene binds with high affinity to both estrogen receptor subtypes, acting as a potent agonist on bone, reducing bone turnover by approximately 20–25% at daily doses of 20 or 40 mg, while functioning as an antagonist in breast and uterine tissues. Consequently, it not only minimises bone loss but also significantly reduces the risk of breast and endometrial stimulation, lowering the

likelihood of endometrial thickening, bleeding, polyps, hyperplasia, and carcinoma. Bazedoxifene additionally demonstrates agonistic activity at the vaginal epithelium, thereby improving vaginal dryness, and exerts favourable effects on lipid metabolism and the vascular endothelium. Compared with raloxifene, the relative absence of vasomotor side effects is considered a clinical advantage.³⁵ When combined with conjugated equine estrogens (CEE), bazedoxifene forms a tissue-selective estrogen complex (TSEC). The SMART trials have demonstrated that bazedoxifene 20 mg combined with CEE 0.45 mg or 0.625 mg provides effective relief of menopausal symptoms while maintaining protection of the breast and endometrium, and represents an effective alternative for symptomatic non-hysterectomised postmenopausal women with a low risk of VTE.³⁶

OSPEMIFENE

Ospemifene is the first and only non-hormonal therapy approved by the U.S. FDA for the treatment of moderate to severe dyspareunia associated with genitourinary syndrome of menopause in postmenopausal women. It is a (SERM) with pronounced estrogen-agonistic effects on the vaginal epithelium and neutral to minimal estrogenic activity on the endometrium. Ospemifene demonstrates tissue-specific actions across multiple systems, exhibiting favourable estrogen-agonist effects on bone and vaginal tissues while remaining largely neutral on the breast and endometrium, and exerting beneficial effects on serum lipid profiles. Its influence on coagulation markers is comparable to that of other SERMs, and vasomotor symptoms, particularly hot flushes, are recognised adverse effects. Ospemifene is available as a 60-mg oral tablet for once-daily administration.³⁷

ARZOXIFENE

An ideal SERM would exert antiestrogenic effects on the breast and endometrium, but pro-estrogenic effects on bone and lipids. Arzoxifene (LY-353381.HCl), a third-generation SERM, meets all of these criteria. Early clinical studies demonstrated antiproliferative effects in breast tissue, including reduced tumour proliferation indices when administered preoperatively, 2 to 6 weeks before resection of the lesion, in women with breast cancer.

The effects of Arzoxifene 20 mg/day on BMD, fractures, uterine safety, and overall safety were further evaluated in a randomised, placebo-controlled trial of postmenopausal women with normal to low bone mass.³⁸ Although longer-term studies showed reductions in vertebral fractures and estrogen receptor-positive breast cancer, Arzoxifene did not demonstrate benefits in non-vertebral fractures, CVD outcomes, or cognitive function. Consequently, further clinical development was discontinued, and regulatory approval was not pursued.

PHYTOESTROGENS

They are phytochemicals derived from plants and natural foods that have a greater affinity for estrogen beta receptors. Refer to Chapter ⁴¹.

SYNOPSIS

- SERMs are a valuable option in menopausal therapy, particularly for women for whom conventional hormone therapy is contraindicated or not preferred. Their use should be individualised, with careful consideration of the indication, such as osteoporosis prevention, vulvovaginal atrophy, or breast cancer risk reduction along with the woman's age, time since menopause, comorbidities, and risk of VTE. Appropriate patient selection and counselling can optimise clinical benefit while minimising adverse effects.
- Tamoxifen is primarily used to prevent breast cancer and recurrence: it improves the lipid profile, increases bone density, and reduces fracture rates, albeit less effectively than raloxifene.
- Raloxifene at 60 mg daily prevented new vertebral fractures, with a rapid 68–70% risk reduction within the first year and a sustained 36–40% reduction at 4 years, with a 76% reduction in the risk of invasive breast cancer. Antifracture efficacy at the hip is lacking, but it reduces the risk of vertebral fractures by 47% in postmenopausal women with osteopenia over 3 years. Raloxifene can be used for the prevention and treatment of osteoporosis, especially in women with an increased risk of breast cancer. Raloxifene and estrogen are associated with a similar increased risk of VTE. Other side effects include hot flushes, which are more likely during the perimenopausal period, and leg cramps.
- Bazedoxifene provides effective relief of menopausal symptoms while antagonising the effects of estrogen on the uterus, endometrium, and breast, making it a suitable option for symptomatic, non-hysterectomised postmenopausal women.

RESEARCH AGENDA

Long-term, comparative studies of the effectiveness and safety of SERMs in different patient populations to guide individualised therapy for osteoporosis and menopausal symptom management.

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COMPLEMENTARY AND ALTERNATIVE THERAPIES

41

Keywords: Ayurveda, homoeopathy, phytoestrogens, Indian herbs

INTRODUCTION

Complementary and alternative medicine (CAM) encompasses a diverse range of medical and healthcare systems, practices, and products that are not currently considered part of conventional medicine.¹ Women often choose CAM therapies because these approaches align with their personal values, beliefs, and philosophical orientations towards health and life. For some, the decision to use CAM arises from dissatisfaction with conventional medical treatments.

Many women perceive natural therapies as inherently safe; however, it is unrealistic to assume that any treatment can provide benefits without the potential for adverse effects. The publication of the Women's Health Initiative (WHI) report on 9 July 2002 significantly influenced women's healthcare decisions, particularly by raising concerns about the long-term risks of menopausal hormone therapy (MHT).

As a result, the management of menopause has evolved into a subspecialty requiring a multidisciplinary approach. In addition to hormonal therapies, newer nonhormonal treatment options are now available for managing menopausal symptoms. Studies have also reported racial and ethnic differences in the use of MHT and CAM. Overall, Black and Hispanic women are more likely to use CAM modalities to manage menopausal symptoms, whereas White women tend to prefer MHT.²

CAM CATEGORIES1

Alternative Whole Medical Systems

Complete systems of theory and practice that have evolved independently of allopathic medicine and are often culturally based.

- *Eastern:* Traditional Chinese medicine (TCM China), Ayurvedic medicine and Unani (India).
- *Western:* Homoeopathy and naturopathy.
- *Ayurvedic medicine:* Ayurveda, which literally means "the science of life", is a natural healing system developed in India. It is a comprehensive medical system that places equal emphasis on the body, mind, and spirit and strives to restore the individual's innate harmony. Primary Ayurvedic treatments include diet, exercise, meditation, herbs, massage, exposure to sunlight and yoga. However, a survey of the Indian medical literature indicates that the quality of published clinical trials generally falls short of contemporary methodological standards regarding randomisation, sample size, and controls.³
- *Homoeopathy:* A key premise of homoeopathy is that every person has an energy called a vital force or self-healing response. When this energy is disrupted or imbalanced, health problems develop. Homoeopathy aims to stimulate the body's own healing responses, and treatment involves administering minute doses of substances that, when given in larger doses, produce characteristic symptoms of illness in healthy people. This approach is called "like cures like". Three commonly prescribed medicines are: (1) Pulsatilla, (2) Sepia and (3) Lachesis. Research studies on homoeopathy have been contradictory in their findings but generally seem to be safe and to improve somatic symptoms and overall health.⁴ However, a recent trial found no significant difference in the Green Climacteric scale, menopause rating scale (MRS), or Utian quality of life (QoL) compared with placebo.⁵
- *Naturopathic medicines:* These employ an array of healing practices, including diet, hydrotherapy, spinal and soft-tissue manipulation using electric currents, ultrasound, and light therapy; therapeutic counselling and pharmacotherapy. Naturopathic physicians collaborate with internists, family care practitioners and gynaecologists, providing for our responsible care continuum. Not covered by health insurance policies, like other CAM services. Overall evidence for naturopathic care and many natural therapies for menopause is promising but limited because of small studies of variable quality or heterogeneous interventions.⁶
- TCM regards menopause as a phenomenon caused by an imbalance of body energy and includes a group of techniques and methods (such as oriental massage, Qi gong, and herbal medicines) to bring the body back into

harmony. A recent systematic review and meta-analysis of Randomised Controlled Trials (RCTs) has shown improvement in perimenopausal insomnia with acceptable safety with Chinese herbal medicines.^{7,8}

- While Chinese herbal medicine may improve menopausal symptoms, there is insufficient evidence specific to premature ovarian insufficiency (POI). There is a clear need for additional, rigorous research on the efficacy and safety of complementary therapies for POI. Evidence does not support the use of complementary medicines as replacements for HT.⁹

Mind-Body Interventions

Examples of mind-body medicine include abdominal breathing, hypnosis, dance, music and art therapy, relaxation, guided imagery, tai chi, Pilates and yoga. These interventions have been shown to improve quality of life with minimal health risks and no side effects.¹⁰

Yoga and adapted mindfulness programmes showed moderate improvements in anxiety and sleep, and small improvements in depressive symptoms and overall menopause symptom score, but study size and follow-up varied.^{11,12}

Cognitive Behavioural Therapy (CBT) is a brief, theory- and evidence-based therapy (four to six sessions) that is acceptable to women and effectively reduces the impact of vasomotor symptoms (VMS), improves sleep, and has benefits for QoL.¹³

Biologically Based Practices

Such practices use substances found in nature, such as herbs, foods and vitamins, derived from traditional systems of medicine in China, India, or Egypt. It also includes reflexology and other practices such as massage, the Feldenkrais method and Rolfing.¹⁴

Manipulation and body-based therapies

It includes acupuncture, acupressure and massage. According to Chinese medicine, during menopause, constitutional balance is affected by stress and emotions, and illnesses need stabilisation. Researchers have conducted a few pilot trials suggesting that acupuncture may modestly alleviate hot flashes.¹⁵ An RCT conducted in Turkey included 61 postmenopausal women who received acupressure and found improvement in MRS and QOL vs. control.¹⁶

Energy therapies

These involve the use of energy fields, such as Reiki and therapeutic touch, and are based on the concept that human beings are infused with subtle energy.

Biologically based therapies

Purchased over the counter or through specialised health professionals include botanicals, animal-derived extracts, vitamins, minerals, fatty acids, amino acids, proteins, probiotics, whole diets, and functional foods. Therapies used mainly in menopause management include phytoestrogens (soy isoflavones and red clover) and herbal remedies (black cohosh, evening primrose oil, dong quai, St. John's wort, cranberry, ginseng, and other Indian herbs).

Phytoestrogens

The primary metabolites (carbohydrates, fats and proteins) formed by plants for their growth are also needed by man for his survival. The secondary metabolites of plants have unique properties, as discovered by man, and act in various ways to promote his well-being

There are two ways in which plants exhibit estrogenic activity in humans: by acting as natural selective estrogen receptor modulators (SERMs), such as phytoestrogens, and by acting as selective estrogen enzyme modulators (SEEMs), such as saponins and tannins..

These function as pro-estrogens when estrogen levels are low and as anti-estrogens when estrogen levels are elevated. Hence, each plant may produce subtle differences in its overall effect.

Phytoestrogens are a group of phytochemicals that exhibit estrogenic activity in the body by acting on estrogen receptors (ERs).^{17,18} They have both genomic and non-genomic effects, displaying weak affinity for ERs and preferentially binding to ER-B over ER-A. They are weak estrogens with both estrogenic and antiestrogenic activity. This property makes them useful in various indications.

Phytoestrogens are broadly classified into four major groups: isoflavones, lignans, coumestans, and stilbenes, of which isoflavones are the most extensively investigated for menopause-related outcomes. Isoflavones, predominantly found in soy and legumes, constitute the principal phytoestrogen class evaluated for menopausal symptom management and cardiometabolic health, with genistein, daidzein, glycitein, biochanin A, and formononetin as the major compounds; the majority of clinical evidence supporting vasomotor symptom relief and lipid profile improvement is derived from this group. Lignans, present in seeds, whole grains, and vegetables, are metabolised by the intestinal microbiota into biologically active enterolignans such as enterodiol and enterolactone, derived from secoisolariciresinol and matairesinol, and are primarily associated with cardiovascular and metabolic health benefits.

Coumestans are less prevalent but biologically potent phytoestrogens, with coumestrol as the principal compound, commonly found in alfalfa sprouts, clover, and split peas. Stilbenes exhibit weak estrogenic but strong antioxidant properties, with resveratrol as the principal compound, occurring in grapes, red wine, berries, and peanuts, and are more strongly linked to cardioprotective and anti-inflammatory effects than to menopausal symptom relief. Soy remains the most extensively studied and commercially promoted phytoestrogen source; however, its biological effects vary according to plant part and type (sprouts contain higher coumestans, and beans predominantly contain isoflavones such as genistein, daidzein, and glycitein), soil and agricultural conditions that influence phytoestrogen concentration and bioavailability, and processing methods, with fermented soy products such as tofu, miso, and tempeh demonstrating enhanced bioavailability and clinical efficacy compared with unfermented forms. Phytoestrogens are biologically active primarily in their glycoside forms, whereas aglycone forms are largely inactive.

Variability in absorption leads to differences in their bioavailability and actions. This is largely influenced by each individual's intestinal flora and by the ability to produce the substance equol. As more studies examine the metabolism and mechanisms of action of phytoestrogens in humans, it is becoming clear that individuals differ in their ability to produce equol. For example, people following a vegetarian diet produce higher levels of equol in their bodies and thus absorb more phytoestrogens from their diets. Such women may exhibit higher estrogen levels. The effect of phytoestrogens is due to the plant's synergistic action. Foods made from soybeans and soy protein formulations may also contain other phytochemicals that enhance the impact of isoflavones.

These effects could be lost when isoflavones are given alone as additives. The effects of the derived active principle (as available in the Indian market) remain unknown. To obtain potential health benefits, it seems preferable to obtain isoflavones from whole foods. However, there is limited quality control of food storage, preservation and preparation, resulting in wide variation in the isoflavone content of foods. This seems to be the rationale for providing phytoestrogen active principles in the form of pills and powders. However, the ready availability of supplements may lead the public to consume larger amounts than are advisable. If isoflavones are added to foods, they should be regulated for purity, standardisation of amount and safety.

It is unlikely that the isoflavones present in the available pills and powders will have equivalent pharmacologic effects, as each product contains different amounts and varying concentrations. Until isoflavone extracts are standardised, it will not be possible to predict outcomes after consumption of the different supplements. In addition, the matrix in which the isoflavones are delivered will affect the release of the agents for absorption and, therefore, will produce differential effects on intestinal metabolism and microflora. As with isoflavone-fortified foods, isoflavone-containing pills and powders require standardisation and regulation.

Until more studies documenting benefits and safety are conducted, clinicians should advise their patients that whole soy foods may be preferable to supplements or soy-enriched or soy-fortified foods. Many of these products are available, each containing a different amount of isoflavones. When assessing patient-specific conditions, the clinician should be aware of this variability and remind the patient to read labels to determine isoflavone content. Clinicians should also warn patients that, at least in India, there are no regulations to ensure the content or quality of such products. More data and studies are needed on the available phytoestrogen formulations.

Isoflavones in the Indian Context

Constitutionally, Indians differ from their Western counterparts. Hence, the spectrum of disease and dosages may differ. There is considerable variation in plasma levels among individuals receiving the same amount of isoflavones. The safety of isoflavones at specific doses has not been established. For example, it is unclear whether the same product (like one roti of soy atta) should be consumed by a woman with osteoporosis and by a woman with an

estrogen-dependent cancer. Even in apparently healthy women, there are questions about the possible overuse of isoflavones. Moreover, the effects on Indian women have not been studied. Since most of the country is vegetarian and there is high consumption of legumes and cereals, the Indian woman may already have plasma levels of phytoestrogens equivalent to those in the Japanese.

Clinical Effects Produced by Phytoestrogens on Various Systems

So far, most studies of menopausal symptoms, such as hot flushes, show only mild benefits. Effects on vaginal dryness are inconclusive. A recent 6-year study involving 1,106 women in Japan demonstrated that soy appears to reduce the incidence of hot flushes associated with menopause.¹⁹ In another double-blind, placebo-controlled study, 104 women were given isoflavones, and the results conclusively proved the effect of isoflavones in reducing the VMS of menopause without any changes in vaginal cytology, any increase in endometrial thickness, and any serious metabolic or hormonal side effects.²⁰ Ciotta and Leanza (2011) reported that long-term treatment with phytoestrogens in postmenopausal women resulted in an approximately 40% reduction in VMS compared with pre-treatment values. The treatment was also associated with a decrease in depressive symptoms and an overall improvement in mood during the postmenopausal period.²¹ Recent studies explored how processed food consumption, body weight, and alterations in the gut microbiome relate to reductions in severe VMS and other menopausal symptoms (Soy vegan Diet).²²

Vaginal Symptoms: The effects on vaginal dryness are inconclusive. A recent study comparing the effects of a soy-based dietary supplement with low-dose hormone therapy on the urogenital system found that the soy-based supplement, when used for 16 weeks, did not exert estrogenic action on the urogenital tract. However, it improved vaginal dryness to a similar extent as hormone therapy.²³ However, a recent study revealed that the use of phytoestrogen is safe and low-risk compared with MHT, and it can relieve urogenital symptoms and promote sexual satisfaction.^{24,25}

Cardiovascular disease: This is the only area where a definite benefit has been established. A meta-analysis of 38 studies examining the effects of soy isoflavones on the cardiovascular system showed that they lowered total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. High-density lipoprotein (HDL) cholesterol was unaffected. However, when administered for at least six months, they have been shown to produce a significant reduction in blood pressure, affecting both systolic and diastolic values, with a more pronounced effect in women with prehypertension or metabolic syndrome.²⁶ Additionally, they have been shown to increase arterial compliance, which may be one mechanism by which they positively influence cardiovascular health. Isoflavones prevent coronary artery disease (CAD) through the following proposed mechanisms: preventing oxidation of lipoproteins, inhibiting cell adhesion, altering growth factor activity, and inhibiting atherosclerosis progression.²⁷ A Large cohort analysis showed an association between moderate dietary intake and lower all-cause mortality.²⁸ An updated review and Meta-analysis studies provided consistent evidence that genistein intake reduces the CVD risk factors of TC, LDL-C, and systolic blood pressure significantly in post-menopausal women with metabolic syndrome.²⁹

Cancer prevention: It has been suggested that phytoestrogens in their natural form do not increase the risk of cancer and may be anti-carcinogenic. The incidence of estrogen-dependent cancers is lowest among Asians who are high consumers of soy, but direct evidence from studies of the isoflavone fraction is conflicting. Experts believe this effect may be due to other constituents, such as saponins, phytosterols, and phytates, in whole foods that contain isoflavones. There appear to be no harmful effects of phytoestrogens on breast, endometrial, or colorectal cancers, and phytoestrogen intake may, in fact, be protective.³⁰

Breast cancer: Whilst phytoestrogens are thought to be protective, there are conflicting reports. It is also suggested that, to reap the full benefits of soy, supplementation should begin at puberty, when it may promote the maturation of breast terminal buds. Additionally, intake of soy isoflavones appears to be safe for breast cancer survivors and may, in fact, reduce mortality and cancer recurrence.^{31,32} A recent meta-analysis of isoflavone consumption and breast cancer risk found a statistically significant inverse dose relationship; every 10 mg/day increase in isoflavone intake corresponded to a 3-7% reduction in breast cancer risk.³³ However, there was no evidence that phytoestrogen had a benefit over placebo in the treatment of breast cancer patients with menopausal symptoms.³⁴

- *Endometrial cancer:* There is insufficient evidence either for or against this. Dietary soy foods in traditional

amounts are probably safe and are associated with a modestly lower EC risk in observational multiethnic cohort studies, but they need not be universally avoided.³⁵

- *Osteoporosis:* Reports are conflicting, although a definite effect on osteoclast activity has been observed. Bone loss is said to be reduced. However, the preventive effects of isoflavones on bone loss and fat accumulation in early postmenopausal women depend on an individual's equol-producing capacity.³⁶ Genistein (54 mg/day), given alone, not only increases bone density in the lumbar spine and femoral neck but also improves the stiffness index, a measure of bone strength. Genistein and equol bind to beta-estrogen receptors and thus exert beneficial effects on bone.³⁷ A long-term 3-year umbrella meta-analysis of 63 trials found a significant increase in BMD at multiple sites and in bone turnover markers, without any effect on the uterus or breast, with isoflavone and vitamin D use.³⁸ To date, however, there are not many trials that have focused on an important endpoint, namely the reduction in the incidence of fractures.³⁹ A recent study examined the effects of genistein on bone loss in a randomised, double-blind, alendronate-controlled trial in postmenopausal women with glucocorticoid-induced osteoporosis (GIO). Two hundred postmenopausal women (taking at least 5 mg of prednisone equivalents) for 3 months or more, and expected to continue for at least another 12 months, were randomised to receive genistein (54 mg/day) or alendronate (70 mg once a week) for 24 months. Regarding bone markers, genistein and alendronate statistically decreased C-terminal telopeptide, while osteocalcin, bone-ALP, and sclerostin showed greater changes in genistein-treated patients. This randomised clinical trial suggests that genistein aglycone represents an additional therapeutic option for patients with GIO.⁴⁰
- Resveratrol, a phytoestrogen belonging to the stilbenes group found in the skin of grapes and red berries, has also been shown to improve BMD in the femoral neck and lumbar spine in postmenopausal women.⁴¹ Although well-designed clinical trials are needed to determine the therapeutic potential of phytoestrogens for bone health, these polyphenolic compounds are being considered cost-effective complementary preventive and therapeutic strategies for the treatment and prevention of postmenopausal osteoporosis.⁴²
- *Cognition:* The effects of soy and soy isoflavones on the cognitive function of postmenopausal women are uncertain at this time. Additional studies are needed to determine whether there is a critical window during the perimenopausal transition during which soy may affect cognitive function.⁴³

In induced menopause, there are no exclusive trials with the use of phytoestrogens. Otherwise, young women with severe, sudden symptoms also need immediate relief. A small-scale comparative study of the effects of phytoestrogens versus HT on menopausal symptoms in cases of surgical menopause showed that women on HT experienced a remarkable decrease in symptoms, with a significant reduction in hot flushes and vaginal dryness. In contrast, in the phytoestrogen group, symptomatology gradually decreased.⁴⁴ In an Indian multicentre trial, 80–90% relief from hot flushes, mood swings, sleep disturbances, and bony pain was observed in both the natural and surgical menopause groups after 3 month's use of 60 mg of isoflavones CR.⁴⁵

QOL (vasomotor, psychosexual, and physical subscales) with soya isoflavones was found to be significantly increased in a study conducted at Johns Hopkins University with 20 g of Soya protein (160 mg isoflavones), not with a placebo made from milk protein.⁴⁶

- *Suggested Intake of Whole Soy Foods:* Optimal cholesterol reduction appears to require approximately 50 mg/day of isoflavones; this amount is found in approximately 25 g/day of soy protein, which corresponds to the health claim allowed by the Food and Drug Administration (FDA). In limited studies, a minimum of 50 mg/day of isoflavones may benefit bone health. However, there are inadequate data to recommend a specific amount to prevent osteoporosis. Most studies on hot flushes have used isoflavone amounts of 40–80 mg/day, and this range may benefit vasomotor symptoms. These effects seem to be dose-related. The most effective dose is 54 mg/day. Genistein reduces the severity and frequency of hot Flushes.⁴⁷ Hence, the recommended intake of soy phytoestrogens is 40–50 mg/day. It is, however, pertinent to note that the Indian diet contains many phytoestrogenic substances. This fact needs to be explored and exploited. An example is Bengal gram, which has three times the estrogenic activity of soy because it contains biochanins (lignans) (Table 1).

Table 1: Types of SERMs and their clinical effects

<i>NAME</i>	<i>USES</i>	<i>EFFECTS/LOCATION</i>
Clomiphene	Anovulation	Antagonist at hypothalamus
Femarelle	Menopausal symptoms, osteoporosis	Agonist breast and bone
Ormeloxifene	Contraceptive	Agonist bone, antagonist breast and uterus
Raloxifene	Osteoporosis, breast cancer prevention	Agonist bone, antagonist breast and uterus
Tamoxifen	Breast cancer	Agonist bone, antagonist breast and uterus
Toremiphene	Breast cancer	Agonist bone, antagonist breast and uterus

Common Indian dietary sources of phytoestrogens are shown in Tables 2 and 3.

Table 2: Common Indian dietary sources of phytoestrogens

<i>Isoflavonoids</i>	<i>Lignans</i>	<i>Saponins</i>
Bengal gram	Linseed	Turmeric
Chick peas	Rye	Liquorice
Cherries	Millet	Ginger
Pareley	Bengal gram	Wild yam
Apples	All pulses	Fenugreek
Mung beans	Sesame and sunflower seeds	Beet root
Whole grains	Legumes and beans	Root vegetables
Alfalfa	Whole grains	Grains
Soya		
Red clover		

Table 3: Common Indian dietary herbs

<i>Name of Herb (common name) (botanical name)</i>	<i>Phytochemical</i>	<i>Actions and uses</i>
Turmeric (Haldi) (<i>Curcuma longa</i>)	Essential oil, resin, alkaloid, curcumin, tumerol	Anti-inflammatory (curcumin is a dual inhibitor of arachidonic acid metabolism). Antioxidant. (particularly by reducing lipid per oxidation). Favorably influences cardiovascular functions. Antimicrobial, inhibits carcinogenesis and tumor promotion.
Cumin (Jeera) (<i>Cuminum cyminum</i>)	Fatty oil, resin, mucilage, gum, protein compounds, maltase, and an essential oil "thymine" rich in corvine obtained from the seeds, contains cuminol or cumin aldehyde a mixture of hydrocarbons, cumene or cymol, terpene.	Seeds-carminative, aromatic, stomachic, stimulant, Astringent have a cooling effect. Anti-inflammatory effect on uterus, Increases lactation.
Fennel (Saunf) (<i>Foeniculum vulgarese</i>)	Oil, flavanoids, plant sterols	Inhibits prolactin, increases weight of reproductive organs.
Fenugreek (Methi) (<i>Trigonella foenumgraecum</i>)	Fresh vegetable contains albuminoids, soluble carbohydrates, albumin and globulin, tannin. Seeds contain a fetid, bitter essential fatty oil, resin, mucilage, albumin, coline and trigonelline (alkaloids), iron in organic form and saponin.	Seeds-mucilaginous demulcent and diuretic, tonic, carminative, emmenagogue, astringent, emollient and aphrodisiac, stimulate the appetite by their action on nervous system. Leaves-cooling and mild aperients. Also, increase lactation.
Cardamom (Ilaichi) (<i>Elattaria cardamomum</i>)	Volatile oil contains terpinyl acetate; cineole free terpinyl, limestone, potassium, starch ligneous fiber and ash containing Mn.	Carminative stimulant stomachic diuretic
Cinnamon	Volatile oil (cinnamaldehyde and eugenol), cinnamic acid, resin, tannin, sugar, mannit, mucilage, ash, etc.	Bark-carminative Antispasmodic Stimulant aromatic hemostatic astringent antiseptic stomachic and germicide. Oil is vascular and nervine stimulant. Used in amenorrhea.
Saffron (Kesar) (<i>Crocus sativus</i>)	Three coloring matters, oil, glucoside crocin, picocrocin, sugar and ash (K & P).	Stimulant Aphrodisiac and stomachic Slightly anodyne and antispasmodic Also has emmenagogue virtues Used in amenorrhoea, dysmenorrhea.
Liquorice (Mulathi) (<i>Glycyrrhiza glabra</i>)	Root-Glycyrrhizin, amorphous powder, isoliquirtin glycoside, asparagin, starch, acid resin, mucilage, phosphoric acid, sulphuric and malic acid, Ca and Mg salts, one steroid estrogen	Eases inflammation and tissue damage in the upper digestive tract Potentiates the anti-inflammatory effect of glucocorticoids, mimics
Ginger (Adrak) (<i>Zingiber officinale</i>)	Aromatic volatile oil contains camphene, phellandrene zingiberine cineol and burneol.	Aromatic Carminative Stimulant to gastrointestinal tract Also acts as a sialagogue and digestive.

Herbs

Different herbs have been used to treat menopausal symptoms. Therapy has focused on symptoms such as hot flushes, loss of libido, general fatigue and exhaustion, reduced ability to fight disease, and joint pain. Effects on the cardiovascular system and bone are emerging and are beginning to be elucidated. Herbs have been studied most extensively in Germany and have been licensed for use there. None of the herbs listed below has FDA approval for use as a drug. Sales, however, are permitted for healthy foods.

Indian herbs used during menopause are generally dietary herbs such as turmeric, ginger, fenugreek, linseed, cumin, fennel, saffron and cinnamon. As these have also been used in the West, their mechanisms of action and side effects are well documented (Table 3).

Certain medicinal herbs, such as ashoka, yashtimadhu, shankhpushpi, and shatavari, are purely indigenous and freely available, both singly and as multi-herbal preparations (Table 2). However, as indicated earlier, the exact mechanism of action and side effects of these herbs are not clearly known.

A summary of the better-known herbs is provided in Tables 4 and 5. Some of the herbs, such as ashwagandha, are also used in men and children, even though they may not be estrogenic; they are useful for symptomatic relief. Ashwagandha or Shatavari extracts have been found to be helpful in reducing overall menopausal symptoms, markers of vascular dysfunction and bone resorption, compared with placebo.⁴⁸

Table 4: Commercially available Indian herbs that can be used for menopausal symptoms

S.No.	Name	Parts used	uses
1.	Amalki (<i>Emblica officianlis</i>)	Dried fruit	Rejuvenator, cleanser, nourisher, balances doshas, especially “pitta”
2.	Anant Mool (<i>Hemidesmus indicus</i>)	Roots	Also called “Sarsaparilla”, blood purifier, promotes diaphoretic actions
3.	Arjuna (<i>Terminalia arjuna</i>)	Bark	Cardiac tonic, used for a variety of heart conditions
4.	Ashoka (<i>Saraca indica</i>)	Bark	Uterine tonic, maintains proper balance of reproductive system, used in bleeding disorders
5.	Ashwagandha (<i>Withania somnifera</i>)	Roots	Rejuvenating tonic, stress reliever, strengthens both body and mind
6.	Salai Guggul (<i>Boswellia serrata</i>)	Plant gum	Reduces pain and inflammation of joints
7.	Brahmi (<i>Hydrocotyle asciaeica</i>)	Roots	Rejuvenates nerves and brain, increases mental clarity, promotes memory and intelligence
8.	Eranda (<i>Ricinus Communis</i>)	Roots	Used for rheumatic conditions and body aches
9.	Gokshura (<i>Tribulus terrestris</i>)	Fruit	Rejuvenating herb for urinary tract and prostatic conditions
10.	Guduchi (<i>Tinospora cordifolia</i>)	Stem	Bitter herb, balances all doshas
11.	Guggulu (<i>Comifora mukul</i>)	Resin	Detoxifying agent. Used to remove impurities from tissues and assist in normal function of joints and nervous system.
12.	Haritaki (<i>Terminalia chebula</i>)	Fruit	Rejuvenates, balances all doshas especially “vatta”
13.	Hibiscus (<i>Hibiscus rosa</i>)	Flower	Cooling herb for flushes, supports functions of kidney
14.	Kapi Kachhu (<i>Mucuna prurita</i>)	Seed	Calms both “vatta” and “pitta”. Used for imbalance of kidney and nervous system

15.	Musta (Cypru rotundus)	Roots	Cooling herb, used to soothe fevers, support digestion and regulate menstrual cycle
16.	Nirgundi (Vitex negundo)	Leaves	Bitter herb, analgesic, anti-inflammatory and carminative
17.	Sandalwood (Sanalam albul)	Wood	Cooling, fragrant powder, used to help lighten and concentrate the mind
18.	Shatawari (Asparagus racemosus)	Roots	Sweet, bitter, cooling herb for body and mind
19.	Vidari Kanda (Ipomomea bigitata)	Roots	Sweet nutritive tonic used as an aphrodisiac and for general debility
20.	Yashti Madhu (Glycyrrhiza glabra)	Roots	Rejuvenator, also acts in menstrual irregularities

Table 5: Common Western herbs used in menopause. Herbs judged possibly effective for perimenopausal symptoms by Germany's Commission

<i>Herbal therapy</i>	<i>Lay press claim</i>	<i>Evidence</i>	<i>Adverse effects</i>	<i>Recommendations</i>
Balm (Melissa officinalis)	Relief of tension, anxiety, stress reactions and depression	Has sedative, antispasmodic, officinalis) antihormonal, and antiviral actions in various animal models; approved by Commission E for treatment of nervous disturbances	No information available, but should be used with caution	Use with caution; a tincture of 2-6 mL 3 times a day, or 2-3 tsp dried herb steeped in 1 cup boiling water 2 times per day.
Black cohosh (Cimicifuga racemosa)	Said to be source of estrogen and progesterone	Approved by Commission E for treatment of dysmenorrhea, PMS, and nervous conditions associated with the menopause	Data on toxicity are limited; ingestion of leaves and roots may cause nausea and vomiting; additive hypotensive effects may occur in patients taking black cohosh along with antihypertensive agents	Commission E recommends doses of 40-200 mg/day, not to exceed 6 months; usually taken as a decoction or ethanol tincture in amounts corresponding to stated dosage
Chaste tree, chasteberry (Vitex agnus castus)	Popular in Europe for treating symptoms of PMS and the menopause; reputed to have both aphrodisiac and anaphrodisiac properties	Approved by Commission E for PMS, mastalgia, menopausal symptoms, and poor lactation; may inhibit secretion of prolactin	May cause an itchy rash and gastrointestinal discomfort; may interact with dopamine- receptor antagonists	Prepared as a tincture; extract provides an average daily dose equal to 20 mg of the crude fruit or 30-40 mg fruit in a decoction

Ginkgo (Ginkgo biloba)	Suggested that herb improves memory and relieves senility	Effective in the treatment of circulatory disorders, vertigo, tinnitus, dementia, mood swings; postulated to act as a free radical scavenger	Gastrointestinal disturbances, headache, allergic reactions; larger doses may produce restlessness; may reduce clotting time, so should be used with caution in patients receiving anticoagulants; severe poison ivy-like dermatitis may occur after contact with fruit pulp	120–160 mg/day of standardized ginkgo leaf extract
Ginseng (Panax quinquefolius)	Considered a “wonder herb” by the Chinese, who have used it for >5,000 years	Controversy exists in the scientific literature regarding its merits; no evidence of efficacy in humans; approved by Commission E to treat fatigue, diminished work capacity, and loss of concentration, but use not to exceed 3 months	Various adverse effects reported; women should be cautioned not to take with hormone therapy in light of case reports of uterine bleeding	Various adverse effects reported; women should be cautioned not to take with hormone therapy in light of case reports of uterine bleeding
Passion flower (Passiflora incarnata)	Said to relieve anxiety, insomnia, restlessness and muscle tension	Insufficient evidence of efficacy or safety; approved by Commission E for “nervous unrest” conditions	Little information available	Insufficient information available
St. John’ wort (Hypericum perforatum)	Touted as a mild tranquilizer, an antidepressant, and an aid for menstrual cramps	Four published clinical trails since 1987 show efficacy in depression compared with placebo	May cause photodermatitis; until further information is available, patients should be aware of possible food and drug interaction warning similar to those that apply to traditional MAO inhibitors	Usual dosage is 2-4 g hypericin in capsule form, 1–2 times per day
Valerian	Said to have sedative and anti-anxiety properties; widely used in France	Approved by the Commission E as a “sedative and sleep-inducing preparation to mediate states of excitation and difficulty falling asleep due to nervousness”; studies in humans support a tranquilizing, sedative and hypertonic effect	Generally thought to be safe, but has been linked to 4 cases of severe liver damage, headaches, excitability, uneasiness and cardiac changes reported in controlled clinical trails; not all active ingredients have been identified	1–2 commercial capsules HS; 2-3 g once or twice a day as an anti-anxiety regimen

CLINICAL PRACTICE OF CAMS IN MENOPAUSE MEDICINE

These are available in a variety of formulations and may be given to women as first-line therapy. If they do not prove beneficial, she may be referred to a good herbalist who can prescribe them for her, based on the Unani/Ayurvedic principles of medicine.

Phytoestrogens and herbs are generating interest among consumers and healthcare providers worldwide as alternatives to HT, especially given the confusion caused by the WHI and the Million Women Study. New products extracted from soy are being developed. One such scientifically researched pill, with the active ingredient isoflavone DT56a, called the “tofu pill”, is also being marketed in India. An RCT of the tofu pill/Femarelle (DT56a) found an increase in lumbar spine BMD of 3.6% at higher doses. It reduces hot flushes and other menopausal symptoms, appears endometrium-sparing, and functions as a phyto-SERM, so flexible dosing is possible with a good safety profile.⁴⁹

Ipriflavone is another such product developed for bone health. A meta-analysis of 63 RCTs concluded that Ipriflavone at 600mg/day and genistein at 54 mg /day were associated with significant improvement in BMD and appear to be effective and safe.⁵⁰

Narrative review of 8 RCTs, including 8,769 women, found that red clover isoflavones improved a broad range of menopausal symptoms, including hot flushes, lipid profiles, bone density, and cognitive impairment, and reduced the risk of breast and endometrial cancer.⁵¹

Most Indian companies also recognise the importance of Indian trials, and almost all have conducted small (though unpublished) trials of their own products, which can be found on the internet. An Indian study found improvement in MRS, with the greatest gain in somatic and psychological symptoms, the least improvement in urogenital symptoms, and no significant change in BMI and BP with soy isoflavone 40 mg twice daily for 12 weeks.⁵²

Unfortunately, herbal formulations pose a complex problem. Most companies use similar herb combinations, but in different dosages or forms, and with different claims. The function of individual herbs remains unclear to both physicians and pharmaceutical companies.

Companies cannot substantiate their claims with trials, nor can they interpret the effects of their products using the principles of modern medicine. Some Indian herbs have been scientifically tested in the past, such as Rauwolfia alkaloids for hypertension and Arjuna for cardioprotection. These are used by physicians.

Rhapontic rhubarb extract (ERr731) systematic review and meta-analysis support its efficacy in relieving menopausal symptoms; a recent German case-control study also found no increase in breast cancer.⁵³

Well-designed large trials are desperately needed to understand the mechanisms of action, clinical indications and side effects of these indigenous formulations in menopausal medicine.

FUTURE DIRECTIONS FOR HERB USE IN MENOPAUSE

Given the mindset of Indian consumers and physicians, it is recommended that herbs and phytoestrogens not be dismissed as “quackery”. These have been used by humans since time immemorial. Physicians in every civilisation have emphasised the importance of a good, nourishing diet, eating what is locally available and relevant to the season. The story of “Soy” has proven to be true.

Therefore, the time has now come to validate the effects of locally used herbs in the Indian context, in line with modern science and medicine, and to prescribe them rationally, using clinical research tools and well-designed, documented RCTs. When prescribing or recommending herbs, it would be essential to fully inform women that very little human data is available on the usefulness of these formulations, but that they can nonetheless be used on a trial basis to evaluate their effectiveness in symptomatic relief. It is also important to convey that the side effects of the herbs have not been studied.

OTHERS

- *Red clover*: Studies have shown effects on phytoestrogens, steroidogenesis, antioxidant activity, calcium metabolism, cell growth and differentiation, and anticancer activity (available in India).⁵⁴ Several studies of a proprietary extract of red clover isoflavones (80 mg) suggest that it may significantly reduce (44%) hot flushes in menopausal women.⁵⁵ Beneficial effects on CVS function (regulation of blood glucose and lipid markers) and

improvement in menopausal symptoms were reported.⁵⁶ Red clover is reported to be safe and well-tolerated in women with a family history of breast cancer.⁵⁷ However, most oncology and menopause society guidelines (International Menopause Society (IMS), North American Menopause Society (NAMS)) recommend avoiding red clover in women with a history of breast cancer until more definitive evidence is available.

- *Black cohosh (Actaea racemosa)*: has been widely used in Germany for years to reduce the intensity and frequency of hot flushes. In the black cohosh group (dose 40 mg/day), the daily number of sweating episodes and sleep quality parameters were assessed compared with placebo.⁵⁸ There has been one human study, which evaluated the efficacy of a topical treatment of black cohosh in diminishing wrinkles.⁵⁹ The clinical trials have shown severe hepatotoxicity. A recent RCT assessed the combined effect of Black Cohosh, Soy isoflavones and SDG lignans and reported improvement in the MRS; Somatic, psychological and urogenital symptoms.⁶⁰
- *Ginseng*: Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) have traditionally been used as tonics and have been shown to increase the maturation index, with no effect on vasomotor symptoms, sex drive or sexual function, but with slight improvements in depression, anxiety and vitality (100–600 mg/day).⁶¹ Korean red ginseng has been reported to improve insomnia, depression and fatigue in postmenopausal women (6 gm for 30 days), with no increase in dehydroepiandrosterone sulphate (DHEA-S) levels.⁶² An Umbrella review of 19 meta-analyses of ginseng showed that it may reduce menopausal symptoms and hot Flushes, but the evidence quality is low.⁶³
- *St. John's Wort (Hypericum perforatum)* is widely used for psychological disturbances during menopause at standard antidepressant dosages (500–600 mg/day).^{64,65} Various studies have found that it can alleviate depression and hot flushes, but the evidence is limited, and more research is needed.
- *Dong quai (Angelica sinensis)*: has been used as a tonic in TCM for many centuries (not for menopause), often combined with other herbs. The usual dose is 3–6 g/day in three doses.⁶⁶
- *Kava kava (Piper methysticum)*: a plant native to the South Pacific, is used for medicinal purposes. Many cases of liver damage and even some deaths have been linked to kava use. As a result, kava has been banned from the market in Switzerland, Germany and Canada, and several other countries are considering similar action. These are not available in India.⁶⁷
- *Evening primrose (Oenothera biennis)*: oil is extracted from the wildflower's seeds and is rich in linoleic acid. It is standardised to 320–360 mg of linoleic acid and 40 mg of gamma-linolenic acid per capsule (dose: 1.5–3 g/day). It is well tolerated but has gastrointestinal (GI) side effects and has been reported to cause immunosuppression, thrombosis, and inflammation, and to increase seizures; the benefit for hot flushes is doubtful.⁶⁸
- *Wild yam (Dioscorea villosa)*: contains diosgenin, which cannot be converted in the body and is converted in the lab to make several steroids, including progesterone. Replacing two-thirds of staple foods with yams for 30 days improves the status of sex hormones, lipids and antioxidants. These effects might reduce the risk of breast cancer and cardiovascular diseases in postmenopausal women.⁶⁹ To date, very few human studies have been published, so leading medical bodies do not endorse wild yam for menopausal symptom relief.
- All the Western herbs are well studied, but their effects on the Indian population are unknown. It is important to study their effects on the Indian woman. Many Indian pharma companies are promoting the use of isoflavones and herbs after the WHI study, as sales of HT dropped. Most Indian companies also recognise the importance of Indian trials, and practically all have conducted small (though unpublished) trials of their own products, which can be found on the internet.

Guidelines

The World Health Organisation has developed a traditional medicine strategy which recommends further research to understand the effects and safety of traditional medicine.⁷⁰

Most International Menopause Societies do not recommend phytoestrogens as the primary preventive or treatment strategy for menopause, as evidence for their efficacy and safety in managing menopausal symptoms remains limited and their efficacy in symptom relief remains unproven. At the same time, they have not written them off, as larger studies are still pending.

The Asia-Pacific Menopause Federation (APMF) Consensus Statement on the Management of Menopause states that several CAM treatments can be safely integrated into care, although their effectiveness has not been adequately studied in many cases. Most complementary and alternative treatments lack evidence-based support. There will always be individuals who benefit from some of these treatments, sometimes for a short period and sometimes longer.⁷¹

The NAMS recommends Selective Serotonin Reuptake Inhibitors (SSRIs), Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs), gabapentin, pregabalin, clonidine, CBT and clinical hypnosis to help alleviate menopausal symptoms.⁷² According to the updated IMS recommendations on preventive strategies for midlife health, high-quality studies to date have not consistently supported the efficacy of complementary or over-the-counter therapies in reducing the severity or frequency of hot flashes or night sweats.⁷³ A formal, updated position statement from the IMS that may provide more clarity, including on specific CAM modalities, is expected in 2026.

Ongoing research on complementary therapies is warranted, given favourable data from small clinical trials. Still, proper regulation of their sale is vital to ensure ethical, safe and cost-effective management of menopause, according to the British Menopause Society (BMS).⁷⁴

The Indian Menopause Society recommends raising awareness of the phytoestrogen-rich foods in the Indian diet. Extracts and capsules of phytoestrogens have not yet been adequately researched for the long term, either internationally or in India.⁷⁵ Prescription of CAM by an allopathic doctor is not legally suggested. Still, during counselling for options, balanced communication with evidence-based medicine is required. If a herbal treatment is chosen, patients should look for the Traditional Herbal Remedy (THR) stamp, which validates the strength and quality.⁷⁶

SYNOPSIS

- Global interest in complementary and alternative medicine, especially soy-based products, is rising due to greater consumer awareness and controversies surrounding HT.
- Given the mindset of Indian consumers and physicians, it is now recommended to validate the effects of locally used herbs in the Indian context, in line with modern medicine, and to prescribe them rationally, using clinical research tools and well-designed, well-documented RCTs.
- The data regarding estrogenic effects of soy are still inconclusive; hence, women with a personal or strong family history of hormone-dependent cancers (breast, uterine, or ovarian) or thromboembolic or cardiovascular events should be cautioned about soy-based therapies.
- Women currently access numerous complementary therapies as first-line treatments for managing menopause before professional help is sought. Whilst these preparations are unlikely to cause harm, they can occasionally lead to significant adverse effects and are usually ineffective.
- As clinicians, we must be familiar with alternative therapies to help inform and guide women as to which options are most likely to be beneficial to them.
- An integrated approach is of utmost importance to address the multifaceted challenges of menopause, also for research and evidence-based clinical practice.

RESEARCH AGENDA

Investigating cultural adaptations, and clarifying how Meditation, mindfulness, and acceptance methods (MMA) constructs can be measured within individual psychotherapy for training recommendations and therapeutic practices.⁷⁷

Research on cognitive-behavioural, behavioural, and mindfulness-based therapies (CBBMBs) with more diverse samples and head-to-head comparisons is needed. Dissemination of CBBMBs for insomnia in clinics where menopausal women seek care is an essential next step.⁷⁸

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Section 10

ENDOCRINES AND MENOPAUSE

42. Menopause And Body Composition,Insulin Resistance ,Metabolic Syndrome

43. Diabetes and Thyroid At Menopause

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MENOPAUSE & BODY COMPOSITION, INSULIN RESISTANCE AND METABOLIC SYNDROME

42

Keywords: Body composition, obesity, metabolic syndrome, insulin resistance

INTRODUCTION

With increasing life expectancy, women may now spend nearly 30–40% of their lives in the postmenopausal period, with important implications for long-term health and quality of life (QoL).¹ The menopausal transition (MT) is characterised by a decline in estrogen levels, leading to significant physiological and metabolic alterations involving lipid metabolism, energy expenditure, insulin sensitivity, and adipose tissue distribution.¹ Although overall weight gain in midlife is largely attributable to chronological ageing, menopause independently accelerates visceral fat accumulation and lean mass decline. A characteristic shift in body fat distribution from a gynoid to an android pattern is commonly observed. This redistribution of fat is strongly associated with adverse cardiometabolic risk profiles.¹ Consequently, the postmenopausal state is accompanied by a marked increase in insulin resistance (IR), dyslipidemia, and the risk of type 2 diabetes mellitus (T2DM), collectively contributing to a substantial rise in cardiovascular disease (CVD) risk.^{2,3}

Obesity in postmenopausal women is linked to adverse metabolic effects and is a major risk factor for CVD, including coronary heart disease, stroke, and hypertension.⁴ It also increases the risk of T2DM, certain cancers (endometrial, breast and colon), urinary incontinence, dementia, and musculoskeletal disorders like osteoarthritis. Additionally, obesity negatively impacts bone health and health-related QoL.⁴ Understanding the interplay between menopause, body composition, and metabolic dysfunction is therefore essential for developing effective preventive and therapeutic strategies in midlife and beyond.

MENOPAUSE AND BODY COMPOSITION

Effect of Menopause on Weight and Body Composition

The MT is associated with progressive changes in body composition (BC), characterised by modest weight gain and a preferential redistribution of adipose tissue toward the abdominal compartment. On an average, women gain approximately 0.5–0.7 kg per year between 50 and 60 years of age, regardless of baseline body mass index (BMI) or racial and ethnic background.^{5,6} Evidence indicates that weight gain during this period is largely attributable to chronological ageing, rather than menopause per se. However, menopause independently accelerates visceral fat accumulation and loss of lean mass, which are primarily driven by ovarian ageing and decline in estrogen levels.^{5,7,8}

Weight gain during midlife is also influenced by lifestyle and metabolic factors, including reduced physical activity, excess caloric intake, declining resting energy expenditure due to loss of lean mass, sleep disturbance related to vasomotor symptoms (VMS), shift work, genetic predisposition, and use of psychotropic medications or chemotherapy.^{6,9} Persistent weight gain during this period can contribute to the onset or progression of obesity. Importantly, changes in BC may occur even in the absence of substantial weight gain, underscoring the limitation of body weight or BMI as a sole indicator of metabolic risk.^{7,8}

Longitudinal data from the Study of Women's Health Across the Nation (SWAN) provide critical insight into menopause-related changes in BC.⁷ Approximately two years before the final menstrual period (FMP), the rate of fat mass accumulation doubles, and lean mass begins to decline. These changes continue until nearly two years after the FMP, after which both fat gain and lean mass loss plateau. In contrast, body weight increases steadily across midlife, without acceleration during the MT. These findings highlight that menopause is characterised by accelerated fat gain and lean mass loss, without a parallel increase in overall body weight, emphasising body composition rather than weight as the principal metabolic change during this period.⁷

Menopause-related alterations in BC affect multiple tissue compartments. Declining bone mineral density (BMD) predisposes to osteoporosis; loss of skeletal muscle mass leads to sarcopenia; cartilage degeneration contributes to osteoarthritis; and visceral fat accumulation increases cardiometabolic risk. The coexistence of increased fat mass and

reduced muscle mass predisposes to sarcopenic obesity, a condition associated with functional impairment, IR, and CVD.^{8,10}

Significant increases in total fat mass, percentage fat mass, truncal fat mass, and visceral adiposity have been demonstrated in longitudinal cohorts of non-obese, premenopausal women, transitioning through menopause. Visceral fat may increase from approximately 5–8% of total fat mass in premenopausal women to 15–20% after menopause, independent of overall weight change.^{7,8,11}

Visceral Adiposity and Metabolic Risk

Abdominal adiposity, assessed by waist circumference (WC) and waist-to-hip ratio, is more strongly linked to adverse metabolic outcomes and mortality than overall body weight or BMI in postmenopausal women.^{12,13} Android fat deposition is associated with a higher risk of hypertriglyceridemia, small dense low-density lipoprotein (LDL) particles, IR, T2DM, hypertension, and increased cardiovascular and all-cause mortality, even in women with a normal BMI.^{1,11,12} Thus, measures of central adiposity, such as WC and waist-to-hip ratio, along with BC assessments using dual-energy X-ray absorptiometry (DXA) or magnetic resonance imaging (MRI), provide more clinically meaningful insights into cardiometabolic risk in this population than body weight alone.^{8,12,14}

Menopause, Ageing and Adipose Tissue

Adipose tissue is an active endocrine organ that secretes adipokines, such as adiponectin and leptin, which regulate insulin sensitivity, inflammation, and vascular function. Adiponectin levels decline with increasing adiposity; this adipokine exerts anti-inflammatory, insulin-sensitising, and anti-atherogenic effects.⁶ In contrast, leptin levels are elevated in obesity due to leptin resistance, and are associated with a pro-inflammatory and pro-atherogenic milieu.^{8,12} These adipokine alterations promote IR and metabolic syndrome (MetS) in postmenopausal women. Although adipose tissue does not synthesise steroid hormones *de novo*, it plays an important role in the uptake, storage, conversion, and local metabolism of sex steroids. Adipocytes express estrogen receptors (Ers), androgen receptors (Ars), and enzymes involved in steroid metabolism, thus influencing regional fat distribution.¹¹ Age, sex, genetic predisposition, and ethnicity are important determinants of individual variability in visceral adipose tissue accumulation.¹³

Estrogen exerts site-specific effects on adipose tissue through ERs expressed on adipocytes. It promotes lipolysis in visceral fat while inhibiting lipolysis in subcutaneous fat. As a key regulator of adiposity, estrogen, particularly estradiol (E2), facilitates the preferential accumulation of subcutaneous fat.⁶ In contrast, androgens positively correlate with abdominal fat accumulation.¹⁵ Estrogens may down-regulate AR density in female adipose tissue, thereby attenuating androgen-mediated fat deposition.^{16,17}

During the reproductive years, estrogen promotes preferential fat distribution towards the subcutaneous gluteofemoral depot, while limiting visceral fat accumulation. Lipoprotein lipase (LPL) is a key enzyme regulating intracellular triglyceride storage. In premenopausal women, LPL activity is significantly higher in femoral and gluteal adipose tissue than in subcutaneous abdominal fat, contributing to the preferential deposition of fat in the gluteofemoral region.^{18,19} The android (around the trunk, upper body, abdomen, chest, shoulders and nape of the neck) and gynoid (around the gluteal and femoral region) distribution of adipose tissue may partially explain the greater CVD risk in men compared with premenopausal women.²⁰

After menopause, declining estrogen levels are accompanied by reduced sex hormone-binding globulin (SHBG), which increases the proportion of bioavailable (free) testosterone. This relative increase in active androgen exposure promotes visceral fat accumulation. Thus, the marked decline in circulating estrogen levels and low SHBG after menopause, combined with relative hyperandrogenism, is therefore thought to contribute to increased visceral fat accumulation in postmenopausal women.²¹

Ferrara and colleagues demonstrated depot-specific metabolic alterations in adipose tissue between perimenopausal and postmenopausal women matched for race and total body fat. Despite minimal age differences (approximately 5–6 years), postmenopausal women exhibited higher LPL activity in both gluteal and abdominal depots, suggesting a metabolic environment favouring fat storage and reduced lipolytic responsiveness. The authors concluded that menopause is associated with depot-specific alterations in adipose tissue metabolism in both gluteal and abdominal regions. These metabolic changes predispose postmenopausal women to increased fat accumulation.²²

Ageing and menopause therefore synergistically promote redistribution of adipose tissue toward visceral

compartments, contributing to IR, sarcopenia, osteoporosis, and heightened cardiometabolic risk. The shift from a gynoid to an android pattern of fat distribution partly explains the rise in CVD risk observed after menopause.

Menopause Hormone Therapy: Weight and Body Composition

Menopause hormone therapy (MHT) primarily influences fat distribution, rather than total body weight. Overall, MHT does not cause significant weight gain or loss, but it may attenuate central (abdominal/visceral) fat accumulation and may modestly improve body composition.

Effects on Weight

Large randomised controlled trials (RCTs) and cohort studies demonstrate no clinically meaningful difference in overall weight gain between women using MHT and those not using it over 1–3 years.^{23–28} Some trials report slightly less weight gain with MHT (approximately 0.5–1 kg over several years), although the magnitude of effect is small.^{25,28,29} A surgical menopause study (risk-reducing salpingo-oophorectomy, RRSO) similarly found no significant effect of hormone replacement therapy (HRT) on weight at 24 months.²⁶

Effects on Body Composition and Fat Distribution

Evidence from RCTs and imaging studies indicates that MHT may reduce visceral (intra-abdominal) fat accumulation after menopause, resulting in lower visceral adipose tissue (VAT) and android fat compared with placebo.^{24,30–34} Current MHT users have lower BMI, visceral fat, and android fat than never-users, but these benefits disappear after discontinuation.³¹ Certain regimens (estradiol + norethisterone, tibolone: estradiol with testosterone) have been associated with increased lean mass and reduced android fat.^{30,35} In obese women, HT users show less visceral fat and lower total fat mass compared with nonusers, despite similar insulin sensitivity.³⁶

While MHT does not significantly alter total body weight, it may exert beneficial effects on fat distribution by limiting central fat gain and modestly preserving lean mass. The magnitude of benefit is small but may contribute to improved cardiometabolic profiles in early postmenopausal women.

Effect of Oral vs Transdermal Estrogen Therapy

The metabolic and body-composition effects of MHT vary by route of estrogen administration, largely due to differences in hepatic first-pass metabolism.^{37,38} Oral estrogen undergoes significant first-pass hepatic metabolism, resulting in higher circulating levels of estrone and estrone sulfate and greater hepatic exposure, whereas transdermal estradiol bypasses this process and maintains more physiologic hormone levels. These differences influence endocrine function, particularly the GH-IGF-1 axis: oral estrogen reduces IGF-1 and increases growth hormone, reflecting decreased hepatic IGF-1 production and leading to reduced anabolic signalling and altered fat metabolism, while transdermal estrogen preserves a more balanced profile.^{39–41} Metabolically, oral estrogen suppresses lipid oxidation and increases carbohydrate oxidation without affecting total energy expenditure, whereas transdermal estrogen does not impair lipid oxidation. In terms of body composition, oral estrogen is associated with a small increase in fat mass and a decrease in lean mass, while transdermal estrogen has minimal impact on fat mass, lean body mass, or visceral fat. Despite these differences, oral estrogen, particularly when combined with progestogen, has been associated with improved insulin sensitivity and a reduced risk of type 2 diabetes, whereas transdermal estrogen tends to have a more neutral metabolic effect.

OBESITY IN MIDLIFE & POSTMENOPAUSAL WOMEN

Obesity is a dysfunctional storage of excess energy and is a serious, treatable, chronic disease. The American Association of Clinical Endocrinology (AACE) has coined a new term for obesity -ABCD or Adiposity-Based Chronic Disease, to highlight the need to recognise it as a chronic disease.⁴² Obesity is characterised by abnormal or excessive fat accumulation that impairs health and predisposes individuals to CVD, metabolic syndrome, and cancer.⁴ The aetiology of obesity is multifactorial, resulting from complex interactions among genetic and epigenetic susceptibility, neurobehavioral pathways, endocrine and immune mechanisms, environmental and sociocultural influences, and medical factors.^{42–44} These interconnected factors affect energy balance, adipose tissue function, and long-term weight regulation, underscoring the need for comprehensive, individualised management approaches.⁴² Certain medications and diseases are also associated with weight gain.⁴⁵

Obesity is a recurring pro-inflammatory state resulting from an imbalance between calorie intake and energy expenditure.⁴⁶ Total energy expenditure (TEE) consists of three primary components: basal or resting metabolic rate

(BMR or REE), the thermic effect of food (TEF), and energy spent through physical activity. In adults, BMR accounts for approximately 60–70% of TEE, with TEF contributing about 10% and physical activity accounting for the remaining 20–30%. BMR decreases linearly with age and is notably lower in postmenopausal women compared to age-matched premenopausal controls.⁴⁷ This decline is partially attributed to reductions in both the quantity and metabolic activity of lean tissue with ageing. Loss of skeletal muscle with ageing and menopause decreases basal metabolic demand, and fat accumulation further diminishes energy expenditure since adipose tissue has a lower metabolic rate than lean tissue.⁴⁸ Although TEF contributes modestly to TEE, evidence suggests the thermic response to food is reduced with ageing, further lowering total energy expenditure in older adults.⁴⁹ Physical activity and non-exercise activity thermogenesis remain the most variable components of TEE, influenced by and varying with exercise frequency, intensity, and duration. Adipocyte number and function influence energy expenditure and are regulated by numerous genomic and non-genomic factors.⁴⁸

Epidemiology of Obesity

Worldwide adult obesity has more than doubled since 1990. By 2022, an estimated 2.5 billion adults were classified as overweight, of whom 890 million or approximately one in eight people in the world, were living with obesity.⁴ Data from *The Lancet* highlight the growing burden of obesity in India, particularly in urban populations. India ranks third globally in absolute numbers of individuals with obesity, following the US and China. Between 1990 and 2022, the prevalence of obesity among Indian women increased by 94% across 188 countries. The incidence of obesity surged by 9% among women, amounting to 4.4 crore, and 5% among men, totalling 2.6 crore.⁵⁰ The proportion of overweight and obese women increases from 4% at a younger age to 34% at middle and older age. This steep increase in the prevalence of obesity in women coincides with the onset of the MT, suggesting a critical window of vulnerability. Nearly 401 million perimenopausal women in India may be predisposed to the risk of menopausal obesity by 2026.⁵¹ Data from 2020 in menopausal women aged 40–60 years showed a high prevalence of excess weight, even in rural populations, with approximately 35.5% classified as overweight or obese (26% overweight and 9.5% obese).⁵² This substantial burden highlights the need for focused attention and a multidisciplinary approach to address overweight and obesity during menopause and reduce long-term morbidity.

Abdominal obesity represents a particularly significant concern. In India, approximately 40% of women are affected by central adiposity, with prevalence highest among women aged 30–49 years, in whom 5–6 out of 10 are abdominally obese. The burden is disproportionately higher in older, urban, wealthier, and non-vegetarian women.⁵³ Findings from the Indian Council of Medical Research – India Diabetes (ICMR-INDIAB) study further underscore this trend, reporting an overall prevalence of abdominal obesity of 39.5%, with substantially higher rates in women (49.6%) than in men (28.8%). Among women, prevalence increased progressively with age, from 28.0% at 20–29 years to 46.0%, 55.2%, and 57.9% in the 30–39, 40–49, and 50–59-year groups, respectively, before declining slightly to 52.4% among those aged 60 years and above.⁵⁴

Health Impact of Obesity

The consequences of obesity can be broadly categorised into cardiometabolic, mechanical, and psychological domains. Obesity and changes in body composition after menopause are major drivers of cardiometabolic diseases such as T2DM, dyslipidemia, hypertension, CVD, hyperuricemia, metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic dysfunction-associated steatohepatitis (MASH), cholelithiasis, polycystic ovary syndrome (PCOS) and MetS.^{55–58} Mechanical issues comprise obstructive sleep apnoea, hypoventilation, osteoarthritis, chronic pain, gastroesophageal reflux disease, urinary incontinence, intertrigo, venous stasis and thrombosis. Psychological impact of obesity manifests as anxiety and depression, low self-esteem, eating disorders, addictions, psychosis, attention deficit, insomnia, posttraumatic stress disorder and cognitive impairment.^{58, 59}

Central and visceral fat accumulation also increases the risk of gynaecologic (endometrial, breast, ovarian) and non-gynaecologic malignancies (colorectal, esophageal, kidney, gallbladder, pancreatic, liver, stomach, and thyroid).^{60,61} Obesity has been found to be protective against breast cancer in premenopausal women, significant mainly among Europeans, but increases breast cancer risk after menopause across Asian, European, North American, and African populations, due to higher postmenopausal estrogen from peripheral aromatisation.^{62–65} Obesity is associated with an increased risk of cervical cancer, particularly adenocarcinoma, and with lower detection rates of precancerous lesions, and the association is consistent but less robust than that for endometrial or breast cancer.⁶⁶

Beyond cardiometabolic and oncologic consequences, obesity also adversely affects bone health and health-related QoL.^{67–70} Postmenopausal women with obesity are up to four times more likely to report vulvovaginal itching and

irritation and have a higher prevalence of urinary incontinence and urgency compared with women of normal weight.⁵⁶

The association between adiposity and VM varies across the MT. Higher central adiposity is linked to more frequent and severe VMS in early menopause, though this relationship may weaken or reverse later.⁵⁶ Weight gain itself has not been consistently shown to increase VMS, but lifestyle-related weight loss can reduce symptom burden.⁷¹ Altered thermoregulation and adipokine changes (such as elevated leptin) may partly explain these findings.⁷²

Obesity and Breast Cancer

The association between obesity and breast cancer is multifactorial and varies by menopausal status. In postmenopausal women, adipose tissue becomes the principal source of estrogen through aromatisation of androgens, leading to higher circulating estradiol concentrations and an increased risk of estrogen receptor-positive breast cancer.^{73,74} Excess body fatness has been classified as a causal factor for postmenopausal breast cancer.⁷³

In addition to estrogen-mediated effects, obesity promotes breast carcinogenesis through several estrogen-independent pathways. Visceral adiposity is associated with insulin resistance, hyperinsulinemia, and increased insulin-like growth factor-1 (IGF-1) signalling, which enhances cellular proliferation and inhibits apoptosis.⁷⁵ Chronic low-grade inflammation within adipose tissue further contributes to tumorigenesis through increased leptin secretion, macrophage activation, and elevated pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF- α), promoting angiogenesis and tumour progression.^{75,76} Conversely, adiponectin, an adipokine with insulin-sensitising and anti-proliferative properties, is reduced in obesity and has been inversely associated with breast cancer risk.⁷⁵ Weight control, particularly after menopause, may therefore reduce breast cancer risk by modulating estrogen production, insulin signalling, and inflammatory pathways.⁷⁶

Menopause and Sarcopenic Obesity

Sarcopenic obesity represents a high-risk phenotype, characterised by the coexistence of excess adiposity with reduced muscle mass and strength, most commonly seen in older adults.⁵⁸ Reduced exercise capacity and declining physical activity during the MT, together with estrogen deficiency, contribute to visceral fat accumulation and accelerated skeletal muscle loss, thereby increasing cardiometabolic and functional risk.^{77,78} Recent longitudinal evidence confirms that significant loss of skeletal muscle mass occurs during the MT independent of ageing, implicating hormonal changes as a key driver of menopause-related sarcopenia.⁷⁹ Sarcopenic obesity is associated with greater functional impairment, frailty, falls, and disability compared with obesity or sarcopenia alone.⁸⁰ In addition, sarcopenic obesity confers amplified cardiometabolic risk due to increased insulin resistance, chronic low-grade inflammation, and adverse lipid profiles, and has been linked to higher all-cause and cardiovascular mortality.^{80,81} Poorer surgical outcomes and reduced tolerance to treatment in chronic disease states have also been reported.⁸¹

Importantly, unstructured weight loss without exercise may worsen muscle depletion. Higher levels of physical activity attenuate this decline, highlighting exercise as a modifiable protective factor.⁷⁹ Exercise training effectively improves body composition by increasing muscle mass, simultaneously reducing fat mass in postmenopausal women.⁸² Management should therefore emphasise intentional weight loss combined with structured physical activity, particularly resistance training alongside aerobic exercise, to preserve lean mass, improve physical function, and reduce metabolic risk. Nutritional strategies, including adequate protein intake, are integral to this approach.⁸⁰

Obesity of Bone

Although obesity is associated with higher bone mineral density (BMD), it does not uniformly protect against fracture. Data from the Global Longitudinal Study of Osteoporosis in Women (GLOW) demonstrated site-specific risk⁸³: obese women are at increased risk of fracture in the ankle, leg, humerus, and vertebral column and at lower risk of wrist, hip and pelvis fracture when compared to non-obese women.⁸⁴⁻⁸⁵

Excess adiposity, particularly visceral fat, may adversely affect bone quality through inflammatory pathways, altered adipokine signalling, and impaired muscle-bone interactions, despite preserved or elevated BMD.⁸⁶ Bone marrow adipocytes (BMAs) are now being recognised as metabolically active, endocrine regulators within the bone microenvironment. BMAs secrete adipokines, inflammatory cytokines, and lipid-derived factors that suppress osteoblast differentiation and activity while promoting osteoclast-mediated bone resorption, thereby contributing to osteoporosis and skeletal ageing.⁸⁷ A central mechanism is disrupted in mesenchymal stem cell (MSC) differentiation,

where precursor cells are diverted toward adipocyte formation rather than osteoblast formation.^{88,89} This lineage shift becomes more pronounced with ageing and the MT, resulting in reduced bone formation capacity. Importantly, expansion of bone marrow adipose tissue is associated with reduced BMD and increased fracture risk, independent of circulating estrogen levels.⁹⁰ These findings suggest that increased marrow adiposity reflects impaired bone quality and may partly explain why obesity does not uniformly protect against fracture in postmenopausal women. Accordingly, obesity should not be considered protective, and fracture risk assessment should incorporate fall risk, body composition, and metabolic factors in addition to BMD.⁸⁵

Assessment of Obesity

Measurement of anthropometric parameters, including BMI and WC, should be incorporated into routine clinical practice as vital clinical signs for health assessment of midlife women. BMI is calculated as weight in kilograms divided by height in meters squared (kg/m^2), and standardised BMI categories are used to stratify risk and guide management.

WHO Asian BMI Classification of obesity recognises that Asian populations have a higher percentage of body fat at lower BMI levels than Caucasians and other ethnic groups.⁹¹ Based on body fat percentage and morbidity data, BMI thresholds for defining overweight and obesity are therefore lower and narrower in Asians than in Western populations. Consequently, obesity in Asian populations should be identified and managed earlier, due to the higher metabolic risk at comparatively lower BMI thresholds.⁹² Refer to Table 1.

Table 1. Criteria for Using BMI in kg/m^2 categories: WHO and Indians

Category	WHO	Indian
Underweight	< 18.5	< 18
Healthy	18.5 - 24.9	18.0 - 22.9
Overweight	25.0 - 29.9	23.0 - 24.9
Obese Grade I	30.0 - 34.9	> 25
Obese Grade II	35.0 - 39.9	
Obese Grade III	≥ 40	

Although BMI is simple and widely used, it may not accurately reflect adiposity or metabolic risk in the Indian population, where excess body fat and metabolic abnormalities occur at lower BMI levels.⁵⁸ This limitation is particularly relevant for identifying women with metabolically obese normal weight (MONW) in clinical settings.⁹³ Measures of central obesity, particularly WC and waist-hip ratio (WHR), have been validated in Indian cohorts and are superior predictors of cardiometabolic risk in this setting. WC and WHR more accurately capture visceral and ectopic fat deposition (liver, muscle, pancreas, epicardium), which plays a key pathogenic role in metabolic dysfunction.⁹⁴

WC is a simple, reproducible, and robust predictor of cardiometabolic risk, and should be routinely measured in clinical practice to assess baseline risk and monitor the impact of lifestyle and pharmacologic interventions.^{92,93,95} WC is measured in the horizontal plane at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest.⁹⁶ Refer to Table 2.

Table 2. Obesity is defined by waist circumference^{96,97}

WHO	Indians	Management
> 80 cm	> 72 cm	Action line 1- Avoid weight gain or lose weight
> 88 cm	> 80 cm	Action line 2- Supervised weight management

A WHR ≥ 0.9 in men and ≥ 0.8 in women indicates central (abdominal) obesity and reflects increased visceral fat accumulation.⁵⁸ Elevated WHR is strongly associated with insulin resistance, cardiometabolic risk, and cardiovascular disease, even in individuals with a normal BMI. For clinical application, obesity is defined in two stages. Refer to chapter ⁴³.

Total body fat percentage measured by dual-energy X-ray absorptiometry (DXA) $> 25\%$ in men and $> 30\%$ in women is generally considered indicative of excess adiposity.⁵⁸ DXA provides a more precise assessment of body composition than BMI, allowing differentiation between fat mass and lean mass, and may identify individuals with normal BMI but excess body fat (normal-weight obesity), who remain at increased metabolic risk.

Investigations in a Patient with Obesity

A baseline evaluation in patients with obesity should include assessment for metabolic, endocrine, and obesity-related comorbidities. Recommended investigations include fasting and postprandial blood glucose, HbA1c, serum creatinine, fasting lipid profile, thyroid-stimulating hormone (TSH), liver function tests, serum electrolytes, uric acid and, where clinically indicated, evaluation of the cortisol axis. Chest X-ray may be considered based on clinical context.⁵⁸ In selected patients, additional investigations may be required. Electrocardiogram (ECG), body composition analysis using DXA scan, abdominal ultrasound or upper gastrointestinal endoscopy, sleep apnoea assessment, and evaluation for diabetes-related complications in patients with established diabetes.⁵⁸

MANAGEMENT OF OVERWEIGHT AND OBESITY IN MIDLIFE

Healthcare providers should be adequately trained in midlife obesity management and menopausal counselling. Management should adopt a multidisciplinary approach involving primary care physicians, dietitians, exercise physiologists, mental health professionals, endocrinologists, and gynaecologists.

Therapeutic Lifestyle Management (TLM)

TLM remains the cornerstone of obesity management in midlife and postmenopausal women.^{93,98,99}

Weight Loss Goals: The goals of weight management should include preventing further weight gain, reducing body weight, and maintaining the achieved lower body weight over the long term.⁵⁸ The short-term goal is a weight loss of 0.5 to 1 kg per week, aiming for a 5–10% reduction over 6 months.^{58,93} Weight reduction should be achieved through caloric restriction, particularly reducing refined carbohydrate intake, along with increased physical activity. Sustained success requires strong family and social support to enhance motivation and long-term adherence.⁹³ A target BMI ≤ 23 kg/m² is recommended for Indian populations.

Medical Nutrition Therapy (MNT): is a structured, evidence-based approach that includes comprehensive nutritional assessment, individualised dietary and culinary counselling, and ongoing follow-up by a trained healthcare professional for the prevention and management of obesity.¹⁰⁰ Effective, patient-centric MNT involves three key steps: understanding the individual's and family's current dietary practices, developing an individualised meal plan, and ensuring careful follow-up.¹⁰⁰ A detailed dietary assessment should evaluate usual meal patterns and eating behaviours such as meal skipping, frequent intake of high-fat, sugar, and salt (HFSS) foods, eating out, and emotional or stress-related eating, and should be assessed using a 24-hour dietary recall.⁹³ A moderate caloric deficit of approximately 500 kcal per day is recommended to achieve gradual and sustainable weight loss. Dietary interventions should emphasise a balanced pattern with moderate carbohydrate intake preferably from low-glycaemic index sources, adequate high-quality protein (around 1.0–1.2 g/kg/day) to help preserve lean body mass, and healthy fats, particularly mono- and polyunsaturated fatty acids, including omega-3s.

Attention should also be given to key micronutrients that are particularly relevant during the MT. Adequate calcium intake (1,000–1,200 mg/day) and maintenance of vitamin D sufficiency are essential for bone health. Iron intake remains important in perimenopausal women who continue to menstruate. A daily fibre intake of 20–30 g supports cardiometabolic and gastrointestinal health. Inclusion of phytoestrogen-containing foods such as soy products, flaxseed, legumes, and whole grains may provide modest additional benefits for vasomotor symptoms and cardiometabolic risk. For better adherence, MNT should follow the 7As principle: accessible, acceptable, accurate, absorbable, affordable, attractive, and appropriate.⁵⁸ It should also appeal to all five senses ("Degustation Pentad") to enhance engagement and compliance.⁵⁸

Physical activity: is a core component of obesity management in postmenopausal women, particularly to reduce central adiposity and IR while preserving bone density and muscle mass, thereby preventing osteoporosis and sarcopenia. Exercise prescriptions should be individualised based on functional capacity and comorbidities, with gradual progression in intensity.⁵⁸ An initial medical evaluation is advisable for women with chronic conditions. At least 150–300 minutes per week of moderate-intensity aerobic activity (or 75–150 minutes of vigorous activity) is recommended.⁵⁸ Aerobic exercise reduces visceral and ectopic fat, improves cardiometabolic health, and enhances cardiorespiratory fitness. Resistance training (2–3 sessions per week) is essential for preserving or increasing muscle mass, maintaining functional capacity, and supporting bone health. Regular physical activity also improves mood, quality of life, and body image. Activity may be accumulated in short bouts (≥ 10 minutes) and integrated into daily routines to enhance adherence.⁵⁸

Non-exercise activity thermogenesis (NEAT), comprising daily activities such as standing, walking, and incidental movement, is an important contributor to total energy expenditure.¹⁰¹ Declines in spontaneous physical activity during midlife may contribute to central fat accumulation. Increasing NEAT through occupational and leisure-time movement can support weight control and cardiometabolic health in postmenopausal women.^{101,102}

Behavioural Techniques: Use goal setting, motivational interviewing, and digital self-monitoring to enhance adherence. Apply problem-solving and cognitive restructuring to manage negative thoughts, with ongoing feedback and relapse prevention for sustained success.⁹³

Monitoring and Follow-up: During the intervention phase, provide intensive counselling with bimonthly progressing to monthly follow-ups (in-person or telehealth).⁹³ In the maintenance phase, ensure lifelong engagement with 3-monthly in-person and monthly digital reviews. Encourage self-monitoring of weight, diet, physical activity, and metabolic or menopausal parameters using digital or app-based tools.^{93,98,99}

Table 3: Criteria for using BMI as a measure of obesity and management interventions⁹²

Category	BMI (kg/m ²)	Management Intervention
Underweight	< 18	Encourage balanced diet and exercise
Healthy	18.0 – 22.9	Encourage balanced diet and exercise
Overweight	23.0 – 24.9	TLM
Obese Grade I	25.0 – 29.9	TLM plus drug therapy if comorbidities* exist
Obese Grade II	30.0 – 34.9	TLM plus drug therapy: If comorbidities* exist, bariatric surgery
Obese Grade III	> 35	TLM, drug therapy, and bariatric surgery

Comorbidities: Hypertension, diabetes, and hyperlipidaemia. WHO: World Health Organisation

Anti-Obesity Pharmacotherapy

If weight loss of $\geq 5\%$ is not achieved after 6 months of intensive lifestyle therapy, initiate anti-obesity medication for women with a BMI ≥ 27 kg/m², alongside ongoing lifestyle measures.^{98,99,103,104} In Indian populations, lower BMI thresholds (≥ 25 kg/m²) with associated comorbidities such as hypertension, dyslipidemia, type 2 diabetes, and obstructive sleep apnoea may be considered, given the higher metabolic risk at lower BMI. Drug therapy should always complement TLM, not replace it.¹⁰⁵ According to the Endocrine Society of India Clinical Practice Guidelines for the Evaluation and Management of Obesity in India 2025 update, pharmacotherapy is individualised based on weight-loss targets and clinical profile.

Semaglutide, one of the potent and efficacious glucagon-like peptide 1 (GLP-1) receptor agonists, at a dose of 2.4 mg weekly injection, is recommended when 10–15% weight loss is targeted.¹⁰⁵ It has demonstrated approximately 15–17% weight loss in the Semaglutide Treatment Effect in People with Obesity (STEP) trials.¹⁰⁶ It reduces visceral

adiposity and improves insulin resistance, and may be particularly useful in postmenopausal women with central obesity, type 2 diabetes, or cardiometabolic risk.¹⁰⁶

Tirzepatide is a glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist and is recommended when 15–20% weight loss is targeted.¹⁰⁷ It has demonstrated a mean weight loss of up to 20% in SURMOUNT trials.¹⁰⁸ It is effective for women with obesity and diabetes or severe central adiposity, and demonstrates a substantial reduction in visceral fat.

Liraglutide 3.0 mg once daily, initiated at a low dose and gradually titrated to minimise gastrointestinal adverse effects, produces clinically meaningful and sustained weight loss along with significant improvements in cardiometabolic risk factors.¹⁰⁹

When GLP-1 receptor agonists are contraindicated, unavailable, or unaffordable, use phentermine/topiramate, bupropion/naltrexone, or orlistat, selected based on tolerance and comorbidities. Refer to Table 4 for a complete list of anti-obesity medications. Anti-obesity medications should be initiated only after comprehensive counselling and continued patient education throughout treatment. Counselling must address expected benefits, limitations, potential adverse effects, cost considerations, and correct administration to ensure safe and effective use.¹⁰⁵

Table 4: Common Anti-Obesity Medications^{105,110}

Drug	Drug Class	Usual Dose	Common Side Effects	Contraindications / Warnings
Orlistat	lipase inhibitor	120 mg TDS before food	Oily stools, faecal urgency, abdominal pain, flatulence, fat-soluble vitamin deficiency	Malabsorption syndrome, cholestasis, hypersensitivity; caution in nephrolithiasis, cholelithiasis, reduced absorption of thyroid hormones, antiepileptics
Liraglutide	GLP-1 receptor agonist	Start with 0.6 mg SC daily; titrate to 3.0 mg	Nausea, vomiting, dyspepsia, diarrhoea, bloating, constipation, increased heart rate, hypo-glycaemia, headache, dizziness, fatigue	Personal/family history of MTC, MEN2; Warnings: injection site reactions, pancreatitis, acute cholelithiasis and cholecystitis, tachycardia, acute kidney injury, chronic kidney disease, suicidal behaviour and ideation
Semaglutide	GLP-1 receptor agonist	SC weekly; titrate to 2.4 mg	GI symptoms, gallbladder disease, rare pancreatitis	Personal/family history of MTC, MEN2; Warnings: injection site reactions, pancreatitis, acute cholelithiasis and cholecystitis, tachycardia, acute kidney injury, chronic kidney disease, suicidal behaviour and ideation
Tirzepatide	Glucose-dependent insulintropic polypeptide & glucagon-like peptide-1 receptor agonist (GIP/GLP-1 RA)	SC weekly; 5–15 mg	GI symptoms, possible gallbladder disease	Personal/family history of MTC, MEN2; Warnings: injection site reactions, pancreatitis, acute cholelithiasis and cholecystitis, tachycardia, acute kidney injury, chronic kidney disease, suicidal behaviour and ideation

Phentermine- Topiramate ER	Phentermine- Norepinephrine releasing drug; Topiramate - GABA receptor modulation	Once daily; titrated dosing	Headache, paraesthesia, dizziness, insomnia, xerostomia, dysgeusia, depression, anxiety, cognitive impairment; CV safety not known	Glaucoma, hyperthyroidism, MAOI administration; Warnings: metabolic acidosis, cognitive impairment, elevated heart rate, nephrolithiasis, hypokalaemia, mood disorders
Naltrexone- Bupropion ER	Opioid antagonist +DA/ NE reuptake inhibitor	8/90 mg (8 mg naltrexone / 90 mg bupropion); titrated to 2 tabs BD	Nausea, vomiting, constipation, diarrhoea, dry mouth, dizziness, anxiety, insomnia, headache	Seizure disorder, uncontrolled HTN, eating disorders, opioid use, abrupt alcohol withdrawal, MAOI use; Warnings: suicidal behaviour and ideation, neuropsychiatric symptoms, seizures, increased BP & HR, hepatotoxicity

Abbreviations: BD (twice daily), BP (blood pressure), CV (cardiovascular), DA/NE (dopamine/norepinephrine), ER (extended release), GABA (gamma-aminobutyric acid), GI (gastrointestinal), HR (heart rate), HTN (hypertension), MAOI (monoamine oxidase inhibitor), MEN2 (multiple endocrine neoplasia 2), MTC (medullary thyroid carcinoma), RA (receptor agonist), SC (subcutaneous), TDS (three times daily)

Next-Generation Anti-Obesity Medications

Several emerging anti-obesity agents in Phase 2–3 trials show substantial efficacy. High-dose oral semaglutide achieves approximately 15% weight loss.¹⁰⁵ Retatrutide (GIP/GLP-1/glucagon triple agonist) demonstrates up to 24% reduction.¹⁰⁵ CagriSema (amylin + GLP-1) and survodutide (GLP-1 + glucagon dual agonist) produce up to 14–16% weight loss.¹⁰⁵ New oral agents such as orforglipron and ecnoglutide achieve 10–15% reductions. Overall, multi-agonists and oral incretin therapies are approaching bariatric-level efficacy and may expand future treatment options.¹⁰⁵

Oral semaglutide 14 mg produces weight loss comparable to 1 mg injectable semaglutide, and higher doses have demonstrated greater efficacy. In the PIONEER PLUS trial, oral semaglutide 50 mg resulted in significantly greater weight loss than 14 mg (–9.2 kg vs –4.5 kg at 68 weeks; $P < 0.0001$) in adults with obesity and type 2 diabetes,¹¹¹ and in the OASIS-1 study oral semaglutide 50 mg produced a placebo-subtracted mean weight loss of –15.6% at 68 weeks in adults with obesity without diabetes.¹¹²

Metformin: Not classified as an anti-obesity drug. Recommended only in obese women with IR, prediabetes, or PCOS, where it improves insulin sensitivity and may modestly reduce weight.¹¹³

Bariatric Surgery and Intra-gastric Devices

Bariatric surgery involves modification of the gastrointestinal tract to induce weight loss, either by reducing gastric volume (restrictive procedures) or by altering the normal alimentary tract pathway, resulting in nutrient malabsorption. In Asian Indian populations, bariatric surgery is indicated at lower BMI thresholds than in Western populations, given the higher cardiometabolic risk at relatively lower BMI. Surgery is recommended for individuals with a BMI ≥ 32.5 kg/m² in the presence of comorbidities, and for those with a BMI ≥ 37.5 kg/m² even without comorbidities.⁵⁸ The most commonly performed bariatric procedures include Roux-en-Y gastric bypass, sleeve gastrectomy, and, less commonly, adjustable gastric banding.

Diabesity is the coexistence of type 2 diabetes and obesity.⁵⁸ Management emphasises diet and physical activity, with recommendations to reduce carbohydrate intake by 10–15%, increase protein intake (up to 1 g/kg/day), and limit fats, particularly in carbohydrate-rich Indian diets.¹⁰⁰

METABOLIC CHANGES DURING MENOPAUSE

Estrogen plays a critical role in metabolic homeostasis through its actions on estrogen receptors alpha (ER α) and beta (ER β). ER α is particularly important in regulating adipogenesis, insulin sensitivity, glucose uptake, lipid oxidation, and inflammatory signalling in metabolic tissues. ER β appears to exert modulatory and, in some contexts, counter-regulatory effects.¹¹⁴ Refer to Table 5 for a list of beneficial effects of estrogen in various tissues which exist prior to menopause.

Table 5: Beneficial Effects of Estrogen on Various Tissues

Organ	Tissue Effects of Estrogen
Pancreas	Improves fasting insulinemia
Liver	Modulates gluconeogenesis, improves hepatic insulin response, reduces hepatic insulin degradation
Adipose tissue	Improves insulin sensitivity in adipocytes, reduces oxidative stress
Skeletal muscle	Improves insulin-stimulated glucose absorption
Cardiac tissue	Mitigates insulin resistance - induced cardiomyopathy, improves cardiac function
Vascular endothelium	Improves Nitric Oxide production, increases vasodilation response

The decline in circulating estrogen levels during MT and the reduced ER α signalling impair peripheral insulin sensitivity, alter lipid metabolism, and favour central fat accumulation.¹¹⁵ Central visceral adiposity exacerbates the release of pro-inflammatory cytokines, excess free fatty acids, and oxidative stress, thereby driving insulin resistance (IR).^{13,116} To add fuel to the fire, there is a relative androgen excess, which further worsens IR. Resting energy expenditure declines during menopause, independent of chronological ageing, further predisposing to visceral adiposity.⁷⁷ Age-related alterations in cortisol metabolism may additionally promote gluconeogenesis and metabolic dysfunction.¹¹⁷

Reduced basal metabolism, central adiposity, dyslipidemia, and IR collectively contribute to the development of MetS. Postmenopausal women, particularly those with obesity, overweight, or PCOS, demonstrate a higher prevalence of MetS and an adverse cardiovascular risk profile.¹¹⁸

Insulin Resistance

IR is a complex metabolic abnormality in which peripheral tissues fail to respond adequately in response to insulin. Under normal conditions, an increase in blood glucose stimulates insulin secretion from pancreatic β -cells and suppresses hepatic glucose production.¹¹⁹ However, IR individuals do not respond to this signalling process, and paradoxically show an increase in both hepatic gluconeogenesis and insulin secretion, which can induce or aggravate hyperglycaemia.¹²⁰ The key factors that promote the emergence of IR include altered insulin signalling, hyperinsulinemia, hyperlipidaemia, and obesity. The main features of IR include impaired skeletal muscle glucose metabolism, glucose intolerance, and compensatory hyperinsulinemia, ultimately increasing the risk of T2DM. Obesity, specifically excess visceral abdominal fat, is considered a major driver of IR. Visceral fat is strongly associated with MetS and CVD, and reducing visceral abdominal fat can significantly improve insulin sensitivity.¹¹⁹⁻¹²¹

The diagnosis of IR is ideally made using hyperinsulinemic-euglycemic clamp studies. However, this is practically not feasible. Alternative assessments include an oral glucose tolerance test (75 g OGTT), Homeostatic Model Assessment for IR (HOMA-IR), glycated haemoglobin (HbA1c), fasting glucose, and fasting insulin levels. In resource-limited settings, clinical markers such as acanthosis nigricans and acrochordons can serve as proxy indicators of IR.¹²²

METABOLIC SYNDROME

MetS is a constellation of interrelated metabolic risk factors that appear to directly promote the development of atherosclerotic CVD.¹²³ MetS has IR as its central underlying pathophysiological mechanism, and is characterised by central adiposity, abnormal glucose metabolism, hypertension, and atherogenic dyslipidemia.¹²⁴ Patients with MetS

are estimated to have an approximately two-fold increased risk of atherosclerotic CVD and a five-fold increased risk of T2DM, as compared to the general population.^{124,125} MetS is also associated with accelerated atherosclerosis, premature CVD, and early onset T2DM.¹²⁶ While pre-menopausal women have a 14–45% prevalence of MetS, it steeply rises to 30–70% after menopause, depending on ethnicity and diagnostic criteria.¹¹⁸ Menopause adversely affects all components of MetS, and surgical menopause may lead to a higher incidence of MetS compared to natural menopause.¹¹⁸ Men are more susceptible to developing MetS than premenopausal women; however, protection in women is significantly reduced when estrogen levels decrease nearing menopause.

Menopause is not only a metabolic shift, but also an inflammatory transition. Declining estrogen levels shift immune cells, such as macrophages and monocytes, both of which express estrogen receptors, toward a more pro-inflammatory state. Postmenopausal women exhibit higher pro-inflammatory cytokine activity and features of immune senescence, reflecting altered immune balance. Estrogen normally exerts anti-inflammatory and insulin-sensitising effects through its actions on immune and metabolic tissues. With menopause, this protective modulation is largely lost, contributing to IR and the development of MetS.¹²⁷

Epidemiology of MetS

A global systematic review with Bayesian modelling (45.5 million adults) showed that MetS prevalence in women increased from 14.7% in 2000 to 31.0% in 2023, affecting an estimated 846 million women worldwide. Prevalence rose with age and urbanisation and increased across nearly all countries, underscoring the growing global burden among women.¹²⁸

In a systematic review, the prevalence of MetS across 15 Asia-Pacific countries showed marked heterogeneity, ranging from 11.9% in a 2003 national survey from the Philippines (using the National Cholesterol Education Program Adult Treatment Panel III criteria) to 49.0% in an urban cohort from Karachi, Pakistan (2004). A higher prevalence was consistently reported among women and in urban populations. Long-term trend data from China, South Korea, and Taiwan showed a progressive increase in MetS prevalence. Despite methodological and diagnostic variability, the Asia-Pacific region faces a substantial and growing MetS burden, with approximately 1 in 5 adults affected in many countries.¹²⁹

In Indian studies, the prevalence of MetS among peri- and postmenopausal women ranges from 34% to 64%, is highest in urban and postmenopausal cohorts, and is largely driven by abdominal obesity and IR.^{130–135} An observational study conducted by the Indian Menopause Society on the prevalence of non-communicable chronic diseases in rural Western India (N=316) found that dyslipidemia, diabetes mellitus, obesity, and hypertension had prevalences of 58%, 25%, 25%, and 20%, respectively.¹³⁶ In a recent cross-sectional comparative study of urban Indian women, the prevalence of metabolic syndrome was significantly higher in postmenopausal women (40%) compared with premenopausal women (12.7%) ($p = 0.004$). Menopause was found to be a significant risk factor for metabolic syndrome in Indian women. Among individual components, raised triglycerides demonstrated the strongest association (odds ratio [OR] 3.41), followed by hypertension (OR 2.08), increased waist circumference (OR 1.73), elevated fasting glucose (OR 1.61), and low HDL cholesterol (OR 1.38).¹³⁷

Abnormal WC was the most prevalent component (87%) of MetS, and, in terms of odds ratios, the correlation was highest with BMI, followed by total cholesterol and waist-to-hip ratio.¹³⁴ The risk of MetS, abdominal obesity, and high blood pressure was highest within 5 years following menopause, and decreased thereafter.¹³²

A large, nationally representative Indian study reported a weighted MetS prevalence of 4.83%, likely underestimated due to underdiagnosis. Higher prevalence was observed among women, urban residents, obese, and physically inactive individuals, with hypertension as the most common component. Nearly one-quarter of affected individuals were untreated or partially treated. Comprehensive care was more likely among older, urban, wealthier individuals and those with comorbidities, whereas middle-aged, working, rural, and otherwise healthier individuals were less likely to receive adequate treatment, highlighting marked disparities in management.¹³⁸ Considerable regional variation in the prevalence of MetS was observed in India, with the highest prevalence in Kerala (19.76%) and the lowest in Assam (1.15%).¹³⁸

A meta-analysis found that MetS is associated with an increased risk of gynaecological cancers, particularly endometrial cancer. Evidence for ovarian cancer was inconsistent, and no significant association was observed for cervical cancer. Despite good study quality, overall evidence certainty was low.¹³⁹

Diagnosis of MetS

According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III, 2005 revision), the diagnosis of metabolic syndrome in women requires the presence of 3 or more metabolic abnormalities¹⁴⁰ out of the following: central obesity: waist circumference ≥ 80 cm; hypertriglyceridemia: serum triglycerides level ≥ 150 mg/dL; low HDL-cholesterol < 50 mg/dL; high blood pressure: systolic blood pressure ≥ 130 mmHg and/or diastolic blood pressure ≥ 85 mmHg or on treatment for hypertension; high fasting glucose: serum glucose level ≥ 100 mg/dl or on treatment for T2DM.¹²³ (as stated in Table 6).

Table 6: Diagnosis of Metabolic Syndrome¹⁴¹

Parameters	Values
Waist circumference	≥ 80 cms
Serum triglycerides	≥ 150 mg/dL
High density lipoproteins (HDL) cholesterol	< 50 mg/dL
Fasting blood glucose	≥ 100 mg/dL
Blood pressure	$\geq 130/85$ mmHg

MANAGEMENT OF METABOLIC SYNDROME

The management of MetS in postmenopausal women should be individualised, taking into account body weight, cardiometabolic risk profile, smoking status, physical activity level, and coexisting conditions. Lifestyle modification remains the cornerstone of therapy, while MHT may provide additional metabolic benefits in appropriately selected women.

In women with normal body weight, prevention of further weight gain may be sufficient, whereas overweight and obese women require structured lifestyle intervention to prevent progressive cardiometabolic deterioration.¹⁴²⁻¹⁴⁴ Comprehensive management includes a hypocaloric diet, regular aerobics and weight training, cessation of smoking, limiting alcohol use, good sleep hygiene, alongside pharmacological therapy when indicated.¹⁴²⁻¹⁴⁴ In general, 45 minutes of brisk walking three times a week helps prevent further weight gain and promotes fat mass reduction, reduced WC, and improved blood pressure, plasma glucose, and lipid levels.¹⁴⁵

In postmenopausal women, preservation of muscle mass and bone health is crucial due to the increased risk of sarcopenia and osteoporosis; therefore, gradual, modest weight loss (approximately 5–7% annually) is recommended. Consuming polyunsaturated and monounsaturated fats, whole grains, low-fat proteins like lean meat, fish, and skimmed dairy products, and a modest reduction in carbohydrates can go a long way toward maintaining good health.¹⁴²⁻¹⁴⁴ Adequate calcium (1000–1200 mg/day) and vitamin D (600–800 IU/day) intake or supplementation are recommended to maintain skeletal health.¹⁴⁶ Regular exercise improves muscle strength, bone quality, glycaemic control, and overall metabolic parameters. Current recommendations advise at least 150 minutes per week of moderate-intensity aerobic activity or 75 minutes per week of vigorous activity in women with T2DM and MetS.^{142-144,146}

Many women with T2DM and MetS eventually require pharmacotherapy. Drug selection should be individualised, taking into account cardiometabolic risk, weight, and bone health considerations in postmenopausal women. Metformin remains first-line therapy and is weight-neutral or modestly weight-reducing. GLP-1 receptor agonists (GLP-1RAs) are now preferred in women with obesity due to their glycaemic and weight-loss benefits.

Thiazolidinediones should be used cautiously in women at risk of osteoporosis. Detailed pharmacologic considerations are discussed in the obesity section of this chapter and Chapter 43.

Menopausal Hormone Therapy

MHT does not prevent age-related weight gain, but may attenuate increases in visceral adiposity and help preserve lean body mass in normal-weight women. Transdermal estrogen is generally preferred in women with metabolic risk factors due to its neutral hepatic and triglyceride effects.¹⁴⁷⁻¹⁴⁹ Estrogens improve insulin sensitivity through direct actions on ER α in the liver, skeletal muscle, and adipose tissue, resulting in reduced hepatic glucose output and enhanced peripheral glucose uptake. MHT has been associated with a 20–35% reduction in the incidence of T2DM, particularly in women initiating therapy close to menopause.¹⁵⁰⁻¹⁵³

In a large cohort of postmenopausal women (N=63,624), 1,220 incident cases of T2DM were identified, and oral MHT was associated with a lower risk of new-onset T2DM compared with transdermal therapy.¹⁵⁴ Oral conjugated equine estrogens (CEE) appear to exert a stronger effect on insulin sensitivity and suppression of hepatic gluconeogenesis, likely due to first-pass hepatic metabolism. However, the progestogen component of combined MHT may attenuate some of the favourable metabolic effects of estrogen in a dose-dependent manner. Progestogens with lower androgenicity (such as norethisterone acetate and drospirenone) are metabolically less androgenic than more androgenic agents such as medroxyprogesterone acetate or levonorgestrel.¹⁵⁴

A meta-analysis of 107 RCTs showed that MHT significantly reduces IR, abdominal adiposity, incident diabetes, dyslipidemia, blood pressure, and procoagulant factors in postmenopausal women. In women with T2DM, MHT also reduces fasting glucose and improves IR, though these benefits are attenuated when progestins are added.^{155,156}

Although MHT favourably influences IR, glycaemia, and other features of MetS, it is prescribed nearly 50% less often in women with T2DM compared with non-diabetic women.¹⁵⁷ MHT in women with T2DM should be individualised after careful cardiovascular risk evaluation.^{158,159} In low-risk patients, oral 17 β -estradiol can be considered, as it exerts greater effects on hepatic glucose regulation compared with transdermal preparations due to first-pass hepatic metabolism.¹⁵⁷ Oral estrogen preparations are generally suitable for perimenopausal or recently postmenopausal women with low cardiovascular risk.^{158,159} In contrast, transdermal estrogen is recommended in women with moderate to high cardiovascular risk due to the lower associated risk of stroke and venous thromboembolism compared with oral therapy.^{158,159}

For postmenopausal women with T2DM and an intact uterus, micronised progesterone, dydrogesterone, or transdermal norethisterone are generally preferred because of their comparatively neutral metabolic effects.¹⁵⁷ Initiation of MHT beyond 60 years of age or more than 10 years after menopause is not recommended, as the risk of thromboembolic and cardiovascular events increases, particularly in those with established atherosclerosis, and cardiovascular benefit is not observed when therapy is started late.^{158,159} In appropriately selected postmenopausal women with T2DM, MHT may be safely and effectively prescribed, provided cardiovascular, metabolic, and skeletal risks are thoroughly evaluated, and the regimen is individualised.^{158,159}

SYNOPSIS

- Declining estrogen during the menopausal transition alters body composition (weight gain 0.7 kg/year, accelerated visceral fat gain and lean mass loss), energy metabolism, and insulin sensitivity. This increases risk for type 2 diabetes, dyslipidemia, hypertension, cardiovascular disease (CVD), obesity-related cancers, osteoporosis, sarcopenia, and reduced QoL. BMI may remain stable despite increased metabolic risk.
- Obesity in midlife is a multifactorial chronic disease of excess fat, increasingly prevalent globally and in India (35–50% of midlife women, 40–50% with central obesity), which elevates cardiometabolic, mechanical, psychological, and oncologic risks and worsens metabolic and vasomotor symptoms.
- Assessment of obesity includes anthropometry (WC, waist-hip ratio, BMI), body composition analysis (DXA/MRI to distinguish fat and lean mass, including normal-weight obesity), and investigations (glucose, HbA1c, lipid profile, liver/kidney function, TSH, uric acid) according to comorbidities.
- Management of obesity prioritises lifestyle interventions, including a moderate-calorie diet rich in protein and fibre, regular aerobic and resistance exercise, increased daily activity (NEAT), and behavioural support through goal setting and self-monitoring. Pharmacotherapy (GLP-1 receptor agonists and other approved agents) is

added if lifestyle changes are insufficient, while bariatric surgery is reserved for individuals with BMI ≥ 32.5 – 37.5 kg/m², depending on comorbidities.

- MetS is a cluster of central obesity, insulin resistance, dyslipidemia, hypertension, and impaired glucose metabolism. Insulin resistance is the key pathophysiological mechanism. MetS doubles ASCVD risk and increases T2DM risk 5-fold.
- Prevalence rises from 14–45% in premenopause to 30–70% in postmenopause; highest in urban and surgical menopause.
- Diagnosis (NCEP ATP III): ≥ 3 criteria out of 5 criteria; waist ≥ 80 cm, triglycerides ≥ 150 mg/dL, HDL < 50 mg/dL, BP $\geq 130/85$ mmHg, fasting glucose ≥ 100 mg/dL.
- Management requires an individualised combination of lifestyle interventions (caloric restriction, regular aerobic/resistance exercise, smoking cessation, alcohol moderation, and sleep hygiene), pharmacotherapy, and possibly MHT for optimal cardiometabolic outcomes.
- MHT can reduce visceral fat, improve insulin sensitivity, and lower the incidence of T2DM; transdermal estrogen is preferred for metabolic risk, and oral estrogen is effective for hepatic glucose regulation. Should be initiated within 10 years of menopause or before 60 years, after cardiovascular and thromboembolic risk assessment.

RESEARCH AGENDA

Longitudinal studies that examine how hormonal changes, genetics, ethnicity, and lifestyle factors influence body composition during the menopause transition.

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DIABETES AND THYROID AT MENOPAUSE

Keywords: Menopause, insulin resistance, diabetes mellitus, hypothyroidism, thyroid nodule

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DIABETES AT MENOPAUSE

INTRODUCTION

Menopause marks the natural end of a woman's reproductive phase and typically occurs earlier in Indian women compared to those in developed countries. A recent systematic review reported the mean age of natural menopause in India at approximately 46.6 years (95% CI: 44.8–48.4).¹ The prevalence of Type 2 diabetes mellitus (T2 DM) in women in the age group of 15- 49 yrs was 2.39% in the urban population and 1.41% in the rural population as per the National Family Health, 2019-21 Survey (NFHS-5).² However, this figure probably underestimates the true burden, as diabetes prevalence escalates sharply with age. Approximately one in five individuals aged 45 years and above in India, equating to about 50.4 million people, were found to have diabetes. The prevalence varied substantially across different states.³

The rapid rise in the prevalence of T2DM across India, combined with increasing life expectancy, heralds a looming public health crisis. The age-adjusted diabetes prevalence in India is projected to rise from 89.8 million in 2011 to 156.7 million by 2050, and alarmingly, approximately 43% of the affected individuals remain undiagnosed.⁴ This trend carries profound implications for menopausal women, who face compounded vulnerability due to gender-specific risk factors. Among endocrine disorders encountered during midlife, diabetes and thyroid dysfunctions are the most prevalent in clinical practice, particularly among those entering menopause. Emerging research has uncovered a significant association between menopause timing and diabetes risk. Early menopause is linked to 20%–32% increased risk of T2DM, potentially due to longer durations of estrogen deficiency and metabolic changes.⁵

POI and early menopause are risk factors for T2D in postmenopausal women, with considerable variation across ethnic groups, and may need to be considered in risk assessments of T2D among women.⁶ Conversely, diabetes itself may influence reproductive ageing; a South Indian study found that diabetic women reached menopause approximately four years earlier (average age 44.7 years) than non-diabetic counterparts (average age 48.2 years).⁷ There is now evidence for an interrelation between the age at menopause, either natural or following oophorectomy, and the onset of diabetes mellitus. There is substantial evidence to suggest that natural menopause, premature or early menopause, appears to be associated with an increased risk of diabetes, prediabetes, and the metabolic syndrome.⁸ Early menopause was significantly higher among diabetic women (21.3%).⁹

ESTROGEN AND DIABETES

Menopause transition, Menopause and Diabetes

The menopausal transition (MT) and menopause are associated with increased visceral fat, elevated inflammatory markers, a relative increase in androgens, and insulin resistance. These changes also increase the risk of cardiovascular disease. Increasing age and obesity by themselves are risk factors for diabetes. With so many metabolic and hormonal changes occurring at MT, it is important to understand the interrelationship of menopause, menopause hormone therapy (MHT) and diabetes mellitus.¹⁰

Central adiposity is associated with a 2-fold increased risk of developing metabolic syndrome. The risk is higher in women with surgically induced menopause.^{11,12} Rather than an earlier menopause, a shorter reproductive span was found to be associated with a greater risk of diabetes mellitus.¹³ It is now recognised that women are more insulin sensitive compared to men, but this metabolic advantage gradually disappears after menopause or when insulin resistance progresses to hyperglycemia and diabetes.¹⁴

Indian studies consistently show that the prevalence of metabolic syndrome (MS) in women rises significantly during the menopausal transition. Across different cohorts, the prevalence ranges from 33% to 59.4% in premenopausal women and approximately 50% to 65.7% in postmenopausal women. Abdominal obesity (seen in up to 87%) is the

most frequent component. Postmenopausal women also show higher rates of elevated blood pressure, low high-density lipoprotein (HDL) cholesterol, and high triglycerides, while the risk of hyperglycemia increases with the duration since menopause. Overall, postmenopausal status is identified as an independent risk factor for metabolic syndrome in Indian women. The effect partly overlaps with age and obesity.^{15,16,17}

In an Indian cohort of 851 women with diabetes, 60.6% reported regular menstrual cycles, while 39.4% experienced disturbances in their cycles, out of which 18.7% (5.3% menorrhagia and 13.4% oligomenorrhea) reported abnormal uterine bleeding (AUB), 4.5% had a history of hysterectomy, and 11.5% were postmenopausal. These findings suggest that almost two out of five diabetic women encounter menstrual health issues, reflecting a close interplay between diabetes, reproductive health, and elevated cardiovascular risk.¹⁸

Estrogen receptors are present in various insulin-sensitive tissues (skeletal muscle, liver, adipose tissue) and organs. Estradiol (E2) affects various energy homeostasis pathways, including the central nervous system, the regulation of food intake and energy expenditure, lipid storage and metabolism in adipose tissue, and insulin sensitivity.¹⁹ Estrogen may positively impact glucose homeostasis by improving and/or modulating glucose metabolism and insulin resistance.²⁰ The energy expenditure at rest, which is 600 Kcal per month, is decreased during MT. This leads to increased fat deposition and, over time, obesity. Estrogen therapy increases this resting energy expenditure and improves energy balance.²¹

Type 1 Diabetes Mellitus and Menopause

Most of the studies on menopause and diabetes have focused on Type 2 DM. With increasing life expectancy, changes at menopause need to be discussed in women with T1DM. The evidence is conflicting for age at menopause in T1DM. Some report an earlier menopause; others do not. Cardioprotective and bone-protective effects of MHT observed in the general population may not be evident in T1DM.²² Management and care of T1DM patients at menopause require a multidisciplinary approach. MHT should be individualised for menopausal symptoms, and the transdermal approach is preferred.

There are fluctuations in glycemic control and insulin sensitivity in women with T1DM at menopause, so continuous glucose monitoring and smart pens should be used to guide appropriate insulin dosing. Whenever vasomotor symptoms are a complaint in T1DM, a differential diagnosis of hypoglycaemia should be considered. Cardiovascular disease risk and metabolic changes are higher in patients with longstanding T1DM, so they should be addressed early through risk assessment and preventive measures.²²

MHT and Glycemic Control

MHT, when initiated early in the MT period, may offer metabolic benefits, including improved insulin sensitivity and glycaemic control.^{23,24} This is particularly effective when therapy is initiated in women under 60 or within 10 years of menopause.²⁴ MHT has been associated with improved glycaemic control in women with T2DM and a reduced risk of developing T2DM in those without the condition. In the E3N cohort study, the incidence of new-onset diabetes was lower in women who had used MHT.²⁵ MHT, particularly oral estrogens, significantly lowers lipoprotein(a) levels, a known cardiovascular risk factor. In addition, in women with hypertriglyceridemia, low doses or transdermal MHT would be a safer choice.²⁶

The 2025 American Diabetes Association guidelines now recommend that postmenopausal women with prediabetes and diabetes undergo an assessment for genitourinary syndrome.²⁷ According to the European Menopause and Andropause Society clinical guidelines, women with T2DM can receive MHT after a careful individual assessment of their cardiovascular and metabolic risk profile.²⁸ As per the North American Menopause Society, MHT significantly reduces the diagnosis of new-onset T2DM.²⁹

The benefit of estrogens on metabolic parameters is mitigated by the use of progestins or progestogens. Women on only estrogens had a lower risk of diabetes mellitus as compared to those on conjugated equine estrogen (CEE) or 17 β -estradiol and medroxy progesterone acetate (MPA). Use of dydrogesterone (DYD) and micronised progesterone (MP) may not adversely affect glucose levels.

RISK FACTORS FOR DIABETES MELLITUS

Various risk factors for diabetes are advancing age, obesity, family history, hypertension, dyslipidemia, personal history of gestational diabetes mellitus or impaired glucose tolerance, polycystic ovarian syndrome (PCOS), ethnicity and physical inactivity.³⁰

METABOLIC SYNDROME, OBESITY AND DIABETES

MS refers to a combination of interrelated health conditions that collectively elevate the likelihood of developing atherosclerotic cardiovascular diseases, such as myocardial infarction (MI), stroke, and peripheral arterial disease, as well as insulin resistance and type 2 diabetes mellitus. The main components of metabolic syndrome are abdominal obesity, high blood pressure, elevated blood sugar, and low levels of HDL. A diagnosis of MS is made if 3 of these 5 components are present.³¹

It is important to note that a revised risk-based obesity classification for Asian Indians has been proposed. This integrates adiposity and metabolic risk. The 2009 obesity guidelines for Asian Indians defined obesity as BMI: Between 23 and 24.9 kg/m², as overweight and 25 kg/m² or more, as obesity and abdominal obesity defined as waist circumference: 80 cm or more in women, and 90 cm or more in men.³² However, lately, apart from these anthropometric definitions, limitations of daily activities, metabolic and cardiovascular morbidities have been added to define two stages of obesity: stage 1 and 2. This provides a risk-based classification of obesity.³³

Stage 1: $\geq 23 \text{ kg/m}^2$ is a must with optional features (waist circumference, waist to height ratio, body fat percentage) with no symptoms suggestive of loss of day-to-day activity due to obesity and no comorbid condition due to obesity (with no major functional or organ impairment).

Stage 2: BMI $\geq 23 \text{ kg/m}^2$ mandatory plus waist circumference/waist to height ratio with body fat optional. And either activity limitations or related metabolic/cardiovascular conditions due to obesity. This approach enables earlier identification of high-risk individuals and aligns with global risk-based definitions of obesity.

Screening for Diabetes²⁷

The 2025 guidelines of the American Diabetes Association suggest screening for asymptomatic adults as follows:

In normal-weight women without risk factors and asymptomatic subjects, screening for diabetes is recommended from age 35. If tests are normal, a repeat test may be performed every 3 years.

In India, opportunistic screening for all women aged 30 years and above should be conducted. It should be done annually for younger women with risk factors.

Testing should be considered at a younger age or should be carried out more frequently (annually) in individuals who are overweight (BMI $> 23 \text{ kg/m}^2$) or obese (BMI $> 25 \text{ kg/m}^2$) and have additional risk factors, including:

- Physical inactivity
- First-degree relative with diabetes
- Members of a high-risk ethnic population (Asian - Americans)
- Women who delivered a baby weighing $> 9 \text{ lb}$ or were diagnosed with GDM
- History of Cardiovascular Diseases
- Hypertensive [blood pressure (BP) $\geq 130/80$] or on therapy for Hypertension
- A HDL cholesterol level of less than 50 mg/dl and or a triglyceride level of more than 250 mg/dL
- An individual with polycystic ovary syndrome
- Impaired fasting glucose or altered glucose tolerance on previous testing.
- Use of medications associated with diabetes (glucocorticoids, antipsychotics, clozapine, olanzapine, and haloperidol, thiazide diuretics, statins, beta-blockers such as metoprolol and atenolol and highly active antiretroviral therapy).
- Other clinical conditions associated with Insulin resistance (severe obesity, acanthosis nigricans, metabolic dysfunction associated with steatotic liver diseases)

Use of the Indian Diabetes Risk Score (IDRS) provides a no-cost, non-invasive, simple, and easily applicable tool for diabetes screening in mass screening programmes. IDRS consists of four components: age, abdominal obesity, family history of diabetes, and physical activity, with a maximum score of 100.^{34,35}

Lab test for screening:

The best test is a fasting plasma glucose test or a non-fasting haemoglobin A1c (HbA1c) test.

If fasting blood glucose is normal (< 100mg/dL) or HbA1c is < 5.7%, retesting should be done at 3-year intervals.

Prediabetes is defined as fasting blood glucose between 100 and 125 mg/dL or HbA1c between 5.7% and 6.4%. In such cases, repeat testing should be done in 1 to 3-year intervals.

Formal Criteria for Diagnosis of Diabetes

HbA1c: When the test is done in a laboratory which has been certified and standardised according to the National Glycohemoglobin Standardisation Program (NGSP), and the level is equal to or above 6.5%.

Fasting plasma glucose equal to or above 126 mg/dL (no calorie intake for at least 8 hours).

Oral glucose tolerance test: With a 75 g glucose load, a 2-hour plasma glucose level equal to or above 200 mg/dL.

In symptomatic women, a random plasma glucose value of 200 mg/dL or higher.

When the results are equivocal, a repeat test must be planned.

Investigations : (ICMR standard treatment workflow Diabetes Mellitus type II)

HbA1c, Creatinine, Potassium, fasting lipid profile, liver function tests, Urine routine examination and spot albumin: creatinine ratio (may best be carried out after initial glycaemic control), ECG. Others like Echo and USG abdomen, as indicated.

All women with diabetes should undergo annual screening for hypertension, dyslipidemia, and microalbuminuria, and have a comprehensive eye examination to detect retinopathy and other microvascular complications.³⁶ They should maintain HbA1c < 7% with strict control of BP, lipids, and weight to reduce cardiovascular and microvascular risk.³⁶

MHT in women with Type 2 diabetes: Use MHT for symptomatic relief of VMS and genitourinary syndrome of menopause, with secondary improvement in sleep and quality of life and a potential metabolic benefit.^{37,38,39} MHT is not indicated for glycemic control. Oral MHT on accepted indications exerts a more substantial favourable effect on glucose metabolism and insulin sensitivity and may reduce the incidence of type 2 diabetes in women without prior disease.^{37,38,40} MHT is not to be prescribed for the prevention of diabetes. Transdermal MHT is preferred in women with obesity, metabolic syndrome, or established type 2 diabetes who are at higher risk of thrombosis, hypertension, or hypertriglyceridemia, as it bypasses hepatic first-pass metabolism and has neutral effects on triglycerides and CRP.^{31,32,34} MHT in women with type 1 diabetes: In type 1 diabetes, data on MHT are sparse and inconclusive; MHT should be used only for usual menopausal indications and not for glycaemic or metabolic benefit.^{38,39,41}

PREVENTION OF DIABETES³³

Lifestyle interventions, such as diabetes self-management education, medical nutrition therapy, and regular physical activity, are essential for managing T2DM and improving quality of life, reducing mortality, hospitalisations, and healthcare costs. Goals include at least 150 minutes of moderate exercise weekly and 5–10% weight loss, which can enhance glycaemic control, induce remission, and improve metabolic and cardiovascular risk factors.⁴² Dietary strategies should be culturally and economically appropriate, focusing on legumes, fresh fruits, non-starchy vegetables, nuts, and seeds, while limiting sugary drinks, added sugars, and highly processed starchy foods. Low-carbohydrate diets can modestly reduce HbA1c, with evidence suggesting a dose-dependent benefit; low-glycaemic-index diets and plant-based eating patterns also improve control. Most dietary trials are short-term, and benefits often diminish beyond 12 months, underscoring the need for sustained interventions and integration with pharmacotherapy.

MANAGEMENT OF DIABETES

Diabetes is widely recognised as a lifestyle-related condition that demands more than medication alone; it calls for lasting changes in daily habits, including healthy eating, regular physical activity, and ongoing monitoring. For women, adopting balanced nutrition and exercise routines is valuable not only in preventing diabetes but also in managing the condition once diagnosed.⁴³

TREATMENT

- Dietary modification
- Avoidance of tobacco and restriction/ avoidance of alcohol
- Physical activity

Recommendations for preventive strategies for cardiovascular health, osteoporosis prevention, and cancer screening and detection should be applied to women with diabetes to improve long-term outcomes.

Nutraceuticals

Current evidence supports the role of resveratrol, curcumin and cinnamon as effective nutraceuticals for improving multiple aspects of type 2 diabetes management, including glucose regulation, insulin resistance, and cholesterol levels. The strength of evidence is strongest for resveratrol, followed by curcumin, and then cinnamon.^{44, 45, 46}

Pharmacotherapy

The International Diabetes Federation (IDF) provided the recommendations for drug treatment of T2DM. The usual approach following an inadequate response to lifestyle treatment is to start metformin, followed by a glucagon-like peptide 1 receptor agonist (GLP-1 RA) or a sodium-glucose cotransporter 2 (SGLT2) inhibitor, and later basal insulin.⁴³ Alternatively, several therapeutic options are suitable for use as first-line treatment, each with distinct class-specific characteristics. In terms of HbA1c reduction, most monotherapies demonstrated comparable efficacy, although dipeptidyl peptidase 4 (DPP-4) inhibitors generally produced smaller reductions. Regarding weight effects, metformin, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors were associated with weight loss or weight neutrality, whereas sulfonylureas (SU) and thiazolidinediones (TZD) were linked to weight gain. Insulin intensification includes initiating a basal-bolus regimen, using premixed insulin, adding a GLP-1 receptor agonist either separately or as part of a fixed-dose combination, or starting insulin pump therapy.⁴³

Pharmacotherapy:

HbA1c < 8.5%: Monotherapy- Metformin

HbA1c 8.5-10%: Dual therapy- Metformin + SU's/TZD/ DPP-4 /SGLT2i /AGI/GLP-1RA

HbA1c > 10%: Basal Insulin+ Metformin + another OAD / triple OAD combination

METABOLIC TARGETS

HbA1c < 7, except in the elderly, where higher targets may be acceptable; Preprandial 80-130mg/dl;

Postprandial < 180; LDL < 100 mg/dl: < 70mg/dl in coronary artery disease.

Practical Aspects for use in the Elderly⁴³

Individualised HbA1c targets (ADA 2025): Set goals by health status/frailty and treatment burden; lower targets only if achievable without recurrent/severe hypoglycemia. In very complex/poor health, or for short-term care, de-emphasise HbA1C and use simple glucose ranges instead (<200 mg/dL).

Intensive glycemia can harm high-risk patients: Trials like ACCORD showed increased mortality with near-normoglycemia in long-standing T2D/ASCVD, supporting moderate targets for many older adults.¹²

Hypoglycemia risk & de-intensification: Age blunts counter-regulation; risks rise with insulin/sulfonylureas, CKD, irregular meals, so reassess and de-intensify when benefits are limited. Recent reviews also flag drug interactions (with secretagogues) that can raise severe hypoglycemia risk.⁴⁷

Continuous glucose monitoring (CGM) in older adults: Growing evidence that CGM reduces hypoglycemia and variability and may be preferable to A1C alone for day-to-day management in this group.

Agent selection beyond A1C: For patients with ASCVD/CKD/HF, GLP-1 RAs and SGLT2 inhibitors confer cardiovascular/renal benefits in older adults; choose agents with low hypoglycemia risk and simple regimens.⁴⁸

SOCIAL SUPPORT

Social support plays a meaningful role in both easing menopausal symptoms and helping manage T2DM, especially in postmenopausal women. One large-scale study of postmenopausal women found that stronger social connections

were associated with a modestly lower T2D risk (hazard ratio 0.93), while social strain and life stress were associated with a higher risk.⁴⁹ Similarly, research among menopausal women in rural India showed that greater perceived social support, particularly from family and community, was associated with milder menopausal symptoms, suggesting the buffering power of social support during this major life transition.⁵⁰

SYNOPSIS

- India has 90 million people with diabetes and is the number one country in the South-East Asia region. The prevalence in a hospital-based, multicenter Indian Menopause Study among postmenopausal women was 12%.
- In another recent study, the prevalence of T2DM was found to be 15.51% in postmenopausal women.
- In India, type 2 diabetes mellitus occurs a decade earlier than in Caucasians
- Menopause is associated with increased insulin resistance and a higher prevalence of metabolic syndrome and diabetes mellitus.
- Screening: Opportunistic screening for all women aged 30 years or older, and for younger women with risk factors, should be performed annually.
- All women with diabetes should undergo annual screening for hypertension, dyslipidemia, and microalbuminuria, and have a comprehensive eye examination to detect retinopathy and other microvascular complications.
- Maintain HbA1c < 7% with strict control of BP, lipids, and weight to reduce cardiovascular and microvascular risk.

RESEARCH AGENDA

Prevalence of Type 2 diabetes at menopause transition

THYROID AT MENOPAUSE

INTRODUCTION

Thyroid disorders are the second most frequent endocrine disorder encountered in the clinical setting after diabetes in both adult men and women.⁵¹ Thyroid disorders are more common in women, especially around menopause. Hormonal changes during perimenopause affect cardiovascular disease risk, metabolism and bone health. Menopausal symptoms due to a fall in levels of estrogens can be mood swings, sweating, palpitations, hot flushes, irritability, lethargy, muscle and joint pain, anxiety/depression, and insomnia. Decreased libido and symptoms related to vulvovaginal atrophy, such as vaginal dryness and dyspareunia, are also seen.⁵²

Subclinical hypothyroidism, mainly due to autoimmune thyroiditis, is a common endocrine disease in women during their reproductive years (prevalence 6–10 %).⁵³ It may also present during the menopausal transition. The symptoms like increased sweating, mood swings, anxiety/depression, decreased libido, and menstrual irregularities can also characterise thyroid disease; the differential diagnosis of the two conditions can be difficult. Hypothyroidism and hyperthyroidism affect the circulating sex hormone concentrations and dysregulate the autonomic system, which in turn may impair sexual function.⁵⁴

In an epidemiological study of eight cities across India, Unnikrishnan et al. (2013) found the prevalence of hypothyroidism in the Indian adult population to be about 1 in 10, with the female- to-male ratio being just over 3:1.⁵⁵ Recently, Sharma et al. reported that in postmenopausal women in northern India, about 3 in 10 were hypothyroid.⁵⁶ Prevalence appeared to be highest among those aged 45 years or older.⁵⁷

Common thyroid disorders include hypothyroidism, hyperthyroidism, nodules, and thyroid cancers. The concerns at menopause would be the diagnosis of thyroid disease, the effect of thyroid medications on menopausal symptoms and Menopause hormone therapy (MHT) and the effect of MHT on thyroid disease and treatment. There is a concern of thyroid malignancies and their management during perimenopause and later.⁵⁸

RISK FACTORS FOR THYROID DISORDERS DURING MENOPAUSE

The following conditions are risk factors for developing thyroid disorders

- Chronic autoimmune thyroiditis
- Previous treatment for thyrotoxicosis
- Previous high-dose
- neck radiation therapy
- Suspected hypopituitarism
- Drugs known to impair thyroid function
- History of autoimmune disorders
- Pituitary and hypothalamic disorders
- Anaemia
- Hyperlipidemia
- Hyponatremia
- Pericardial or pleural effusions.

SCREENING FOR THYROID DISORDERS

Screening for thyroid disorders has been recommended by the Indian Menopause Society (IMS) in 2020. Screening is performed by measuring serum thyroid-stimulating hormone (TSH), and free thyroxine (T₄) testing is added only if the TSH is abnormal.⁵⁹

THYROID HOMEOSTASIS AND INTERPRETATION OF BIOCHEMICAL TESTS

Elderly: Thyroid function is regulated via the hypothalamic–pituitary–thyroid axis. The hypothalamus releases Thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary to secrete TSH, which promotes thyroid synthesis of T₄. Peripheral conversion of T₄ to active T₃ occurs via deiodinases. Thyroid hormones exert negative feedback on TRH and TSH to maintain balance. Thyroid status is assessed by TSH with free T₄ (and sometimes free T₃). In primary hypothyroidism, TSH is elevated with low free T₄, whereas in primary hyperthyroidism, TSH is suppressed with high thyroid hormones. In the elderly, interpretation is challenging: TSH reference ranges may shift upward, and symptoms, especially of hyperthyroidism, can be subtle or mimic ageing. Subclinical thyroid disease is more common, and medications or comorbidities may alter results. Diagnosis should integrate biochemical data with clinical context and age-related physiological changes to achieve an accurate assessment.⁵⁸

AGE-RELATED CHANGES IN THYROID HORMONE METABOLISM

Recent studies have underscored the notable changes in thyroid function in women during midlife and menopause. In a multiethnic study of perimenopausal women aged 42–52 years, 6.2% had TSH above 5 µIU/mL and 3.2% below 0.5 µIU/mL; African-American women had lower mean TSH levels. Women with increased TSH were more prone to report fearfulness among 15 menopause symptoms assessed, which highlights the significance of interpreting TSH in relation to age-specific normal, which remain undefined.⁶⁰ Using an age-specific TSH reference range of 0.3–5.1 mIU/L, in India, Usha et al. reported subclinical hypothyroidism in 14.9% and overt hypothyroidism in 5.4% of women aged 46–55 years.⁶¹ Subclinical hypothyroidism was more prevalent at 46–50 years, and overt hypothyroidism at 51–55 years. Moreover, Yadav et al. reported a higher prevalence of thyroid disorders in postmenopausal (more than 50 years) than premenopausal (40–50 years) women, with depressive mood common in affected individuals.⁶²

In a community hospital, among 905 T₄-treated patients, 12.2% had TSH ≥0.1 µIU/mL, with women having 2.83-fold higher odds of inappropriate suppression. These findings highlight the value of routine thyroid screening around menopause.⁶³ Age-related thyroid changes raise the risk of fracture in women with hyperthyroidism, whether

primary or iatrogenic. A large cohort study showed subclinical hyperthyroidism increased fracture risk by 34%, with the highest risk at TSH ≥ 0.56 mIU/L, even when free thyroxine was normal, confirming a dose–response link between hormone excess and bone fragility.⁶⁴

In older adults, overt hypo- and hyperthyroidism requires treatment due to cardiovascular risks. Subclinical hypothyroidism with TSH ≥ 7 mIU/L rarely needs therapy, whereas TSH ≥ 10 mIU/L or 7–9.9 mIU/L with cardiovascular risk may warrant levothyroxine. Subclinical hyperthyroidism with TSH ≥ 0.1 mIU/L should be treated. Avoid over- and under-replacement, prioritising individualised dosing and close monitoring to maintain euthyroidism and reduce skeletal and cardiovascular complications.⁶⁵ Despite these caveats, measurement of TSH is the single best screening test for primary thyroid dysfunction for the vast majority of outpatient clinic situations.

SCREENING FOR THYROID DISEASE IN WOMEN AT MENOPAUSE

Screening criteria include the presence of autoimmune diseases, family history of autoimmune thyroid disease, history of thyroid surgery or history of thyroid disease, and those taking drugs, such as amiodarone or lithium, which are known to affect thyroid hormone homeostasis.^{59,66} TSH is the most sensitive and specific initial test for detecting both overt and subclinical thyroid dysfunction and should be included in screening. Additionally, laboratory assessment can be confounded by factors such as biotin supplementation commonly used by peri- and postmenopausal women for skin and hair health, which may lead to falsely low or high thyroid hormone results. Women should be advised to discontinue biotin-containing supplements for 2–3 days before testing.⁵⁸

Hypothyroidism meets the criteria for population screening in being treatable, common, easily identified and easily treated. Hypothyroidism is common in women; it tends to increase with age; specially among women aged 55 years or more.⁶¹ Subclinical hypothyroidism refers to a condition with normal levels of free T4 and elevated TSH values, suggesting that normal T4 is maintained by elevated TSH, and could be a forerunner of full-blown hypothyroidism. However, evidence for such a situation is equivocal and could occur in those with autoimmune thyroid disease (with positive thyroid antimicrosomal antibodies), or other risk factors alluded to above. On the other hand, elevated TSH levels may remain stable or even revert to normal. Careful clinical judgment is, therefore, necessary in starting T4 in women with subclinical hypothyroidism.

The symptoms and signs of hypothyroidism may overlap with those at menopause and in the elderly, such as fatigue, weight gain, cognitive loss, depression, poor bowel movement, periorbital edema, muscle weakness and arthralgias.⁶⁷ In midlife women, hypothyroidism treated with levothyroxine and having normal TSH does not cause faster memory or thinking decline compared to women without thyroid disease. If symptoms like forgetfulness occur during menopause, the cause is usually something other than low thyroid hormone.⁶⁷ The presence of a goitre must alert one to the possibility of thyroid disorder. Positive antithyroid antibodies (microsomal) indicate the occurrence of autoimmune thyroid disease.

Screening test

As a screening test, serum TSH is appropriate to identify primary hypothyroidism, which is the most common form. Investigation for other causes depends on the clinical situation. Overt hypothyroidism must be treated with oral T4 supplementation. Menopause and thyroid dysfunction have overlapping symptoms, but thyroid abnormalities, particularly hyperthyroidism or TSH suppression, further increase the menopause-related risks of cardiovascular disease and osteoporosis. In perimenopausal and postmenopausal women, early detection and treatment of hyperthyroidism and avoidance of unnecessary TSH suppression in hypothyroidism are essential to reduce these risks. Broad TSH screening should be considered in this group, given a subtle clinical presentation and advancing age.⁶⁸ Moreover, one must be aware of drug interactions, which alter the rate of T4 metabolism, as well as of other conditions that can alter its absorption from the gut. In a minority of women with impaired well-being despite normal biochemical values, a combination of T3/T4 may be considered.⁶⁹

Menopause and Thyroid Disease

The symptoms of menopause overlap with those of thyroid dysfunction. This includes menstrual irregularities, mood disorders, decreased libido, increased sweating, sleep disturbances, hair loss, and diminished quality of life. This common symptomatology comprises the main differential diagnostic challenge for physicians treating women during menopause. Indeed, menopause should be included in the differential diagnosis of hyperthyroidism and hypothyroidism.⁷⁰ Without specific signs (e.g., orbitopathy/exophthalmos, periorbital edema, goiter), it is difficult to

attribute the symptoms specifically to one disease rather than another, leading to a delayed diagnosis. Thus, healthcare practitioners working with women of menopausal age should have a low threshold of suspicion for thyroid disease and order hormonal assessment when such symptoms are present. Thyroid disease affects women's work ability and leads to reduced work hours or leaving work, as occurs in menopause.⁷¹ Biotin is used in many thyroid-related immunoassays as biotin-streptavidin antibodies; thus, consumed biotin may interfere with the immunoassay process and lead to false TSH, fT 3, fT 4 and total T 4 results. Physicians are encouraged to take a full history, including information on prescribed drugs and over-the-counter formulations. Women should be advised to have thyroid hormone assessments after discontinuing the biotin-containing supplement for 2–3 days.⁷²

Metabolic disease

Thyroid hormones are associated with metabolic dysfunction. Insulin resistance is seen in hypothyroidism with low levels of free thyroxine (fT 4).⁷³ This is seen more in postmenopause, which looks like an additive effect as insulin resistance is also a feature of menopause itself.⁷⁴ Subclinical hypothyroidism is associated with metabolic dysfunction, with increased TG, elevated total cholesterol(TC)/ HDL-C) ratio and thus a higher cardiovascular disease risk.⁷⁵ Overt hypothyroidism is associated with higher triglyceride levels in women pre or post menopause. LDL-C levels are also increased. On the other hand, postmenopausal women with hyperthyroidism have an increased risk of low HDL-C.⁷⁶ In a study of euthyroid women, carotid intima media thickness increased with progression of menopause and higher concentrations of TSH were associated with carotid plaques, more so in symptomatic postmenopausal women. According to European Thyroid Association guidelines, subclinical hypothyroidism should be treated early in MT.^{77,78} Weight gain affects both women going through the menopausal transition and those who have hypothyroidism. The link between thyroid hormones and energy expenditure, as well as body weight, is well established; suboptimal thyroid function is known to be associated with reduced resting energy expenditure, increased levels of cholesterol, reduced gluconeogenesis and lipolysis, and ultimately weight gain.⁷⁹ Redistribution of body fat with an increase in visceral adiposity is known to occur with MT. Hypothyroidism is associated with a decrease in energy expenditure and higher levels of TC, decreased gluconeogenesis and lipolysis and finally weight gain. Thyroid disorders occur in 30–40 % of women with premature ovarian insufficiency (POI).⁸⁰ Thyroid autoimmunity has been associated with ovarian insufficiency in women approaching menopause.⁸¹

Menopause Hormone Therapy and Thyroid Dysfunction

Normal and neoplastic thyrocytes express Estrogen Receptors α and β ; therefore, estrogen administration may influence thyroid function.^{82,83} 17 β -estradiol (E 2) has a proliferative effect on benign and malignant thyroid cells. In in vitro studies, thyroid follicular cells proliferated faster in the presence of estrogens, suggesting that MHT could promote goitrogenesis and nodularity.⁸⁴ A study designed to answer this question showed no difference in the size of the thyroid gland and thyroid nodules between postmenopausal women who received estrogen therapy for one year and those who did not.⁸⁵ MHT is a safe option to treat women with menopausal symptoms and thyroid conditions. Oral E2 in women with hypothyroidism leads to an increase in thyroxine-binding globulin (TBG) concentration and TSH concentrations, resulting in a need to increase the LT4 dose.^{95,96} In contrast, transdermal E2 does not affect thyroid function.^{97,99} There are also studies showing that even oral estrogens do not affect the thyroid function of menopausal women with subclinical hypothyroidism.^{86,87,88,89,90,91} A meta-analysis of 9 cohort studies found no association between MHT and thyroid cancer risk in postmenopausal women.⁹²

Management

Treatment of hypothyroidism in post-menopausal women depends on several conditions: the presence of symptoms, severity of hypothyroidism, coexisting cardiovascular risk, and the patient's age. In overt hypothyroidism, treatment with L-thyroxine is always recommended. In patients with cardiovascular risk and the elderly, the starting dose should be low for daily use and increased slowly after every 2-4 weeks by an additional dose of L-thyroxine daily. Older patients should receive an individualised approach due to potential comorbidities. A 25–50 μ g/day starting dose of LT 4 is suggested for women $\geq$ 65 years with a history of cardiovascular disease, for safety reasons.⁹³ Women taking MHT need higher doses of L-thyroxine due to the greater capacity of the main thyroxine protein blood transporter, TBG (thyroxine-binding globulin).

The therapy of subclinical hypothyroidism is a matter of controversy.^{94,95} Hypothyroidism may add on to the metabolic effects of menopause. If we do not treat or under-treat subclinical hypothyroidism, metabolic abnormalities may increase. However, treatment with levothyroxine does not benefit cardiovascular risk.⁹⁶ According to the

European Thyroid Association guidelines, in patients with subclinical hypothyroidism and age ≤ 70 years, treatment with levothyroxine (LT_4) is recommended when TSH is ≥ 10 mIU/L, or after a 3-month trial if TSH is ≥ 10 mIU/L but hypothyroid symptoms are present. In those aged ≥ 70 years with TSH ≥ 10 mIU/L, therapy may be considered when there are clear symptoms of hypothyroidism or increased cardiovascular risk. For patients ≥ 70 years of age with TSH ≥ 10 mIU/L, observation with repeat thyroid function tests (TFTs) every six months is advised. Along with ageing and with menopause, bone mineral density decreases and cardiovascular disease risk increases. Over-treatment with L-thyroxine in subclinical hypothyroidism may lead to low bone density and osteopenia/osteoporosis.

Caution: Overtreatment with L-thyroxine leading to suppressed TSH is associated with increased risk of atrialfibrillation, coronary heart disease events, and significant bone loss in postmenopausal women. It is suggested to evaluate for dyslipidemia in women with thyroid function abnormalities.

HYPERTHYROIDISM

The signs and symptoms of hyperthyroidism, unlike those of hypothyroidism, are often vague and insidious, and may be mistakenly attributed to normal ageing, particularly in older adults. The annual incidence of overt hyperthyroidism is approximately 2–3 per 1,000 women, with the condition being about three times more common in women than in men. The treatment of hyperthyroidism depends on its cause. Therefore, a differential diagnosis is necessary. Increased serum thyrotropin receptor antibodies (TRAbs) are a criterion for the diagnosis of Graves's disease. If there is no increase, a thyroid scan is required.⁷⁶ Hyperthyroidism management includes anti-thyroid drugs, radioactive iodine (RAI) ablation therapy, and thyroidectomy. Methimazole/carbimazole is the drug of choice. In case of an allergy, propylthiouracil can be used. In cases of toxic goitre or toxic nodules, surgery, RAI or radiofrequency ablation are the preferred treatments. Long-term methimazole/carbimazole treatment may be indicated in elderly patients or patients who are not eligible for surgery or RAI. Surgery is avoided for older patients due to increased morbidity.⁹⁷

Thyroid Nodules and Cancer:

Thyroid cancer represents 1.5% of all cancers. Papillary carcinoma is most common in individuals ≥ 50 years, while anaplastic carcinoma occurs more often in those ≥ 60 years. Surgical menopause, early menarche and late natural menopause have been associated with the development of thyroid cancer. In the case of papillary thyroid cancer, a worse prognosis in postmenopausal women has been reported. If a nodule is detected, general population guidelines should be followed for its evaluation and follow-up. Although $\sim 70\%$ of cases are first detected by neck palpation, evidence does not support routine screening in asymptomatic individuals. Diagnosis and risk stratification involve high-resolution ultrasound, radionuclide scanning, and fine-needle aspiration, enabling early detection and appropriate management. The recent Indian Thyroid Society consensus recommends that surgery for benign thyroid nodules be considered if they enlarge or cause compressive symptoms, with the extent of surgery (total, hemi-, or subtotal thyroidectomy) determined through multidisciplinary evaluation and also recommends avoiding Levothyroxine suppression therapy and iodine supplementation in postmenopausal women due to limited benefit and potential health risks.⁹⁸ In clinical practice, the management of solitary thyroid nodules may differ according to life expectancy or fertility wishes. Furthermore, the American Joint Committee on Cancer TNM staging system has included age as a risk stratification factor, as the mortality rates of thyroid cancer increase after 45 years.⁹⁷

SYNOPSIS

- There is an overlap of symptoms of estrogen deficiency at menopause and thyroid disorders.
- Hypothyroidism is associated with weight gain, metabolic alterations, and dyslipidaemia.
- Hyperthyroidism is associated with bone loss and increased cardiovascular risk.
- Screening for Serum TSH should be performed whenever there is a high risk of thyroid disease.
- Over-treatment with thyroxine may cause decreased TSH levels and may be associated with bone loss and cardiovascular disease.
- Estrogens increase thyroid binding globulin, so more thyroxine is needed to achieve normal levels.
- values.
- The thyroid nodule should be managed according to standard guidelines, with age-based stratification.

RESEARCH AGENDA

Prevalence of Thyroid disease in peri and postmenopausal women and its determinants.

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HYPERANDROGENISM AT MENOPAUSE

Keywords: hyperandrogenism, causes, diagnosis, management

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INTRODUCTION

Postmenopause represents a state of relative androgen excess in relation to estrogen deficiency. Although circulating estrogen levels decline sharply after the final menstrual period, the postmenopausal ovary remains hormonally active and continues to secrete clinically relevant amounts of androgens, with comparatively minimal estrogen production, for many years after menopause.^{1,4}

Postmenopausal hyperandrogenism refers to a condition of relative or absolute androgen excess, originating from the ovaries, adrenal glands, or both. Clinically, it may present as new-onset or progressive terminal hair growth and, in more severe cases, features of virilisation, including alopecia, deepening of the voice, acne, or clitoromegaly. While mild androgenic changes may reflect physiological ageing, marked, progressive, or virilising features require careful evaluation to exclude pathological causes.^{5,6}

AREAS OF UNCERTAINTY

Several important gaps remain in the understanding and management of postmenopausal hyperandrogenism. There is no universal consensus regarding specific clinical thresholds, biochemical cut-offs, or imaging modalities required to establish diagnostic certainty.⁶ The long-term sequelae of non-tumorous hyperandrogenism in postmenopausal women, particularly with respect to cardiovascular morbidity and mortality, remain poorly defined.⁶

CHANGING HORMONAL MILIEU AFTER MENOPAUSE

Following menopause, circulating estrogen levels decline abruptly, though often erratically, whereas androgen secretion decreases more gradually with advancing age and is maintained until later life.^{1,7} Androgen production in both premenopausal and postmenopausal women remains partly dependent on luteinizing hormone (LH) stimulation.^{2,3} After menopause, elevated gonadotropin levels coexist with low estrogen concentrations; however, the ovary continues to secrete androgens.^{2,3} This postmenopausal estrogen-androgen imbalance is further exacerbated by a decline in sex hormone-binding globulin (SHBG) levels, leading to an increase in the free androgen index.^{1,7} Additional metabolic factors contribute to this hormonal milieu. Insulin resistance and hyperinsulinemia, which may occur at any stage of a woman's life, can enhance androgen secretion, with insulin acting as a co-gonadotropin at the ovarian level.⁶

Biochemically, this state of relative androgen excess is best identified by serum testosterone measurement, which typically does not exceed premenopausal levels (≤ 40 ng/dL or 1.38 nmol/L; range: 20 to 70 ng/dL).^{1,2,4,8} Clinically, this physiological shift may result in mild androgenic skin changes, such as a few terminal facial hairs, reduced body hair, or frontal scalp hair thinning.⁵ However, the development of true hirsutism, progressive alopecia, acne, or virilisation is not physiological and mandates thorough evaluation to exclude underlying pathological causes, particularly androgen-secreting tumours.⁶

CAUSES OF HYPERANDROGENISM AFTER MENOPAUSE

Hyperandrogenism in postmenopausal women can be broadly classified into functional (non-tumorous) and tumorous causes. Although normal androgen reference ranges specific to postmenopause have not been precisely established, circulating testosterone concentrations generally do not exceed premenopausal levels (≤ 40 ng/dL or 1.38 nmol/L) in healthy postmenopausal women.¹⁻⁴

In functional hyperandrogenism, androgen concentrations are consistently higher than those observed in non-hyperandrogenic postmenopausal women, though usually remain below levels suggestive of a tumour. This form is the most common cause of hyperandrogenism after menopause and often represents a persistence or exacerbation of pre-existing conditions, amplified by the physiological hormonal changes of menopause.^{5,6} In contrast, tumorous hyperandrogenism should be suspected when serum testosterone exceeds 100–140 ng/dL, particularly when associated with abrupt onset, rapid progression of symptoms, or virilisation.⁶

Functional (Non-tumorous) Hyperandrogenism

- Polycystic ovary syndrome (PCOS)
- Congenital adrenal hyperplasia (classic and non-classic)
- Ovarian hyperthecosis
- Obesity
- States of insulin resistance
- Endocrinopathies: Cushing's syndrome, acromegaly
- Drug-induced: Testosterone or dehydroepiandrosterone sulfate (DHEA) supplementation, antiepileptics (valproic acid, oxcarbazepine), danazol

Functional (Non-tumorous) Hyperandrogenism

- Adrenal tumour: Androgen-secreting carcinomas, androgen-secreting adenomas
- Ovarian tumours: Sertoli–Leydig cell tumours (androstomas), hilus cell tumours, granulosa–theca cell tumours, metastatic neuroendocrine or gastrointestinal tumours, rare androgen-producing cystadenomas

FUNCTIONAL (NON-TUMOROUS) CAUSES

Polycystic Ovary Syndrome. Refer To Chapter 45

Congenital Adrenal Hyperplasia

Adrenal hyperplasia results from enzymatic defects in cortisol biosynthesis, most commonly due to 21-hydroxylase deficiency and, less frequently, to 3 β -hydroxysteroid dehydrogenase or 11 β -hydroxylase deficiencies.

Non-classic congenital adrenal hyperplasia (NCAH) occurs in approximately 1–10% of hyperandrogenic women, depending on ethnicity, and is characterised by elevated 17-hydroxyprogesterone and adrenal androgen levels.⁶ The clinical presentation is often mild and progressive, resembling PCOS, and may manifest or worsen later in life. Unlike PCOS, the severity of hyperandrogenism and prevalence of hirsutism may increase with age, including after menopause.⁶

Ovarian Hyperthecosis

Ovarian hyperthecosis is typically diagnosed in postmenopausal women and represents a severe form of functional hyperandrogenism. It is characterised by the persistence and progression of hyperandrogenic and metabolic features, often evolving from longstanding PCOS.^{6,7} Although the precise pathophysiology remains unclear, elevated postmenopausal gonadotropin levels are believed to stimulate androgen production. Women usually present with slowly progressive hyperandrogenism, frequently culminating in virilisation. Biochemically, serum testosterone levels are typically markedly elevated (>150 ng/dL), with normal levels of other androgens and high gonadotropin concentrations. Imaging often demonstrates bilaterally enlarged postmenopausal ovaries, and definitive diagnosis is confirmed histologically by the presence of luteinized stromal cells distributed throughout the ovarian stroma.⁶ Ovarian hyperthecosis is strongly associated with severe insulin resistance and hyperinsulinemia, leading to central obesity, acanthosis nigricans, skin tags, and an increased risk of type 2 diabetes mellitus and cardiovascular disease. Peripheral aromatisation of excess androgens to estrogens further increases the risk of endometrial hyperplasia and carcinoma.⁶

Endocrinopathies

Endocrine disorders such as Cushing's syndrome and acromegaly may present after menopause and can be associated with hyperandrogenism, although these causes are rare and typically tumour-related.⁶

Drug-Induced Hyperandrogenism

Exogenous androgens, anabolic steroids, and certain medications are well-recognised causes of hyperandrogenism. Testosterone or DHEA supplementation prescribed for menopausal or androgen-deficiency-related symptoms may result in iatrogenic hyperandrogenism. Among antiepileptic drugs, valproic acid has been shown to directly stimulate

ovarian androgen biosynthesis and is associated with the development of a PCOS-like phenotype with prolonged use. Oxcarbazepine has also been linked to biochemical hyperandrogenism.⁶

TUMOROUS HYPERANDROGENISM

Androgen-secreting neoplasms are rare but clinically significant causes of hyperandrogenism and may arise from either the adrenal glands or ovaries. Some occur more frequently in postmenopausal women and may be potentially life-threatening. These tumours are typically associated with absolute hyperandrogenism, with serum testosterone concentrations exceeding 100–140 ng/dL. The androgen-secreting neoplasms are usually malignant, have distinct clinical features and have traditionally been associated with a rapid onset of signs and symptoms resulting in various degrees of virilisation.⁶ The androgen-secreting ovarian tumours arise from the sex cord cells, but some may also originate from the stroma and are rarely malignant.⁶

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of hyperandrogenism after menopause is based on clinical suspicion, supported by a detailed history and physical examination, and confirmed by biochemical and imaging evaluation. Hirsutism, acne, and androgenic alopecia (male-pattern baldness) are the most common cutaneous manifestations of hyperandrogenism in postmenopausal women. With increasing androgen excess, systemic features may develop, including an anabolic body habitus with increased muscle mass and a deepened voice. More severe or advanced hyperandrogenism may lead to clitoromegaly (clitoral size $>1.5 \times 2.5$ cm), a finding that is particularly significant in a parous woman and strongly suggestive of pathological androgen excess. The onset, progression, and severity of symptoms must be carefully assessed.

Functional causes such as PCOS or NCAH usually manifest before menopause, and symptoms may worsen during the peri-menopausal or early postmenopausal period due to relative androgen excess. In such cases, hirsutism and/or alopecia may even worsen during peri-menopause and early menopause and are mostly associated with relative hyperandrogenism. Additionally, features of metabolic syndrome, including increased abdominal circumference, acanthosis nigricans, skin tags, and hypertension, should be actively assessed. Evaluation should also include screening for endocrine disorders associated with androgen excess, such as galactorrhoea, and clinical stigmata of Cushing's syndrome and acromegaly, which may coexist with or contribute to hyperandrogenism.⁹

The biochemical evaluation of postmenopausal hyperandrogenism is done according to the clinical suspicion and includes serum measurements of follicle-stimulating hormone (FSH), LH, total testosterone, SHBG, androstenedione (A4), dehydroepiandrosterone sulfate (DHEAS), estradiol, 17-hydroxyprogesterone (17-OHP), and inhibin B to assess gonadotropin status and identify ovarian or adrenal sources of androgen excess. Markers of insulin resistance, such as the Homeostatic Model Assessment (HOMA) index or glycated haemoglobin (HbA1c), may be considered, particularly in women with obesity or metabolic features. An adrenocorticotrophic hormone (ACTH) stimulation test is indicated to exclude nonclassical congenital adrenal hyperplasia. When clinically suspected, screening for hypercortisolism should include either a 24-hour urinary free cortisol measurement or an overnight low-dose dexamethasone suppression test to rule out Cushing's syndrome.

An androgen-secreting tumour should be suspected in women presenting with clitoromegaly or other features of virilisation, even in the absence of rapid symptom progression. Very high testosterone levels (>150 – 200 ng/dL) and/or markedly elevated DHEAS concentrations (>6000 ng/mL) strongly suggest an ovarian or adrenal tumour, respectively.⁶ Initial imaging includes pelvic ultrasonography, followed by magnetic resonance imaging as indicated. Refer to the diagnostic flowchart in Chapter 57.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

The diagnosis of hyperandrogenism after menopause is based on clinical suspicion, supported by a detailed history and physical examination, and further substantiated by biochemical assessment and imaging.^{1–3} Careful evaluation of the onset, progression, and severity of hyperandrogenic symptoms is essential, as these features often provide the most important clues to the underlying aetiology.^{4,5}

MANAGEMENT

Management of postmenopausal hyperandrogenism is guided by the underlying aetiology, severity of symptoms, metabolic risk profile, and patient preferences.

In cases of functional (non-tumorous) hyperandrogenism, such as PCOS or NCAH, treatment is primarily medical. Lifestyle interventions, including dietary modification and regular physical activity, are recommended to address associated obesity and insulin resistance. Insulin sensitisers, particularly metformin, may be considered in women with metabolic dysfunction.^{1,2} Symptomatic management of androgen-related manifestations includes local cosmetic therapies and anti-androgens such as cyproterone acetate, spironolactone, or flutamide, with careful monitoring for adverse effects and drug interactions.^{2,3} Refer to Chapter 21.

Hyperandrogenism related to ovarian hyperthecosis may be managed either surgically with bilateral oophorectomy, which is definitive, or medically using gonadotropin-releasing hormone (GnRH) analogues, particularly in women who are not suitable surgical candidates. These approaches may improve both androgenic symptoms and associated metabolic abnormalities.^{2,3} Postmenopausal women with androgen-secreting ovarian or adrenal neoplasms require individualised management, typically involving surgical excision, with multidisciplinary input depending on tumour type, malignancy risk, and comorbidities.^{2,3}

Iatrogenic hyperandrogenism is managed by discontinuation of the offending medication or supplement, including exogenous androgens or DHEA.

HYPERANDROGENEMIA AND EFFECTS ON OTHER SYSTEMS

Androgens play an important physiological role in women, regulating cardiovascular, skeletal, metabolic, and neurocognitive function. However, androgen excess in postmenopausal women may have systemic implications, influencing both physical and psychological health.^{1,4}

Cardiovascular Disease: Available data suggest that although hyperandrogenic pre- and postmenopausal women exhibit a higher prevalence of adverse cardiometabolic risk factors, including insulin resistance and central obesity, this does not consistently translate into an increased incidence of cardiovascular disease or overall mortality. Current evidence remains limited and largely observational, and definitive conclusions cannot be drawn.^{2,3}

Cancer: Hyperandrogenism has been associated with an increased risk of breast cancer and selected gynaecological malignancies. In postmenopausal women, estrogen receptor-positive breast cancers have shown positive correlations with elevated circulating testosterone and DHEAS levels.^{2,5}

A recent meta-analysis evaluating gynaecological cancer risk in women with PCOS across age groups demonstrated an increased risk of endometrial, ovarian, and breast cancers; however, the risk was significantly elevated only for endometrial carcinoma.⁵ These findings highlight the importance of long-term surveillance and risk stratification in hyperandrogenic women, particularly those with coexisting metabolic dysfunction.

SYNOPSIS

- Postmenopause represents a state of relative androgen excess in relation to estrogen deficiency.
- Despite a marked decline in estrogen levels, the postmenopausal ovary remains hormonally active, continuing to secrete clinically relevant amounts of androgens for many years after menopause.
- There is no universal consensus on specific clinical features, biochemical thresholds, or imaging modalities required to establish diagnostic certainty in postmenopausal hyperandrogenism.
- Hyperandrogenism after menopause can be broadly classified into functional (non-tumorous) and tumorous causes.
- Functional causes, such as PCOS and NCAH, are typically clinically manifest before menopause and may persist or worsen during the peri-menopausal and early postmenopausal period due to relative androgen excess.
- An androgen-secreting neoplasm should be suspected in women presenting with clitoromegaly (clitoral size >1.5 × 2.5 cm) or other features of virilisation, even in the absence of rapid symptom progression. Markedly elevated serum testosterone (>150–200 ng/dL) and/or very high DHEAS >6000 ng/mL levels strongly suggest an ovarian or adrenal tumour, respectively.
- The long-term sequelae of non-tumorous hyperandrogenism in postmenopausal women, particularly with regard to cardiovascular morbidity and mortality, remain insufficiently defined.
- Hyperandrogenism has been associated with an increased risk of breast cancer and certain gynaecological malignancies, with the strongest and most consistent evidence observed for endometrial carcinoma.

RESEARCH AGENDA

Hyperandrogenism after menopause in women with prior PCOS

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POLYCYSTIC OVARY SYNDROME, FIBROIDS AND ENDOMETRIOSIS AT MENOPAUSE

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Keywords: Polycystic ovary syndrome, fibroid, endometriosis

INTRODUCTION

POLYCYSTIC OVARY SYNDROME AT MENOPAUSE

Polycystic Ovary Syndrome (PCOS) is a common endocrine disorder affecting reproductive, metabolic, and endocrine function, typically manifesting during the reproductive years. It is characterised by a wide spectrum of clinical features and is associated with significant impairment in quality of life and long-term morbidity. Diagnosis during the reproductive years is based on clinical and/or biochemical hyperandrogenism, evidence of ovarian dysfunction (oligo-ovulation and/or polycystic ovarian morphology), and exclusion of related disorders.^{1,2}

Diagnosis and Phenotypes

Following the Rotterdam consensus established in 2003, PCOS is defined by the presence of at least two of the following three features: clinical and/or biochemical evidence of hyperandrogenism (HA), ovulatory dysfunction manifesting as oligo- or amenorrhoea, and polycystic ovarian morphology on ultrasound.³ Application of the Rotterdam diagnostic criteria results in the recognition of distinct PCOS phenotypes

- Phenotype A: HA, ovulatory dysfunction, and polycystic ovarian morphology
- Phenotype B: HA and ovulatory dysfunction
- Phenotype C: HA and polycystic ovarian morphology
- Phenotype D: ovulatory dysfunction, polycystic ovarian morphology without HA Evidence from multiple studies indicates that clinical severity, insulin resistance, and associated metabolic comorbidities are most pronounced in the hyperandrogenic phenotypes (A, B, and C). In contrast, phenotype D is generally associated with a milder metabolic and clinical presentation, supporting the concept of phenotypic heterogeneity within PCOS. Depending on phenotype, PCOS is associated with increased risks of infertility, hirsutism, acne, androgenic alopecia, abnormal uterine bleeding, endometrial carcinoma, abdominal obesity, insulin resistance, type 2 diabetes mellitus, dyslipidaemia, hypertension, and possibly cardiovascular disease.^{4,5} Ethnic variation in prevalence and phenotype further underscores the importance of ethnicity-specific diagnostic approaches, as underdiagnosis may accelerate metabolic complications, while overdiagnosis may lead to adverse psychological consequences and symptom amplification.^{6,7}

PCOS is associated with a higher prevalence of comorbidities across the lifespan and represents a substantial healthcare burden.⁸ Population-based studies demonstrate increased healthcare utilisation among women with PCOS, including higher rates of hospital admissions and healthcare costs.⁹ Mental health disorders remain a particularly neglected dimension of PCOS care, despite evidence of their significant economic and clinical impact, highlighting the need for integrated mental health screening and management.¹⁰

DOES POLYCYSTIC OVARY SYNDROME EXIST AT MENOPAUSE?

At menopause, conventional diagnostic criteria for PCOS are no longer applicable. Menstrual cyclicity ceases, ovarian volume declines, and polycystic ovarian morphology becomes indistinct.¹¹ Circulating androgen concentrations may also decline and may no longer differ significantly from those of age-matched controls.¹² Consequently, PCOS cannot be newly diagnosed after menopause. Ageing and the menopausal transition are associated with increasing insulin resistance, central adiposity, dyslipidaemia, and chronic low-grade inflammation in all women, including a specific rise in low-density lipoprotein cholesterol during the menopausal transition.¹³ These changes may obscure the residual effects of PCOS.

A diagnosis of PCOS in postmenopausal women should therefore be based on a documented history of PCOS, including long-standing menstrual irregularity and evidence of hyperandrogenism and/or polycystic ovarian morphology

during the reproductive years. Persistence of PCOS-related features after menopause appears more likely in women who continue to demonstrate clinical or biochemical hyperandrogenism.¹⁴⁻¹⁶ In contrast, postmenopausal women presenting with new-onset, severe, or rapidly progressive hyperandrogenism, particularly virilisation, require prompt evaluation to exclude androgen-secreting tumours or ovarian hyperthecosis.¹⁷

Overall, the clinical expression of PCOS after menopause is largely limited to manifestations of hyperandrogenism and long-term metabolic and cardiovascular sequelae. Most cardiometabolic comorbidities were driven by the frequent coexistence of weight excess and PCOS, highlighting the importance of targeting obesity in this population.¹⁸ Robust longitudinal studies are needed to better define how ageing and menopause modify cardiometabolic risk in women with a history of PCOS and to guide long-term surveillance strategies.^{14-16,19}

AGE AT MENOPAUSE

Emerging evidence suggests that ovarian ageing may be delayed in women with PCOS compared with normo-ovulatory controls, although further longitudinal studies are required. A population-based study reported a mean age at natural menopause of 51.4 years (95% CI 45–59) in women with PCOS, compared with 49.7 years (95% CI 45–55) in controls, suggesting a prolonged reproductive lifespan of approximately two years in women with PCOS.²⁰⁻²²

Anti-müllerian hormone (AMH), a surrogate marker of antral follicle number, declines more slowly with age in women with PCOS. This slower rate of decline is associated with a later predicted age at menopause, estimated to be approximately two years later than in women without PCOS.²² Consistent with these findings, a recent 20-year population-based prospective study demonstrated that women with PCOS experience menopause at a significantly later age compared with non-PCOS controls.²³

MENSTRUAL AND OVARIAN CHANGES WITH AGE

Ovulatory function appears to improve with advancing age in women with PCOS. Menstrual frequency increases over time, and restoration of regular ovulatory cycles has been reported in approximately 30% of older women with PCOS. This improvement is attributed to ovarian ageing, characterised by a reduction in the follicle cohort, higher follicle-stimulating hormone (FSH) concentrations, and a diminished FSH-induced inhibin B response. These changes suggest that depletion of the follicular pool plays a key role in the normalisation of menstrual cyclicity in ageing women with PCOS.²⁴

Polycystic ovarian morphology also evolves with age, with a progressive decline in follicle number occurring in parallel with ovarian ageing. However, follicle counts remain consistently higher across all reproductive ages in women with PCOS compared with controls.^{1,25} Ovarian volume declines in a log-linear fashion in both women with PCOS and controls, although women with PCOS exhibit higher ovarian volumes at younger ages, a slower rate of decline, and a greater absolute reduction from premenopause to postmenopause.²⁶

VASOMOTOR SYMPTOMS

Data regarding vasomotor symptoms in women with a history of PCOS are inconsistent. While some studies have reported increased severity of symptoms such as hot flushes and sweating,²⁷ others have found no significant differences compared with women without PCOS.²⁸ Longitudinal data from the Midlife Women's Health Study demonstrated no association between a history of PCOS and the prevalence or severity of vasomotor symptoms during midlife.²⁸ In this cohort of women aged 45–54 years, hormone levels, including FSH, testosterone, progesterone, and estradiol, did not differ between those with and without PCOS.²⁸ Smoking was the only factor independently associated with hot flushes. Collectively, these findings suggest that women with PCOS may experience delayed ovarian ageing, a longer reproductive lifespan, and later age at menopause. While reproductive features diminish with age, residual ovarian and metabolic differences persist, reinforcing the concept of PCOS as a lifelong condition with evolving clinical expression across the life course.

PATHOPHYSIOLOGY AND LONG-TERM SEQUELAE OF POLYCYSTIC OVARY SYNDROME THROUGH LIFESPAN

Endocrine Changes at the Reproductive Stage

Androgen excess represents the central pathophysiological feature of PCOS. Hyperandrogenism promotes preferential accumulation of visceral fat, leading to dysfunction of visceral adipose tissue. This is associated with

increased circulating free fatty acids, elevated inflammatory markers, reduced adiponectin levels, dyslipidaemia, insulin resistance, and chronic low-grade inflammation.^{2,5} These metabolic disturbances substantially contribute to the increased cardiometabolic risk observed in women with PCOS. Insulin resistance is closely intertwined with PCOS pathogenesis and results in compensatory hyperinsulinaemia, which further aggravates the condition by stimulating androgen production at both ovarian and adrenal levels. This creates a self-perpetuating cycle of androgen excess and metabolic dysfunction that may occur independently of obesity.^{29,30}

PCOS is a heterogeneous disorder encompassing a broad spectrum of phenotypes. At one end, severe intrinsic androgen excess alone may be sufficient to produce the PCOS phenotype, whereas at the other, relatively mild androgen excess may manifest clinically only in the presence of additional contributing factors such as marked abdominal adiposity. Importantly, all women with PCOS are thought to have an underlying defect in androgen secretion, as obesity alone does not result in PCOS in the absence of this primary abnormality.⁴

Given these mechanisms, long-term management strategies targeting androgen excess are critical not only for controlling hyperandrogenic symptoms but also for mitigating future metabolic and cardiovascular complications. Ovulatory women with PCOS generally demonstrate a less severe metabolic phenotype than anovulatory women, although their metabolic risk remains higher than that of unaffected controls. In contrast, non-hyperandrogenic PCOS phenotypes tend to exhibit the most favourable metabolic profile, often approaching that of women without PCOS.^{31,1}

Endocrine Changes at Menopause

The menopausal transition (MT) is associated with significant hormonal and metabolic changes. As menopause occurs alongside ageing, the development of metabolic disorders during this period likely reflects the combined influence of chronological ageing and pre-existing metabolic risk factors.¹³ Menopause is characterised by declining estrogen levels, rising gonadotropins, and relatively stable or mildly increased androgen concentrations. Sex hormone binding globulin (SHBG) levels are higher in postmenopausal women but lower in those with obesity, influencing androgen bioavailability.^{32,33}

Androgen metabolism appears to be more strongly influenced by ageing than by menopause itself.³⁴ Dehydroepiandrosterone sulphate (DHEAS), the principal adrenal androgen, declines progressively with age and shows no consistent temporal association with the menopausal transition.³⁵ Despite ovarian senescence, the postmenopausal ovary remains hormonally active, contributing substantially to circulating testosterone and androstenedione through continued stromal activity and peripheral conversion.³⁶⁻³⁸

Clinical manifestations of PCOS may attenuate with advancing age. Some women develop more regular ovulatory cycles and experience partial or spontaneous improvement in hyperandrogenic symptoms such as hirsutism. Studies indicate that free and total testosterone levels in women aged 42–47 years with PCOS are approximately 50% lower than those observed in younger women aged 20–42 years, suggesting that hyperandrogenism may diminish prior to the MT in a subset of patients.^{31,39}

However, evidence also indicates that PCOS-related endocrine abnormalities may persist beyond menopause. Several studies have demonstrated that postmenopausal women with a history of PCOS exhibit significantly higher circulating concentrations of total and free testosterone, androstenedione, dehydroepiandrosterone sulphate, progesterone, and 17-hydroxyprogesterone compared with age-matched postmenopausal controls.^{15,16} These persistent hormonal alterations are frequently accompanied by adverse metabolic and inflammatory profiles. Collectively, these findings suggest that while hyperandrogenism may attenuate with ageing in some women with PCOS, a substantial subset continues to exhibit androgen excess after menopause. This persistent endocrine milieu may contribute to the sustained metabolic and cardiovascular risk observed in later life among women with PCOS.⁵

Insulin Resistance in PCOS at the Reproductive Stage

Insulin resistance (IR) is a core metabolic abnormality in PCOS, affecting approximately 60–80% of women overall and up to 95% of those with obesity, independent of age and reproductive status.⁴⁰ Impaired glucose tolerance (IGT) occurs more frequently in women with classical hyperandrogenic phenotypes and represents a strong predictor of future type 2 diabetes mellitus (T2DM) and an increased risk of gestational diabetes mellitus. Obesity and a positive family history of T2DM further amplify this risk.^{41,42}

A large systematic review and meta-analysis confirmed that women with PCOS have a significantly higher prevalence of IGT, T2DM, and metabolic syndrome compared with women without PCOS, even in BMI-matched analyses,

highlighting the intrinsic metabolic risk associated with the syndrome.⁴³

Longitudinal population-based studies have further demonstrated a markedly increased incidence of T2DM in women with PCOS across the life course compared with the general female population.⁴⁴ Longitudinal studies in postmenopausal women have demonstrated a substantial increase in waist circumference and total fat mass. The MT is associated with increased overall adiposity and a preferential redistribution of fat to the abdominal compartment.^{43,45} Obesity affects approximately 30–70% of women with PCOS and is strongly linked to visceral adiposity, which plays a central role in the development and progression of insulin resistance. A recent meta-analysis encompassing more than 35 studies reported a pooled obesity prevalence of nearly 50% among women with PCOS.⁴³

Importantly, studies from India and other South Asian populations demonstrate that women with PCOS exhibit higher fasting insulin levels and greater IR than white women with PCOS from Western populations. Increased visceral adiposity is frequently observed even at relatively low body mass indices, underscoring the limitations of BMI alone in assessing metabolic risk in South Asian women and highlighting the need for ethnicity-specific risk stratification and surveillance strategies.^{46,47}

Insulin Resistance at Menopause

Hyperinsulinaemia and IR persist in a substantial proportion of women with PCOS after menopause and are associated with an increased susceptibility to T2DM in later life. Longitudinal and cross-sectional studies demonstrate that insulin sensitivity does not normalise with cessation of ovarian function and may remain impaired despite age-related declines in androgen levels.^{44,48} The long-term metabolic risk observed in postmenopausal women with PCOS appears to reflect the cumulative burden of IR beginning in reproductive life and extending beyond menopause, rather than the MT itself.^{18,49} This persistent metabolic dysfunction contributes to the higher incidence of T2DM, metabolic syndrome, and cardiovascular risk factors observed in ageing women with a history of PCOS, underscoring the importance of lifelong metabolic surveillance, particularly in those with hyperandrogenic phenotypes or obesity.⁵⁰

Dyslipidaemia and PCOS at the Reproductive Stage

Women with PCOS commonly exhibit an atherogenic lipid profile, characterised by elevated triglycerides, increased low-density lipoprotein (LDL) cholesterol, and reduced high-density lipoprotein (HDL) cholesterol compared with women without PCOS.⁵¹ These lipid abnormalities contribute significantly to the increased cardiometabolic risk observed in PCOS across the life course. A recent systematic review and meta-analysis confirmed that LDL cholesterol and non-HDL cholesterol levels are significantly higher in women with PCOS, irrespective of body mass index, with more pronounced dyslipidaemia observed in hyperandrogenic phenotypes.¹⁹ This finding underscores the intrinsic contribution of androgen excess to lipid disturbances in PCOS, beyond the effects of obesity alone.

IR plays a central and independent role in the development of dyslipidaemia in PCOS, influencing hepatic lipid metabolism and lipoprotein composition regardless of adiposity.⁵² Data from Indian populations further demonstrate a strong association between IR and adverse lipid profiles in women with PCOS, highlighting the need for routine lipid screening and early cardiometabolic risk assessment, particularly in South Asian women who may develop dyslipidaemia at lower body mass indices.⁵³

Dyslipidaemia at Menopause

Atherogenic changes in lipid and apolipoprotein profiles appear to be specifically related to ovarian ageing. Prospective studies have demonstrated significant increases in total cholesterol, low-density lipoprotein cholesterol, and apolipoprotein B in the period surrounding the final menstrual period, suggesting that women experience a unique deterioration in lipid profiles during this transition.^{54,55}

Long-term prospective data indicate that dyslipidaemia is more prevalent in postmenopausal women with a history of PCOS compared with women without PCOS. Follow-up studies demonstrate persistent elevations in total cholesterol, LDL cholesterol, and triglyceride levels in women previously diagnosed with PCOS, even after the menopausal transition.^{27,56} These findings suggest that adverse lipid profiles associated with PCOS do not resolve with menopause and may contribute to the sustained cardiometabolic risk observed in later life. Consequently, continued lipid surveillance after menopause is warranted, particularly in women with hyperandrogenic phenotypes, insulin resistance, or obesity.

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Metabolic Syndrome at the Reproductive Stage

Metabolic syndrome is strongly associated with an increased risk of cardiovascular disease (CVD) and all-cause mortality. Meta-analyses have demonstrated that women with PCOS have more than a threefold higher prevalence of metabolic syndrome compared with women without PCOS, a finding that persists even after adjustment for body mass index (BMI).^{5,43} This increased prevalence reflects the high burden of central obesity, IR, dyslipidaemia, and hypertension that characterise many PCOS phenotypes, particularly those with hyperandrogenism. Long-term follow-up studies of women with a prior diagnosis of PCOS have further confirmed a significantly higher prevalence of metabolic syndrome in later life, compared with age-matched controls. This risk appears to be especially pronounced in women with abdominal obesity, underscoring the central role of visceral adiposity in driving cardiometabolic risk in PCOS.⁵⁷⁻⁵⁹

Metabolic Syndrome at Menopause

During the perimenopausal and postmenopausal years, women with a history of PCOS, particularly those with persistent androgen excess, continue to demonstrate a high prevalence of metabolic syndrome, and the prevalence is 30%–40% among South Asians.^{18,49,57,60}

Cardiovascular Disease at the Reproductive Stage

Given the high prevalence of CVD risk factors in many women with PCOS at a young age, it is generally believed that CVD is significantly accelerated in this population. Indeed, women with PCOS display a higher prevalence of subclinical arterial disease markers such as decreased flow-mediated dilatation,⁶¹ increased carotid intima-media thickness,⁶² and increased coronary artery calcification.⁶³

Longitudinal studies following women with PCOS and controls from early reproductive life into menopause are limited. Available evidence indicates that women with PCOS are exposed to adverse cardiometabolic risk factors, including insulin resistance, dyslipidaemia, central obesity, and hypertension earlier and for a longer duration than women without PCOS. However, some studies indicate that with advancing age, cardiometabolic parameters in control women tend to deteriorate to levels comparable with those observed in women with PCOS.^{64,65}

This prolonged lifetime exposure to components of the metabolic syndrome in women with PCOS begins in early adulthood and persists across the reproductive years.^{5,58,66} Despite this extended exposure, only a small number of longitudinal and retrospective cohort studies have assessed cardiovascular morbidity and mortality in women diagnosed with PCOS during their reproductive years and followed into later life. Studies in perimenopausal women with PCOS have reported a substantially increased relative risk of premature ischaemic heart disease, highlighting the persistence of cardiometabolic vulnerability beyond the reproductive years. Most studies have not demonstrated a significant increase in the hard endpoints like myocardial infarction, cardiovascular mortality, or all-cause mortality compared with control populations. An increased risk of stroke, however, has been reported in some cohorts, particularly among women with PCOS who also have obesity, T2DM, or other established cardiovascular risk factors.^{67,68}

Cardiovascular Disease at Menopause

Evidence evaluating cardiovascular disease outcomes specifically after menopause in women with PCOS remains limited and heterogeneous. Longitudinal data suggest that although women with PCOS experience adverse cardiometabolic exposure earlier and for longer, the worsening of cardiometabolic profiles after menopause is not substantially greater than that observed in women without PCOS.^{27,69,70}

Importantly, emerging data indicate that subgroups of women with PCOS may remain at increased cardiovascular risk after menopause, particularly those with persistent hyperandrogenism.⁵⁶ Hyperandrogenism in premenopausal women is associated with an increased prevalence of cardiovascular risk factors and higher cardiovascular disease and mortality, independent of body mass index. In contrast, among postmenopausal women, elevated cardiovascular risk associated with hyperandrogenism appears to be largely mediated by obesity.⁷¹

It has been proposed that differences in endocrine balance and metabolic status between women with and without hyperandrogenism may diminish after menopause, as androgen excess often improves with age, while the menopausal transition itself is associated with relative androgen dominance and increased abdominal adiposity.⁷¹ Supporting this, long-term follow-up studies have shown that although reproductive hormone differences persist after menopause in women with PCOS, premenopausal differences in body fat distribution, such as increased waist-to-hip ratio, tend to disappear after menopause, largely due to weight gain among control women.²⁷

A meta-analysis restricted to population-based cohorts did not demonstrate a significant increase in overall cardiovascular events among ageing or menopausal women with PCOS compared with controls, suggesting that cardiovascular risk may attenuate with ageing in many women.⁵⁶ Systematic reviews and population-based cohort studies emphasise the substantial heterogeneity of available evidence and the generally low quality of long-term outcome data, precluding definitive conclusions regarding cardiovascular morbidity and mortality in postmenopausal women with PCOS.^{18,56}

To conclude, across studies, obesity consistently emerges as the dominant driver of cardiometabolic risk, highlighting the importance of lifelong weight management and lifestyle interventions in women with PCOS.^{18,56} Current evidence suggests that while cardiovascular risk factors are clearly increased in reproductive-aged women with PCOS, it remains uncertain whether this translates into increased cardiovascular morbidity or mortality after menopause. Cardiovascular risk may attenuate with ageing in many women; however, a subgroup, particularly those with persistent hyperandrogenism, obesity, or metabolic dysfunction, may remain at elevated risk.

The limitations of the present evidence are that data on actual CVD events in women with PCOS are inconclusive.^{23,27,53,69,70} Large, well-phenotyped prospective cohort studies with longer follow-up are lacking. Most available studies on this topic have been limited by retrospective or cross-sectional designs, incomplete PCOS diagnoses, phenotypic stratification, small sample sizes, inadequate measurement of CVD events, inclusion of younger women, and/or failure to follow women into the late postmenopausal years, when CVD usually manifests.

Evidence of early cardiovascular disease, including increased carotid intima-media thickness, has also been demonstrated in women with PCOS irrespective of BMI or blood pressure, suggesting that vascular changes may begin early and progress across the life course.²⁹ Collectively, these findings support the need for continued cardiometabolic surveillance after menopause in women with a history of PCOS, particularly those with hyperandrogenic phenotypes, central obesity, or IR.

Neuropsychological Manifestations at the Reproductive Stage

PCOS is increasingly recognised as a condition with significant neuropsychological and mental health implications during the reproductive years. Compared with women without PCOS, affected women demonstrate a higher prevalence of depression, anxiety disorders, reduced quality of life, body image dissatisfaction, and disordered eating behaviours.^{72,73} These associations are consistently reported across observational studies and systematic reviews.

Both biological and psychosocial mechanisms contribute to psychological morbidity in PCOS. Proposed biological contributors include hyperandrogenism, insulin resistance, chronic low-grade inflammation, and hypothalamic-pituitary-adrenal axis dysregulation, all of which may influence mood regulation. In parallel, clinical manifestations such as hirsutism, acne, obesity, and infertility exert substantial psychosocial stress, contributing to low self-esteem and impaired quality of life.⁷⁴

Gaps in healthcare delivery for women with PCOS represent a systemic and recurring issue rather than isolated events. Persistent knowledge deficits among healthcare professionals contribute to unmet informational needs and fragmented care in PCOS. Inadequate counselling, particularly regarding lifestyle modification and long-term health implications, has been shown to negatively affect patient understanding, engagement, and satisfaction with care. Consequently, many women report feeling insufficiently informed and compelled to assume an advocacy role in managing their condition, underscoring the need for improved clinician education and structured, patient-centred

PCOS care pathways. Recognition of these factors has led to a growing consensus that mental health assessment should be an integral component of routine PCOS care during the reproductive years.^{75,76}

Neuropsychological Manifestations at Menopause

Emerging longitudinal data suggest that depressive and anxiety symptoms may persist into midlife and the menopausal transition in women with a history of PCOS. The menopausal transition itself represents a period of increased vulnerability to mood disturbances, and women with PCOS may constitute a particularly susceptible subgroup due to pre-existing metabolic and endocrine vulnerabilities.⁷⁷

Cognitive complaints, including difficulties with attention, executive function, and memory, have also been reported in women with PCOS, although evidence specific to postmenopausal women remains limited and heterogeneous.⁷⁸ Sleep disturbances, most notably obstructive sleep apnoea, are more prevalent in women with PCOS and are strongly associated with obesity and metabolic dysfunction. These sleep disorders may persist beyond reproductive age and further exacerbate mood symptoms and cognitive impairment.⁷⁹

Collectively, these findings underscore the importance of lifelong neuropsychological surveillance in women with PCOS. Contemporary guidance emphasises that long-term management should include structured mental health screening, appropriate counselling, and referral pathways, particularly during the MT and postmenopause.^{1,80}

Bone Health at the Reproductive Stage

Women with PCOS are exposed to a complex interplay of factors that may influence bone health across the reproductive lifespan, including hyperandrogenism, insulin resistance, obesity, chronic low-grade inflammation, and prolonged oligo- or amenorrhoea. Androgens exert anabolic effects on bone, which may contribute to preserved or increased bone mineral density (BMD) in women with PCOS during reproductive life.⁸¹

Several cross-sectional and longitudinal studies have reported normal or higher BMD in premenopausal women with PCOS compared with age-matched controls, particularly at the lumbar spine and femoral neck. Hyperinsulinaemia may further enhance bone mass by stimulating osteoblast activity and suppressing bone resorption.⁸² In addition, obesity, common in PCOS, is associated with increased mechanical loading and greater peripheral estrogen production, both of which may exert protective effects on bone.⁸³⁻⁸⁵

However, these potentially favourable influences may be offset by adverse factors commonly observed in PCOS, including vitamin D deficiency, chronic inflammation, and metabolic dysfunction, which can negatively affect bone quality and long-term skeletal health.

Bone Health at Menopause

Data on bone health after menopause in women with PCOS remain limited. Following menopause, declining estrogen levels result in accelerated bone loss in all women. It is unclear whether the relative advantage in BMD observed in premenopausal women with PCOS persists after menopause. Available evidence suggests that postmenopausal women with PCOS are not protected against age-related bone loss and may experience rates of bone loss comparable to those of women without PCOS.⁸⁶ Given the high prevalence of insulin resistance, metabolic syndrome, obesity, and vitamin D deficiency in women with PCOS, bone health assessment should be considered, particularly in postmenopausal women with additional risk factors for osteoporosis or fracture.¹ Long-term prospective studies are required to clarify fracture risk and skeletal outcomes in ageing and postmenopausal women with PCOS.

Skeletal Muscle in the Reproductive Years

Skeletal muscle is the principal site of insulin-mediated glucose disposal and plays a central role in the metabolic disturbances associated with PCOS. IR in PCOS is partly attributable to intrinsic defects in skeletal muscle insulin signalling, which are evident even in lean women and are therefore independent of adiposity. Studies consistently demonstrate impaired insulin-stimulated glucose uptake in skeletal muscle in PCOS, contributing to compensatory hyperinsulinaemia and increased cardiometabolic risk.⁸⁷

At the molecular level, skeletal muscle in women with PCOS exhibits post-receptor insulin signalling abnormalities, including reduced insulin receptor substrate-1 (IRS-1) activity, impaired phosphatidylinositol 3-kinase (PI3K) signalling, and decreased glucose transporter type 4 (GLUT4) translocation.⁸⁸ These defects are accompanied by increased intramyocellular lipid accumulation and low-grade inflammation, further impairing insulin sensitivity.⁸⁹

Hyperandrogenism may additionally influence skeletal muscle metabolism. While androgens exert anabolic effects on muscle mass and strength, excess androgen exposure in PCOS has been associated with altered muscle fibre composition, mitochondrial dysfunction, and reduced oxidative capacity, which may exacerbate insulin resistance.⁸⁷ Collectively, these findings support the concept of a primary skeletal muscle abnormality in PCOS that contributes to lifelong metabolic risk.

Skeletal Muscle at Menopause

Ageing and the menopausal transition are associated with progressive declines in skeletal muscle mass and function, reduced mitochondrial efficiency, and worsening IR in all women.^{90,91} In women with PCOS, the presence of long-standing IR and metabolic dysfunction may increase susceptibility to sarcopenic obesity, characterised by reduced muscle mass in the setting of excess adiposity.

However, data specifically examining sarcopenia and muscle function in postmenopausal women with PCOS remain limited. Available evidence suggests that the cumulative metabolic burden of PCOS across the life course may predispose to adverse muscle and metabolic outcomes in later life, underscoring the need for targeted surveillance and intervention.

Exercise interventions represent a cornerstone of management. Both aerobic and resistance training have been shown to improve skeletal muscle insulin sensitivity, enhance mitochondrial function, increase muscle mass, and reduce insulin resistance, independent of weight loss, in women with PCOS. Resistance training may be particularly beneficial in counteracting age-related muscle loss and improving metabolic health during midlife and postmenopause. Given the central role of skeletal muscle in glucose homeostasis, strategies aimed at preserving and improving muscle function, especially structured physical activity and resistance training, should form an integral component of long-term PCOS management, including during and after the menopausal transition.¹ Further longitudinal studies are required to clarify the impact of PCOS on muscle ageing, sarcopenia, and physical function in later life.

Cancers During the Reproductive Stage

Women with PCOS are exposed during reproductive life to multiple biologically plausible pro-carcinogenic factors, including chronic anovulation, prolonged unopposed estrogen exposure, hyperinsulinemia, obesity, dyslipidemia, and chronic low-grade inflammation.^{92,93} Among malignancies, the association between PCOS and endometrial cancer is the most consistent and well-established. Systematic reviews and meta-analyses demonstrate an approximately two- to three-fold increased risk of endometrial cancer in women with PCOS, largely mediated by obesity, insulin resistance, and persistent ovulatory dysfunction rather than PCOS alone.

Large population-based cohort studies confirm this association, consistently reporting increased endometrial cancer incidence in women with PCOS compared with the general population. In contrast, evidence linking PCOS to ovarian or breast cancer during reproductive life remains inconsistent. When analyses adequately adjust for confounding factors such as body mass index, diabetes, parity, and hormonal exposure, most contemporary studies do not demonstrate a clear independent increase in risk for these malignancies.⁹⁴⁻⁹⁷

Cancers at Menopause

Data examining cancer risk in postmenopausal women with a history of PCOS are limited but increasingly reassuring. Long-term cohort studies suggest that although women with PCOS may experience higher cancer incidence at younger ages, overall cancer risk after menopause appears comparable to that of women without PCOS. The excess risk observed earlier in life appears to attenuate with age, likely reflecting resolution of ovulatory dysfunction, declining androgen levels, and convergence of metabolic risk profiles between women with and without PCOS.

Persistent cancer risk after menopause seems confined to subgroups with ongoing obesity, T2DM, or prolonged hyperinsulinemia, rather than PCOS itself.⁹⁵ Contemporary reviews conclude that current evidence does not support routine cancer surveillance beyond standard population-based screening guidelines solely on the basis of a past PCOS diagnosis, though heightened vigilance is reasonable in women with multiple metabolic comorbidities.

MANAGEMENT OF MENOPAUSE IN WOMEN WITH POLYCYSTIC OVARY SYNDROME

Management of menopause in women with PCOS is broadly similar to that of women without PCOS; however, additional considerations are required because PCOS is a lifelong condition associated with persistent metabolic,

cardiovascular, and endometrial risks. Contemporary evidence supports a life-course approach, with continued surveillance beyond the reproductive years, particularly for cardiometabolic health and endometrial safety.¹

Women with a current or prior diagnosis of PCOS should undergo ongoing assessment for obesity, IR, T2DM, dyslipidaemia, hypertension, and metabolic syndrome, as these risks often persist or worsen after menopause, especially in those with central adiposity or a family history of cardiometabolic disease. Regular screening should therefore continue after menopause in accordance with general population guidelines, with a lower threshold for investigation in high-risk individuals.¹ Endometrial surveillance remains important in women with a history of chronic anovulation, prolonged amenorrhoea, abnormal uterine bleeding, or persistent endometrial thickening, as PCOS-related endometrial cancer risk is largely mediated by long-standing unopposed estrogen exposure and metabolic dysfunction rather than menopausal status alone. Prompt evaluation is required when symptoms occur.

Lifestyle modification remains the cornerstone of management during and after the menopausal transition. Weight management, regular physical activity, and dietary interventions continue to provide substantial benefits for metabolic health, cardiovascular risk reduction, and overall quality of life in ageing women with PCOS. Pharmacological therapies commonly used earlier in life, such as metformin, antihypertensive agents, and lipid-lowering therapy, may remain appropriate after menopause and should be individualised based on comorbidities and global risk assessment. MHT may be prescribed according to standard indications and contraindications. A history of PCOS alone is not a contraindication to MHT; however, treatment decisions should be guided by an individual woman's cardiometabolic risk profile, obesity status, and personal preferences.¹ Overall, optimal menopausal care in women with PCOS requires an integrated, multidisciplinary approach, recognising PCOS as a condition with evolving manifestations across the lifespan rather than one confined to the reproductive years.¹

FIBROIDS AT MENOPAUSE

INTRODUCTION

The term “fibroid”, short for fibromyoma, was introduced in the 19th century to describe the firm, fibrous nature of these smooth muscle tumours. The terminology was established by Rudolf Virchow, who classified and described these tumours in his early pathological studies of uterine neoplasms.⁹⁸ Uterine fibroids are the most common pelvic tumours in women of reproductive age, with a prevalence of approximately 35% based on clinical diagnosis, 50% on ultrasonography, and up to 80% in hysterectomy specimens.⁹⁹

Leiomyomas are benign, monoclonal smooth muscle tumours of the uterus. Although their exact aetiology remains unclear, uterine leiomyomas are well established as sex steroid-dependent masses. They tend to enlarge during the reproductive years and may enlarge further during the MT due to high, erratic estradiol levels. Fibroids have not been observed before menarche and generally decrease in size after menopause.^{100,101} Because uterine leiomyomas are hormonally responsive tumours, many established risk factors are those associated with prolonged or increased lifetime exposure to endogenous estrogen. These include early onset of menarche, nulliparity, delayed menopause, obesity, certain dietary patterns, and a positive family history of fibroids.¹⁰²

Fibroids express both estrogen and progesterone receptors, a finding that has led to the development of several medical therapies, including mifepristone, an antiprogesterone; selective progesterone receptor modulators such as ulipristal acetate; gonadotropin-releasing hormone (GnRH) analogues such as buserelin and goserelin; and GnRH antagonists such as elagolix, relugolix and linzagolix.^{103,104} Administration of combined estrogen-progestin therapy has been shown to promote fibroid growth during the reproductive years.¹⁰¹

FIBROIDS AT MENOPAUSAL TRANSITION

The incidence of clinically symptomatic uterine fibroids (UFs) is highest during the perimenopausal period and typically declines after menopause. A large cohort study reported that more than 30% of newly diagnosed fibroids occurred in women aged 45–49 years.¹⁰⁵

Management of fibroids during the MT depends on presenting symptoms, fibroid size and location, patient age, desire for fertility, and estimated time to menopause. As uterine fibroids often shrink and become asymptomatic with menopause, the majority of women do not require surgical intervention and may be managed conservatively with medical therapy and/or hysteroscopic removal of symptomatic submucosal fibroids.¹⁰⁶ Abnormal uterine bleeding (AUB) accounts for over 70% of gynaecologic consultations in perimenopausal and postmenopausal women.¹⁰⁷

Because AUB has a broad differential diagnosis, careful evaluation is essential to exclude serious conditions such as endometrial carcinoma or complex atypical hyperplasia and to ensure appropriate management.¹⁰⁴ Specific therapy is generally reserved for large fibroids or those that continue to grow during the MT; in such cases, hysterectomy may be considered definitive management. Evaluation of the endometrium is recommended before offering conservative treatment in this age group. Selective progesterone receptor modulators (SPRMs) may induce endometrial changes due to unopposed estrogenic stimulation, leading to endometrial thickening. Persistent endometrial thickening for more than three months after discontinuation of ulipristal acetate and resumption of menses warrants further evaluation.^{108,109} The characteristic histologic findings associated with these agents are termed progesterone receptor modulator-associated endometrial changes and may be mistaken for endometrial hyperplasia.¹¹⁰

FIBROIDS AT POSTMENOPAUSE

Uterine fibroids typically become quiescent after menopause; however, a subset of women may continue to experience symptoms. In obese postmenopausal women, increased peripheral conversion of androstenedione to estrogen in adipose tissue, mediated by aromatase enzyme activity, creates a relatively estrogenic environment that may promote continued fibroid growth.¹¹¹ Any increase in the size of uterine masses or the occurrence of postmenopausal bleeding requires prompt evaluation to exclude uterine malignancy, particularly leiomyosarcoma.¹¹²

Postmenopausal Fibroids and Hormone Therapy

The management of vasomotor symptoms (VMS) with menopausal hormone therapy (MHT) in women with fibroids remains controversial, as fibroids are hormone-dependent tumours and MHT is the gold standard for the treatment of VMS. A state-of-the-art review by Moro et al. evaluated five studies involving 237 women that assessed the effects of tibolone, with comparisons to various estrogen–progestogen combinations.¹¹³ Except for one study, no significant increase in fibroid size was observed. The conclusion was that women with uterine fibroids who undergo MHT should be monitored regularly to assess for potential changes in fibroid size. If there is evidence of tumour growth, discontinuation of hormonal therapy should be considered. Additionally, the lowest effective dose of progestogen should be prescribed to minimise potential stimulatory effects on leiomyoma growth.

Overall, the available literature suggests that tibolone does not cause a statistically significant increase in asymptomatic fibroid size and may even reduce fibroid volume in postmenopausal.^{114–117} Two studies, including a total of 102 women treated with raloxifene, demonstrated a significant reduction in fibroid size.¹¹⁸ Thirteen studies comprising 914 women compared different estrogen–progestin regimens, most commonly transdermal estrogen (used in nine studies) combined with medroxyprogesterone acetate (MPA) at varying doses (used in ten studies). Higher MPA doses were associated with larger fibroids. Although the data are conflicting, they suggest that uterine fibroids may be influenced by MHT, without representing an absolute contraindication to hormonal therapy.

The choice of the most appropriate MHT regimen is therefore crucial to minimise fibroid growth and related symptoms. Raloxifene appears to be a relatively safe option for postmenopausal women at risk of osteoporosis or breast cancer who have asymptomatic fibroids.¹¹⁹ Based on current evidence, uterine fibroids are not considered an absolute contraindication to MHT.

Counselling and individualised risk–benefit analysis should guide shared decision-making regarding MHT use.¹⁰¹ When MHT is prescribed in women with fibroids, the lowest effective estrogen dose should be used, along with the minimal effective dose of progestin. Periodic clinical and ultrasonographic follow-up is recommended, particularly during the first years of treatment, and hormonal therapy should be discontinued if leiomyomas demonstrate progressive growth.^{106,113}

While uterine artery Doppler indices have been explored as potential markers of fibroid vascularity, current evidence does not conclusively support their use as reliable predictors of fibroid growth during menopausal hormone therapy.^{120–122} In contrast, studies in premenopausal women have demonstrated correlations between fibroid vascularity and heavy menstrual bleeding.^{121,122}

ENDOMETRIOSIS AND MENOPAUSE

INTRODUCTION

Endometriosis is a chronic disease that requires a lifelong management strategy to maintain quality of life and prevent associated complications. It is primarily an estrogen-dependent condition affecting women during their reproductive

years, typically beginning at menarche or in early adulthood. Rarely, endometriosis may present after menopause, either as a continuation of pre-existing disease or, less commonly, as de novo lesions.¹²³⁻¹²⁵ Women with a history of endometriosis may experience natural, premature, early, or age-appropriate menopause, or may undergo surgical or medical menopause, which can similarly occur prematurely, early, or at the expected age.^{125,126}

The hypo-estrogenic environment of menopause generally leads to regression of endometriotic lesions and improvement in pain symptoms, a phenomenon also observed during pregnancy and with drug-induced pseudomenopause.^{127,128} However, some ectopic endometrial implants may remain hormonally active after menopause, resulting in persistent or recurrent pain and other endometriosis-related symptoms.¹²⁹ In addition, de novo postmenopausal endometriosis has been reported, particularly in the presence of exogenous estrogen exposure.¹³⁰ Endometriotic lesions in postmenopausal women may also be asymptomatic and incidentally detected during pelvic imaging or surgical procedures performed for unrelated indications.¹³¹

DEFINITION

Endometriosis is defined by the World Endometriosis Society as a chronic inflammatory condition characterised by the presence of endometrium-like tissue outside the uterus.¹³² It is predominantly a disease of reproductive-aged women and is associated with chronic pelvic pain, dyspareunia, dysuria, dyschezia, dysmenorrhoea, and infertility.¹³³ Based on the depth of invasion, endometriosis may be classified as superficial peritoneal disease or deep infiltrating endometriosis (DIE), the latter defined by penetration of endometriotic tissue ≥ 5 mm below the peritoneal surface.¹³⁴ Endometriosis may involve multiple pelvic sites, including the uterus (adenomyosis), ovaries (endometriomas), pelvic peritoneum, bladder, ureters, rectum, colon, uterosacral ligaments, rectovaginal septum, vaginal wall, and pouch of Douglas.¹³² Rarely, implants may occur at extrapelvic or distant sites, such as the lungs, liver, pancreas, surgical scars, inguinal region, and central nervous system, leading to a wide spectrum of clinical presentations.¹³⁵

Disease severity is commonly classified using the revised American Society for Reproductive Medicine (rASRM) staging system, which categorises endometriosis into stages I (minimal), II (mild), III (moderate), and IV (severe). Although widely used, this system correlates poorly with symptom severity and does not adequately reflect deep or extrapelvic disease.¹³⁶

ENDOMETRIOSIS AND MENOPAUSE TRANSITION

Current international guidelines provide limited specific recommendations for managing endometriosis in women approaching menopause, largely due to insufficient evidence. Endometriosis can be treated with medical or surgical interventions. Medical therapies generally provide comparable symptom relief, with approximately 80–85% of patients reporting improvement.¹³⁷ However, while total hysterectomy with bilateral salpingo-oophorectomy has traditionally been considered definitive treatment, recurrence rates after so-called “curative” surgery still range between 5–10%.^{138,139} The American College of Obstetricians and Gynaecologists recommends hysterectomy with bilateral salpingo-oophorectomy as definitive treatment for women with severe, refractory pelvic pain, adnexal masses, or repeated failed conservative procedures who no longer desire fertility.¹⁴⁰ However, ovarian conservation at the time of hysterectomy has been associated with a higher risk of symptom recurrence (RR 6.1; 95% CI 2.5–14.6) and need for reoperation (RR 8.1; 95% CI 2.1–31.3).¹⁴¹ In contrast, long-term follow-up data suggest that complete excision with hysterectomy may provide durable symptom control regardless of oophorectomy status.¹⁴² The World Endometriosis Society consensus further emphasises that most recommendations are based on reproductive-age populations and acknowledges that the role of hysterectomy with or without oophorectomy remains controversial due to limited high-quality evidence.¹⁴³

POSTMENOPAUSE AND ENDOMETRIOSIS

Information on postmenopausal endometriosis is largely derived from case reports and small case series, and the clinical spectrum of the disease in this population has not yet been clearly defined.^{123,124} Based on published cohort data, the prevalence of postmenopausal endometriosis is estimated to be $<3\%$.¹³² Early case series reported that approximately 2–5% of women diagnosed with endometriosis were within seven years of menopause.¹⁴⁴ A large retrospective study evaluating the age distribution of 42,079 German women with histologically confirmed endometriosis found that 2.55% were postmenopausal (aged 55–95 years), 17.09% were perimenopausal (aged 45–55 years), and 80.36% were premenopausal (aged 0–45 years).¹⁴⁵

Pathogenesis of Endometriosis After Menopause

Postmenopausal endometriosis is generally considered to represent either persistence or recurrence of pre-existing disease, or, less commonly, the development of de novo lesions.¹³² Progressive endometriosis after menopause most often occurs more than 10 years after the menopausal transition and without elevated systemic or exogenous estrogen exposure. This suggests the presence of estrogen-independent mechanisms, including genetic or epigenetic changes, increased local estrogen production, or enhanced tissue sensitivity.¹⁴⁶ Estrogen plays a central role in the development and progression of premenopausal endometriosis.

The pathogenesis of postmenopausal endometriosis appears to be dependent on the availability of extraovarian estrogen, which may arise through several mechanisms, including coelomic metaplasia, continued gonadal steroidogenesis, exogenous estrogen exposure, peripheral aromatisation in adipose tissue, and in situ aromatisation within endometriotic implants.^{146,147}

A well-described pathogenic mechanism involves a local estrogen-driven feed-forward loop. Aromatase expression has been demonstrated within endometriotic implants and the eutopic endometrium of affected women. Locally produced estrogens stimulate cyclooxygenase-2 (COX-2) activity, increasing prostaglandin E₂ (PGE₂) synthesis, which, in turn, further enhances aromatase activity.¹²⁵ This autocrine and paracrine mechanism may explain how endometriotic lesions remain biologically active and symptomatic in the hypo-estrogenic postmenopausal milieu. Extraovarian estrogen sources include adipose tissue, adrenal glands, endometrial stroma, and exogenous exposures, such as phyto-estrogens, MHT, and tamoxifen.¹²⁹ Given this pathogenic background, aromatase inhibitors (AIs) have been proposed as a therapeutic option in postmenopausal endometriosis, as they disrupt local estrogen production by inhibiting aromatase activity and thereby suppress intralesional estrogen synthesis.¹⁴⁸

Diagnosis

Diagnosis of postmenopausal endometriosis remains challenging, as the clinical presentation is variable and not well defined. Recurrent or persistent disease after menopause commonly presents with low back pain, rectal pain, painful defecation, deep dyspareunia, rectal or vaginal bleeding, haematuria, flank pain, or, in severe cases, hydronephrosis and renal impairment. A high index of suspicion is needed; no specific biomarkers or imaging criteria reliably detect postmenopausal recurrence.¹³³

In peri- and postmenopausal women, transvaginal and transrectal ultrasound may detect persistent ovarian endometriomas, which typically present as unilocular cysts with homogeneous low-level internal echoes, often described as a “ground-glass” appearance. Interpretation can be challenging due to age-related pelvic anatomical changes and the frequent coexistence of other pathologies, such as fibroids or adnexal tumours. Importantly, neither ultrasound nor magnetic resonance imaging is definitive for diagnosing postmenopausal endometriosis nor reliably excluding ovarian malignancy. Consequently, the presence of suspicious imaging features, including papillary projections, solid components, or ascites, should prompt referral to a gynaecologic oncology multidisciplinary team for further evaluation and consideration of surgical management.

The gold standard for diagnosis remains diagnostic laparoscopy with visual inspection and histological confirmation of suspicious lesions. However, the requirement for histological confirmation is debated: macroscopically suspected lesions are not always histologically confirmed, and occult microscopic endometriosis may be identified in biopsies of macroscopically normal peritoneum in women with and without visible disease.¹⁵⁰

Cancer antigen 125 (CA-125) is a nonspecific tumour marker that may be elevated in endometriosis, bowel disease, and malignancy, and its levels vary with menopausal status, limiting diagnostic utility.¹⁵¹ In contrast, human epididymis protein 4 (HE4) tends to remain within normal ranges in benign endometriosis, thus offering significantly higher specificity than CA-125 in distinguishing benign endometriosis from malignant disease, making it a useful adjunct in postmenopausal women presenting with pelvic masses.^{151,152} The combination of HE4, CA-125 and CEA (carcinoembryonic antigen) can improve sensitivity and specificity when evaluating ovarian masses.^{151,152}

ENDOMETRIOSIS AND EARLY AGE AT MENOPAUSE

Women with endometriosis face a higher risk of earlier menopause (1–3 years), with a 7-fold increase in surgical menopause occurring approximately 19 months earlier and natural menopause occurring about 5 months earlier. This is due to repeated ovarian inflammation, surgeries such as endometrioma excision, and decreased ovarian reserve.^{153,154} It remains debatable whether endometriosis itself leads to a reduction in ovarian reserve or whether

the observed decline is primarily attributable to conservative surgical treatment for endometriosis, particularly ovarian surgery.^{125,155-158} Molecular, histological, and morphological evidence support a toxic effect of ovarian endometriomas on adjacent ovarian cortical tissue, independent of mechanical stretching caused by cyst size.^{159,160} Data evaluating the direct effect of ovarian endometriomas on the age at menopause are limited. In a case-control study, serum AMH levels were significantly reduced in women with stage III-IV endometriosis, suggesting diminished ovarian reserve.^{21,161} Surgical treatment, especially for bilateral endometriomas, has been shown to influence the age at menopause and is associated with an increased risk of premature ovarian insufficiency (POI).^{133,141} A substantial proportion of women with severe endometriosis (approximately 12% in some cohorts) undergo total hysterectomy with bilateral salpingo-oophorectomy, often at a relatively young age.^{123,162} This results in abrupt estrogen deprivation, leading to severe menopausal symptoms and an increased long-term risk of osteoporosis and cardiovascular disease.¹⁶³ Conversely, ovarian preservation has been associated with a six-fold increased risk of recurrent pain and an eight-fold increased risk of reoperation, highlighting the complex balance between symptom control and long-term health outcomes.¹⁴¹

RECURRENCE OF ENDOMETRIOSIS AND MALIGNANT TRANSFORMATION

Endometriosis lesions may recur following surgical menopause, particularly in women receiving MHT after hysterectomy and bilateral salpingo-oophorectomy performed for severe, refractory disease at an early age.¹²⁹

Risk factors for recurrence among women receiving MHT include large peritoneal implants (>3 cm) and, most importantly, incomplete surgical excision. Recurrence rates have been reported as 2.4% per year in women with smaller lesions, and 22.2% per patient in cases of incomplete versus complete surgery.¹⁴² A Cochrane Database systematic review identified only two randomised trials assessing the risk of recurrence associated with MHT following surgical menopause, underscoring the limited high-quality evidence in this area.¹⁶⁴ Although endometriosis is a benign proliferative disorder, malignant transformation occurs in approximately 0.7–1.0% of cases, most commonly involving ovarian endometriotic lesions.¹⁶⁵

Postmenopausal endometriosis may show a higher tendency to infiltrate, affecting extragonadal areas such as the bowel, bladder, ureter, or surgical scars. Endometriosis shares several biological features with malignancy, including enhanced proliferative capacity, resistance to apoptosis, angiogenesis, and the ability to invade ectopic sites.¹⁶⁶ The risk of malignant transformation appears to increase years after menopause, particularly in the presence of unopposed estrogen exposure, which is known to increase the incidence of endometrial hyperplasia and carcinoma.¹⁶⁷ Malignancy should therefore be suspected when endometriotic lesions enlarge, become nodular, or present with new-onset postmenopausal bleeding or pelvic pain.^{168,169} Given that endometriosis consists of ectopic endometrioid tissue, similar estrogen-driven mechanisms may promote reactivation or neoplastic transformation.¹³⁵ Several hypotheses explain the association between endometriosis and malignancy. Endometriosis may represent a premalignant lesion in a subset of cases, with shared environmental, endocrine, epigenetic, and genetic risk factors contributing to both conditions. Alternatively, endometriosis may serve as a metaplastic precursor within the malignant transformation pathway.^{135,147,166,167}

Consistent with this, epidemiologic studies indicate that women with endometriosis have an approximately 50% increased risk of epithelial ovarian cancer, with particularly strong associations observed for clear cell, endometrioid, and low-grade serous ovarian carcinomas.¹⁶⁵ Endometriosis is often identified incidentally during pelvic surgery performed for other indications. In one series, it was detected during procedures for ovarian cysts, ovarian or endometrial malignancy, and atypical endometrial hyperplasia, while only a minority of affected women had a prior diagnosis of endometriosis. The ovary was the most common site of involvement.¹⁴⁰ Histopathologic evaluation of ovarian endometriotic cysts revealed that although most lesions lacked hyperplastic changes, over one-third demonstrated hyperplasia, atypia, or carcinoma, underscoring the potential for occult disease and malignant progression, particularly in postmenopausal women.¹²⁴

MANAGEMENT OF ENDOMETRIOSIS AFTER MENOPAUSE

The first-line management of symptomatic postmenopausal endometriosis is surgical treatment, followed, when indicated, by medical therapy, most commonly aromatase inhibitors or progestogens.^{130,133} The limited effectiveness of gonadotropin-releasing hormone (GnRH) agonists or antagonists and oral contraceptive pills in postmenopausal women is likely related to their primary mechanism of action, suppression of ovulation, which is no longer relevant after menopause. This reduced efficacy reflects the profound hormonal changes of menopause, particularly the

marked decline in ovarian estrogen production.^{170,171} Vigilant clinical follow-up and histopathological assessment of any enlarging or symptomatic lesion are crucial. Magnetic resonance imaging (MRI) is the preferred imaging modality for evaluation.¹⁷²

Surgical Management

Surgery is considered the treatment of choice for new-onset symptomatic postmenopausal endometriosis, owing to diagnostic uncertainty, the risk of associated malignancy, and the potential for malignant transformation.^{124,126,132} Surgical intervention serves a dual purpose: it allows definitive diagnosis through histological confirmation and provides symptom relief, particularly pain reduction.¹²⁶ Despite complete excision, recurrence after surgery is not uncommon, and second-line medical therapy may be required.¹⁴⁵

Prior to undertaking surgery for suspected recurrence, alternative causes of pelvic pain, including irritable bowel syndrome, interstitial cystitis, myofascial pain syndromes, and vertebral pathology, should be excluded, and patients should be counselled regarding the potential risks and complications of radical surgery.¹⁷³ Procedures such as presacral neurectomy or uterine nerve ablation have not demonstrated additional benefit in reducing postoperative symptom persistence and may be associated with adverse effects, including chronic constipation and bladder dysfunction.¹⁷⁴

Medical Management

Medical therapy may be considered for patients with benign imaging findings who are poor surgical candidates or who experience recurrence of pain following surgical treatment. The options are aromatase inhibitors and progestones.

Follow-up

For women who decline surgical management, standardised surveillance strategies are not well established. Annual transvaginal ultrasound is commonly recommended for known endometriomas, given the approximately 1% lifetime risk of malignant transformation. In cases of previously identified deep endometriosis, an initial follow-up with ultrasound or magnetic resonance imaging at six months may be considered, followed by individualised surveillance intervals based on lesion behaviour and clinical symptoms. Given the potential for malignant transformation in women with longstanding disease, particularly those with persistent lesions later in life, careful risk stratification is essential. Recognised risk factors include prolonged disease duration exceeding ten years, large ovarian endometriomas, older age at diagnosis or postmenopausal presentation, and exposure to unopposed estrogen therapy, which may stimulate residual endometriotic tissue.

Aromatase Inhibitors

In postmenopausal women with recurrent disease after surgery or in those for whom surgery is contraindicated, AIs represent a potential therapeutic option.¹⁴⁸ Aromatase catalyses the conversion of androstenedione and testosterone into estrone and estradiol, respectively. While ovarian estrogen production ceases after menopause, aromatase remains active in extraovarian tissues, including adipose tissue, and is also expressed within endometriotic implants.^{125,146,147} Third-generation AIs (exemestane, letrozole, and anastrozole) selectively inhibit aromatase and are widely used in the adjuvant treatment of hormone receptor-positive postmenopausal breast cancer.¹⁷⁵

Given that postmenopausal endometriosis is rare, data on AI use in this population are limited to small case series and observational reports. In a small clinical series of five postmenopausal women with recurrent symptomatic endometriosis, prolonged AI therapy resulted in significant pain reduction, including improvement in urinary and gastrointestinal symptoms, and a decrease in lesion size on imaging.¹⁷⁶ One patient who did not respond to short-term exemestane experienced symptomatic improvement after switching to letrozole, suggesting potential interindividual variability in response. AIs are associated with side effects related to profound estrogen suppression, including hot flashes, vaginal dryness, arthralgia, and an increased risk of bone mineral density loss.¹⁷⁷ Therefore, assessment of osteoporosis risk factors and baseline bone mineral density is recommended prior to initiating therapy. In selected cases, low-dose estrogen add-back therapy may be considered with caution.¹⁷⁸

During reproductive life, estrogen is produced predominantly by the ovaries, and first-line medical therapy aims to suppress ovarian function using gonadotropin-releasing hormone (GnRH) analogues, progestogens, or combined estrogen-progestogen therapy. In contrast, after menopause, AIs specifically target extraovarian and intralesional estrogen production and may therefore offer a mechanistically appropriate treatment option. A randomised controlled trial in premenopausal women demonstrated that combining AIs with GnRH agonists prolonged the pain-

free interval and reduced symptom recurrence after surgery, supporting the biological rationale for AI use in refractory disease.¹⁷⁸

Progestogens

Progestogens are widely used and effective in the management of endometriosis-related pain in premenopausal women. Their primary mechanisms include negative feedback on the hypothalamic–pituitary–ovarian axis, induction of anovulation, and decidualization and atrophy of endometriotic lesions via direct action on progesterone receptors.¹⁷⁹ In theory, progestogens may be used in postmenopausal endometriosis for their direct antiproliferative effects on ectopic endometrial tissue, independent of ovarian suppression. Natural progesterone is generally preferred due to its more favourable metabolic and cardiovascular profiles.¹⁸⁰ Continuous exposure to levonorgestrel, such as with the levonorgestrel-releasing intrauterine system (LNG-IUS), induces profound endometrial atrophy through a local mechanism. This localised effect may also benefit the management of endometriosis-related symptoms in postmenopausal women. However, to date, no studies have specifically evaluated the use of the LNG-IUS in postmenopausal endometriosis, and evidence remains based on extrapolation from premenopausal populations.

MANAGEMENT OF MENOPAUSAL SYMPTOMS IN WOMEN WITH A HISTORY OF ENDOMETRIOSIS

Endometriosis significantly affects quality of life across both premenopausal and postmenopausal stages, with persistent pain, sexual dysfunction, and psychosocial burden contributing to reduced overall well-being.¹⁸¹ Surgical or medically induced menopause often relieves endometriosis-related symptoms but may precipitate significant vasomotor symptoms, vaginal dryness, dyspareunia, mood disturbances, and sleep disruption, particularly in women with abrupt hypo-estrogenism. Quality of life in the early postmenopausal period can be assessed using tools such as the Menopause-Specific Quality of Life (MENQOL) questionnaire.

Few studies have investigated hormone therapy in postmenopausal women with a history of endometriosis. Concerns include the potential reactivation of residual endometriotic implants and the theoretical risk of malignant transformation. Although available evidence suggests that recurrence risk may increase with MHT, it is insufficient to justify withholding treatment in severely symptomatic patients.¹⁸² Similarly, endometriosis is associated with a slightly increased baseline risk of ovarian cancer; current evidence does not support routinely withholding menopausal hormone therapy solely due to fear of malignancy.^{182,183}

Management with MHT needs to be individualised and is patient-centric. A study on pre- and post menopausal women with endometriosis showed that a focus on lifestyle management and psychological care markedly improved pain and dyspareunia. Management of genitourinary syndrome is similar to that of women without endometriosis. Risk stratification should include evaluation of residual disease and factors such as obesity, which may increase peripheral estrogen production. Patients must be counselled regarding the limited quality of available data.

The decision to initiate MHT in women with prior endometriosis should be individualised. In women who underwent early bilateral prophylactic salpingo-oophorectomy with no residual lesions and who experience moderate or severe menopausal symptoms, especially before age 45, the benefits of MHT likely outweigh the potential risks.¹⁸⁴ In such cases, MHT is generally considered appropriate. Conversely, in women with incomplete surgery or residual disease, particularly those with minimal menopausal symptoms and menopause at a typical age, avoidance of MHT may be reasonable.

Estrogen Threshold Theory and Clinical Implications

Estradiol exerts differential effects across target tissues, reflecting a hierarchy of organ sensitivity in which calcium metabolism and gonadotropin secretion are most responsive, followed by vaginal epithelium and lipid metabolism. Similarly, estradiol-dependent diseases demonstrate variable responsiveness, with breast cancer being highly estrogen-sensitive and endometriosis relatively less sensitive.¹⁸⁴

The estrogen threshold hypothesis proposes that endometriotic lesion activity is dependent on circulating estradiol concentrations within a specific biologic range. Estradiol levels below approximately 20 pg/mL are generally associated with lesion regression but are also linked to significant hypo-estrogenic adverse effects, including vasomotor symptoms and accelerated bone loss. In contrast, concentrations above roughly 60 pg/mL tend to support lesion viability and growth.¹⁸⁴ Partial suppression of estradiol to a low physiologic range, approximately 20–45 pg/mL, may therefore permit regression of endometriotic lesions while minimising bone loss and climacteric

symptoms.¹⁸⁴

This concept provides the biological rationale for the use of gonadotropin-releasing hormone (GnRH) agonists or antagonists combined with add-back menopausal hormone therapy in premenopausal women, allowing sustained symptom control with acceptable tolerability. In postmenopausal women, endogenous estradiol levels are typically already below this threshold; however, exogenous estrogen exposure through menopausal hormone therapy may exceed individual lesion sensitivity thresholds in some patients, potentially contributing to disease reactivation.

Hence, at postmenopause, the decision on the type, dose, and delivery mode of MHT depends on age, such as residual disease after surgery and obesity, which increase aromatase activity in peripheral tissues, resulting in higher systemic estrogen levels; the effect of disease stage and extent on recurrence rates and comorbidities; and the presence of comorbidities. When MHT is prescribed, combined estrogen–progestogen therapy is preferred over unopposed estrogen to reduce the theoretical risk of disease reactivation or malignant transformation in women with surgically induced menopause or natural menopause.¹⁸⁵

Continuous combined preparations appear preferable to sequential preparations as symptoms of endometriosis are known to fluctuate cyclically. Continuous combined preparations have been widely used as an add-back therapy with ovarian suppression in the medical treatment of endometriosis, and data on this therapeutic approach support the view that it is an optimum preparation. Regarding the timing of MHT after surgically induced menopause, available evidence suggests that immediate initiation of estrogen therapy does not increase the risk of endometriosis recurrence compared with delayed treatment. Hickman et al. reported no significant difference in recurrence rates between women who commenced estrogen replacement therapy immediately after surgery and those who delayed initiation, indicating that there is no clear benefit to postponing MHT following definitive surgical treatment. Therefore, when clinically indicated, hormone therapy does not need to be routinely delayed after surgery. Alternative therapies, such as tibolone, may also be considered.¹⁸⁶

Ongoing monitoring, potentially including clinical assessment, ultrasound evaluation, and, where appropriate, CA-125 and HE4 testing, may be considered, although evidence guiding surveillance strategies remains limited.¹⁸⁷

ADENOMYOSIS

Adenomyosis is an estrogen-dependent condition that usually becomes clinically inactive or less active after natural or surgical menopause; symptomatic postmenopausal adenomyosis is rare.^{188,189} If indicated, MHT is administered as ccMHT or tibolone, and continued clinical vigilance for recurrence, abnormal bleeding, or uterine enlargement is suggested.

SYNOPSIS

- Postmenopausal endometriosis is rare (<3%) but clinically significant due to diagnostic uncertainty and malignancy risk
- Postmenopausal endometriosis may have a greater tendency to spread and involve extragonadal organs and structures that may develop into constrictive and/or obstructive lesions. Surgical treatment is the first-line therapy to exclude malignancy in cases of postmenopausal endometriosis, but drug treatment may be an option in cases of pain recurrence after surgery.
- MHT may increase the risk of endometriosis symptoms and disease recurrence after surgically induced menopause, and theoretically, there is potential for malignant transformation. Current data are, however, insufficient to justify not administering HRT for symptomatic women after surgically induced menopause.
- The evidence is currently insufficient to support any conclusions about the optimal MRT regimen for women with endometriosis. Few data suggest a higher malignancy risk with estrogen-only MRT compared with combined MHT. Hence, continuous combined MHT is preferred over unopposed estrogen. Tibolone may be offered
- Patients with endometriosis receiving MHT should be monitored regularly for pain recurrence.
- Aromatase inhibitors may be considered for recurrent disease when surgery is not feasible
- Nonhormonal therapies such as SSRIs/SNRIs, gabapentin, and lifestyle-based interventions may be considered for vasomotor symptom control in women at high risk of recurrence.

RESEARCH AGENDA

Is endometriosis associated with an early age of menopause?

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