

# **Dysfunctional uterine bleeding in a Perimenopausal / Menopausal woman**

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**Q:**If a 48 year old woman comes with intermenstrual bleeding with occasional menorrhagia presents to the OPD, and pelvic examination shows a normal uterus with non tender pelvis and a normal looking cervix, what should be the line of management?

**A:**This is a case of dysfunctional uterine bleeding, as no obvious cause for bleeding can be found. Intermenstrual bleeding is generally the hallmark of oestrogen deficiency in the perimenopausal lady, like the one mentioned here. In this case, since there are occasional bouts of menorrhagia, there is a possibility of endometrial polyps. However, in the perimenopausal period the patients may present with episodes of ovulatory bleeding (which are predictable, because they are regular), interspersed with episodes of anovulatory bleeding which is erratic. This becomes confusing to the patient and the physician. This happens due to decreased inhibin levels, and variable estradiol levels with normal FSH levels.

In this patient, pelvic examination is normal. Thyromegaly and hypothyroidism should be looked for and treated, if present. Pelvic ultrasound, both abdominal (suprapubic) and transvaginal, is recommended as a first-line procedure for the etiological diagnosis of Abnormal uterine bleeding(AUB) (Grade A)<sup>3</sup>. Doppler ultrasonography provides additional information useful for characterizing endometrial and myometrial abnormalities (Grade B).

Endometrial biopsy should be performed in women older than 35 years of age, or younger if risk factors for endometrial hyperplasia or malignancy are present. Thus it is indicated in this patient.

If no abnormality is seen, then put her on conventional Combined oral contraceptive pills (COCs) with 30mcg EthinylEstradiol, as her intermenstrual bleed may be because of estrogen breakthrough. This will also correct her Menorrhagia. Continue for at least six cycles and then stop the COCs. Intermittent anovulation during the perimenopause may be associated with physical complaints like hot flashes, and night sweats. Oral contraceptive pills regulate menstrual cycles, decrease vasomotor symptoms, improve bone mineral density, and decreases the need for surgical intervention for DUB<sup>1</sup>. Additionally, endometrial and ovarian cancer rates are reduced in women using oral contraceptive therapy. Generally, oral contraceptives are well tolerated and enhance menstrual health and quality of life for the perimenopausal woman.

Uterine exploration: Hysteroscopy or hysterosonography can be suggested as a second-line procedure when ultrasound suggests an intrauterine abnormality or if medical treatment fails after 3–6 months (Grade B)<sup>3</sup>.

**Q:** What should be looked for in Transvaginal ultrasound(TVUS) in a patient with peri menopausal bleeding PV with normal pelvis on per vaginal examination?

**A:** A uterus appearing normal on pelvic examination sometimes has endometrial polyps or tiny submucous fibroids which may not be revealed on pelvic examination but which can be picked up on TVUS. In premenopausal women, endometrial thickness varies between the proliferative phase (4 to 8 mm) and the secretory phase (8 to 14 mm), and TVUS should be scheduled between days 4 to 6 of menstrual cycle, when the endometrium is the thinnest<sup>1</sup>. A cut off of 5mm of endometrium is useful in ruling out endometrial cancer in post menopausal women. A thin endometrium can reassure the physician that there is no

endometrial pathology and medical treatment can be embarked upon. A patient with thick endometrium needs further evaluation with endometrial biopsy, saline sonography or hysteroscopy.

Q: What is Endometrial sampling? Should Endometrial sampling be done for all women with increased thickness of endometrium?

A: Endometrial sampling is a technique of taking a biopsy of the endometrium to rule out malignancy. Generally, this was done by dilatation and curettage in the past, but now, it has been found that sampling the endometrium using special devices like an endometrial pipelle can also rule out malignancy. It is necessary to rule out malignancy this way for women in the reproductive and perimenopausal age group, ie: >45 years with abnormal uterine bleeding. It is also deemed necessary when high risk factors for malignancy, are present, viz; Age > 45, history of infertility, family history of colonic carcinoma, and nulliparity<sup>4,5</sup>. All post menopausal women presenting with uterine bleeding, and women on Tamoxifen/Letrozole post-CA Breast should also undergo endometrial sampling.

Q: What is sonohysterogram? When does the gynaecologist order this investigation?

A: Sonohysterogram or SIS ( Saline Infusion Sonography ) infuses saline into the endometrial cavity during Trans vaginal ultrasonography (TVUS) to enhance the image. Many alternate terms have been used to describe this technique: echohysteroscopy, hydrosonography, sonohysteroscopy, sonohysterogram, sonohysterosalpingography, and sonoendovaginal ultrasound. SIS allows the clinician to evaluate the uterus for intracavitary lesions more accurately than TVUS. The indications for SIS are<sup>3,6</sup>:

1. Abnormal bleeding in premenopausal or postmenopausal patients
2. Evaluation of an endometrium that is thickened, irregular, immeasurable or poorly defined by conventional transvaginal ultrasound (TVUS).
3. Irregular endometrial appearance by TVUS in women using tamoxifen.
4. The need to differentiate between sessile and pedunculated masses of the endometrium.
5. Presurgical evaluation of intracavitary fibroids.

Q: If endometrial sampling is normal, what should be the first line of management?

A: In the perimenopausal age, anovulatory bleeding is more likely to be the cause of DUB. This has to be tackled with progestogens or oral contraceptive pills as first line of management. In hypertensive and diabetic patients, oral contraceptives with high dose oestrogen may be harmful. Some patients cannot tolerate hormones. Some patients may not respond to hormone treatment or may take treatment irregularly leading to more irregularities in bleeding. Alternative medical treatment methods or conservative surgical measures have to be resorted to in such patients.

Derangements in the local haemostatic mechanism may cause ovulatory bleeding. Antiprostaglandins like Mefenamic acid and antifibrinolytic agents like Tranexamic acid may be useful in the management of such patients. Patients with ovulatory DUB must be evaluated for intracavitary uterine pathology (with SIS or hysteroscopy), since hormonal dysfunction is not the likely cause of bleeding. Intracavitary causes like endometrial polyps or submucous fibroids have to be ruled out. If such pathology is diagnosed, there is an option of hysteroscopic resection in centres with facilities for such procedures.

Q: Should hysteroscopy be done for all patients with dysfunctional uterine bleeding?

A: All patients with DUB need not undergo Hysteroscopy. However, all patients of ovulatory DUB are best evaluated with a hysteroscope, because patients with ovulatory DUB are more likely to have intracavitary uterine pathology, since hormonal dysfunction is not the likely cause of bleeding. In these

patients, if on TVS, the endometrial thickness is irregular, the endo-myometrial interface is ill defined, then hysteroscopy offers a better chance of diagnosis. Patients with anovulatory DUB, where concomitant intra-cavitary lesions are suspected, may also be offered hysteroscopy<sup>2,6</sup>.

Q: What are the medical treatment modalities available for treatment of DUB?

A: Combined Oral Contraceptive pills, Progesterone Preparations, NSAIDs, I/V CEEs for acute bleeding (not available in India), Danazol, (not very frequently used due to unacceptable side effects), GnRH Analogues, LNG IUS : Mirena, Antifibrinolytic Agents : Tranexamic Acid.

Q: What is Tranexamic acid? What is the dose and how long in an index month can it be given?

A: Tranexamic acid is an Antifibrinolytic Agent and is a synthetic lysine derivative which blocks lysine-binding sites on plasminogen. It prevents plasmin from binding to fibrin, thus inhibiting fibrinolysis. Tranexamic acid has been shown to reduce menstrual bleeding by approximately 50%<sup>7,8</sup>. In most studies tranexamic acid was administered from days 1 to 4 or 5 of menses in a dose of 4 g/day<sup>1,7,8</sup>. Maximum of 4 gms can be given per day in divided doses. It has been studied in the dose of 1.95gm daily was also found to be effective in one study<sup>9</sup>.

Q: What is ormeloxifene? For how many months can treatment with ormeloxifene be given?

A: Ormeloxifene (also known as centchroman) is one of the selective estrogen receptor modulators, or SERMs, a class of medication which acts on the estrogen receptor. It is best known as a non-hormonal, non-steroidal oral contraceptive which is taken once per week. Ormeloxifene may be effective for dysfunctional uterine bleeding and advanced breast cancer. It can be used for the treatment of DUB at any age. However, it is not suitable for women desiring pregnancy, due to its contraceptive effects. Doses: Dysfunctional uterine bleeding: 60 mg twice a week for the 1st 12 weeks and then 60 mg once a week for up to next 12 weeks<sup>10</sup>

Q: Is there any difference in medical treatment if there is metabolic syndrome?

A: Women with metabolic syndrome tend to be diabetic and hypertensive in the perimenopausal age. Giving high dose oral contraceptive pills may be harmful in these patients. Such patients can be treated by giving them withdrawal bleeds without allowing them to go into prolonged periods of amenorrhoea. If she has PCOS, metformin may be helpful. Progestogens or antifibrinolytic agents will have to be chosen instead of COC's. Ormeloxifene is a new option. The LNG-IUD, is another option.

Q: What is LNG-IUD? What are the effects and side effects?

A: The LNG-IUS is an intrauterine delivery system, which delivers levonorgestrel @ 20mcg per day. The IUS has a similar shape to the Nova-T 380 copper IUD with the vertical stem containing a mixture of 52 mg levonorgestrel and polydimethyl siloxane (PDMS), surrounded by a rate-controlling PDMS capsule<sup>11</sup>. The total length of the system is 32 mm, and the T-shaped plastic frame is impregnated with barium sulphate, making the device radio-opaque. Two threads are attached to the loop at the base of the IUS to aid removal. This system allows a steady, local release of 20 mg levonorgestrel per day initially, and has few systemic side-effects (approximately the equivalent of taking two progestogen-only pills/week). Following insertion of an IUS, women frequently complain of menstrual disturbance. Approximately 17% of women will complain of prolonged bleeding (>8 days) in the first month of use, with this falling to 3% at

3 months. Some complaints include mood changes, nausea, headache, bloating, breast tenderness, fluid retention and skin problems.

Q: How long can you give medical treatment?

If COC pills, progestagens, tranexamic acid, NSAIDs are used, then minimum of 6 months therapy is indicated. If LNG—IUS is used then it may even be continued for upto 5 years for extended contraceptive benefits<sup>2,3,8</sup>.

Q: In a woman with simple hyperplasia, in the perimenopausal period, is there any need for hysterectomy?

A: If medical treatment is not effective or is contraindicated, then first choice is hysterectomy as Ablation Techniques are contraindicated in women with hyperplasia due to the fact that hyperplasia is a risk factor for Endometrial CA. More so if the patient is obese, hypertensive and diabetic, as these are co-risk factors<sup>1,2,3</sup>.

Q: In a woman with cystic glandular hyperplasia, in the perimenopausal age, is there any need for hysterectomy?

A: WHO classifies hyperplasia into two varieties, simple or complex types, each with atypical or non-atypical pathology. Studies have found high concentrations of progesterone receptors in hyperplasia without atypia whereas lower levels were found in atypical hyperplasia<sup>12,13</sup>. Hyperplasia without atypia may disappear completely with progesterone therapy. Progesterone therapy has to be given for 6 months. LNG IUD is another option.

However, studies have shown discrepancies between endometrial pipelle specimens of endometrium /D&C samplings and hysterectomy specimens of endometrium<sup>12</sup>. So ideally, if a pipelle sample shows hyperplasia, a hysteroscopic directed biopsy should be taken to rule out atypical hyperplasia. If a hysteroscopic directed biopsy is negative for atypia, progesterone treatment may be tried. In women who show atypia, either on hysteroscopy or on pipelle sampling, the clinician must be worried that the patient may be harbouring endometrial carcinoma. A hysterectomy may be prudent in these women. Ablative procedures are not currently recommended for such patients.

Q: What are the other options beside hysterectomy for a woman who cannot tolerate medical treatment due to side effects or if she has a failure of medical treatment?

A: Endometrial Ablation Techniques: where controlled injury of the basal layer of the endometrium is done in order to treat DUB by creating intrauterine adhesions or an iatrogenic Asherman's Syndrome-like situation.

Hysteroscopic resection was the first efficacious ablation therapy for DUB. It was introduced in 1976 by Neuwirth et al. and offered a surgical alternative to hysterectomy. Subsequently, laser ablation, radio-frequency monopolar resection, and rollerball ablation were developed. These are commonly called First Generation Techniques.

Later the second generation techniques followed, Second-generation techniques mostly involve tissue heating as the method of endometrial destruction. They are blind in nature, not being performed under direct hysteroscopic vision with the exception of the HydroTherm Ablator™. They therefore, avoid the risks of fluid distension media. Some techniques may be performed under local anaesthesia. For all methods, the woman should have no desire to retain her fertility. The uterus should be of 12 week

size or less. Cryoablation, Free fluid thermal ablation, Impedance-controlled bipolar radiofrequency, ELITT, Photodynamic endometrial ablation, Thermal balloon endometrial ablation are some of the second generation ablation techniques<sup>14,15,16</sup>. Thermal balloon endometrial ablation is the most popular among these in India.

Q: What are the complications of the Ablation Techniques?

A: Endometrial ablation and endometrial resection both performed under hysteroscopic view, are safe procedures with a low morbidity. Peri-operative complications of hysteroscopic resection/Ablation procedures are: Perforation with the possibility of bowel injury, haemorrhage, visceral burn, genital tract burn and cardiovascular problems due to intravasation of distension fluid, characterised by hyponatraemia, water intoxication, cerebral edema and cardiac overload.

Second generation endometrial Ablation techniques, not employing the hysteroscope, like the thermal ablation system, have fewer complications.

Q: What is the failure rate of ablation methods? Is it better to do hysterectomy for once and for all?

A: Failure rate measured by re-intervention rates is dependent on the method of ablation chosen. Broadly it varies between 6% to 30% for various methods. Choosing hysterectomy over the ablation techniques depends upon individual patient counseling, her needs, whether she is compliant enough for further follow-ups, and whether the case is high/ low risk for surgery/anaesthesia<sup>14,15,16</sup>.

Q: What is the role of D&C in the management of DUB?

A: Dilatation and curettage (D&C) causes a temporary reduction of menstrual blood loss for the first month, but at following cycles, the amount of blood loss tends to increase as compared to the blood loss before the D&C. Therefore, D&C must be considered obsolete in the treatment of dysfunctional uterine bleeding, but unfortunately it is still performed on a large scale in women suffering from dysfunctional uterine bleeding<sup>1,2,3</sup>.

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