Leading Article

Unscheduled bleeding following HRT- assessment and management

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Abstract

Menopause is defined as permanent cessation of monthly menstrual periods due to permanent depletion of ovarian follicular activity which results in reduced production of ovarian steroids. This in turn causes short term and long term complications in postmenopausal women. Hormone replacement therapy (HRT) is considered as the treatment of choice in the management of these complications. However unscheduled bleeding following HRT is a well known complication. Diagnosis of unscheduled bleeding is confirmed after careful assessment and exclusion of secondary endometrial pathologies. This can be managed effectively by adjusting or changing the hormone profile in HRT preparations.

Key words - unscheduled bleeding, hormone replacement therapy, menopause.

Introduction

Menopause is defined by World Health Organization (WHO) as permanent cessation of monthly menstrual periods due to permanent depletion of ovarian follicular activity^{1,2}. However it is a retrospective diagnosis after one year period of absent

menstruation following final menstrual period. Average age of menopause is considered to be 52.4 years³. Menopause is associated with Estrogen deficiency which subsequently causes short term and long term complications. Short term complications includes vasomotor symptoms, commonly known as menopausal symptoms, mood changes and urogenital symptoms, whereas long term complications includes osteoporosis, increased risk of cardiovascular diseases and pelvic organ prolapse^{4,5,6}.

Various treatment modalities are currently on practice which includes pharmacological and non-pharmacological modalities. However, most effective treatment modality for postmenopausal symptoms is considered to be hormone replacement therapy (HRT)^{7,8}. Main indications for HRT includes presence of menopausal symptoms, surgical menopause before natural menopause and premature menopause/ovarian failure⁸.

Unscheduled vaginal bleeding following HRT reduces the patient's compliance in long term use and results in discontinuation of HRT^{9,10}. This is considered to be the main cause for discontinuation of HRT⁹. According to available data, around 25-50% of patients discontinue HRT due to unscheduled bleeding⁹. Most importantly there is no well-established data on management of unscheduled bleeding.

Pathophysiology of menopause

Menopause is characterized by cessation of menstruation due to cessation of ovulation, which is considered to be due to permanent cessation of ovarian follicular activity. This in turn reduces the ovarian production of estradiol, which is the most active biological form of estrogens and inhibins (inhibin A and inhibin B). Due to reduced circulatory inhibins, the negative feedback on pituitary and hypothalamus is lost and circulatory follicular

stimulating hormone (FSH) level is elevated^{11,12}. This process is believed to be happen over a period of time and is called menopausal transition (MT). During menopausal transition, FSH is the first hormone to be increased and inhibin A and inhibin B decrease gradually. Finally, Serum estradiol is decreased¹³. However, there is no single biochemical or serological marker to diagnose menopausal transition or perimenopause effectively.

Hormone replacement therapy

HRT is considered to be the most effective treatment modality of postmenopausal symptoms^{7,8}. It reduces the short term complications like vasomotor symptoms, mood changes and genito-urinary symptoms. It also has the advantage of reducing the risk of osteoporosis, cardiovascular disease and pelvic organ prolapse. Estrogen only therapy or estrogen and progesterone combined HRT therapy is prescribed depending on the absence or presence of the uterus respectively. Combined HRT therapy can be subclassified as combined sequential therapy or combined continuous therapy. Combined sequential HRT is used in patients who have postmenopausal symptoms but still menstruating and during early phase of post menopause (preferably during first year following menopause)^{8,14}. This regimen is later converted to combined continuous HRT when desired age of menopause is achieved (usually after 1 year of commencement of combined sequential HRT or by age of 54 years)^{8,14}.

Unscheduled bleeding following HRT

Unscheduled bleeding following HRT is a known complication. It's frequency, timing and severity depends on the scheduling, type and strength of estrogen and progesterone¹⁵. Exact mechanisms of unscheduled bleeding is poorly understood. Continuous combined HRT can cause unscheduled bleeding (break through bleeding) often during first six months after initiation of treatment and can last even after 12

months^{16,17,18}. Combined sequential HRT can have heavy vaginal bleeding at the end of progesterone phase (withdrawal bleeding), spotting before withdrawal bleeding (due to breakthrough bleeding) or irregular per-vaginal bleeding^{16,17,18}.

Up to 80% of women who started on combined continuous HRT can have unscheduled bleeding and usually settle by six months^{19,20,21,22,23,24}. 3-10% of them have persistent unscheduled bleeding even after 9 months²¹. Up to 8%-40% of patients who started on combined sequential HRT will experience unscheduled bleeding (withdrawal bleeding / breakthrough bleeding / irregular bleeding)^{22,23,24,25}.

Postmenopausal bleeding versus unscheduled bleeding following HRT

Postmenopausal bleeding is defined as bleeding from vagina following one year after last menstrual period irrespective of the cause, whereas unscheduled bleeding following HRT is considered to be due to hormonal imbalance caused by scheduling, type and strength of different estrogen and progesterone preparations, in the absence of secondary endometrial pathology¹⁶.

Assessment of unscheduled bleeding

Persistent Unscheduled bleeding following HRT, has to be investigated. Assessment of unscheduled bleeding includes detailed history taking, thorough examination and relevant investigations. Menstrual diaries are useful in assessing the timing, frequency and severity of the bleeding. Compliance of the HRT has to be assessed. Diagnosis of unscheduled bleeding is made only after exclusion of secondary causes including endometrial hyperplasia and endometrial malignancy.

Transvaginal scan (TVS) is the initial investigation of choice to assess the endometrium²⁶. It is a quick, painless, easily available, highly effective investigation modality and it gives the advantage of simultaneous evaluation of uterine or ovarian

pathology^{27,28,29}. It has high sensitivity and specificity in assessing postmenopausal endometrial pathology^{27,28,29}. Endometrial thickness of more than 5 mm, in patients treated with combined continuous HRT, requires further assessment of the endometrium, whereas endometrial thickness of less than 5 mm safely excludes endometrial pathology^{18,30,31,32}. Mean endometrial thickness of patients treated with combined sequential HRT is higher compared to those who are not treated with sequential HRT¹⁸. In addition to that, the endometrial thickness will be vary depending on the date of the combines sequential HRT cy-

Definitive diagnosis for secondary causes is made by histological assessment, which can be done by either pipelle endometrial sampling, dilatation and curettage or hysteroscopy. Dilatation and curettage is no longer recommended for endometrial sampling though it is still used in low resourced centers.

Pipelle endometrial sampling is an outpatient procedure with high sensitivity and specificity^{34,35}. A meta-analysis involving 39 studies found that 99.6% detection rate of endometrial pathology with pipelle endometrial sampling³¹. This procedure is considered to be low cost, easily available and causing minimal discomfort³⁵.

Figure 01 Assessment of unscheduled bleeding following HRT

cle¹⁸. Therefore endometrial thickness measured within first half of the cycle is taken in clinical practice¹⁸. Further, evidence suggests to take cut-off value of 8mm in patients treated with combined sequential HRT since less than 8mm is highly unlikely due to a malignant cause^{18,33}.

Hysteroscopy remains the gold standard of assessing the endometrial pathology³⁶. It has very high sensitivity and specificity and a detection rate of 95% of endometrial pathologies³⁷. It also has the advantages of visualizing focal abnormalities and taking direct biopsies. However it has few drawbacks including high cost.

Management

Management of unscheduled bleeding following HRT depends on scheduling, type and strength of the different HRT preparations. Management includes three main principles, firstly to exclude other endometrial pathology, secondly to identify the bleeding pattern (withdrawal/breakthrough/irregular) and thirdly to treat the unscheduled bleeding.

Unscheduled bleeding caused by combined continuous HRT, lasting more than 6 months without any high risk factors or lasting less than 6 months with high risk factors (older age group, irregular endometrium, focal lesions, haematometron and pyometron) has to be investigated and possible secondary causes need to be excluded^{14,17}. This can be managed with reducing the estrogen dose, increasing the progesterone dose, changing the type of progesterone, changing to combined sequential HRT and inserting Levonorgestrel releasing intra uterine system (IUS)^{17,18,21,38}.

Unscheduled bleeding (withdrawal bleeding) due to combined sequential therapy can be managed with reducing the estrogen dose, increasing the progesterone dose and changing the pro-

gesterone type. Spotting before the withdrawal bleeding (due to breakthrough bleeding) can be managed with increasing the estrogen dose. Irregular bleeding throughout the cycle can be managed with trying different HRT preparation or increasing the progesterone dose^{17,18,21,38}.

Unscheduled bleeding which is not responding to medical treatment can be managed with stopping HRT and converting to nonhormonal / nonpharmacological method, ablation techniques and surgical resection of the endometrium¹⁸. If all these options fail, last resort would be the hysterectomy¹⁷.

Conclusion

Unscheduled bleeding following HRT is a common complication and the commonest cause for discontinuation of HRT. Exclusion of secondary causes is the mainstay of diagnosis of unscheduled bleeding following HRT. Persistent unscheduled bleeding has to be assessed carefully. It can be managed by changing the regimens depending on the scheduling, type and the strength of different HRT preparations.

Figure 02 Management of unscheduled bleeding following HRT

Disclosure of interests

No conflicts of interest

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