



# The 6<sup>th</sup> Scientific Meeting of the Asia Pacific Menopause Federation

Singapore | 20 – 23 Apr 2017

23 Apr 2017

## Abnormal uterine bleeding in the perimenopause

Perimenopausal menstrual problems are among the most common causes for family practitioner and specialist referral. Often it is due to the hormone changes associated with this stage of life, but occasionally can result from significant pathology. The investigation and management of perimenopausal menstrual problems are discussed here.

The most common presenting problem is heavy and irregular menses. It is difficult to assess the heaviness of flow clinically. Therefore, it may be more appropriate to ascertain the degree of incapacity experienced. Passage of clots and a change in menstrual pattern causes concern for many women as this is perceived as abnormal. Menstrual irregularity is a considerable nuisance and occurs when the incidence of anovulation increases.

‘Red-light symptoms’ for referral are inter-menstrual bleeding, worsening pain and a pelvic mass.

The history should include information regarding tamoxifen use or the presence of polycystic ovarian syndrome that suggest a higher risk of endometrial cancer. An examination includes general, abdominal and pelvic examination.

Investigation is usually relatively simple. It is essential to measure haemoglobin when there is heavy menstrual loss. An ultrasound is usually performed to assess the pelvic organs and appearance of the endometrium. Hysteroscopy is required only if structural abnormality is identified (eg, fibroids, polyps, thick endometrium, etc.) or if it is not



possible to get an adequate quality scan. Endometrial biopsy is performed in women over 45 years, and in those under 45 years with menstrual irregularity or where treatment for heavy menses has failed.

Medical treatments may be hormonal (levonorgestrel-releasing intrauterine system, combined oral contraceptive or progestogens) or non-hormonal (tranexamic acid or mefenamic acid). Selective progesterone receptor modulators are used for women with fibroids. Surgical treatment includes hysterectomy and endometrial ablation. Radiological treatment (uterine artery embolization) is useful for women with fibroids.

Perimenopausal bleeding problems can usually be successfully treated and endometrial cancer is uncommon, although the incidence is rising.



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## Perimenopausal abnormal uterine bleeding

- Abnormal bleeding in the perimenopause may commonly be due to anovulatory bleeding and leiomyomas. Endometrial carcinoma or hyperplasia are rare
- 'Red-light symptoms' are intermenstrual bleeding, post-coital bleeding, pelvic pain and pressure symptoms
- Investigations include haemoglobin, but other haematological tests need only be done in those with additional symptoms
- Ultrasonography is the first-line investigation. Hysteroscopy is only needed when an abnormality is suspected within the uterine cavity, eg, fibroids, polyps or thick endometrium
- Endometrial biopsy is required when endometrial cancer is suspected, but not if endometrial thickness is <4 mm. This can usually be done as an outpatient
- Treatment may be medical or surgical, depending on the cause and the presence/absence of fibroids or polyps
- Medical treatment with hormones is usually contraceptive. Non-hormonal methods are needed in patients with fertility concerns
- Fibroids can be treated medically with selective progesterone receptor modulators, surgically (myomectomy or hysterectomy) or radiologically (uterine artery embolization)



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## Primary ovarian insufficiency and perimenopause

Primary ovarian insufficiency (POI) is a syndrome of amenorrhoea, sex steroid deficiency and elevated gonadotropins in a woman aged more than two standard deviations below the mean age estimated for her reference population.

POI occurs spontaneously in 1% of women before the age of 40 years.

An early menopause (before age 45 years) will also occur in approximately 5% of women, whilst iatrogenic

POI will affect approximately 5% of women prior to age 40 years as a result of surgery, radiotherapy or chemotherapy.

Women with POI will experience all the usual menopausal symptoms, but also have an increased risk of osteoporosis-related fractures, heart disease, stroke, cognitive impairment, Parkinson's disease and early death. Symptoms and risks are all greater following a surgical menopause.

For most women, POI will signal the end of their reproductive life, although as many as 50% with iatrogenic



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POI will experience a return of menses and 5–10% will become pregnant. The diagnosis of POI and the uncertainty of its consequences may also give rise to significant psychological distress.

There is a strong association between POI and autoimmune endocrine disorders, including thyroid disease, Addison's disease and diabetes.

Almost 1 in 4 women with POI will develop autoimmune thyroiditis and 3% will develop adrenal insufficiency or diabetes.

Hormone therapy is the cornerstone of treatment for POI, unless there is a clear contraindication to its use. There

is clear evidence that hormone replacement therapy (HRT) will alleviate menopausal symptoms and reduce the risk of adverse health outcomes.

It is important to note that HRT is not contraceptive. Women concerned about contraception should use barrier methods, particularly in the first year following diagnosis.

The 2016 International Menopause Society Global Consensus Statement recommends that HRT be continued in women with premature ovarian insufficiency at least until the age of the natural menopause.<sup>1</sup>

## References

1. De Villiers TJ, et al. *Maturitas* 2016;91:153–155.

## Premature ovarian insufficiency

- Premature ovarian insufficiency (POI) is loss of ovarian follicular activity before the age of 40 years
- The prevalence is usually stated to be 1%, but may be higher
- Any young woman with more than 3 months of menstrual irregularity should be investigated with a follicle-stimulating hormone (FSH) level. If this is raised, the test should be repeated in 6 weeks together with  $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG), thyroid-stimulating hormone (TSH), prolactin, thyroid and adrenal antibodies, FMR 1 and karyotype
- If POI is proven, further tests should include bone density assessment and ovarian ultrasound
- Untreated POI leads to an increased risk of cardiovascular disease, stroke, osteoporosis and fracture, and perhaps cognitive impairment
- For most women hormone replacement therapy is the cornerstone of treatment and should be continued until at least age 50 years. Dose and type of therapy may need modification over time
- Regular monitoring of general well-being, psychological health, possible autoimmune endocrinopathies, cardiovascular and bone health is required



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## Non-hormonal management of the menopause

Menopausal symptoms can usually be treated effectively by hormone replacement therapy (HRT). However, HRT is not suitable for all, and for these reasons, there is an interest in non-hormonal alternatives. Vasomotor symptoms (VMS) are the most commonly reported, and often the most difficult to manage effectively with non-hormonal therapies.

Most guidelines suggest that women can be offered HRT first for VMS, after a discussion of benefits and risks. However, there is a group of women for whom hormonal therapy is not suitable. Half of the more than 500,000 women living with breast cancer in the UK will not adhere to the recommended 10 years of tamoxifen, often as a result of the severity of the associated hot flushes. We must be able to advise women on safe and effective treatment alternatives, particularly for these women, to help them continue a potentially life-saving treatment.

Simple measures, such as cooling techniques and avoiding triggers, should be mentioned, alongside lifestyle modifications, such as losing weight, stopping smoking and exercise.

Non-hormonal pharmacological treatments are available. Clonidine, selective serotonin reuptake inhibitors and gabapentin have all shown a significant improvement in flushing, whilst vitamin E and evening primrose oil appear to be of little or no benefit. However, adverse effects may limit the use of these drugs.

Soy isoflavones may be more effective with longer term use than other phytoestrogens, but black cohosh, or any compound with oestrogenic properties, should be used



with extreme caution in women with a history of breast cancer or any other oestrogen-dependent disease.

A potential novel treatment, neurokinin B antagonists, may offer relief to many women with severe flushing who cannot use hormonal therapy.

Other alternatives have been studied, such as cognitive behavioural therapy (CBT), which can be delivered in a group or self-taught, and has been developed to help women self-manage VMS. CBT reduces the impact, but not frequency, of flushing. Acupuncture may have some beneficial effects, although it is difficult to demonstrate superiority to sham.

It is important that women are aware of all the treatment options before making any decisions.





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## Non-hormonal alternatives for vasomotor symptoms

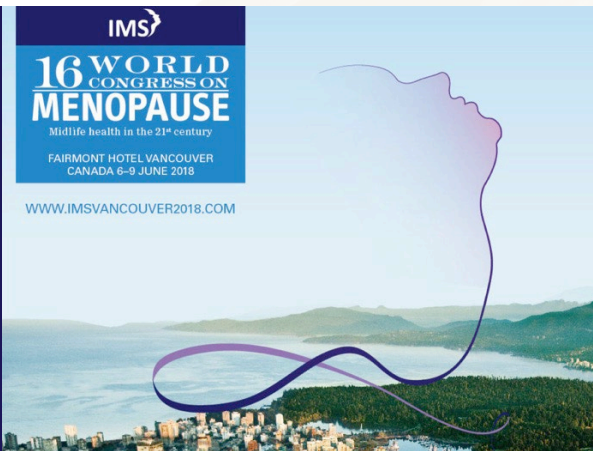
- Non-hormonal alternatives to hormone replacement therapy are usually required for women with breast cancer
- Many women cannot tolerate long-term tamoxifen because of severe vasomotor symptoms (VMS)
- Simple life-style measures, such as cooling, weight loss, identifying trigger factors, etc. should be discussed
- Non-hormonal alternatives include drugs, such as clonidine, selective serotonin reuptake inhibitors and gabapentin
- Cognitive behavioural therapy is useful for decreasing the impact rather than the frequency of VMS
- Hypnosis and acupuncture may be effective, but the evidence is unclear since the 'placebo effect' in randomized, controlled trials of any treatment is often over 30%
- Other treatments, such as stellate ganglion blockade, are available
- New options that block the kisspeptin/neurokinin B/dynorphin pathway may be useful in the future



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