Managing premature menopause: what is the best approach?

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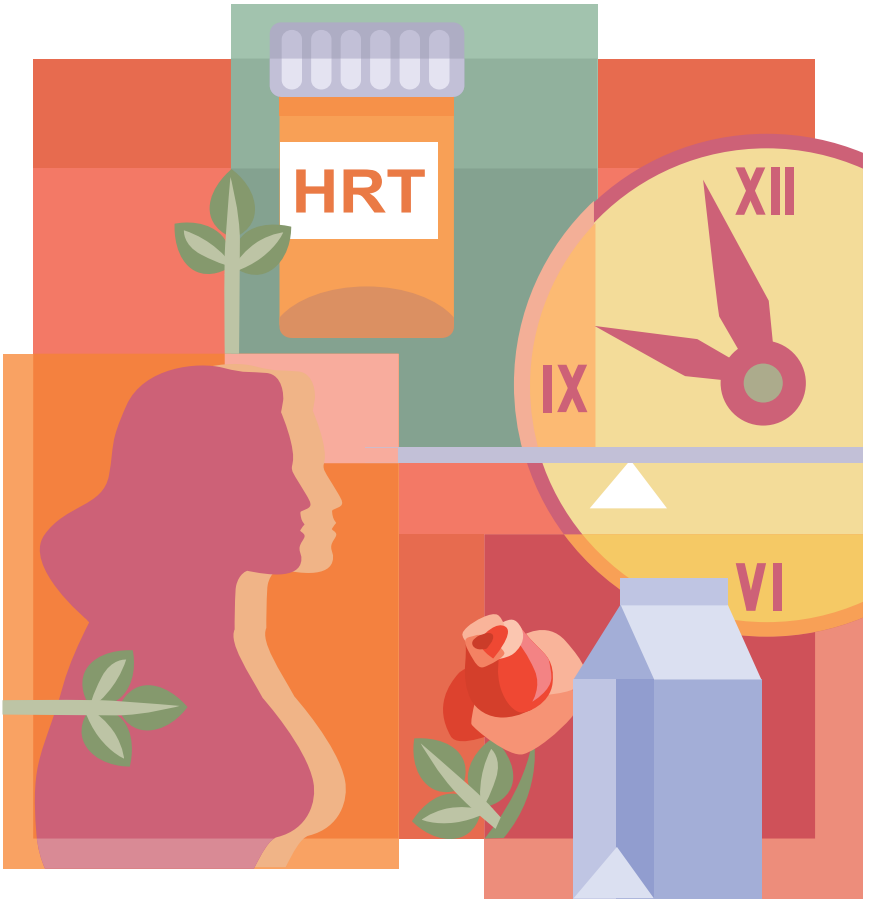
Premature menopause presents a diagnostic and management challenge to clinicians. A multidisciplinary approach is recommended, with management directed at symptom control, screening, prevention and management of long-term complications, and provision of psychological support and information about the condition.



Key points

- **The diagnosis of premature menopause should be considered in young women presenting with menstrual disturbance/amenorrhoea. The diagnosis should be conveyed in a sensitive manner.**
- **Women with premature menopause experience significant psychological distress.**
- **Hormone replacement therapy (unless contraindicated) should be given to women with premature menopause until 51 years of age.**
- **Long-term consequences of premature menopause, such as osteoporosis, need to be screened for and managed.**
- **Provision of information to affected women about premature menopause is essential.**

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Premature menopause, defined as menopause occurring before the age of 40 years, presents a diagnostic and management challenge to clinicians. Premature menopause includes spontaneous premature menopause (premature ovarian failure/insufficiency [POI]) and induced premature menopause (occurring secondary to medical intervention, including bilateral oophorectomy, chemotherapy or radiotherapy).

Spontaneous POI affects 1% of women, with the incidence of induced menopause being potentially higher. At diagnosis, 25% of women with breast cancer are premenopausal, with 10 to 100% of these women developing premature menopause following chemotherapy depending on age and dose, type and duration of chemotherapy.

Causes

The cause of spontaneous POI is unknown in most women[1] and these women are classified as having idiopathic normal karyotype POI. Other causes of premature menopause are shown in the box on page 28.[2]

Clinical presentation and sequelae

The clinical presentation of premature menopause is variable and includes menstrual disturbance, amenorrhoea, menopausal symptoms and infertility, which may all occur concurrently. Severe menopausal symptoms, psychological distress and sexual dysfunction are commonly experienced, with evidence suggesting that the symptom profile and severity varies depending on the cause of premature menopause. Women with POI

Causes of premature menopause[2]

- Spontaneous normal karyotype premature ovarian insufficiency
- Genetic (e.g. *FMR-1* gene premutation, Turner syndrome)
- Autoimmune associated (e.g. thyroid, adrenal and coeliac disease, hypoparathyroidism, pernicious anaemia, type 1 diabetes mellitus, myasthenia gravis, vitiligo, autoimmune hepatitis, connective tissue disorders, autoimmune polyglandular syndromes)
- Medically induced (e.g. bilateral oophorectomy, chemotherapy, radiotherapy, hysterectomy, pelvic surgery)
- Metabolic (e.g. galactosaemia)
- Viral (e.g. mumps oophoritis)

Diagnostic criteria for premature menopause[1]

- At least four months of amenorrhoea (or disordered menses)
- Menopausal range of FSH levels (>40 IU) on at least two occasions one month apart
- Exclusion of secondary causes of amenorrhoea including pregnancy

experience less severe symptoms than those with medically induced premature menopause,[3] and women with breast cancer experience more severe symptoms than those without.[4]

Observational studies indicate that long-term complications of premature menopause include an increased risk of osteoporosis, cardiovascular disease, dementia, cognitive decline and Parkinson's disease, with evidence that use of hormone replacement therapy (HRT) until the age of 45 to 50 years minimises these risks.[5] In addition, women with POI may be at risk of long-term complications related to the specific cause of POI. Approximately 20% of women with POI have an autoimmune disorder, most commonly thyroid dysfunction. Women with POI and positive adrenal autoantibodies have a 50% chance of developing adrenal insufficiency.[1]

Diagnosis

Diagnosing premature menopause can be difficult due to the varied presentation and, at times, difficulty interpreting hormone results. In a study of women in Australia with premature menopause, diagnosis took longer than two years in 23% of women, with at least two clinicians consulted on average.[3] Diagnostic criteria for premature menopause are shown in the box on this page.[1] The diagnosis can be difficult in the setting of chemotherapy/tamoxifen treatment in women with breast cancer.

Use of antimullerian hormone in diagnosing premature menopause appears promising but routine use is not advisable currently. Following diagnosis, investigations to determine the cause of premature menopause and screening for complications are necessary. Disclosure of the diagnosis of premature menopause can be traumatic for women; 89% of women in one study reported moderate to severe emotional distress at the time,[6] and women should be informed in a sensitive and supportive manner. Osteoporosis, sexual dysfunction and weight gain were the most common fears reported.[3]

Management

A multidisciplinary approach is usually necessary in women with premature menopause, with management directed at symptom control, screening, prevention and management of long-term complications, and provision of psychological support and information about the condition. Specialist referral of patients is usually required to confirm the diagnosis and cause of POI and institute therapy. Referral of women to an infertility specialist is necessary if fertility is desired.

Lifestyle measures

Lifestyle measures for women with premature menopause include diet (avoidance of triggers of hot flushes such as spicy foods, adherence to a low-fat diet, maintenance of body mass index in the normal range and adequate calcium intake), smoking cessation and exercise. These are aimed at symptom control and prevention of long-term complications, such as cardiovascular disease and osteoporosis. Women with premature menopause perceived that lifestyle measures and reducing stress were the most effective treatments for menopausal symptoms.[3,7]

Hormonal therapies

HRT is the most effective method for relieving vasomotor and urogenital symptoms[8] experienced during the menopause, with observational studies indicating benefit regarding the prevention of long-term complications.[5] There are no large scale, randomised, controlled trials involving HRT in women with premature menopause and the results from the Women's Health Initiative should not be extrapolated to this group of women.

Current recommendations from national and international societies including The Endocrine Society,[9] The North American Menopause Society[10] and Australasian Menopause Society recommend the use of HRT (unless oestrogen is contraindicated) in women with premature menopause until the age of 51 years (the average age of natural menopause). An increased risk of venous thromboembolism (VTE), as observed with use of the combined oral contraceptive pill (COCP), is considered the main risk associated with use of HRT in this group, although the risk of VTE may be reduced with use of transdermal oestrogen.[10] Data are lacking regarding the optimal form of HRT for women with premature menopause, although transdermal oestradiol is recommended by some authors.[1] The usual contraindications to HRT (e.g. breast cancer, higher grade endometrial cancer, previous VTE or stroke) apply. A progestin should be used in women with an intact uterus with cyclical or continuous dosing depending on time since menopause and patient preference (a regular withdrawal bleed is psychologically important for some women). Higher doses of oestrogen may be required for the

management of symptoms in women with premature menopause compared with those with natural age menopause. Additional use of vaginal oestrogen preparations may be necessary for relief of urogenital symptoms. HRT is not contraceptive.

The low-dose COCP may be preferred by some women with premature menopause; however, recurrence of symptoms and potential cumulative lack of oestrogen during the inactive pill phase means that continuous oestrogen preparations are preferable. Use of the COCP should be avoided in adolescents and women in whom breast development has not commenced to prevent abnormal breast development.

Nonhormonal therapies

Nonhormonal therapies are effective in the management of women with vasomotor symptoms in whom oestrogen is contraindicated. These therapies include gabapentin, clonidine, selective serotonin reuptake inhibitors and selective noradrenaline reuptake inhibitors (off-label uses).[11] However, fluoxetine and paroxetine should not be used concurrently with tamoxifen due to interference with tamoxifen metabolism and reduced tamoxifen efficacy.[12] Nonhormonal vaginal moisturisers and lubricants are used if vaginal oestrogen is contraindicated (e.g. aromatase inhibitor treatment).[12]

Alternative and complementary therapies

Cognitive behavioural and mindfulness therapies are effective in the management of menopausal symptoms in women with breast cancer.[13] Efficacy and safety data regarding the use of herbal therapies, acupuncture and phytoestrogens are inconclusive or lacking for menopausal women in general and lacking for women with premature menopause.[9-12] There are no data regarding efficacy and safety of compounded bioidentical hormone therapy and their use is not supported by The Endocrine Society, Australasian Menopause Society or The North American Menopause Society.[9,10]

Testosterone therapy

Testosterone therapy remains controversial in women with premature menopause, with some evidence suggesting benefit regarding sexual function, bone mineral density and wellbeing.[14] However, there are no TGA-approved preparations formulated for women and long-term safety remains unclear.

Monitoring long-term health effects

There are no evidence-based guidelines regarding monitoring of the long-term health effects of women with premature menopause. Assessment of cardiovascular risk factors, including blood pressure,

Useful websites on premature menopause

Australasian Menopause Society
http://www.menopause.org.au

Jean Hailes for Women's Health
http://www.jeanhailes.org.au
http://www.earlymenopause.org.au

The North American Menopause Society
http://www.menopause.org

The US Endocrine Society: Hormone Health Network
http://www.hormone.org

yearly fasting lipids and glucose, is reasonable with use of lipid-lowering agents and antihypertensives as necessary. Strict control of hypertension is crucial for women with Turner syndrome because of an increased risk of aortic dilation/dissection.

Vitamin D deficiency is common in women with premature menopause and should be screened for and treated. Bone density monitoring using dual-energy x-ray absorptiometry (available with Medicare rebate for women aged under 45 years with six months of amenorrhoea) should be repeated every two years. Fracture risk scoring using FRAX does not apply to women under 40 years of age. HRT is the preferred treatment for low bone density in women with premature menopause. Bisphosphonates and other antiresorptive agents should not be used routinely and specialist referral is necessary for women with low bone density and a contraindication to HRT.

Women with premature menopause appear to have a reduced risk of breast cancer (except where premature menopause occurs secondary to breast cancer therapy) and mammography follows usual screening recommendations. Yearly thyroid function assessment and measurement of early morning serum cortisol and adrenocorticotropic hormone levels are necessary if thyroid or adrenal autoantibodies are detected.

Psychological support and/or counselling

Provision of psychological support and/or counselling is crucial because women with premature menopause experience significantly greater anxiety and depression, negative body image, decreased sexual function and impaired self-esteem and confidence compared with premenopausal women.[3] The age of the woman, reason for premature menopause, the individual and the social context of each woman who experiences premature menopause are factors affecting psychological wellbeing. GPs may be able to initiate referral of the patient to a psychologist or psychiatrist under the Medicare Australia provisions. Referral to a support group may also be helpful (Australian Early Menopause Network; http://www.aemn.com.au).

Infertility

Infertility as a consequence of premature menopause causes significant psychological distress for some women. Oocyte donation is the only proven method of achieving a pregnancy in women with premature menopause and referral to an infertility specialist is required if pregnancy is desired. Women with POI have a reported approximately 5 to 10% life-time chance of pregnancy.[15]

Provision of information

Provision of information to affected women about premature menopause is essential. In one cross-sectional, observational study of 77 women with premature menopause in Australia, less than 40% received information at the time of their diagnosis.[3] This is a cause of dissatisfaction whereas providing information helps to improve the emotional state of women with this condition.[6] The internet was perceived as an information source;[3] however, concerns exist regarding the accuracy of the information. Useful websites on premature menopause are listed in the box on this page.

Summary

Diagnosis and management of women with premature menopause is complex. The role of the GP is important in being alert to this diagnosis and in addressing the physical and psychological issues confronting affected women, often in partnership with a multidisciplinary team. The best approach to managing women with premature menopause is consideration of the diagnosis, use of HRT (unless contraindicated) continued until the age of 51 years (thereby addressing both symptoms and long-term consequences) and provision of psychological support and information. **ET**

References

1. Nelson LM. Primary ovarian insufficiency. N Engl J Med 2009; 360: 606-614.
2. Goswami D and Conway GS. Premature ovarian Failure. Human Reprod Update 2005; 11: 391-410.
3. Deeks AA, Gibson-Helm M, Teede H, Vincent A. Premature menopause: a comprehensive understanding of psychosocial aspects. Climacteric 2011; 14: 565-572.
4. Howard-Anderson J, Ganz PA, Bower JE, Stanton AL. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. J Natl Cancer Inst 2012; 104: 386-405.
5. Shuster LT, Rhodes DJ, Gostout BS, Grossardt BR, Rocca WA. Premature menopause or early menopause: long-term health consequences. Maturitas 2010; 65: 161-166.
6. Groff A, Covington S, Halvorsen L, et al. Assessing the emotional needs of women with spontaneous premature ovarian failure. Fertil Steril 2005; 83: 1734-1741.
7. Sayakhot P, Vincent A, Teede H. Breast cancer and menopause: perceptions of diagnosis, menopausal therapies and health behaviors. Climacteric 2012; 15: 59-67.
8. Maclennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. Cochrane Database Syst Rev 2004; 18(4): CD002978. Available online at: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD002978/frame.html (accessed September 2012).
9. Santen RJ, Allred DC, Ardoin SP, et al. Postmenopausal hormone therapy: an Endocrine Society scientific statement. J Clin Endocrinol Metab 2010; 95(7 Suppl 1): s1-s66.
10. The 2012 hormone therapy position statement of The North American Menopause Society. Menopause 2012; 19: 257-271.
11. Rada G, Capurro D, Pantoja T, et al. Non-hormonal interventions for hot flushes in women with a history of breast cancer. Cochrane Database Syst Rev 2010; 8(9): CD004923. Available online at: http://www.mrw.interscience.wiley.com/cochrane/clsysrev/articles/CD004923/frame.html (accessed September 2012).
12. Hickey M, Saunders C, Partridge A, et al. Practical clinical guidelines for assessing and managing menopausal symptoms after breast cancer. Ann Oncol 2008; 19: 1669-1680.
13. Ayers B, Smith M, Hellier J, Mann E, Hunter MS. Effectiveness of group and self-help cognitive behavior therapy in reducing problematic menopausal hot flushes and night sweats (MENOS 2): a randomized controlled trial. Menopause 2012; 19: 1-11.
14. Graziottin A, Basson R. Sexual dysfunction in women with premature menopause. Menopause 2004; 11(6 Pt 2): 766-777.
15. Bidet M, Bachelot A, Bissauge E, et al. Resumption of ovarian function and pregnancies in 358 patients with premature ovarian failure. J Clin Endocrinol Metab 2011; 96: 3864-3872.

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