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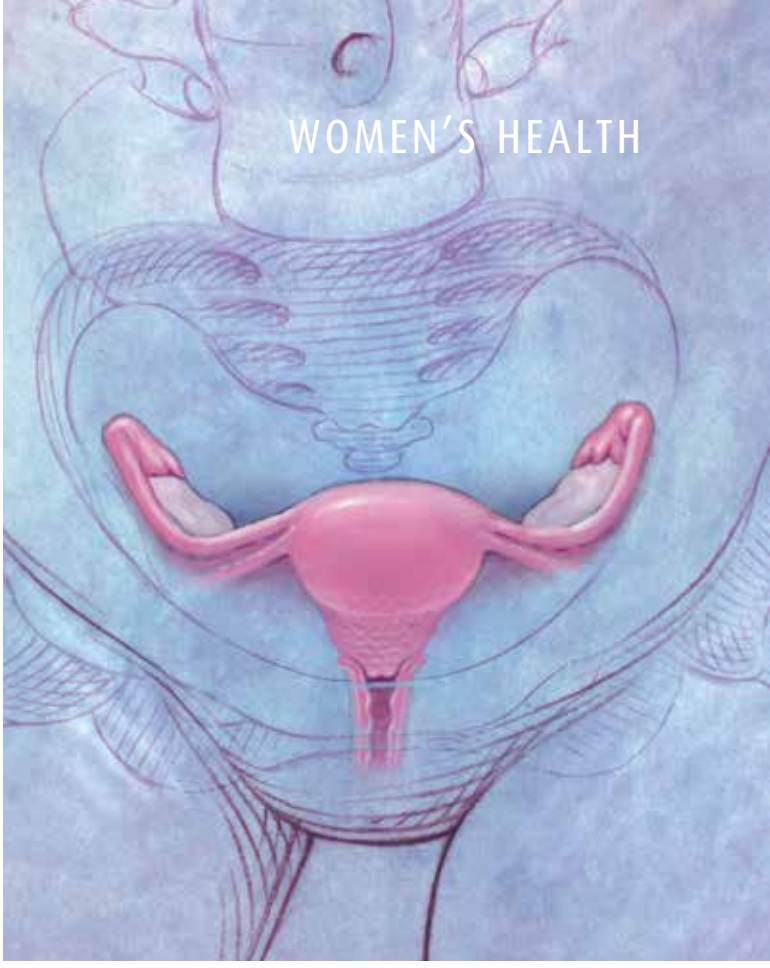

Primary ovarian insufficiency

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A diagnosis of primary ovarian insufficiency can have a huge impact on a young woman and a multidisciplinary team is desirable to ensure her physical and psychological wellbeing.

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DEFINITION

Primary ovarian insufficiency (POI; also known as premature ovarian failure/dysfunction/insufficiency or premature menopause) is characterised by amenorrhoea, sex hormone (oestrogen, progesterone and testosterone) deficiency and elevated gonadotrophins levels in a woman aged more than two standard deviations below the mean age of menopause estimated for her reference population.[1] In practical terms, it occurs spontaneously in 1% of women before the age of 40 years. POI is defined as a disorder in ovarian function in any woman before the age of 40 years, irrespective of the cause.

Although most cases of POI are idiopathic, common causes include familial links and genetic disorders such as monosomy X, trisomy X and fragile X syndrome. Autoimmune links with thyroid and adrenal insufficiency, coeliac disease and diabetes also affect up to 15% of women with POI. POI may also be a result of metabolic disease and infection.

POI will also affect about 8% of women before the age of 40 years as a result of surgery, radiotherapy or chemotherapy, and an early menopause may also arise due to smoking or malnutrition.[2] Thus, almost one woman in 10 under the age of 40 years will be affected by early depletion of ovarian function.

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DIAGNOSIS

The diagnosis of POI should be considered in any woman under the age of 40 years with a history of menstrual irregularity of more than three months.

Initial assessment should include a thorough history, including a family history, physical examination and blood tests to measure levels of follicle-stimulating hormone (FSH), thyroid-stimulating hormone, prolactin and oestradiol.[3] If the patient's FSH level is elevated then the measurement should be repeated in two weeks together with:

- measurement of anti-mullerian hormone (AMH) levels. AMH is a protein hormone secreted by granulosa cells in developing ovarian follicles. It can thus provide an insight into the remaining quantity, but not quality, of follicles (eggs) and the number of fertile years a woman has remaining. AMH does not change during the menstrual cycle and is not affected by hormonal contraception
- measurement of thyroid and adrenal antibodies
- chromosomal studies, which should include a search for the *FMR1* gene mutation, the cause of fragile X syndrome.

Young women with POI should ideally be seen in a tertiary referral centre with access to a multidisciplinary team. Sufficient time should be set aside for counselling to discuss possible aetiology, the long-term consequences of the diagnosis and the emotional impact the diagnosis has had on the young woman and her family.

Once the diagnosis has been made, her bone mineral density should be assessed, an ultrasound performed to exclude autoimmune oophoritis and an appointment made to discuss both

1. CONSEQUENCES OF PRIMARY OVARIAN INSUFFICIENCY

- Increased risk of cardiovascular disease
- Early loss of bone and an increased risk of osteoporotic fracture
- Impaired cognitive function
- Infertility
- Adverse Impact on psychological health
- Comorbidities associated with other endocrine syndromes
- Premature death

fertility issues and her psychological welfare. It is important to direct the young woman to appropriate sources of information, to support groups and, with permission, to involve her family.

CONSEQUENCES OF POI

Although it is assumed that the consequences of POI (see Box 1) are due to long-term hormone depletion, it remains possible that POI arises as a result of an accelerated ageing process, which affects all tissues and organs in the body.[4,5]

Apart from the common occurrence of oestrogen-deficiency symptoms, such as hot flushes, night sweats, muscle and joint pains, and vaginal dryness, women with early menopause experience an increased risk of heart disease, osteoporosis, fracture, cognitive impairment and all-cause premature mortality.

Cardiovascular disease

Following loss of ovarian function, levels of total cholesterol and LDL-cholesterol rise within the first three years. Lesser changes are seen in levels of HDL-cholesterol, blood pressure and insulin resistance.[6,7] The most likely explanation for increasing cardiovascular disease after the menopause is accelerated atherosclerosis, which has been elegantly demonstrated in animal models.[8] This increase in risk appears to be greater after a surgical menopause when, in some studies, the relative risk was reported to be four times higher than in women going through the menopause at the usual natural age.[9]

The Framingham Heart Study also found that the risk of stroke increased after an early menopause.[6] This is a paradoxical finding as the use of hormone replacement therapy (HRT) in older postmenopausal women is associated with a small increase in risk of ischaemic stroke.[10] However, a number of studies have confirmed this finding and have been summarised in a recent meta-analysis.[11]

There is clear evidence from a number of studies that HRT will prevent this increased risk of cardiovascular disease if it is administered until at least age 45 years.[12,13] The International Menopause Society, in a global consensus statement published in 2013, recommends that HRT be continued in women with POI until the age of the natural menopause.[13]

Osteoporosis

Early menopause leads to early loss of bone mineral density and an increased risk of osteoporotic fracture. In the Study of Women's Health Across the Nation (SWAN), the risk of osteoporosis was found to be significantly increased in women of all ethnic groups with POI compared with premenopausal age-matched women.[14] Similar data have been reported in several other studies.

Impaired cognitive function

Cognitive function has been reported to be impaired in patients with POI. In studies performed at the Mayo Clinic, Rocca and colleagues reported an increased risk of cognitive impairment and Parkinson's disease among women undergoing early bilateral oophorectomy compared with control women, a finding confirmed by several other observational studies.[15-17] In a recent study, Bove and colleagues showed that early age at surgical menopause was associated with a faster decline in global cognition, and that this decline was reversed with HRT use initiated within five years of surgery and continued for at least 10 years.[18] The study also found that age at natural menopause did not have the same link with cognitive decline.[18] Although these data are not universally concordant, they suggest altered memory and cognitive function are related to early loss of sex hormones. The use of menopausal hormone therapy, at least until the age of 45 years, has been shown to prevent these neurological changes.

Impact on psychological health

The impact of POI on psychological health is substantial. For many young women the diagnosis is delayed and poorly communicated.[2] Often in patients with POI, the underlying cause is never defined and the uncertainty of the diagnosis, fear of the consequences, faintly held hope of spontaneous return of ovulation and limited management options are distressing. POI may lead to long-lasting anxiety, depression, loss of self-esteem and impaired wellbeing.[19]

The diagnosis of POI must be made promptly and then communicated sensitively to the patient. Access to multidisciplinary teams is desirable to expedite counselling, information communication and expert advice on management. About 8% of young women under the age of 40 years will experience POI as a result of having received chemotherapy or radiotherapy for cancer.[20] Survival from childhood cancer is high and of all breast cancers diagnosed in western women, 25% will be in women younger than 50 years. In Asian communities the peak age of incidence of breast cancer is in the fourth decade of life making premenopausal breast cancer even more common in these communities.[21] These young women require special consideration.

Fertility

Idiopathic POI leads to infertility. Although 50% of women with idiopathic POI will experience some return of cyclical menstrual activity, it is not possible to predict in whom this will occur nor how long it will last; however, some insight can be gained from measurement of AMH.

Similarly, 5 to 10% of women with idiopathic POI will become pregnant without any intervention. For those women hoping to conceive pregnancy will be welcome, but for others, who believe their reproductive life has concluded, it may be an unwanted surprise. Therefore contraception may need to be discussed. For women with POI hoping to become pregnant, the only interventions proven to be effective are oocyte and embryo donation. For some, adoption and fostering may be an option.[22]

The possibility of return of ovarian function following chemotherapy depends on the type of chemotherapy administered, the duration of therapy and the age of the patient. Where possible, consideration should be given to the collection and storage of oocytes before commencing treatment. The psychological effect of the diagnosis of a life-threatening disease adds to the psychological impact of POI and creates further uncertainties regarding fertility and sexuality.

Autoimmune endocrine conditions

Premature menopause may also be associated with other autoimmune endocrine conditions including thyroid disease, Addison's disease, diabetes and systemic lupus erythematosus. Almost one in four women with POI will develop autoimmune thyroiditis and 3% will develop adrenal insufficiency or diabetes. Autoimmune polyglandular syndromes may also occur.[1] Consequently, it is important to screen for at least thyroid and adrenal antibodies when a diagnosis of POI is entertained and long-term screening for these conditions is an important component of patient follow up.

MANAGEMENT

Hormonal treatments

The cornerstone of management of women with POI is HRT, which should be continued until the usual natural age of the menopause.[13] Younger women, particularly those with a surgical menopause, may require higher doses of oestrogen than women passing through the menopause at the usual age. The mean oestradiol level in a normal menstrual cycle has been calculated to be 367 pmol/L[23] and this level will usually be achieved with the use of a 100 µg oestradiol patch. Testosterone therapy should also be considered in younger women, particularly when libido is an issue, but never before other possible causes of loss of libido and sexual dysfunction have been considered.[24] Although measurement of hormone levels is not a usual part of menopause management, testosterone levels should be measured before commencing testosterone therapy.

Many young women will prefer to use the combined oral contraceptive pill to treat their POI. There are certainly social advantages in using an oral contraceptive in younger women rather than HRT more commonly used by older women; however, there is limited evidence suggesting that the combined oral contraceptive pill has less effect on bone mineral density than HRT.[25]

Nonhormonal treatments

Some women will be unable to use hormone therapy because of a history of hormone-dependent cancer or other contraindications. In these women every effort should be made to encourage an active lifestyle, healthy eating patterns, regular exercise and an ideal body mass index. Cardiovascular health should be monitored and consideration given where necessary to pharmacological interventions to control lipids, blood sugars and blood pressure when healthy lifestyle measures have failed. Similarly, bone density may be maximised with adequate exercise, dietary calcium and vitamin D, but if bone loss persists then treatment with bone-sparing agents should be commenced.

If vasomotor symptoms are problematic for women unable to use hormonal therapy then several nonhormonal drug options are available. These include clonidine, low-dose selective serotonin reuptake inhibitors (SSRIs) and serotonin–noradrenaline reuptake inhibitors (SNRIs) including paroxetine, venlafaxine, escitalopram and citalopram (SSRIs and SNRIs used off label). Gabapentin at a dose of 300 to 900 mg per day has also proven effective in controlling menopausal vasomotor symptoms (off-label use).[26]

Women with POI who experience vaginal dryness and dyspareunia should be advised on the use of lubricants and moisturisers and also reassured that topical vaginal oestriol preparations are almost always safe to use when indicated.[13]

2. KEY POINTS

- Primary ovarian insufficiency (POI) affects up to 8% of women before the age of 40 years.
- POI is due to an accelerated loss of or a diminished initial number of ovarian follicles.
- POI should be considered in any young woman with more than three months of menstrual irregularity.
- POI increases the risk of osteoporosis, fracture, heart disease, cognitive impairment and premature death.
- The cornerstone of treatment is hormone replacement therapy.

CONCLUSION

POI is more common than we think. Always consider it in any young woman with four months or more of menstrual irregularities, convey the diagnosis with sensitivity and involve as many colleagues as is necessary to deal with the multiple challenges associated with this diagnosis. Treat patients as you would for any other endocrine deficiency disorder and ensure there is regular and long-term follow up. See Box 2 for the key points of this article. MT

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A list of references is included in the website version (www.medicinetoday.com.au) and the iPad app version of this article.

COMPETING INTERESTS: None.

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