Spontaneous Premature Ovarian Insufficiency

Definitions and Epidemiology

Menopause occurring spontaneously in women younger than 40 years of age affects approximately 1% of women. This was previously referred to as premature ovarian failure; however, the preferred term is now ***premature (or primary) ovarian insufficiency (POI)***[1] Premature menopause is menopause occurring before age 40 years and includes surgical removal of ovaries (bilateral oophorectomy). POI may also be included under this heading although cessation of ovarian function in POI is not always irreversible. Menopause occurring between 40-45 years of age is called ***early menopause***, with spontaneous early menopause affecting approximately 5% of women.

Factors associated with an earlier menopause include smoking, nulliparity, hysterectomy, HIV infection, illicit drug use, a family history of early menopause and adverse life events[2]. There is no evidence that early menopause is associated with the use of oral contraceptives, fertility drugs or artificial hormones in the environment. Childhood caloric restriction, emotional stress at a young age, lower socioeconomic position and environmental toxins are factors identified in some but not all studies[1,2].

Diagnosis of POI often has long term physical and psychological consequences, so women may need emotional support and ongoing medical follow-up.

Causes of POI[1]

- In 90% of women with spontaneous premature ovarian insufficiency, the cause is unexplained[1].
- Genetic causes include Turner syndrome, and Fragile X syndrome carrier..
- POI can be associated with autoimmune disorders. Autoimmune thyroid disease is the most common association with POI; however, adrenal, parathyroid, type 1 diabetes, pernicious anaemia, myasthaenia gravis and connective tissue disorders are also associated.
- Rare metabolic causes include galactosaemia
- Chemotherapy and radiotherapy including the ovaries (pelvic or total body irradiation) are associated with POI. Older age, greater cumulative dose and chemotherapy regimens containing cyclophosphamide are associated with greater risk[3].

Diagnosis

- At present there is no specific predictor of POI . Although Anti-mullerian hormone has been identified as a potential predictor of menopause, problems with assay sensitivity/ reliability prevent routine use currently. Diagnosis is often delayed as the woman or her doctor do not consider the possibility of menopause as a cause of her symptoms. Evaluation of symptoms and exclusion of secondary causes of amenorrhea is necessary. Diagnostic criteria1 include FSH levels> 40IU on 2 occasions at least 1 month apart following 4-6 months of amenorrhea (where the women is not receiving any hormone therapy).
- Diagnosis can be stressful and difficult decisions may need to be made. A woman should be comfortable with her doctor as several consultations may be needed to establish the best management of this condition and plan for the future.

What are the consequences?

- Loss of fertility, which for many women can be devastating.
- Loss of menstrual periods. This may be the first indicator of early ovarian insufficiency. Sometimes in the lead-up, the time between periods becomes longer or erratic. However, there is no specific menstrual pattern which signals that early menopause is about to occur.
- Symptoms of oestrogen deficiency. These include hot flushes, mood change, sleep disturbance, vaginal dryness or poor lubrication during sexual arousal. These symptoms may occur even while the woman is still having menstrual periods. The onset of symptoms may occur gradually or suddenly especially after surgical removal of the ovaries (oophorectomy). Symptoms may be more severe in comparison to women experiencing natural menopause[4]
- Emotional turmoil. Women often feel confused, sad, jealous of other women's pregnancies or old before their time. Depression and anxiety are commonly experienced. Psychological counseling can ease this distress. Use of hormone replacement therapy (HRT) may help mood. Support from the woman's partner, family and friends is important.
- Information regarding the long-term consequences of POI are derived from observational cohort studies. These studies indicate a 2-3 fold increased risk of osteoporosis and a 40% greater risk of cardiovascular disease[5]. Breast cancer risk may be reduced slightly. There may also be an increased risk of cognitive problems, dementia, diabetes mellitus and Parkinson's disease. Greater risk is associated with younger age of menopause. Taking HRT until 45-50 years may minimize these long term risks.

Fertility issues:

- There is still a low chance (1-5% over a lifetime) of becoming pregnant spontaneously (unless a woman has had an oophorectomy) so if a woman does not want a pregnancy she should use contraception even if diagnosed with POI.
- Some women choose not to become a parent, others may want to adopt or foster children.
- Some women try IVF or drugs to stimulate egg production but these have a low chance of success
- Most women with POI who achieve pregnancy use eggs from another woman donated either anonymously or by a friend or relative. Another option is achieving pregnancy using embryos donated by another couple.

Hormone Replacement Therapy:

- Compared with post-menopausal women aged over 50 years who take hormone therapy (referred to as "menopausal hormone therapy" or MHT), hormone therapy in women with POI can be considered as "hormone replacement therapy" (HRT) as the hormone therapy in this instance is replacing the hormones which the ovaries would otherwise be producing.
- Unless contra-indicated (for example women with breast cancer), young women with early menopause are advised to take HRT to relieve the symptoms of oestrogen deficiency and prevent long term complications. Higher oestrogen doses may be required compared with older women for symptom relief and for bone protection. Current recommendations are to continue HRT until the age of average menopause at approximately 50 years[6, 7].

- Options include oestrogen tablets, patches, or gels. Oestrogen alone therapy is used in women who have had a hysterectomy (see AMS information sheet: Menopause-Oestrogen Only Therapy). Oestrogen combined with a progestogen is required if a women has not had a hysterectomy (see AMS information sheets: Menopause – Combined Hormone Replacement Therapy and Menopause- Oestrogen Only Therapy).In addition, regular vaginal oestrogen can be used to improve comfort during sexual activity.
- The combined oral contraceptive pill (OCP) can be used as a replacement hormone up to the age of 50 if the woman has no contraindications to its use including risk factors or a personal history of venous blood clots, , hypertension or is a current smoker and older than 34 years. Continuous or extended cycle use of the OCP is often necessary as women may experience a return of symptoms when the inactive tablets are taken.
- Women on HRT who become fatigued and have reduced libido may have low levels of testosterone. However, low levels of testosterone present on blood testing may not be diagnostic and testosterone treatment in women is still being researched. There are no testosterone products for women approved by the Therapeutic Goods Administration. Any woman taking supplements of testosterone should also be taking HRT as there is very little information on the use of testosterone therapy alone in women. (See AMS information sheet: Low Libido and Testosterone Therapy)

Prevention of bone loss:

- Osteoporosis is common in women who have had oestrogen deficiency at a young age. Measurement of bone density is an important part of managing POI. It is important to check bone mineral density every two years, particularly if the woman decides against taking HRT as use of HRT prevents bone loss.
- A healthy lifestyle is important to maintain bone health. Women with early menopause should avoid smoking, engage in regular weight-bearing exercise, and ensure adequate dietary intake of calcium and vitamin D.
- If a woman suffers a bone fracture from osteoporosis, there are several proven therapies available to reduce her risk of further fractures

Prevention of cardiovascular disease:

- Years of oestrogen deficiency may accelerate a young woman's chance of developing cardiovascular disease. Some studies suggest that this risk is minimized in women who take HRT.
- Women with early menopause should avoid risk factors for vascular disease by not becoming overweight, by exercising regularly, avoiding smoking, controlling diabetes and high blood pressure, and preventing high levels of cholesterol and triglycerides.

Key Points

- Spontaneous POI affects approximately 1% of women aged <40 years and the cause is unknown in most women.
- Diagnosis can be difficult/ delayed. Diagnostic criteria1 include FSH levels> 40IU on 2 occasions at least 1 month apart following 4-6 months of amenorrhea with exclusion of secondary causes of amenorrhoea
- Consequences of POI include menopausal symptoms, psychological distress, infertility, and an increased risk of osteoporosis, cardiovascular disease and possibly cognitive problems.
- HRT (unless contraindicated) is recommended until age 50 years to treat symptoms and minimize the risk of long term health problems. The OCP is an alternative option for women who are medically eligible to use an oestrogen-containing method (the usual contraindications apply).
- Donor egg/embryo is usually required to achieve a pregnancy.

Further information:

- The Jean Hailes Foundation: www.jeanhailes.org.au
- ACCESS: Australia's National Infertility Network www.access.org.au
- NZ Early Menopause Support www.earlymenopause.org.nz
- The Daisy Network Premature Menopause Support Group: www.daisynetwork.org.uk
- Fertility NZ, the NZ national fertility support network: www.fertilitynz.org.nz
- Turner Syndrome Association of Australia www.turnersyndrome.org.au
- Turner Syndrome Society of the United States: www.turner-syndrome-us.org
- www.endocrineonline.org.uk

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