

Spontaneous Premature Ovarian Insufficiency

KEY POINTS

- Spontaneous POI affects up to 4% of women aged <40 years and the cause is unknown in most women.
- Diagnosis can be difficult/ delayed. Diagnostic criteria¹ include FSH levels > 25 IU on 2 occasions at least 1 month apart following 4-6 months of amenorrhoea 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.
- MHT/HRT (unless contraindicated) is recommended until at least usual age of menopause 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.

Definitions and Epidemiology

Loss of ovarian function occurring in women younger than 40 years of age is called **premature ovarian insufficiency (POI)**¹. POI may also be referred to as **primary ovarian insufficiency, premature menopause or premature/ primary ovarian failure**). POI can occur spontaneously affecting up to 4% of women and may vary with ethnicity². POI may also occur secondary to medical treatments, including chemotherapy, radiotherapy or surgery (see AMS Information Sheet [Early menopause due to chemotherapy and radiotherapy](#)). Approximately 11% of female childhood cancer survivors developed premature ovarian insufficiency (based on hormone criteria) in one cohort although the frequency varies³. Menopause occurring between 40-45 years of age is called **early menopause**¹, with spontaneous early menopause affecting approximately 12% of women².

Factors associated with an earlier age at menopause include smoking, nulliparity, hysterectomy, HIV infection, low bodyweight, a family history of early menopause and adverse life events⁴. There is no evidence that early menopause is associated with the use of oral contraceptives, fertility drugs or artificial hormones in the environment⁵. Low birthweight, poor childhood growth, emotional stress at a young age, lower socioeconomic position and environmental toxins are factors identified in some but not all studies⁴.

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

Causes of POI¹

- In 90% of women with spontaneous premature ovarian insufficiency, the cause is unexplained¹.
- Recent studies have identified candidate genes involved in DNA repair, cell energy metabolism and the immune response in the pathogenesis of POI⁶. However, the only genetic causes able to be identified in the clinical setting currently are karyotype abnormalities such as Turner syndrome or Fragile X syndrome premutation carriers.
- 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, myasthenia 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, chemotherapy regimens containing cyclophosphamide and combined radiotherapy and chemotherapy are associated with greater risk³ (see AMS Information Sheet [Early menopause due to chemotherapy and radiotherapy](#)).
- Surgical premature menopause/ occurs with bilateral oophorectomy.

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 currently¹. 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 > 25IU on 2 occasions at least 1 month apart following 4-6 months of amenorrhea (where the woman is not receiving any hormone therapy)⁷.
- 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.

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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 menopause. Symptoms may be more severe in comparison to women experiencing natural menopause⁴
- 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 menopausal hormone therapy (MHT), also known as 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^{8,9}, increased risk of type 2 diabetes mellitus¹⁰, and a 50% greater risk of cardiovascular disease^{5,11,12}. Breast cancer risk may be reduced slightly¹³. There may also be an increased risk of cognitive problems, dementia and Parkinson's disease¹⁴. Greater risk is associated with younger age of menopause. Taking MHT until 45-50 years may minimize these long-term risks¹.

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 MHT, hormone therapy in women with POI can be considered as 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

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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}. Decision to continue thereafter is similar to the decision with menopause at the usual age.

- Options include oestrogen tablets, patches, or gels. Oestrogen alone therapy is used in women who have had a hysterectomy (see AMS information sheet: [Oestrogen Only Menopausal Hormone Therapy](#)). Oestrogen combined with a progestogen is required if a woman has not had a hysterectomy (see AMS information sheets: [Combined Menopausal Hormone Therapy](#) and [Oestrogen Only Menopausal Hormone Therapy](#)). In addition, regular vaginal oestrogen can be used to improve dyspareunia.
- 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 preferred as women may experience a return of symptoms when the inactive tablets are taken and to optimize bone health¹⁵.
- Women on HRT who 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 although Androfemme 1% is registered and approval has been sought. 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: [Sexual Difficulties in the Menopause](#)).

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 loss¹⁶.
- 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. However, specialist consultation is recommended to consider future fertility requirements and impact of anti-resorptive therapy.

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Prevention of cardiovascular disease:

- POI is associated with an increased risk of cardiovascular disease (CVD). Some studies suggest that this risk is minimized in women who take HRT.
Women with early menopause should minimize CVD risk by maintaining normal weight, exercising regularly, ceasing smoking, maintaining a healthy diet, controlling diabetes mellitus and high blood pressure, and preventing or treating high levels of cholesterol and triglycerides.

Further information:

- Early Menopause: Experiences and Perspectives of Women and Health Practitioners: <https://healthtalkaustralia.org/early-menopause-experiences-and-perspectives-of-women-and-health-professionals/>
- 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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