

# 12 Premature ovarian insufficiency

## At a glance

- ▶ Diagnosis of premature ovarian insufficiency should follow careful investigation and if necessary, referral to a specialist menopause service.
- ▶ A minimum of two follicle-stimulating hormone measurements at least six weeks apart should be used to confirm the diagnosis.
- ▶ All women with premature ovarian insufficiency (POI) should be offered psychological support during the process of diagnosis and especially during the initial phase of realisation and acceptance.
- ▶ Hormone replacement either with the combined oral contraceptive pill or with HRT is recommended for all women with POI at least until age of natural menopause (51 years).
- ▶ The choice of combined oral contraceptive pill or HRT will depend on a number of factors, including the wishes of the woman.
- ▶ The hormonal needs of a younger women may differ from those of a women going through menopause at average age and higher doses of estrogen are often required.
- ▶ Management of POI is about long-term health promotion as well as immediate symptom relief and resolving fertility issues.
- ▶ Women with non-surgical POI should be aware of the small risk of spontaneous pregnancy; appropriate contraceptive advice is essential.
- ▶ NICE guidance suggests that women who are or will be rendered menopausal at a young age should be referred to a menopause specialist.

## Introduction

Premature ovarian insufficiency (POI) is a condition in which the ovaries stop functioning normally in women who are younger than 40 years. The condition is sometimes described as 'premature ovarian failure' and 'premature menopause' but these terms are misleading because women with ovarian insufficiency do not always stop menstruating and the

ovaries do not always permanently fail. It is important to keep in mind that some women present with oligomenorrhoea, suggesting sporadic ovarian activity, so the diagnosis of POI does not always mean that pregnancy is impossible. Menopause implies permanent cessation of ovarian activity, and menstruation and POI may be seen as the start of a continuum which finally ends in premature menopause.

### Definition

Premature menopause should be defined as menopause that occurs at an age more than two standard deviations below the mean estimated for the reference population. In the absence of reliable estimates of age of natural menopause in developing countries, the age of 40 years is now universally agreed as the cut-off point for a menopause to be premature. It may take months or years to progress from stages of ovarian insufficiency to true menopause. Women who undergo a menopause between 40 and 45 years are deemed to have an 'early menopause'. The extent of investigation and assessment in this group will depend on a variety of factors. However, the limited data available for this group suggest that they also have an increased morbidity if not adequately treated with hormone therapy. As such, women who have an early menopause should be managed in a similar way to those with POI, with the recommendation that they should take HRT at least until the average age of menopause.

### Aetiology

POI is not uncommon. It is estimated to affect 1% of women younger than 40 years and 0.1% of those under 30 years. Data suggest that the rate may be as high as 7% when both spontaneous and iatrogenic menopause are taken into account. In some countries such as China and India, POI rates as high as 15–20% have been reported but these rates require validation. POI can occur at any age, even in teenagers, and presents as primary or secondary amenorrhoea or oligomenorrhoea, with or without menopausal symptoms. Some causes are known but in the great majority of cases no cause is found (Table 12.1). It is common for women to present with fertility issues, which, after investigation, leads to a diagnosis of POI.

### Chromosome and gene abnormalities

The most common genetic causes of POI are X chromosome abnormalities ranging from numerical defects, deletions, X-autosome translocations

**Table 12.1****Causes of premature ovarian failure**

Presentation	Cause
Primary	Chromosome and gene abnormalities Enzyme deficiencies Autoimmune disease
Secondary	Chemotherapy and radiotherapy Bilateral oophorectomy or surgical menopause Hysterectomy without oophorectomy/uterine artery embolisation Infection

and isochromosomes. Some women presenting with POI will have known chromosome abnormalities linked to the condition, such as those with Turner syndrome, Down's syndrome, *FMRI* (fragile X syndrome) and blepharophimosis, ptosis and epicanthus inversus syndrome (BPES). Research indicates that various gene mutations are also associated with POI. In practical terms, such testing is often not available to most women presenting with POI. Testing (mainly for X chromosome abnormalities) is particularly indicated in women with an identifiable family history of early ovarian insufficiency and especially if occurring under the age of 30 years. The aim of several research groups around the world is to increase sensitivity of genetic screening through the analysis of genomic biobanks and ultimately to develop a test for the prediction of menopausal age.

**Enzyme deficiencies**

A number of enzyme deficiencies have been found to be associated with increased risk of POI. The most common of these is the autosomal recessive condition of galactosaemia, in which there is a deficiency in the enzyme galactose-1-phosphate uridyltransferase, identified at a young age. Rarer deficiencies include:

- cholesterol desmolase deficiency: patients with this enzyme deficiency can barely produce any steroid hormone. They have enlarged lipid-filled adrenals, lack ovarian function and rarely survive to adulthood.
- 17-alpha-hydroxylase deficiency: this is a form of congenital adrenal hyperplasia. Patients have impaired adrenal and ovarian steroid hormone synthesis. They develop hypertension, hypokalaemia and ovarian failure.

- 17-20-desmolase deficiency: although this enzyme is a part of the 17- $\alpha$ -hydroxylase cytochrome P450 complex, an isolated deficiency is possible. In this case, only ovarian insufficiency develops. Patients who have 17-alpha-hydroxylase/17-20-desmolase deficiency also have low serum estrogen, high gonadotrophins, enlarged ovaries with multiple cysts and amenorrhoea.

### Autoimmune disease

Androgens, estrogen and progesterone all influence immune functions; estrogen in the form of 17- $\beta$  estradiol has been particularly associated with profound influences on the immune system. When women with POI are tested, laboratory evidence of autoimmune disease is much more prevalent than clinically significant disease and it is not known if progression always occurs. The most commonly found antibodies are thyroid, adrenal and lupus related. Other autoimmune disorders, such as myasthenia gravis, rheumatoid arthritis and systemic lupus erythematosus have also been reported in association with POI but such cases are infrequent. Testing for thyroid antibodies and function should be part of the standard diagnostic work-up, owing to the frequency of association, but testing for other autoimmune conditions should be predicated on symptoms and signs that are suggestive of the condition.

### Chemotherapy and radiotherapy

The likelihood of ovarian insufficiency after chemotherapy or radiotherapy depends on the agent used, the dosage, the interval between treatments and, particularly, the age of the woman. The closer she is to the age of natural menopause, the more likely it is that there will be ovarian insufficiency.

Radiation-induced ovarian insufficiency usually results in sterility when the total dose exceeds 6Gy. As with chemotherapy, however, prepubertal girls are more resistant to irradiation. Normal menstruation after treatment does not necessarily mean that the ovaries are unaffected and premature menopause can occur, resulting in a shorter reproductive time span. A successful term pregnancy also depends on a normal uterine environment that is not only receptive to implantation but also able to accommodate normal growth of the fetus. The degree of damage to the uterus depends on the total dose of radiation and the site of irradiation. The prepubertal uterus is more vulnerable to the effects of pelvic irradiation, with doses of radiation of 14–30Gy likely to result in uterine dysfunction. High doses of pelvic radiotherapy in young women will have

long-term effects on the uterine vasculature and development. Adverse pregnancy outcomes have been described for women treated with total body irradiation and include increased risk of early pregnancy loss, preterm birth and delivery of infants with low or very low birth weight. An excess risk of infants of low birth weight and preterm birth also exists among mothers who received abdominal irradiation for Wilms' tumour in childhood.

### Bilateral oophorectomy or surgical menopause

Bilateral oophorectomy results in immediate menopause, which may be intensely symptomatic. The implications of this procedure require detailed discussion with the woman, in view of the increased morbidity and mortality in those who cannot or will not take estrogen replacement.

### Hysterectomy without oophorectomy/uterine artery embolisation

Uterine artery embolisation is a safe alternative to surgery for treatment of fibroids. This procedure, together with hysterectomy without oophorectomy, has been associated in a small proportion of women with earlier onset of menopause, perhaps because of compromised ovarian blood supply and loss of ovarian follicles.

The diagnosis of POI in women who have had a hysterectomy may be difficult, as not all have acute symptoms, and, in the absence of a uterus, the sign of amenorrhoea is absent. A case can be made for annual estimates of levels of follicle-stimulating hormone in women who have had a hysterectomy/uterine artery embolisation before the age of 40 years. Until this becomes routine practice, these women should be encouraged to report menopause symptoms, which may not always be classic hot flushes and sweats. They may include new or worsening problems, such as tiredness, insomnia, low or fluctuating mood, poor cognition or reduced sexual desire.

### Infection

Tuberculosis and mumps are infections that have been implicated most commonly. The increasing incidence of tuberculosis and the emergence of multidrug-resistant strains of bacilli is of concern. In most cases, normal ovarian function returns after infection with mumps. Malaria, varicella and *Shigella* infections have also been implicated in POI.

## Long-term health effects

Early menopause is associated with a decreased risk for breast cancer, lower bone density and increased risk for fracture, increased cardiovascular disease, reduced cognition and decreased life expectancy. Published data on health risks are largely from cohort studies of women with surgical menopause rather than natural menopause. There is a lack of studies assessing long-term outcomes in spontaneous POI, where the estrogen deficiency is less extreme than surgical menopause. The FRAX® scoring system that assesses the risk of osteoporotic fracture (see Chapter 11) does not apply in women below the age of 40 years.

## Presentation and assessment

The most common presentation is secondary amenorrhoea or oligomenorrhoea in a woman younger than 40 years, which may be accompanied by hot flushes and vaginal dryness. Presentation often starts with fertility difficulties. Assessment will include family history of early menopause, full personal and family medical and medication history, and a careful menstrual history. Symptom assessment is important, while recognising that it is often not symptoms which bring women for investigation but anxiety about fertility or long-term health issues (Box 12.1).

### Box 12.1

#### Summary of investigation of premature ovarian insufficiency

- ▶ Serial measurement of follicle-stimulating hormone (at least two measurements, six–eight weeks apart)
- ▶ Thyroid function tests
- ▶ Autoantibody screen (thyroid and adrenal). Other specific antibodies if indicated (ovarian antibody tests are too non-specific for routine use)
- ▶ Karyotyping should be offered if the onset of amenorrhoea or oligomenorrhoea is before age 30 years or in women of any age in whom Turner syndrome mosaicism is suspected
- ▶ Baseline measurement of bone mineral density through dual-energy x-ray absorptiometry
- ▶ Investigations for secondary disease if indicated; for example, in Addison's disease, diabetes, vitamin D deficiency

The Premature Ovarian Insufficiency Register (<https://poiregistry.net>) has been established with a view to improving data collection and analysis in this field. All healthcare professionals who manage young women with POI are encouraged to register at the website and enter their anonymised patient data. These data can then be used to analyse the aetiology and presentation of POI and to assess the short- and long-term outcomes of women with POI.

### Anti-müllerian hormone as predictor of ovarian reserve

Anti-müllerian hormone (AMH) is produced by the granulosa cells of preantral and small antral follicles, and its levels can be assessed in serum. Since the number of ovarian follicles declines with increasing age, AMH levels might be used as a marker for ovarian ageing. Used widely in preparation for in vitro fertilisation (IVF), measurement of AMH can be a useful tool to predict ovarian response. Commercial tests are now available to purchase that claim to assess 'ovarian reserve'. Evidence that it can be useful to predict age of menopause is less comprehensive and not yet at a stage where AMH testing to predict age of menopause is used in routine clinical practice. A number of research centres are now working on the reliability of diagnostic models for menopause prediction.

## Management

### Counselling and support

The diagnosis of POI is a difficult one to receive and women may require several visits for questions and discussions. Written information and directions to reliable internet resources should be offered. Psychological support from a counsellor should be made available to all women with POI, because of the profound impact this diagnosis can have.

National and international support groups for POI exist (such as [daisynetwork.org.uk](http://daisynetwork.org.uk)) and these provide helpful psychological support for many women. Women need to be aware that, in the absence of bilateral oophorectomy, ovulation may occur again, often intermittently, and cyclical menstrual bleeding or even spontaneous pregnancy can result. Contraception should therefore be discussed, together with fertility issues, and tailored to the individual's desires and wishes. With an increasing number of healthy young women undergoing risk-reducing bilateral salpingo-oophorectomy there is a need for specific counselling and support within this group. Coordination of care and

advice between primary care, genetic counsellors, oncologists and gynaecologists is essential.

### Hormone replacement therapy

Hormone replacement therapy (HRT) is recommended to treat the symptoms of POI and to prevent adverse effects of estrogen deficiency. Use of HRT is recommended at least until the average age of natural menopause (51 years in the UK). This view is endorsed by regulatory bodies such as the Medicines and Healthcare products Regulatory Agency, the National Institute for Health and Care Excellence in the UK and by national and international menopause and fertility societies in their guidelines.

Very little research has been undertaken to determine the optimal hormone replacement regimen in POI. To date, only three small prospective randomised controlled trials have been conducted comparing HRT with the combined oral contraceptive pill.<sup>1-3</sup> These studies suggest that while both regimens are effective, bone mineralisation and cardiovascular risk markers are more favourable in HRT users.

In the absence of good evidence, it seems most appropriate to provide physiological replacement of the hormone deficiency using usual regimens of HRT tailored to the individual, recognising that doses may need to be higher than in older women. However, if the woman does not wish to become pregnant, or if she expresses a preference for it, the combined oral contraceptive pill is a reasonable starting option for hormone replacement. It provides synthetic estrogen with progestogen cyclically. This regimen may be preferred by some women, as it is a medication with which they are familiar, it is not associated with menopause and is more 'peer friendly'. Packets may need to be run together to avoid breakthrough symptoms in the hormone-free interval.

There is no evidence that estrogen replacement increases the risk of breast cancer to a level greater than that found in normally menstruating women and women with POI do not need to start mammographic screening early.

For the vast majority of young women, the benefits of estrogen replacement will outweigh any risks. For more complex cases, there may need to be consultation across multidisciplinary teams, such as oncological surgeons, oncologists or other physicians. With good availability of resources, time and expertise, these women could be successfully managed in primary care by healthcare professionals with an interest in menopause. However, if the diagnosis is unclear or where there are complex issues alongside POI, care by a menopause specialist is mandatory.

Many women with POI report reduced libido or sexual function despite apparently adequate doses of estrogen replacement. This may be due to the complex psychosexual impact of POI but also to androgen deficiency, which is particularly common in women who have undergone oophorectomy. Consideration should therefore be given to additional treatment with testosterone replacement and psychosexual counselling where appropriate (see Chapters 6 and 7).

### Lifestyle and complementary approaches

Women will often ask about the option of complementary therapies. Even if complementary therapies help with symptoms, they are not thought to offer long-term health protection in women with POI and should not be considered an alternative to hormone replacement. This is a good opportunity to discuss other lifestyle factors that can help prevent bone loss and reduce cardiovascular risk. These include maintaining a healthy weight, ensuring adequate intake of calcium, excluding vitamin D deficiency, weight-bearing and cardiovascular exercise, limiting caffeine and alcohol intake and smoking cessation.

### Fertility and contraception

It is important to ascertain whether the woman wishes to have children and to remember that, even if she has already had children, this can be a painful discussion. The myth that premature ovarian insufficiency is final and infertility inevitable should be explained in the context of age and the chance of spontaneous conception discussed (estimate 5–15%, dependent on age). For those not wanting children, reliable contraception should be provided instead of, or alongside, HRT, perhaps using an intrauterine system as part of her HRT regimen.

For those who need fertility support, donor oocyte IVF is the treatment of choice, although it is only considered by approximately 50% of women with POI, for personal or cultural reasons. Women with spontaneous, karyotypically normal POI have similar success rates to women who undergo conventional IVF. The availability or otherwise of fertility support on the NHS should be discussed, as well as the option of adoption or remaining child free.

In women having chemotherapy or radiotherapy, IVF with embryo freezing prior to treatment currently offers the highest likelihood of a future pregnancy. However, this depends on having a partner with whom the woman wishes to have a family. Recent technical advances in oocyte cryopreservation have improved live birth rates after freezing of mature

eggs but is still less successful than embryo freezing. Cryopreservation of ovarian tissue is still largely experimental, although pregnancies have been reported. This technique is an option for prepubertal girls where ovulation induction is not possible.

## Summary

Women with premature ovarian insufficiency will need support over many years, with their physical and psychological needs changing over time. They will need regular monitoring and sometimes a change in their hormone replacement, as well as risk assessment for long-term health conditions.

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## Web resources

Daisy Network: [daisynetwork.org.uk](http://daisynetwork.org.uk)

Premature Ovarian Insufficiency Register: <https://poiregistry.net>