

# MEETING THE CHALLENGES OF 'EARLY MENOPAUSE'

Though relatively uncommon, primary ovarian insufficiency – sometimes referred to as 'premature' or 'early' menopause – is an important condition that GPs will encounter from time to time. Here, Marie Gerval and Etienne Horner look at how GPs can avoid missed or delayed diagnosis and ensure optimum management of this complex condition.

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Premature ovarian insufficiency (POI) describes a syndrome consisting of the occurrence of amenorrhoea, elevated/menopausal levels of gonadotropins and oestrogen deficiency in women under the age of 40 years.<sup>1,2</sup> While it is not common, POI is by no means rare in specialist practice. It arises from a genetically pre-determined reduced number of ovarian follicles at birth, accelerated follicular atresia, or follicular dysfunction.<sup>3</sup>

At least one in 100 women under the age of 40 are affected, and it is possible to have an early menopause in the teens, 20s and 30s, with 0.1% of under 30s and 0.01% under 20s experiencing this syndrome.<sup>2</sup>

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## Diagnosis and evaluation

There is at present a lack of standardised diagnostic criteria for establishing POI, which can lead to delayed diagnosis and poor management of both the immediate and long-term sequel development of this condition. However the typical presentation of women is menstrual disturbances, which may or may not be accompanied by hot flushes as a result of oestrogen deficiency.<sup>8</sup> Others may present after failed attempts at ovulation induction for infertility.

The diagnosis should always be considered in young women presenting with secondary amenorrhoea of greater than three months.

Detailed history-taking should include the following considerations:

- A family history of autoimmune diseases, POI, fragile X or other X chromosome defects; developmental delay is also significant
- Any history of infections such as mumps oophoritis, tuberculosis, malaria, varicella and shigella

- Severe disorders such as poorly controlled diabetes mellitus or malnutrition, which could underlie secondary amenorrhoea
- Cessation of menses might be caused by thyroid dysfunction, androgen excess (e.g. polycystic ovary syndrome), hypothalamic dysfunction or hyperprolactinaemia.

After excluding pregnancy, the core diagnostic criteria are 3–4 months of amenorrhoea or menstrual irregularity and two serum follicle stimulating hormone (FSH) values of greater than 40 IU/L more than one month apart in a woman less than 40 years old.<sup>4,5</sup>

Unless insufficiency results from removal of ovaries, chemotherapy or radiotherapy (in which case the cause is clear and onset of symptoms abrupt), spontaneous POI is thought to develop over several years – it is a continuous spectrum.

However some individuals develop amenorrhoea after a pregnancy or stopping of hormonal contraceptives, when the insidious nature of the process has been masked.

POI is not an early menopause. Unlike the menopause, which is an irreversible permanent condition, the cessation of ovarian function in POI is not necessarily permanent.<sup>7</sup> Spontaneous pregnancies can arise in 5–10% of women as a result of intermittent ovarian function in 50% of women in the early stages of the disorder.<sup>11,12</sup>

## Investigations

Additional baseline investigations include:

- Serum LH
- Prolactin
- TFT
- DEXA bone scan
- Transvaginal pelvic ultrasound scan

Although it is not currently possible to predict which women will develop POI, anti-Müllerian hormone

(AMH) is currently thought to be the most reliable measure of reduced ovarian reserve and may play a role in predicting the remaining time to final menstrual period.<sup>13</sup>

Further tests are required to identify the small number of women who may have an underlying cause for their diagnosis. These investigations include:

### Chromosomal studies (karyotype)

When ovarian insufficiency presents as primary amenorrhoea, approximately 50% of cases will be associated with an abnormal karyotype.<sup>14</sup> Having this information may influence the family planning decisions of other family members. It is therefore recommended to obtain a karyotype in all women with POI.

### Genetic studies

Obtaining a family history of POI is an essential part of the evaluation. Women who have relatives with spontaneous POI should be referred for genetic counselling. Approximately 14% of women with familial POI have a premutation in the FMR1 gene.

### Auto-immune antibodies

Screening for associated autoimmune diseases is recommended, as POI is frequently associated with autoimmune disorders, particularly hypothyroidism (25%), Addison's disease (3%) and diabetes mellitus (2.5%).

### Iatrogenic POI

Surgical removal of ovaries and hysterectomy for benign gynaecological causes, and chemotherapy and radiotherapy for treatment of malignant disease are the most common known causes of POI.

Chemotherapy depletes oocyte numbers and affects their structure and function. The induced POI can be temporary; however, the chance of spontaneous recovery of ovarian function decreases with the age of the patient.

Radiotherapy may affect the ovaries depending on the radiation field. There is little risk of POI in women treated with radiation fields outside the pelvis.<sup>6</sup>

### Psychological health

After a diagnosis of POI, patients may experience a sense of helplessness, anger, sadness and guilt. The loss of reproductive capacity may also lead to self-esteem and relationship difficulties. Expressing appropriate concern and establishing exactly how much the patient knows and wants to know are important parts of the counselling process.<sup>20</sup>

Directing patients to support groups such as the Daisy Network (<http://www.daisynetwork.org.uk>) and Women's Health Concern ([www.womens-health-concern.org](http://www.womens-health-concern.org)) can offer helpful information.

In some cases, a psychologist or psychiatrist may need to evaluate levels of depression, anxiety and coping mechanisms, and group or medical therapy may be required.

### Subfertility

Spontaneous pregnancies can occur in 5–10% of those with spontaneous POI due to the intermittent resumption of ovarian function that occurs. However, only egg donation has demonstrated high success rates and this is considered the main treatment of choice for women who wish to attempt conception.<sup>2,21</sup>

Some women will seek egg donation from a family member, and it is essential that the family is fully counselled regarding the risk of a possible donation of an ovum with genetic abnormalities, including the predisposition for POI, that are currently unable to be tested for.

### Oestrogen deficiency

Women with POI sometimes have no symptoms but can often present with signs of oestrogen deficiency, including vasomotor symptoms, atrophic vaginitis, dyspareunia, labile mood, insomnia, poor memory and concentration and general tiredness.

Women with POI are also at significant risk of osteoporosis, cardiovascular disease and possibly Alzheimer's disease.<sup>23,24</sup> Hormone therapy should be initiated in these women, not merely for symptom control, but also to maintain long-term health. Some

**TABLE I. SUMMARY OF MANAGEMENT OF SPONTANEOUS PREMATURE OVARIAN FAILURE (POF)**

#### Definition

- At least 3–4 months of amenorrhea in association with menopausal levels of serum FSH concentration on two occasions
- Initial assessment and investigations
- Good history, including family history
- Tests: Serum FSH, LH, prolactin, TSH, oestradiol; if FSH in menopausal range, repeat.

#### Further investigations

- Chromosomal and genetic studies: karyotype, FMR1 gene mutation if family history of POF, fragile X syndrome or mental retardation
- Auto antibodies: autoimmune screen for polyendocrinopathy, thyroid antibodies, anti-adrenal antibodies, ovarian antibodies
- DEXA: estimation of bone mineral density
- Pelvis ultrasound

#### Management

A diagnosis of POI brings with it 3 critical issues:

- The effect of the diagnosis on psychological health
- Consequent infertility
- Short and long term effects of oestrogen deficiency.

women may need HRT before amenorrhea is established because of troublesome symptoms.

As yet, no randomised trials have been conducted to determine the ideal dose, regimen or delivery system for women with POI receiving HRT.

Oestrogens should be accompanied by progestogen therapy for endometrial protection. Therapy may be administered orally or transdermally, sequentially to induce a regular withdrawal bleed or in a continuous combined manner to achieve amenorrhea. The ultimate choice between bleed vs. non-bleed regime should be that of the patient, following appropriate counselling. Treatment should be initiated with a low dose and increasing as required until symptom control is achieved.<sup>25</sup>

There are no data comparing the different routes of administration and the various treatment regimes. However, women with POI will generally require higher doses of oestrogen to achieve symptom relief than postmenopausal women.<sup>3</sup>

HRT does not provide contraception and, in women who desire reliable protection from pregnancy, the use of the oral contraceptive pill is appropriate. However, standard oral contraceptive pills contain synthetic steroid hormones at a greater dose than is required for physiological replacement. Therefore, not only may they not be ideal, they may also be less effective in the prevention of osteoporosis.<sup>3</sup>

Although there is little information, the levonorgestrel intrauterine system (Mirena IUS) may be suitable for patients with POI who choose the continuous combined HRT regime and require contraception.

## Osteoporosis

Osteoporosis is a major contributor to morbidity and mortality in today's society. Women with POI have significantly lower bone density compared with controls,<sup>26,27</sup> with the period of accelerated bone loss occurring during the initial 4–5 years after the menopause. Depending on the age of diagnosis, many patients may not yet have reached their peak bone density (thought to occur in mid–late 20s) and will therefore be at further risk of developing osteoporosis. HRT in the doses discussed above will maintain age appropriate bone density and significantly reduce fracture incidence.<sup>28</sup>

To complement the role of HRT for the long-term prevention of osteoporosis, patients should be given general health advice. A supplementary intake of calcium (1000–1500mg/day) and vitamin D should be encouraged, as should general and weight-bearing exercise. Smoking should be strongly discouraged.

Response to therapy should be followed on a two-yearly basis by using DEXA bone mineral density measurements.

## Cardiovascular disease

An association between early menopause and increased mortality from cardiovascular disease has been

established for many years, with an estimated 80% increase in risk of mortality from ischaemic heart disease in those with menopause under the age of 40 compared with those with menopause at 49–55 years.<sup>29,30</sup>

## Cognitive function

It has been suggested that patients with early menopause may be at increased risk of dementia or reduced cognitive function, based on studies involving women who underwent oophorectomy prior to menopause. However, definitive conclusions cannot be drawn in the case of women under the age of 40 years with non-surgical aetiologies.

## Oestrogen replacement

Young women with POI have pathologically low levels of oestradiol compared to their age-matched peers. The risk/benefit ratio for women with POI is different from that of women using HRT after reaching their menopause at the average age of 54 years. The findings of the Women's Health Initiative studies of absolute increased risk of breast cancer, cerebrovascular and cardiovascular disease with HRT use in older postmenopausal women do not apply to younger women with POI.<sup>28,33,34</sup>

Oestrogen administration replaces the oestrogen which should have been produced by the ovaries in a manner similar to treatment with thyroxine replacement in hypothyroid individuals. Their baseline risk of breast cancer and cardiovascular disease is much lower, and the risk of osteoporosis during their lifetime is much higher than for the older women.

Expert opinion concurs that HRT for women with POI up to the normal age of natural menopause will not only alleviate symptoms but also reduce the risk of chronic disease. At the average age of the natural menopause the use of HRT can be reviewed and if the patient so wishes this can be continued with appropriate counselling and medical review until 60 years of age minimum.

### TABLE 2. SUMMARY OF MANAGEMENT OF PREMATURE OVARIAN FAILURE

- Provide counselling, information and emotional support
- Provide hormone replacement therapy/combined oral contraceptive pill up to average age of natural menopause (approx. 54 years of age) with yearly review
- Provide calcium and vitamin supplements and encourage weight-bearing exercises
- Provide contraception if required and advice on fertility issues
- Monitor response to therapy and bone density according to individual requirements

## Conclusion

Premature ovarian failure has a significant impact on the physical and psychological health of young women affected by this disorder. Effective intervention should involve early diagnosis, sensitive and sympathetic management and counselling of the individual and the use of hormone therapy to alleviate symptoms of oestrogen deficiency and to reduce the burden of long-term disease. Regular long-term follow-up and review on an annual basis are essential.

## KEY POINTS

1. Counselling should include explanation that remission and spontaneous pregnancy can still occur, and the difference between POI and the normal menopause should be highlighted
2. Further investigations to identify the small minority of women with an underlying aetiology must be targeted in order to avoid wasting resources
3. Specific areas of management include the provision of counselling and emotional support, and advice on diet and nutritional supplement, HRT and reproductive health care, including contraception and fertility issues
4. Appropriate information should be given in a sensitive manner, including information about national self-support groups for POI, such as the Daisy Network in the UK ([www.daisynetwork.org.uk](http://www.daisynetwork.org.uk))
5. If the aim is to replace hormones as close to physiological levels as possible, therapy should generally continue at least until the estimated age of natural menopause (on average, 54 years)
6. In the absence of good long-term randomized prospective data, treatment should be individualized according to choice and risk factors
7. Cyclical progesterone/progestogen, e.g. 200 mg Utrogestan, should initially be given for at least 12 days each month to induce a withdrawal bleed, and women should be given the option of moving on to a continuous combined regimen after a year or so
8. Women with POI should be informed that HRT does not provide effective contraception
9. Women for whom fertility is a priority should be counselled to seek assisted conception by in-vitro fertilisation using donor gametes or embryos

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