PREMATURE OVARIAN INSUFFICIENCY IN PRIMARY CARE

Premature ovarian insufficiency is frequently underdiagnosed and poorly managed, with many health professionals unaware of the condition. Menopausal expert Dr Louise Newson looks at how patients living with condition can be cared for in general practice

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CASE STUDY

Lisa is a 34-year-old lady who has been seeing one of your partners over the past few months with increasing fatigue. She works as a teacher in a secondary school and has recently married. She has been trying to conceive for the past year without any success. She has never been pregnant before. Your partner has done various blood tests on her which have all come back as normal so she comes to see you to ask for your advice.

On further questioning, you find that she has only had three periods in the past year whereas her periods used to be regular. She has not experienced any hot flushes or night sweats. She tells you that her mother had an early menopause aged 38 years. You arrange for her to have her FSH levels done as these were not done in her previous blood tests. She has two levels done six weeks apart and they are both raised. You discuss with her the likely diagnosis of premature ovarian insufficiency in view of the raised FSH levels and you refer her to one of the local menopause experts to discuss appropriate future management for her.

Premature ovarian insufficiency (POI) is the menopause occurring in women under 40 years of age.[1] Idiopathic POI is a syndrome consisting of menstrual disturbance (amenorrhea or oligomenorrhoea), elevated gonadotrophins and oestrogen deficiency. Idiopathic POI is not the same as an early menopause. The menopause is an irreversible permanent condition, whereas the cessation of ovarian function in POI may not always be permanent.

Epidemiology

POI is more common than most healthcare professionals realise; at least 1% of women under the age of 40 are affected. Around 0.1% of women aged under 30 and 0.01% of women aged under 20 have this condition.[2] However, this condition is still underdiagnosed and often not optimally managed. Many healthcare professionals are still unaware of this condition.

The term premature ovarian insufficiency encompasses both spontaneous POI and POI which occurs as a result of iatrogenic interventions, such as oophorectomy or some types of chemotherapy.

Aetiology

POI does not usually develop by the same mechanism as the normal menopause, which is follicle depletion. It arises from a genetically pre-determined reduced number of ovarian follicles at birth, accelerated follicular atresia or follicular dysfunction.

The underlying aetiology is still poorly understood. In the vast majority of cases of spontaneous POI no underlying cause will be identified.

The commonest cause for POI is iatrogenic, namely:

- Surgical removal of ovaries and hysterectomy
- Radiotherapy
- Chemotherapy – this can be temporary, as recovery of ovarian function can occur, especially in younger women.

Some women develop POI due to mutations in the follicle-stimulating hormone (FSH) receptor.[3] Numerous studies have demonstrated the presence of mutations and polymorphisms in genes associated with development, recruitment and oocyte atresia in women with POI.[4]

There is a family history of POI in around 20-30% of cases.[5] X linked chromosomal abnormalities (e.g., Turner syndrome) occur in around 13% of women with POI. They are more frequent in those who present with primary amenorrhoea (in around 50% of women).

Another cause of POI is steroidogenic cell autoimmunity lymphocytic oophoritis, which is a specific autoimmune attack against growing ovarian follicles.[6] This is usually diagnosed by 21Oh-Ab or

adrenocortical antibodies (ACA) as it is associated with evidence of adrenal autoimmunity (see later). There is often a family history of autoimmune conditions in these women.

POI may be associated with various infections. However, only mumps oophoritis has been considered a cause of POI.

Cigarette smoking and lower socio-economic class are associated with increased risk of POI.[7]

Presentation

The most common presentations are primary or secondary amenorrhoea. However, abnormal bleeding patterns also include oligomenorrhea. As these irregular menstrual cycles occur during adolescence, diagnosis can be very difficult in young women. This condition should be suspected in any woman who presents with secondary amenorrhoea of more than three months' duration. Amenorrhoea may develop after a pregnancy or after cessation of hormonal contraceptives which is often not recognised as being POI.

All clinicians should ask about any symptoms of oestrogen deficiency in women who present with oligomenorrhoea or amenorrhoea. However, it is important to note that hot flushes and vasomotor symptoms are present in around 75% of women with POI.[2]

Other symptoms may include mood changes, sleep disturbance, poor concentration, joint stiffness, dry eyes, low libido and lack of energy. Symptoms may be transient or intermittent and they can vary in their severity. This variability is due to the fluctuations in ovarian activity that may occur. Symptoms are less likely in young women with primary amenorrhoea.

Genito-urinary symptoms such as vaginal dryness, irritation, urinary frequency and urinary incontinence can often occur as a consequence of low oestrogen levels.

Health risks of POI

POI is associated with reduced bone mineral density (BMD) and osteoporosis. This has been associated with the presence, degree and duration of oestrogen deficiency.

Numerous studies have shown that women with POI have an early onset of cardiovascular disease, especially coronary heart disease due to their low oestrogen levels.[8] They have an increased cardiovascular morbidity and mortality regardless of the underlying cause of their ovarian insufficiency.

Women with POI are more likely to develop early signs of endothelial dysfunction and premature atherosclerosis. Women with POI have significantly higher triglyceride and marginally lower HDL levels compared to women without this condition. Again, this is due to the low oestrogen levels they have.

In addition, the diagnosis of POI can have a significantly negative impact on psychological well-being and a woman's quality of life.

Cigarette smoking and lower socio-economic class are associated with increased risk of POI

Sexual problems can be very common in these women and can be a primary effect of the physiological changes that occur, or secondary to the emotional burden of the diagnosis, including any associated reduced fertility.

There is some evidence that an earlier menopause (either naturally or due to an oophorectomy) is associated with an increased risk of dementia, although some studies have not demonstrated this association.

Investigations

Although proper diagnostic accuracy in POI is lacking, the following are usually used as diagnostic criteria:

- Oligo/amenorrhea for at least 4 months; and
- An elevated FSH level > 25 IU/l on two occasions at least 4 weeks apart[1]

POI should not be diagnosed (or excluded) on a single blood test.[11]

Other investigations may include:

- Chromosomal analysis is recommended for all women with non-iatrogenic POI
- Fragile-X permutation testing. This requires careful counselling before the test is performed, including permission from the patient to perform the test. This is because a positive test can have implications on their family members
- 21Oh-Ab or adrenocortical antibodies (ACA) should be considered in women with POI of unknown cause or if an immune disorder is suspected
- Thyroid (TPO-Ab) antibodies should be performed in women with POI of unknown cause or if an immune disorder is suspected. If this is positive then a TSH level should be undertaken
- TSH should then be measured every year in those women with a positive TPO-Ab test.

Those women who have negative autoantibody tests only need repeat tests if they develop symptoms. Routine screening for diabetes is not recommended in women with POI. There is no need to screen for infection as a possible underlying cause in women with POI.

Anti-Mullerian hormone may be a measure of reduced ovarian reserve.[9,10] It is usually only undertaken

if there is diagnostic uncertainty. Ultrasound is not usually helpful in making a diagnosis of POI but may sometimes be undertaken to exclude other pathology.

A dual-energy X-ray absorptiometry (DEXA) bone scan should be undertaken at diagnosis and then usually every several years to assess bone mineral density. The amount of ionising radiation used in a DEXA scans is very small. If a woman has normal bone density and is taking HRT then they do not always need to have DEXA scans in the future.

POI does not usually develop by the same mechanism as the normal menopause, which is follicle depletion

Management

Lifestyle

It is recommended to consider referral to healthcare professionals with the relevant experience to help women manage all aspects of physical and psychological health related to their condition.

General lifestyle and dietary measures to reduce the risk of cardiovascular disease and osteoporosis should be undertaken. These women should be given advice on how to reduce cardiovascular risk factors by not smoking, taking regular exercise (especially weight-bearing) and also maintaining a healthy weight.

It is important that women with POI are routinely asked about their sexual well-being and sexual function. Many women do not often talk about problems they may have regarding symptoms related to these.

Bone Health

Adequate dietary intake or supplementation of calcium (1,000mg/day) and vitamin D (800IU/day) is recommended.

HRT (see later) is the most effective treatment to maintain bone health and prevent osteoporosis.

Bisphosphonates can be considered under specialist guidance; however, they are not recommended in pregnancy. Bisphosphonate actually remain incorporated in bone for a long time. It is recommended that oral bisphosphonates should not be taken for at least one year before pregnancy. There are actually no trials of the use of bisphosphonates in women with POI.

Cardiovascular health

Any modifiable risk factors for cardiovascular disease need to be addressed and managed appropriately. Women should have their blood pressure and weight recorded annually.

Fertility

Women with POI should be informed that there is a small chance of spontaneous pregnancy. These women should be therefore advised to use contraception if they wish to avoid pregnancy. Spontaneous conception occurs in around 5% of women with POI. Ovarian activity is more likely in those early in the natural history of this condition.

There are no interventions that have reliably shown to increase natural conception rates. Oestrogen treatment may increase the ovulation rate in some women. Oocyte donation is the most common option for fertility treatment in these patients.

It is important that women with idiopathic POI or following most forms of chemotherapy are reassured that if a spontaneous pregnancy does occur then it is not associated with a higher obstetric or neonatal risk compared to the general population.

Wellbeing and quality of life

Women with POI may have complex physical and psychological needs; therefore, a multidisciplinary approach is very important. Some women may need referral to a psychologist or psychiatrist.

Women with POI have an increased risk of depression and also often have lower levels of self-esteem. Any associated depression or anxiety needs to be addressed and managed appropriately.

Sexual and genitourinary function

Local oestrogen treatments are safe to be given in the long-term and should be put on a repeat prescription. Women who are receiving systemic HRT may still need topical oestrogen. Vaginal lubricants and moisturisers can also be very beneficial and should be discussed with patients.

Systemic oestrogen may positively influence sexuality in women with POI. Psychosexual treatments may be of benefit for some women either in combination with HRT or as an alternative.

Testosterone replacement is often also given to these women, although it is not currently licensed in women in the UK. They should be counselled about this and be made aware that the long-term efficacy and safety of testosterone is still unknown. The recommendations states that if androgen therapy is started, then the effects of treatment should be evaluated after 3-6 months and should possibly be limited to 24 months.

Hormone replacement therapy

Women with POI should be given hormone replacement therapy (HRT) until at least the average age of the menopause (51 years). After this age then women will need to be counselled regarding the risks of HRT. This is not just for symptom control but also to maintain their long-term health and reduce the risk of osteoporosis and cardiovascular disease. HRT also reduces the risk of cognitive impairment.

The main goal of HRT for women with POI is to

mimic normal physiological endocrinology with regard to oestrogen replacement. Oral contraceptives contain the potent synthetic estrogen ethinylestradiol, which in effect provides more steroid hormone than is needed for physiological replacement, with unfavourable effects on lipid profile, on haemostatic factors and with an increased risk of thromboembolic events related to the progestogen and first pass effect of the liver. 17ß oestradiol is the active component of the main ovarian oestrogen and is associated with less risks. [Table 1]

Micronised progesterone is body identical to progesterone. It is micronised (finely ground) to improve absorption. It is made from the yam. It has a better cardiovascular safety profile compared to synthetic progestogens.[9] Transdermal oestrogen should be considered in those women with an increased risk of VTE or stroke such as those with a history of migraine, hypertension or those women who are obese, as these preparations are not associated with an increased thrombotic risk.[1]

Treatment with HRT can be given sequentially to induce a regular withdrawal bleed or as a continuous combined preparation to achieve amenorrhea.

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Women with POI will generally require higher doses of oestrogen to achieve symptom relief compared to postmenopausal women.[3]

NB: Any risks of HRT (for example, breast cancer risk) do not apply to younger women with POI taking HRT. The risk/benefit of HRT for women with POI is completely different from that of women using HRT for their menopause who are older than 51 years. It is essential that these women are made aware of this.

Women should be informed that there is still a lack of good evidence to support the efficacy and safety of

TABLE 1: HRT THERAPIES

Systemic	Brand	Oestogen	Progestogen	Formulation
Sequential combined therapy	Climagest	Estradiol (1mg, 2mg)	Norethisterone	Tabs
	Clinorette	Estradiol (2mg, 2mg)	Norethisterone (1mg)	Tabs
	Cyclo-progynova	Estradiol (2mg)	Norgestrel (1mg)	Tabs
	Elleste Duet	Estradiol (1mg, 2mg)	Norethisterone (500mcg)	Tabs
	Evorel Sequei	Estradiol (50mcg)	Norethisterone (1mg)	Patches
	Femoston	Estradiol (1mg, 2mg)	Dydrogesterone (10mg)	Tabs
	Fem Seven Sequi	Estradiol (50mcg)	Levonorgestrel (10mcg)	Patches
	Novofem	Estradiol (1mg)	Norethisterone (1mg)	Tabs
	Prempak-C	Estradiol (625mcg, 125mcg)	Norgestrel (150mcg)	Tabs
	Tridestra	Estradiol (2mg)	Medroxyprogesterone (20mg)	Tabs
	Trisequens	Estradiol (2mg, 2mg, 1mg)	Norethisterone (1mg)	Tabs
Continuous combined therapy	Angeliq	Estradiol (1mg)	Drospirenone (2mg)	Tabs
	Climesse	Estradiol (2mg)	Norethisterone (700mcg)	Tabs
	Elleste Duet Conti	Estradiol (2mg)	Norethisterone (1mg)	Tabs
	Evorel Conti	Estradiol (50mcg)	Norethisterone (170mcg)	Patches
	Femoston Conti	Estradiol (50mcg, 1mg)	Dydrogesterone (2.5mg, 5mg)	Tabs
	FemSeven Conti	Estradiol (50mcg)	Levonorgestrel (7mcg)	Patches
	Indivinia	Estradiol (1mg, 2mg)	Medroxyprogesterone (2.5mg, 5mg)	Tabs
	Kliofem	Estradiol (2mg)	Norethisterone (1mg)	Tabs
	Kliovance	Estradiol (1mg)	Norethisterone (500mcg)	Tabs
	Nuvelle Continuous	Estradiol (2mg)	Norethisterone (1mg)	Tabs
	Premique Low Dose	Conj. Oestr (300mcg)	Medroxyprogesterone (1.5mg)	Tabs
	Premique	Conj. Oestr (625mcg)	Medroxyprogesterone (5mg)	Tabs

TABLE 1: HRT THERAPIES (CONTINUED)

Systemic	Brand	Oestogen	Progestogen	Formulation
Gonadomimetic	Livial	Tibolone (2.5mg)		Tabs
Unopposed oestrogen	Bedol	Estradiol (2mg)		Tabs
	Climavel	Estradiol (1mg, 2mg)		Tabs
	Elleste Solo	Estradiol (1mg, 2mg)		Tabs
	Elleste Solo MX	Estradiol (40, 80mcg)		Patches
	Estraderm MX	Estradiol (25, 50, 75 100mcg)		Patches
	Estradot	Estradiol (25, 37.5, 50, 75 100mcg)		Patches
	Evorel	Estradiol (25, 50, 75 100mcg)		Patches
	FemSeven	Estradiol (50, 75 100mcg)		Patches
	Hormonin	Estriol/ Estradiol/Oestrone 1 strength		Tabs
	Oestrogel	Estradiol (0.06%)		Gel
	Premarin	Conj. Oestr (300mcg, 625mcg, 1.25mg)		Tabs
	Progynova	Estradiol (1mg, 2mg)		Tabs
	Progynova TS	Estradiol (50, 100mcg)		Patches
	Sandrena	Estradiol (500mcg, 1mg)		Gel
	Zumenon	Estradiol (1mg, 2mg)		Tabs
Adjunctive progestogen	Climanor		Medroxyprogesterone (5mg)	Tabs
	Mirena		Levonorgestrel (20mcg/24 hours)	IUS
	Utrogestan		Progesterone (100mg, 200mg)	Caps

(Adapted from *MIMS*)

most alternative and complimentary treatments. They also need to be informed that alternative therapies are marketed as food supplements rather than medical treatments. This means that they are not subject to rules of standardisation (of, for instance, the formula and constitution of the herbal preparation), or the need for studies supporting their efficacy and safety.

CASE STUDY

Lisa was diagnosed with POI and assessed by a local gynaecologist. She was started on a 17ß oestradiol patch as she had a DVT three years previously after a long flight and this will not increase her VTE risk. She was also given micronised progesterone, 200mg to take each day for two out of four weeks, as she is still having periods she needs to have cyclical HRT. She has already noticed that her energy levels have greatly improved. Six months after HRT she stops having periods and is delighted to find out she is pregnant.

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