PRIMARY CARE
WOMEN'S HEALTH FORUM

**THIS RESOURCE IS INTENDED FOR UK HEALTHCARE PROFESSIONALS ONLY**

# A Guide to Managing Premature Ovarian Insufficiency in Primary Care

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*This resource has been produced on behalf of the PCWHF. Remember that this is guidance and to please use your clinical judgement on a case-by-case basis.*

## Premature Ovarian Insufficiency (POI) is the decline of ovarian function under the age of 40 years leading to elevated gonadotropins, hypo-oestrogenic status and menstrual disturbance (amenorrhoea/oligomenorrhoea).

It is important to remember that POI is not a rare disease - recent global prevalence estimates are 3.5-3.6%. It is also best practice to avoid use of the term premature ovarian failure (POF) as it can be emotive and inaccurate.

## Causes of POI

- **Genetic**

Previously, most cases were labelled as idiopathic, but research increasingly suggests many genetic causes (mainly X-linked e.g. Turner Syndrome and Autosomal dominant).

- **Autoimmune ovarian damage**

Often linked to other autoimmune conditions especially adrenal and thyroid autoimmunity.

- **Infections**

Mumps, Tuberculosis, malaria, CMV, HIV.

- **Iatrogenic**

Bilateral oophorectomy, ovarian cystectomies, chemotherapy, GnRH analogues, radiation, pelvic vessel embolisation, and smoking.

The possibility of POI being a consequence of medical interventions should be discussed with women as part of the consenting process.

## When to suspect

**When it comes to diagnosis, consider:**

- If there has been a case of oligo/amenorrhoea for at least four months in women not using hormones.
- Peri-menopausal symptoms e.g. vasomotor symptoms (affecting 80% of women with POI), insomnia, joint pain, labile mood, low energy, low libido, impaired memory and concentration.
- Family history of POI/early menopause or other risk factors (see causes of POI).

## Criteria

- Absent/infrequent periods of more than four months.
- Patient is under 40 years old.
- Elevated FSH on at least two occasions (4-6 weeks apart) – (variable cut-off ranges, see table on next page).

## What are the challenges?

- Delayed diagnosis is common.
- More than 50% of women see over three clinicians before diagnosis.
- A diagnosis takes five years in 25% of women.
- 5%-10% of women are asymptomatic.
- Ovarian function may fluctuate initially, so bloods and symptoms can fluctuate too.
- The condition may be mistaken for other conditions or not considered at all.
- The delay of diagnosis can have a significant impact on a woman's health and wellbeing.

## Diagnostic workup

**Primary care:**

| Test | Rationale |
|---|---|
| bHCG | Exclude pregnancy |
| FSH and oestradiol levels | 2 FSH levels 4-6 weeks apart, variable cut off values depending on guidelines (BMS >40IU/L, ESHRE >25IU/L). If still menstruating should be tested day 2-3.<br><br>Low FSH and low oestradiol suggests hypothalamic amenorrhoea. |

**Likely secondary care (depending on local access/pathways):**

| | |
|---|---|
| Anti-Mullerian Hormone (AMH) | Assess ovarian reserve. Only if diagnostic uncertainty. No diagnostic cut-off established and future prediction of POI using AMH is unreliable. |
| Karotype, FMR1 premutation | Screening for genetic causes. Other genetic tests may be performed, depending on history at specialised centres. |
| TSH, TPO anybody, Adrenal cortex/21-hydroxylase antibody | Screen for linked autoimmune conditions and quantify risk of future problems. |
| Transvaginal ultrasound scan | Assess ovarian reserve (antral follicle count). |
| DEXA | Baseline bone mineral density (BMD). |

## Management

- If initial investigations confirm or you strongly suspect POI, refer to gynaecology/menopause/fertility services. The gold standard here is for a multidisciplinary approach.
- Signpost to the POI peer support group, the Daisy Network.

## HRT

- HRT is recommended until at least the average age of menopause to treat symptoms and as primary prevention of cardiovascular disease (CVD) and osteoporosis.
- Limited evidence for optimum regime/dose/route.

## Type:

- Combined (oestrogen + progesterone) required if uterus is intact.
- Route of HRT should be individualised, and patient preference considered to improve compliance.
- Transdermal oestrogen avoids first-pass hepatic metabolism so there is no increased VTE/stroke risk.
- Micronised progesterone is recommended as body-identical, not pro-thrombotic and more breast friendly.
- 52mg-LNG-IUDs are an alternative, providing contraception and endometrial protection even at higher doses of oestrogen.
- Typically need high oestrogen doses: 75-100mcg/3 or 4 pumps/2mg oral oestradiol.
- Titrate to symptoms but may benefit from oestradiol levels (aiming for 250-500mmol/L) to achieve levels for primary prevention of osteoporosis & CVD.

## Regime:

- Sequential if pregnancy is desired or planning oocyte donation fertility treatment (stimulates regular endometrial proliferation).

## Combined oral contraceptive pill (COCP)

- May be more acceptable and familiar to younger women.
- Provides contraception.
- Requires risk assessment for use as per FSRH UKMEC.
- Dose of oestrogen may not be high enough to manage symptoms.
- Ethinyloestradiol in COCP is pro-thrombotic and may not have the CV benefits of HRT.

## Monitoring

- Once on established hormone therapy, women should have an annual review.
- Setting up reminders to proactively follow women up is recommended to improve compliance.

## Impact of POI

From a patient concerns POI survey in 2011, it was revealed that the top five concerns were fertility, responsiveness to sex, long-term use of HRT, fatigue and outlook on life.

## Cardiovascular health

- If untreated, POI increases risk of cardiac conditions including ischaemic heart disease and overall cardiovascular mortality.
- HRT reduces blood pressure, improves lipid profile, arterial compliance and overall cardiovascular mortality.

## Primary care role

- Offer lifestyle advice.
- Prescribe hormonal treatment at least until average age of menopause (COCP does not have the same proven CV benefits).
- Annual reviews to include BP/BMI/HbA1c/lipids.

## Bone health

- At increased risk of osteoporosis (incidence 8-14%).
- HRT or COCP are the most effective treatments.

## Primary care role

- Offer lifestyle advice: weight bearing exercise, 800-1000IU Vit D daily and a calcium rich diet.
- Prescribe hormonal treatment until at least the average age of menopause.
- Seek specialist review if HRT is contraindicated or fragility fracture has occurred on HRT.
- No evidence for non-hormonal bone sparing agents.
- Baseline DEXA at diagnosis.
- Future DEXA monitoring depends on baseline DEXA, HRT compliance and other risk factors.

**Note:** FRAX tool is not validated in women younger than 40 years old.

## Cognitive health/dementia

- There is likely to be a window of opportunity for cognitive benefit if HRT is started in the perimenopause.

## Psychosexual and psychosocial health

- A diagnosis of POI can have a significant impact on psychological wellbeing and quality of life.
- High levels of depression, stress, low self-esteem and low life satisfaction can be seen following a diagnosis of POI.
- Hypoactive Sexual Desire Disorder (HSDD) is more common, and it is important to routinely enquire about sexual wellbeing and function.
- Adequate oestrogen replacement is first line for improving sexual function. Testosterone can be considered.
- Proactively ask about genitourinary symptoms of the menopause (GSM) and treat with topical treatments including vaginal lubricants, moisturisers and oestrogens.
- Consider referral for specialised psychological support.

## Fertility

- No proven treatments to increase rates of autologous oocyte pregnancies.
- Egg donation offers best chance of pregnancy.
- HRT can sometimes stimulate ovulation of remaining oocytes: HRT is not a contraceptive.
- Naturally conceived pregnancies can occur in up to 5% of women (most in the first year).
- Contraception is recommended if women wish to avoid pregnancy.
- Further research is needed for safety/efficacy of stem cell therapies, platelet rich plasma and primordial follicle activation.

## Breast cancer

- Most women can be reassured.
- Women with POI generally have a lower risk of breast cancer than general age matched population.
- Breast cancer risk is not increased by HRT in POI vs age matched healthy women.

**References and Further Reading:**


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