

Premature ovarian insufficiency: When ovaries retire early

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ABSTRACT

Introduction: Premature ovarian insufficiency (POI) refers to loss of ovarian activity before the age 40 years. POI has significant detrimental effects on health (infertility, cardiovascular diseases, type 2 diabetes, reduced bone density, dementia), well-being and longevity. This summary is a practical toolkit for health-care professionals (HCPs) looking after women with POI.

Method: A workgroup comprising specialists in gynaecology, reproductive medicine, endocrinology, genetics and family medicine reviewed relevant guidelines and literature on POI to establish recommendations for the diagnosis and management of POI in Singapore.

Result: A summary to assist HCPs manage POI was produced, outlining: (1) the aetiology and consequences of POI; (2) making the diagnosis; (3) hormone therapy (HT) prescribing options including for those with additional medical conditions; (4) counselling women with POI about HT; and (5) long-term management of POI.

Conclusion: Timely diagnosis and management of POI is vital to prevent long-term adverse consequences, except infertility. HT is the mainstay of treatment and there are no alternatives as effective. Contraindications are very few; estrogen-sensitive cancer is the main contraindication, and caution in prescribing may be needed with established coexisting cardiovascular disease. Estrogen dosage is higher than when treating normal menopause, and as a result, the patient might require more progesterone for endometrial protection. Minimising cardiovascular risk factors by following a healthy lifestyle is important. POI is a significant public health issue and it is imperative that women have affordable access to appropriate HT. Large-scale research on POI in Asian women is needed.

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CLINICAL IMPACT

What is New

- Untreated POI has health consequences, affects quality of life and reduces longevity.

Clinical Implications

- Women at risk should be counselled regarding measures to reduce risk of POI and about fertility preservation options, when appropriate.
- Women with POI should be treated with hormone therapy until usual age of menopause as primary prevention for cardio-metabolic diseases and osteoporosis; contraindications are few.
- All stakeholders need to improve access to medical treatment for women with POI.

INTRODUCTION

Premature ovarian insufficiency (POI, also known as primary ovarian insufficiency) refers to loss of ovarian activity before the age of 40 years, leading to hypergonadotropic hypogonadism and 4 months or more of menstrual disturbance.¹ In ovarian insufficiency, the ovarian dysfunction is not necessarily definitive, which is why the terms premature menopause and premature (or primary) ovarian failure are not accurate. Twenty-five percent of women with POI may experience fluctuating ovarian function and intermittent menstrual disturbance or symptoms of hypogonadism.² Women with POI are at risk of long-term consequences including infertility, cardiovascular disease (CVD), type 2 diabetes, low bone mineral density (BMD), sexual dysfunction, reduced quality of life and premature mortality. Hormone therapy

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(HT) is therefore recommended (in most women) to mitigate these long-term complications. Early menopause occurs between the ages of 40 and up to 45 years. It is recognised to have similar long-term consequences as POI; as such HT is also indicated in this group of women.

METHOD

A workgroup consisting of specialists in gynaecology, reproductive medicine, endocrinology, genetics and family medicine reviewed relevant guidelines and literature on POI to establish recommendations for the diagnosis and management of POI in Singapore. A consensus document on the management of POI was published in 2024 after collaboration between European, North American and Australian specialist societies, plus the International Menopause Society.¹ Our review supports the recommendations but with an emphasis on Asian women, especially where their needs may differ from other populations. We conducted a search on PubMed using keywords, which include: "premature ovarian insufficiency", "hormone therapy" and "Asian". Relevant studies published in English were included.

RESULTS

Prevalence

Recent global studies have estimated the prevalence of POI and early menopause to be 3.5–3.7% and 12.2%, respectively.^{3,4} The prevalence of POI was higher in medium and low Human Development Index countries.³ In a large cross-sectional study in the US, the prevalence of POI appears to be lower in Asian women: Chinese at 0.5% (95% confidence interval [CI] 0.1–1.9) and Japanese at 0.1% (95% CI 0.02–1.1), compared to Caucasian at 1.0% (95% CI 0.7–1.4), African-American at 1.4% (95% CI 1.0–2.1) and Hispanic at 1.4% (95% CI 0.8–2.5).⁵ However, studies from China, Korea and India report the prevalence of POI at 2.2–3.2% and early menopause at 7.2–16.2%.^{6–8} This might reflect the roles of genetics and environment influencing the prevalence of POI. To our knowledge, there is no study on rates of POI in Singapore to date.

Aetiology

The aetiology of POI is diverse; it can be divided into non-iatrogenic or iatrogenic causes (Table 1). Non-iatrogenic POI can be associated with chromosomal or genetic defects, autoimmune diseases and environmental factors. In approximately 60% of cases, no cause is found and it is currently described as idiopathic.⁹ There is increasing evidence, however, that idiopathic POI may be genetic in origin¹⁰ and

may represent a syndrome of premature ageing. Iatrogenic causes of POI include chemotherapy, abdomino-pelvic radiation and pelvic surgeries, especially repeated ovarian surgeries.

In view of the long-term health consequences of POI, efforts should be made to reduce its incidence. Modifiable factors may include advising women to stop smoking, reducing ovarian surgeries for benign ovarian conditions and modifying treatment regimens for malignant and chronic disease to protect ovarian function. Women facing any gonadotoxic treatment should be counselled about the risks; when there is sufficient time and the individual is well enough, she should be offered a referral to a reproductive medicine specialist to discuss fertility preservation options.

Long-term consequences

The key long-term consequences are shown in Table 1 and summarised below. Women with POI are at risk of premature mortality, largely due to CVD, which may be worsened by the presence of other modifiable CVD risk factors.¹¹ Although the exact mechanism is unclear, adverse changes in lipid profile and impaired endothelial function related to estrogen deficiency may lead to premature atherosclerosis.¹³ Women with POI have a 50% increased risk of type 2 diabetes compared to those aged between 45 and 55 years at menopause.^{14,15} The impact of POI on CVD may be disproportionately higher in Asians compared to Caucasians as Asians are at risk of higher visceral fat, insulin resistance and dyslipidaemia at a lower level of body mass index (BMI).¹⁶

Low BMD (z score less than 2 standard deviations below age-matched pre-menopausal populations) is another consequence of POI, associated with earlier age at onset, later induction of puberty and reduced use of estrogen replacement.¹ Certain causative factors for POI may themselves be associated with lower BMD, such as Turner's syndrome, some chemotherapies (e.g. for breast cancer) and possibly autoimmunity.¹ The prevalence of low BMD in POI was estimated to be 8–14% in an American study, with African-American or Asian women more commonly affected than Caucasians.¹⁷ However, ethnicity was not an independent predictor, and instead may have been a marker for a combination of modifiable risk factors, especially reduced use of HT. Evidence from an Australian cohort supports the biologically plausible expectation that POI is associated with an increased risk of fracture.¹⁸

Evidence for the association between age at natural menopause and all-cause dementia has been inconsistent.^{19,20} However, more recent studies show that shorter lifetime endogenous estrogen

exposure may be associated with higher risk of all-cause dementia.^{21–23} For example, a recent UK Biobank study with a large cohort of 160,080 women reported that compared to women with age at menopause of 46–50 years, women with non-iatrogenic POI or early menopause (age 41–45 years) had a higher risk of all-cause dementia, with hazard ratio (HR) of 1.36 (95% CI 1.01–1.83) and 1.19 (95% CI 1.03–1.37); respectively. However, late natural menopause (over 55 years) was linked to lower risk of dementia (HR 0.83, 95% CI 0.71–0.98).²³ Women with surgical menopause before the age of 40 years (HR 1.94; 95% CI 1.38–2.73) and after the age of 55 years (HR 1.65; 95% CI 1.21–2.24) were both linked to an increased risk of all-cause dementia.²³

POI is an irreversible cause of infertility, although natural pregnancies may occur in an estimated 5% of women, with most occurring within the first year of POI onset.² Infertility may contribute to reduced quality of life in several domains, including psychological and psychosexual well-being. Inadequate estrogen replacement may contribute to dyspareunia and poor sexual health.

Clinical presentation

The clinical presentations of POI can be variable. The most common presenting symptom is menstrual disturbance, particularly amenorrhoea. Amenorrhoea may be followed by temporary resumption of cycles, which may be regular or irregular. There may be symptoms of low estrogen, including vasomotor symptoms (VMS) such as hot flushes and night sweats, vaginal dryness and/or dyspareunia. Other symptoms such as joint pain, labile mood, low energy, low libido as well as impaired memory and concentration may be present.

Symptoms experienced by women with POI may vary in intensity and can be intermittent due to fluctuations in ovarian activity. Some experience few or no VMS, especially when the onset of POI occurs at a very young age (before or during early adulthood). This may indicate that VMS are due to estrogen withdrawal rather than estrogen deficiency. Women who undergo surgical POI often have more sudden onset and severe symptoms, and have a greater risk of impaired cognitive function at least in the short-term.

Diagnosis

Fig. 1 is a diagnostic algorithm for POI. POI is diagnosed when there is or has been an episode of menstrual disturbance for at least 4 months and an elevated follicle-stimulating hormone (FSH) level of ≥ 25 IU/L.¹ FSH test only needs to be repeated if there is any doubt about the diagnosis.

The FSH level must be interpreted with caution in women using hormonal contraceptives or hormone replacement therapy (HRT) within the last 6 weeks.

Serum anti-mullerian hormone (AMH) is produced by small ovarian antral follicles. The number of these follicles and therefore serum AMH declines throughout the reproductive years. AMH cannot predict when menopause will occur and is not useful to diagnose POI as it can be undetectable for years before the onset of menstrual disturbance.

Further evaluation

In the absence of clear iatrogenic causes of POI, genetic and autoimmune screening should be offered to evaluate possible underlying causes and associations.

Genetic

The prevalence of chromosomal abnormalities in women with POI is 10–12%, of which the majority are X chromosomal abnormalities, e.g. Turner's syndrome.^{25,26} Women diagnosed with Y chromosome gonadal dysgenesis are at high risk of gonadoblastoma,²⁷ and should be advised to have their gonads removed. Karyotype analysis should be offered in all cases of unexplained POI.¹ If there are financial reasons to limit testing, a pragmatic approach would be to offer it to those with young onset (usually taken to be under the age of 30 years) or those planning for a pregnancy.

Fragile X (*FMR1*) premutation is present in 0.8–7.5% of women with non-iatrogenic POI and up to 13% in women with a positive family history of POI.²⁸ However, in Asian studies, there was a lower incidence (0.5–1.6%) of fragile X premutation among Chinese women with POI,^{29,30} and no association between fragile X premutation and POI in an Indian population.³¹ Since being a carrier of fragile X syndrome has significant implications for the individual and their family, we recommend referring the woman to genetic services for counselling prior to performing *FMR1* premutation testing. For cost considerations, clinicians may offer karyotype first, then *FMR1* premutation testing if the karyotype is normal.

Whole genome analysis is likely to uncover further genetic causes for POI in the foreseeable future.³² In the current literature, there are approximately 100 monogenic causes identified.¹⁰ Other studies have suggested that the majority of cases are likely oligogenic or polygenic in nature, with 2 or several different genes having synergistic effects.¹⁰ Genetic variants have to be classified as pathogenic (class 5) or likely pathogenic (class 4) for POI according to the American College of Medical Genetics and Genomics criteria.³³ Interna-

Table 1. Aetiology and consequences of premature ovarian insufficiency.

Aetiology		Long-term consequences without HT
Non-iatrogenic POI	Iatrogenic POI	
Idiopathic (most common cause of non-iatrogenic POI) Genetic causes (10%) • Turner's syndrome (45XO): most common genetic cause • Fragile X pre-mutation: prevalence may be lower in Asians than other populations • Y chromosome gonadal dysgenesis • Autosomal gene mutations, e.g. BPES^a Autoimmune associations (20%) • Addison's disease • Autoimmune polyendocrine syndromes 1 and 2 • Autoimmune thyroid disorders, especially Hashimoto's thyroiditis • Other autoimmune conditions: coeliac disease, type 1 diabetes mellitus, myasthenia gravis, systemic lupus erythematosus, thrombocytopenic purpura, vitiligo, alopecia, pernicious anaemia, rheumatoid arthritis, Crohn's disease, Sjogren's syndrome, primary biliary cirrhosis Inborn error of metabolism (rare cause) • Galactosaemia^a Environmental associations • Smoking: associated with earlier onset of menopause	Chemotherapy • Particularly cyclophosphamide and other alkylating agents; dependent on cumulative dose and combination of cytotoxic agents Radiotherapy to the pelvis and/or abdomen • Dependent on cumulative dose and field of exposure Bilateral oophorectomy • Other pelvic surgery has been associated with early age of menopause and/or reduced ovarian reserve, including single oophorectomy, hysterectomy, uterine artery embolisation, bilateral or repeated ovarian surgery for cysts or endometriosis	Infertility Increased risk of: • Low bone mineral density, osteoporosis and possibly of fractures • CVD: coronary artery disease, heart failure and stroke • Type 2 diabetes • All-cause dementia and cognitive impairment (probably resulting from CVD) • Premature mortality Reduced quality of life, including: • Psychosexual well-being • Psychological well-being Reduced risk of breast cancer

BPES: blepharophimosis syndrome; CVD: cardiovascular disease; HT: hormone therapy; POI: premature ovarian insufficiency

^a These are usually diagnosed in infancy.

Aetiology segment is modified from Nguyen HH, Milat F, Vincent A. Premature ovarian insufficiency in general practice: Meeting the needs of women. Aust Fam Physician 2017;46(6):360-6, with permission from The Royal Australian College of General Practitioners.²⁴

Superscript number: refer to REFERENCES

tional large cohort studies, including a Chinese study,³⁴ have shown gene positivity in up to 26% and 36.7% of women with sporadic and familial POI, respectively.^{2,35} Higher gene positivity was observed in syndromic POI (58.3%)³⁵ and in women with primary amenorrhoea (28.5%) compared to secondary amenorrhoea (17.8%).³⁴ The recent 2024 European Society of Human Reproduction and Embryology guidelines on POI has made a conditional recommendation that next-generation sequencing can be offered to all women with non-iatrogenic POI after genetic counselling.¹ This is available for women with POI in some countries, such as China, the UK and France. However, in most countries including Singapore, it is still not part of routine screening for POI, unless there are specific clinical indications (e.g. blepharophimosis, ptosis and epicanthus inversus syndrome).

Autoimmune

Autoimmune disorders are more frequent in women with POI than in the general population, and non-iatrogenic POI is more frequent in women with certain autoimmune disorders.¹ The most clinically important autoimmune conditions associated with POI are adrenal insufficiency in the context of autoimmune polyendocrine syndrome, and thyroid hormone disorders.

The prevalence of Addison's disease (autoimmune adrenal insufficiency) is estimated to be 40–60 cases per 1 million population in Western countries, but only 4.17 per 1 million population in Korea.³⁶ Between 10–20% of women with Addison's disease have POI, while approximately 2.5–20% of women with POI develop adrenal autoimmunity.³⁷ Antibodies against 21-hydroxylase antibodies (21OH-Ab) are currently the marker with the highest diagnostic accuracy for autoimmune POI and should be looked for in women with non-iatrogenic POI. Although currently there is no specific treatment option for autoimmune POI, the diagnosis is clinically relevant for identifying subclinical or latent autoimmune adrenal insufficiency.¹ Women with a positive 21OH-Ab should be referred to an endocrinologist for testing of adrenal function and to rule out Addison's disease.

Approximately 20% of adults with idiopathic POI will experience autoimmune thyroid hormone disorders, most commonly Hashimoto thyroiditis.¹ Thyroid function should be assessed by measuring thyroid-stimulating hormone (TSH) at diagnosis and repeated every 5 years or earlier if symptoms of hypothyroidism occur. TSH should also be measured when the woman desires pregnancy due to the detrimental effects of hypothyroidism on fetal neurodevelopment. Testing for thyroid

peroxidase (TPO) antibodies should not be performed for screening purposes in women with POI due to the high prevalence of positive TPO antibodies in the general community.³⁸

Hormone therapy

Hormone therapy (HT) is indicated for POI, primarily to reduce the risks of CVD, type 2 diabetes, low BMD (with potential future fracture risk) and possibly dementia and cognitive impairment, irrespective of the presence or severity of symptoms of low estrogen. HT can be provided as physiological hormone replacement therapy (HRT) or combined hormonal contraception (CHC). There are few contraindications to HRT, the main one being personal history of estrogen-sensitive cancer. Healthcare professionals (HCPs) prescribing HT for women with POI after cancer treatment should ensure the cancer was not estrogen-sensitive and check with the patient's oncologist if in doubt. The contraindications to CHC are the same with functioning ovaries (refer to the UK Medical Eligibility Criteria for Contraceptive Use guideline³⁹).

HT should be initiated early unless contraindicated and this includes for girls requiring pubertal induction, who should be referred to a paediatric endocrinologist for management (which is outside the scope of this review). HT should be continued until the usual age of menopause (approximately 50 years). Thereafter, ongoing HRT could be considered on the basis of personalised risk-benefit assessment, including need to improve bone health. Table 2 provides a summary for counselling women with POI about HT.

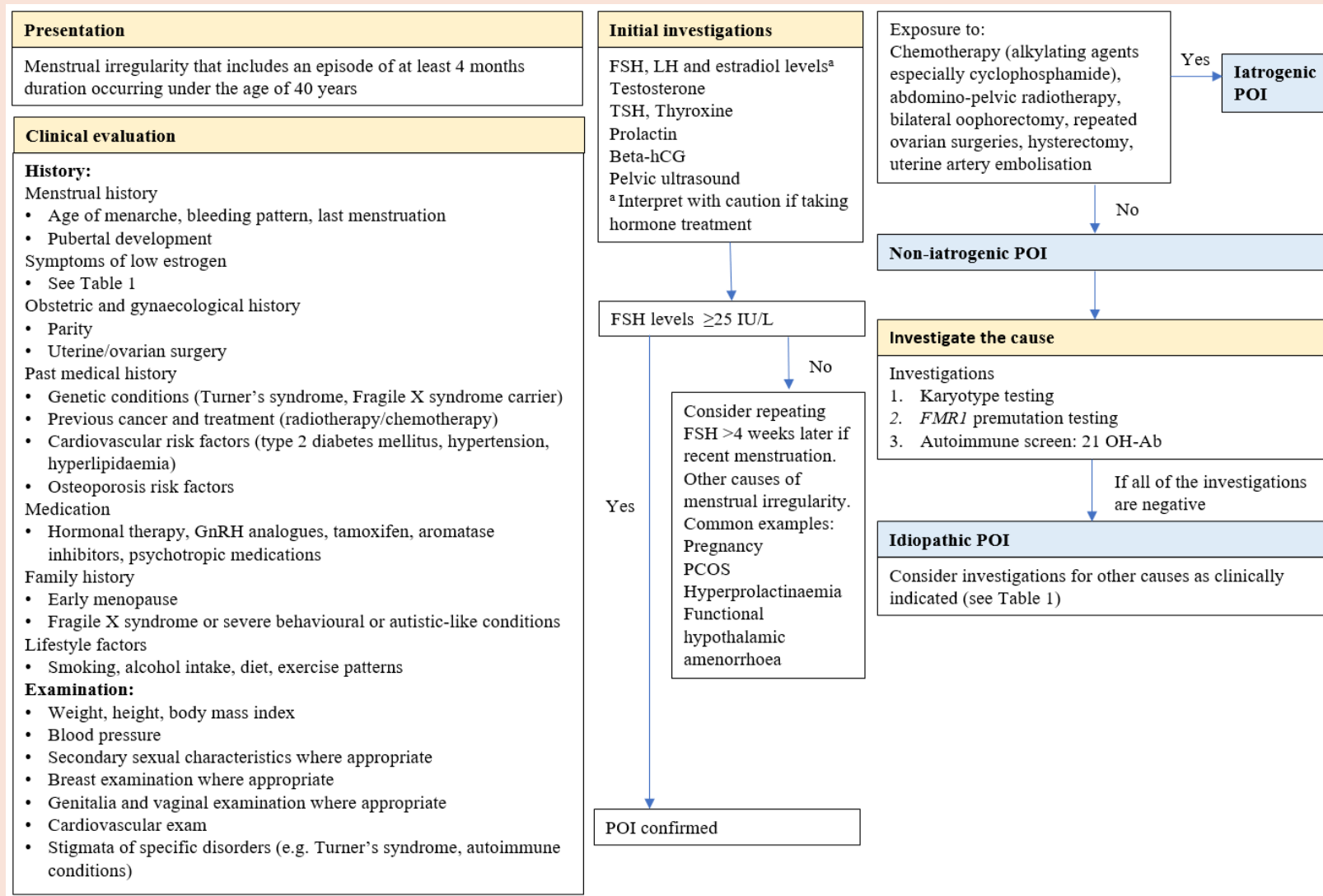
HRT is not a contraceptive, and women desiring pregnancy should be reassured that HRT will not interfere with their chance (albeit low) of natural pregnancy. If pregnancy is not desired, sexually active women should be advised on the need for contraception.

Various factors require consideration in the selection of HT preparations. HT should be individualised to improve adherence, taking into account personal preferences including any need for contraception. CHC may be more appealing due to familiarity with its use among younger women. Although there may be theoretical advantages to transdermal estradiol with oral cyclical progesterone or Mirena (52 mg levonorgestrel intrauterine device [IUD]; Bayer, Leverkusen, Germany), most young women prefer oral HT.⁴⁰ Fig. 2 includes an algorithm to assist with this decision-making process.

HT regimens

HT must consist of an estrogen plus a progestogen

Fig. 1. Premature ovarian insufficiency diagnostic algorithm.



FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; hCG: human chorionic gonadotropin; LH: luteinizing hormone; PCOS: polycystic ovarian syndrome;

POI: premature ovarian insufficiency; TSH: thyroid-stimulating hormone; 21-OH-Ab: 21-hydroxylase antibodies

Modified from Nguyen HH, Milat F, Vincent A. Premature ovarian insufficiency in general practice: Meeting the needs of women. Aust Fam Physician 2017;46(6):360-6, with permission from The Royal Australian College of General Practitioners.²⁴

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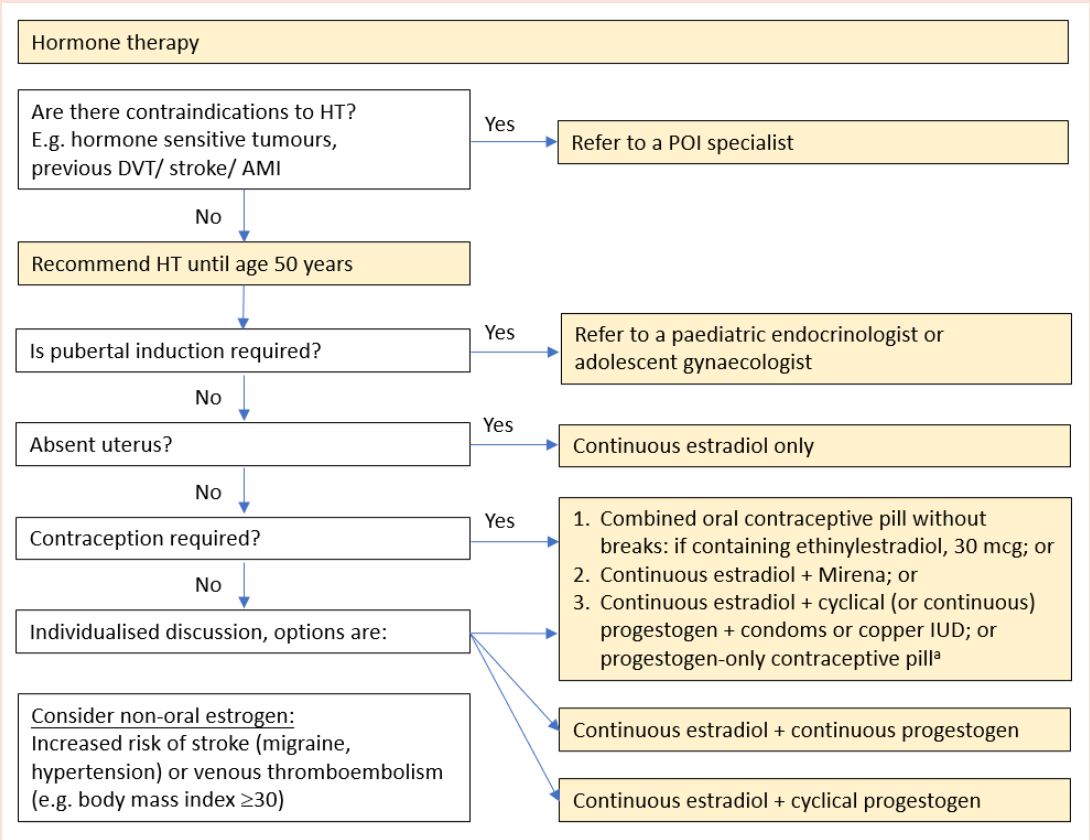
Table 2. Counselling women with premature ovarian insufficiency about hormone therapy.

Points for counselling

- HT is **indicated for women with POI or early menopause** (unless contraindicated) until the usual age of menopause (50 years of age).
- HT **protects your long-term health**, by reducing the risk of developing cardiovascular disease, type 2 diabetes, low bone density and dementia.
- HT can provide **relief of symptoms of low estrogen** and improve quality of life.
- Women with POI taking HT until the age of 50 years **are not thought to have higher risk of breast cancer** than women with normal ovarian function.
- Different formulations of HT allow for **personalised therapies** according to women’s preferences and risk factors.
- Women who have a uterus require both estrogen replacement and **progestogen for protection of the endometrium**.
- HT can be physiological HRT or CHC.
- HRT is **not a contraception** and has fewer side effects than **CHC**.
- Transdermal HT has minimal or no increased risk of venous thromboembolism.
- **Complementary therapies are not a substitute for HT.**
- Women with POI need **long-term follow-up** with a healthcare professional.

CHC: combined hormonal contraception; HT: hormone therapy; HRT: hormone replacement therapy; POI: premature ovarian insufficiency

Fig. 2. Algorithm for prescribing hormonal therapy.



AMI: acute myocardial infarction; DVT: deep vein thrombosis; IUD: intrauterine device; HT: hormonal therapy; POI: premature ovarian insufficiency
^a Progestogen-only contraception pill does not provide adequate endometrial protection within a hormone replacement therapy regime, hence additional progestogen is required.

for endometrial protection in those with an intact uterus and those who have a history of endometriosis, as combined HT may reduce the risk of activating or causing malignant transformation of endometriosis.^{1,41} Estrogen alone can be used otherwise.

Sequential HRT (sHRT: progestogen for 12–14 days/month) is prescribed for women who prefer monthly withdrawal bleeds, while continuous HRT (cHRT) is for those who do not. sHRT is preferable for women who are within 1 year of their last menstrual period to reduce unscheduled bleeding, as well as in women who wish to maximise their (low) chance of natural pregnancy or planning to have embryo transfer as a result of oocyte donation in the near future.⁴² Long sHRT regimens with progestogen for a minimum of 12 days every 3 months can be considered for women who struggle to tolerate progestogens, although the risk of endometrial cancer with such regimens is higher. Extrapolating from older postmenopausal women using HRT, sHRT may be associated with a lower risk of breast cancer but a higher risk of endometrial cancer compared to cHRT.

If CHC is prescribed, it should be taken continuously, i.e. without any days omitting hormone, as this results in reduced total exposure to estrogen, and VMS can occur, which may be distressing. If breakthrough bleeding occurs, a break of 4–7 days can be taken at the end of every 2nd or 3rd calendar strip of pills to allow a withdrawal bleed.⁴²

Type of estrogen

There have been no studies published to date to inform which of the current commercially available HT options are best for women with POI. Most of the research has been for hormone contraception in younger women or HRT for use by older women with usual age at menopause. A UK trial is ongoing at the time of writing which randomises combined oral contraception or HRT for women with POI.⁴³

Estradiol (also known as 17-beta estradiol or E2) is the main and most potent estrogen produced by the pre-menopausal ovary. Natural estrogen is commercially available as estradiol hemihydrate, and is found in oral and transdermal (patch, gel and spray) formulations or as the oral pro-drug estradiol valerate. Oral estradiol undergoes extensive hepatic first-pass metabolism, resulting in low bio-availability of estradiol (under 5%), high levels of the weak natural estrogen estrone and also a variety of other metabolites. These may be responsible for the side effects noted in older postmenopausal women, e.g. increased risk of venous thromboembolism (VTE) and stroke. In

contrast, transdermal estradiol undergoes little metabolism and in the older age group appears not to affect the clotting cascade or VTE risk.^{44,45}

Ethinyl estradiol (EE) is a synthetic estrogen that was developed for CHC, i.e. for women of reproductive age. EE is much more potent than estradiol and causes unfavourable effects on lipid profile and blood pressure, and increases the risk of VTE and stroke. These adverse effects are increased in smokers, those with obesity and those aged over 35 years. Side effects are also dependent on the progestogen delivered alongside EE in the doses used for CHC. Oral CHC may be less favourable for maintenance of BMD compared to HRT;⁴⁶ this could be because EE is less beneficial than natural estradiol or due to the suppressive effect on insulin-like growth factor 1 production by CHC. It is not known if the risk-benefit ratio of CHC may be improved in the newer pills containing the natural estrogens (estradiol or estetrol produced by the feto-placental unit). Estetrol is a weak estrogen thought to have fewer adverse effects than EE and is available with drospirenone as an oral contraceptive in some countries (Australia, US and Europe; licence granted in Hong Kong, Taiwan and Japan in 2024). An HRT version may be available soon.

Most POI specialists do not recommend prescribing conjugated equine estrogen since it contains estrogens not found in humans and is more thrombogenic than estradiol, unless a natural estrogen product is not available and CHC is contraindicated.¹ Tibolone, a synthetic molecule that can stimulate estrogen, progestogen and androgen receptors,⁴⁷ is not recommended. Its safety with long-term use or in pregnancy is unknown. It does not improve BMD in women with POI,⁴⁸ and is unlikely to favour pregnancy due to its thinning effect on the endometrium.

Progestogen for endometrial protection

There are no data to indicate the preferred progestogen for endometrial protection in women with POI. In older postmenopausal women, micronised progesterone (Utrogestan, Besins Healthcare, Monaco) and dydrogesterone (Duphaston, Abbot Laboratories, Chicago, IL, US: a synthetic isomer of natural progesterone) may be preferable over synthetic progestogens, e.g. medroxyprogesterone acetate or norethisterone, as they are associated with a lower risk of breast cancer⁴⁹ and avoid the androgenic and thrombotic side effects of norethisterone. The 52 mg levonorgestrel IUD (Mirena) may also be considered to avoid systemic effects of progestogens or when contraception is

required. The Mirena probably provides protection against endometrial hyperplasia within an HRT regimen for up to 5 years⁵⁰ and this is supported by the Faculty of Sexual and Reproductive Health (UK). Depot preparations of medroxyprogesterone acetate, oral progestogen-only contraceptive pills, vaginal progesterone gel and compounded micronised progesterone creams should not be used for endometrial protection due to concerns that their hypoplastic effects are inadequate.¹

HT dosage

Women with POI generally require higher doses of estrogen for prevention of long-term sequelae, especially for bone health, than those required to control menopausal symptoms in older women. The recommended doses of estrogen for women with POI are oral estradiol 2 to 4 mg or transdermal estradiol 50–100 mcg patches or 2–3 mg gel daily (or 2–3 estradiol sprays).¹ Doses required to attain maximum BMD in the youngest of those with POI (post-puberty) are probably at the higher end of these ranges.¹ Future studies are needed to determine the optimal dosage across the reproductive age range. Ethnicity needs to be taken into consideration in such studies, not only because of different background levels of prevalence and risk for cardio-metabolic disease and osteoporotic fractures. Asian women have significantly higher serum estradiol levels during treatment with transdermal estradiol compared with Caucasian women, suggesting an ethnic difference in steroid metabolism.⁵¹ This may have implications for treating POI in Asians. If CHC containing ethinyl estradiol is used for HT, 30 mcg taken continuously is needed, instead of 20 mcg or 30 mcg cyclically.

The dose of progestogen required for endometrial protection depends on the dose of estrogen and the regimen. For a standard estradiol dose of oral 2 mg per day, continuous regimens require 5 mg dydrogesterone or 100 mg of micronised progesterone, while cyclical regimens require 10 mg dydrogesterone or 200 mg micronised progesterone for 12–14 days per month.⁵² Women who require higher doses of estrogen may require an increased dose of progestogen to ensure adequate endometrial protection.

Monitoring of HT

Women should be reviewed every 3 months while starting on HT to allow for any necessary adjustments. Once optimum HT is established, consultations should occur at least annually. At each visit, HCPs should enquire about symptoms of estrogen deficiency, any unscheduled bleeding, adherence to therapy and reiterate the reasons for needing HRT, including the requirement for

progestogen protection of the endometrium.

Serum measurement of estradiol levels is not required routinely but may be helpful to check compliance or absorption if symptoms persist despite a seemingly adequate dose (for estradiol preparations only). It is reasonable to aim for physiological estradiol levels as found in the serum of women with normal menstrual cycles of approximately 200–400 pmol/L.⁵³ Serum estradiol levels do not increase in a linear fashion with oral estradiol.⁵⁴

Risks of HT

There is a lack of studies investigating the risks of HT for women with POI. Untreated POI is associated with a reduced risk of breast cancer, likely due to reduced lifetime exposure to estrogen.^{55,56} Large studies have not found an increased risk of breast cancer in women less than 50 years taking HRT.^{56,57} A more recent report brings this into question, noting an increased risk of breast cancer in the small number of women identified starting HRT between 30 and 39 years of age.⁵⁸ Statistical significance may be due to index case selection. Although Asian women have lower incidence rates of invasive breast cancer than women of European origin, its incidence in East and Southeast Asia has increased rapidly over the past 40 years.⁵⁹ Given that women with POI will usually be taking HT for over a decade, it is a reminder that the HT of choice should be those with the minimal risk of breast cancer.

CHC administered via any route is associated with risk of VTE and very small risk of thrombotic stroke. Oral HRT has similar adverse effects in older, postmenopausal users and may occur in women with POI, especially in the presence of other risk factors (e.g. smoking and obesity). This risk can be mitigated by using transdermal estrogen,^{44,45} and it is the preferred estrogen for women with migraine or hypertension, or who are at increased risk of VTE (e.g. BMI ≥ 30).^{1,60} The choice of progestogen used alongside estradiol replacement may also influence VTE risk, although there was no adverse effects of different progestogens on the clotting cascade with transdermal estrogen.⁶¹ Nonetheless, using a progestogen with a low thrombogenic profile would be reasonable (e.g. Mirena, oral micronised progesterone or dydrogesterone).

Prolonged use of progestogen is associated with a small risk of meningioma, but not for micronised progesterone, dydrogesterone and Mirena.⁶²

Non-hormonal and complementary therapy

Many Asian women accept menopause as a natural process and would prefer natural or herbal treatment (37%) over HT (19%) for the treatment

of menopausal symptoms.⁶³ Women with POI may also turn to complementary therapies, but they should be advised that these do not replace HT for the prevention of long-term sequelae of POI.

Women with a personal history of hormone-sensitive cancer who are unable to take HT may benefit from non-hormonal pharmacologic (e.g. selective serotonin reuptake inhibitors) and non-pharmacologic therapies (e.g. cognitive behavioural therapy). These can be helpful in relieving menopausal symptoms in older peri- and postmenopausal women, but evidence specific to POI is lacking.

A new class of centrally-acting drugs, neurokinin (NK) blockers, to reduce VMS in peri-menopausal women was launched for women age 45 to 55 years in Australia, the UK and the US in 2022. The licence applications are pending for various markets, including Singapore. NK blockers may have a future role for women with POI for whom HT is contraindicated.

Management of POI

The diagnosis of POI can be extremely distressing for women. Several consultations may be required to provide emotional and psychological support, including for sharing the diagnosis with family and/or partner. All women with POI should be given lifestyle advice and long-term follow-up to monitor their cardiovascular, bone and psychological health, as summarised in Table 3. Women with POI who are keen for fertility should be offered referral to a reproductive medicine specialist.

Lifestyle intervention

Women with POI should be given lifestyle advice to optimise bone and cardio-metabolic health and to reduce risks of dementia. They should be advised to avoid smoking, moderate alcohol intake and maintain a healthy body weight (BMI of 18.5–22.9 kg/m²). Diet should be low in fat and salt but rich in calcium and vitamin D—the recommended daily dietary intake for bone health is calcium 1000–1200 mg and vitamin D 600–800 IU.⁶⁴ The average Singaporean diet contains 625 mg calcium daily.⁶⁵ Women who are not getting enough dietary calcium and vitamin D should receive supplementation. Vitamin D measurement could be considered for all women diagnosed with POI, since the prevalence of deficiency in Singapore is up to 42%,⁶⁶ possibly contributing to low BMD. Vitamin D can be obtained with 5–30 minutes of sun exposure between 10 am and 3 pm, for at least twice a week. Women should be advised to do 150–300 minutes/week of moderate-intensity aerobic for cardio-metabolic health, ideally including some weight-bearing (e.g. dancing, jogging, skipping

rope), muscle-strengthening (e.g. light weights, elastic band exercises) and balance exercises (e.g. yoga, pilates, tai chi) for bone health.

Fertility options

Women should be informed that 5% of women with POI spontaneously conceive, especially within the first year of amenorrhoea.² There is no reliable intervention to increase ovarian activity and natural conception rates. Oocyte or embryo donation are the only proven treatments to achieve pregnancy.¹ Several novel approaches have recently been described, including in vitro activation of follicle growth in biopsied ovarian tissue, administration of mesenchymal stem cells and injection of platelet rich plasma into the ovary. More robust studies are required to determine if these treatments are effective. The opportunity for fertility preservation is missed in women with established POI.

Fitness for pregnancy requires assessment in the preconception period as some women with POI may be of high obstetric risk, such as women with Turner's syndrome, those who have had pelvic irradiation (also associated with a reduced chance of pregnancy), mediastinal irradiation or high-dose anthracycline exposure. Women who are planning pregnancy with egg donation are at higher risk of obstetric complications such as hypertensive disorders in pregnancy.

Relatives of women with POI

The risk of POI in a woman who has a relative diagnosed with POI may be up to 15%.¹ Female relatives (such as sisters or daughters) of women with non-iatrogenic POI who are concerned about their risk for developing POI should be advised that they may be at risk, and informed of the signs and symptoms of POI, with the recommendation to seek medical advice if these occur. Unfortunately, there are no established methods for predicting or preventing POI in this group of women. Some relatives may wish to consider earlier family planning and/or fertility preservation options, although the role of fertility preservation in women with a familial link to POI is not established. There may be financial constraints or legal restriction in some countries for egg freezing.^{68,69} Relatives of women with the fragile X premutation should be offered genetic counselling and testing.

DISCUSSION

POI affects an estimated 3.5% of women globally and the long-term consequences of POI, especially on CVD and osteoporosis, should make health

Table 3. Long-term management of premature ovarian insufficiency.

Long-term management of POI**1. Cardiovascular risk factors**

- **Blood pressure, weight and smoking** status: monitor each visit
- **Lipid profile and diabetes screening:** assess at diagnosis
 - Treat/reassess according to local CVD risk assessment tools (none currently available weighted for POI/age of menopause) and protocols

2. Bone health risk factors

- **Vitamin D:** consider screening at baseline and treat if deficient
 - **DEXA scan:** consider at diagnosis (especially if diagnosis or start of HT was delayed, low BMI or family history of osteoporosis)
 - Normal BMD (z score >-2.0) and adequate HT: value of repeat DEXA scan within 5 years is low
 - Low BMD (z score ≤-2.0): repeat DEXA 1–3 years after HT commenced
- If BMD declines despite seemingly adequate HT, compliance should be checked, screening for other secondary causes of osteoporosis undertaken and consideration given to increasing dose of estrogen/changing preparation. Referral to an osteoporosis specialist may be required: bisphosphonates should be avoided unless there is no chance of future pregnancy (including from egg donation).

3. Fertility

- Adjust HT according to fertility plans: e.g. stop/start contraceptive HT or sHRT
- Refer to reproductive medicine specialist if patient wishes to consider fertility treatment

4. Sexual dysfunction

- **Enquire** after sexual function
- Optimise **HT**
- Treat persisting urogenital symptoms (e.g. **vaginal estrogen, moisturisers and lubricant** to treat dyspareunia)
- Review medications potentially impacting sexual function (e.g. antidepressants)
- **Psychosexual counselling** if required
- **Testosterone** therapy: consider for HSDD especially in surgical POI but:
 - Insufficient evidence regarding efficacy and long-term safety to support routine use⁶⁷
 - No licenced testosterone preparation for females available in Singapore currently

5. Quality of life

- **Psychological symptoms:** e.g. grief at the loss of femininity and fertility, fear of long-term health consequences, concerns regarding impact on relationship with their (future) partner
 - Refer for psychological support when needed
 - Signpost to support groups and educational resources

6. Autoimmune screening (for idiopathic or autoimmune POI and Turner's syndrome)

- **TSH measurement** every 5 years or if symptoms develop
- Low threshold to investigate symptoms suggestive of other autoimmune conditions

7. Cancer screening

- **Enquire after unscheduled vaginal bleeding**, investigate and manage as indicated
- Breast and cervical cancer screening **as per national guidelines**

BMD: bone mineral density; BMI: body mass index; CVD: cardiovascular disease; DEXA: dual-energy x-ray absorptiometry; HSDD: hypoactive sexual desire disorder; HT: hormonal therapy; POI: premature ovarian insufficiency; sHRT: sequential hormone replacement therapy; TSH: thyroid-stimulating hormone

policymakers prioritise and allocate health resources for preventive and treatment interventions for affected women. Healthcare policies should ensure that appropriate HT choices are available and more affordable. Fertility-sparing treatments for cancer and non-cancer conditions should be used whenever possible to reduce iatrogenic POI, with more research into these options. Artificial reproductive techniques and fertility preservation should be made more available for women at risk of POI.

There are barriers for prescribing HT, for both women and HCPs, often still related to the publication of the Women's Health Initiative Studies in 2002, which reported an increased breast cancer prevalence associated with HRT use. HCPs may have had inadequate training in menopausal medicine, resulting in a lack of confidence for prescribing these treatments, even for women with POI. Many women have a lack of knowledge of as well as concerns about the risks of HRT, that is, not understanding the differences between its use to manage symptoms of normal menopause in contrast to reducing the consequences of POI. These barriers need to be broken, by providing training and education to HCP to provide evidence-based counselling to women with POI, in order for them to make informed decisions about their health.⁷⁰

The field of genetics in POI is expanding and it is hoped that this will allow a better understanding of the condition, its prognosis and development of novel prevention or treatment strategies. Last, setting up a POI registry and collaborative research across the region can facilitate much needed large-scale research to be conducted for Asian women with POI.

CONCLUSION

The diagnosis and management of POI can be challenging for HCPs. Practitioners should include POI in their differential diagnosis of women presenting with onset of menstrual irregularity under 40 years of age and be able to confirm the diagnosis, investigate the underlying cause and screen for factors that may potentiate the long-term consequences. Women should be started on HT, unless contraindicated (for which there are very few). Multidisciplinary team involvement is often required. Women require long-term follow-up to monitor therapies and to screen for consequences of POI.

Ethics statement

Not applicable.

Declaration

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