# Premature Ovarian Insufficiency

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**ABSTRACT**

Premature ovarian insufficiency (POI) is a clinical syndrome defined by the presence of ovarian dysfunction before the age of 40 years. The prevalence of POI is around 1%. The following diagnostic criteria are mostly adopted nowadays: (i) oligo/amenorrhea for at least four months, and (ii) FSH levels > 25 IU/l on two occasions more than four weeks apart. POI can be the result of iatrogenic, genetic and autoimmune causes. Karyotyping should be performed in all women with non-iatrogenic POI, while fragile X premutation testing is also indicated. Screening with anti-21OH Abs (or alternatively adrenocortical Abs) and anti-TPO Abs should also be considered. No causal relationship between smoking and POI has been proved, but smoking has been associated with early menopause. In the majority of cases, the cause of POI is not identified and these women are described as having idiopathic POI. Untreated POI is associated with increased risk of type 2 diabetes mellitus and reduced life expectancy, largely due to cardiovascular disease. POI is also associated with reduced bone mineral density and increased risk of fracture. These women should maintain a healthy lifestyle with appropriate diet and exercise. Women with POI should also receive hormone replacement therapy with standard doses of oral (17ß-$E_2$ 2-4 mg or CEE 0.625-1.25 mg) or transdermal (17ß-$E_2$ 50-100 µg) estrogens and progestogens (natural progesterone 200 mg or dihydrogesterone 10-20 mg or norethisterone 1-5 mg) up to the age of normal menopause (50 years). There is a small chance of spontaneous pregnancy, therefore women with POI should be advised to use contraception, if they wish to avoid pregnancy. There are no interventions that have been reliably shown to increase ovarian activity and natural conception rates, therefore oocyte donation is, so far, the established option in the event of fertility issues.

**KEYWORDS**

Premature, ovarian, insufficiency, FSH, amenorrhea, oligomenorrhea, HRT.

## Introduction

Premature ovarian insufficiency is a clinical syndrome defined by the presence of ovarian dysfunction before the age of 40 years [1]. It was first described in the early 1940s by Dr. Albright, a Harvard endocrinologist, who, at the time, called it primary ovarian insufficiency [2]. The word "primary" refers to the level of the defect, in this case the ovary, while "premature" refers to the timing, in this case before 40 years of age. Furthermore, the term "failure" has also been extensively used. However, as some of these women may present recurrent ovarian function, "insufficiency" is more appropriate. Therefore, the term premature ovarian insufficiency (POI) should be used to describe this condition, both in the clinical and in the research setting [1, 3, 4].

The aim of this review is to present the current diagnostic criteria of POI and the prevalence of the syndrome, as well as to list the possible causes of this clinical condition. Furthermore, the authors discuss the appropriate diagnostic assessment approach, consider the short-term and long-term complications, and conclude with the appropriate combined therapeutic strategies for these women.

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## Diagnostic criteria

POI is characterized by menstrual disturbances before the age of 40 years accompanied by raised gonadotrophins and low estradiol concentrations. The latter lead to estrogen deficiency symptoms, such as hot flashes, night sweats and sexual dysfunction. Hormonal confirmation is needed. Although proper diagnostic accuracy is lacking, the following diagnostic criteria are mostly adopted nowadays: (i) oligo/amenorrhea, which means menstrual cycles longer than 35 days or absence of menses for at least four months, and (ii) FSH levels > 25 IU/l measured on two occasions more than four weeks apart. Anti-Mullerian hormone is an indicative marker of ovarian reserve, but it should not be routinely used for the diagnosis of POI [1, 4].

## Prevalence

It is estimated that approximately 1% of women present POI worldwide, while the prevalence is estimated to be around 0.1% in women under 30 years of age, and around 0.01% in the under 20s. This varies according to specific population characteristics, such as ethnicity. For example, Afro-American women present POI in higher percentages (around 1.4%), while the prevalence is much lower in women of Japanese origin (around 0.1%) [5, 6, 7]. The cut-off age of 40 years is two standard deviations below the age of normal natural menopause in the western world, which is around 50 years [1, 3].

If a woman experiences menopause after 40 and before 45 years of age, this situation is called early menopause. In clinical practice, women in these two groups (menopause before 40 or between 40 and 45 years) often receive similar advice in terms of hormone replacement therapy (HRT), and cardiovascular and bone disease risk [1, 3, 4].

## Etiology

POI could be the result of iatrogenic, genetic or autoimmune causes. However, in the majority of cases (50-90%) the cause is not identified and these women are described as having unexplained or idiopathic POI. An association of smoking with early menopause has been described, however no causal relationship between smoking and POI has been proved [1].

POI presents often after medical interventions affecting the ovaries, such surgery, chemotherapy and radiotherapy [5, 8, 9]. Some rather promising developments in the oncology world have, however, resulted in increases in the numbers of women with iatrogenic POI in recent years. First of all, there has been a significant improvement in the prognosis of childhood cancers over the last two decades, with long-term survival rates of more than 80% [5, 8]. In addition, an increasing number of premenopausal women carrying the BRCA gene mutation nowadays undergo risk-reducing surgery including prophylactic oophorectomy [5].

Chemotherapeutic agents can have a direct toxic effect on the ovaries. This varies with different agents and is more common with alkylating agents, which can result in POI in approximately 40% of treated cases. The risk is also influenced by the dose of medications and the age of the woman at the time of treatment [10, 11, 12]. The toxic effects of radiotherapy are mostly related to the site of the treatment and are more common with pelvic, abdominal and whole body irradiation. The effect of radiotherapy is also dose and age dependent [8, 13].

Genetic causes of POI include chromosomal abnormalities, mainly of the X chromosome, such as Turner syndrome or mosaic for Turner syndrome. Some cases with gonadal dysgenesis and the presence of Y chromosomal material can be also detected. Of course, such chromosomal abnormalities are mainly already present early in life, causing often primary amenorrhea [14, 15, 16]. Fragile X premutation is also present in quite a large percentage of cases, especially with familial POI. More specifically, the prevalence of POI in female carriers of fragile X premutation is between 13% and 26%. Moreover, 0.8% to 7.5% of women with sporadic POI are carriers, while in women with familial POI this percentage can be as high as 13% [14, 16, 17]. The fragile X mental retardation 1 (FMR1) gene is located on the long arm of the X chromosome. Full mutation of this gene causes fragile X syndrome, which presents with a broad spectrum of intellectual disability, hyperarousal, social difficulty, anxiety, aggression and autism.

POI is associated with a premutation, implicating expansion of a cytosine-guanine-guanine (CGG) trinucleotide repeat sequence in the first exon and promoter of FMR1. Normal alleles have 5 to 44 CGG repeats, intermediate alleles 45 to 54 repeats, premutation presents with 55 to 200 repeats, while the presence of more than 200 CGG repeats is consistent with full mutation [17]. Some other rare autosomal genetic causes associated with POI have been described, but these are usually part of generalized syndromes, such as the blepharophimosis ptosis epicanthus inversus syndrome [16]. Moreover, recent data deriving from animal genetic models, next generation sequencing studies and genome-wide association studies have indicated possible mutations and polymorphisms associated with POI in more than 60 candidate genes, again with high genetic heterogeneity [18, 19].

POI could also be the result of autoimmune destruction of ovarian tissue [1, 4]. In this case it is associated mainly with adrenal autoimmunity, and secondarily with thyroid autoimmunity. Specifically, 60-80% of cases with autoimmune POI may present positive adrenal autoantibodies, while 20-30% positive thyroid autoantibodies [20]. The latter condition is itself, of course, very common nowadays in the form of Hashimoto's autoimmune thyroiditis. Type 1 diabetes can also be associated with POI, but in smaller percentages of cases (2-3%). In the event of coexistence of two or more autoimmune endocrine disorders in the same patient, there must be a high suspicion of autoimmune polyendocrine syndrome [20, 21].

Environmental chemicals may also disrupt female reproductive function. Adverse effects of endocrine disruptors on animal ovaries have been described, while serum levels of bisphenol-A and phthalate metabolites have been found to be increased in women with POI. The possible effects of endocrine disruptors during pregnancy with female embryos shed light on the fascinating hypothesis of a fetal origin of adult POI [22].

## Diagnostic assessment

Chromosomal analysis (for Turner syndrome or Y chromosomal material detection) should be performed in all women with non-iatrogenic POI. Therefore, karyotyping is a front-line test for all these women. Fragile X premutation testing is also indicated, while autosomal genetic testing is not at present indicated in women with POI, unless there is evidence suggesting a specific mutation [1]. The measurement of anti-ovarian autoantibodies has not yet been validated and is not recommended. However, screening with anti-21 hydroxylase autoantibodies (anti-21OH Abs) or alternatively adrenocortical autoantibodies and anti-thyroid peroxidase autoantibodies (anti-TPO Abs) should be considered in women with POI of unknown cause or if an autoimmune disorder is suspected. Patients with positive

anti-21OH Abs should be investigated for possible adrenal insufficiency, while patients with positive anti-TPO Abs should be investigated for possible hypothyroidism. With regard to adrenal insufficiency, morning cortisol measurement is the test of choice, followed by a dynamic synacthen test, if needed. TSH measurement is the first-line test for hypothyroidism, followed by measurement of peripheral thyroid hormones (T3 and T4), if needed [1, 4].

## Short- and long-term health consequences

POI has both short- and long term health consequences in affected women (Table 1). The former are the result of reduced endogenous estrogen concentrations and include vasomotor symptoms, such as hot flashes and night sweats, sexual dysfunction, decreased energy, and impaired memory and concentration. Sexual dysfunction is due to both decreased libido and vaginal atrophy. In the long term, women with POI have fertility problems and this is usually the main concern of both patients and physicians. However, if they remain untreated these women may develop type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [1, 3, 4].

A recent meta-analysis published by our group indicated that women with POI indeed present a 50% increased risk of T2DM [23]. More specifically, this meta-analysis included 191,762 women in total, including 21,664 cases with T2DM, and it was found that women with early menopause and POI are at higher risk of T2DM compared with those aged between 45 and 55 years at menopause (OR 1.15, 95% CI 1.04-1.26, p = 0.003; I2 61%, p = 0.002 and OR 1.50, 95% CI 1.03-2.19, p = 0.033; I2 75.2%, p = 0.003, respectively). Similar differences emerged when women with early menopause and POI were compared with those aged >45 years at menopause (OR 1.12, 95% CI 1.01-1.20, p = 0.02; I2 78%, p = 0.001 and OR 1.53, 95% CI 1.03-2.27, p = 0.035; I2 78%, p = 0.001, respectively) [23].

There is early evidence that these women are at higher CVD risk and this was confirmed by a recent, well performed meta-analysis, which included 10 studies, 190,588 women in total, with follow-up of 4 to 37 years and 9,440 events [2,026 ischemic heart disease (IHD), 6,438 stroke, 976 total CVD]. The researchers concluded that POI is associated with increased risk of IHD (HR 1.69, 95% CI 1.29-2.21, p=0.0001), and increased risk of total CVD (HR 1.61, 95% CI 1.22-2.12, p=0.0007), while no increased risk was found for stroke (HR 1.03, 95% CI 0.88-1.19, p=0.74) [24].

POI is also associated with reduced bone mineral density (BMD) and increased risk of fracture later in life. A recent meta-analysis published by our group included 462,393 women in total with 12,130 fractures; it emerged that the women with early menopause presented an increased fracture risk (OR 1.36, 95% CI 1.11–1.66, p = 0.002, I2 81.5%). No distinct effect on the site of fracture was found [25]. Last but not least, there is observational evidence of impaired cognitive function in the long term in women with POI [1, 4].

**Table 1** Short term and long term health consequences of women with Premature Ovarian Insufficiency (POI).

| Short-term consequences | Long-term consequences |
|---|---|
| Vasomotor symptoms (hot flashes, night sweats) | Impaired fertility |
| Sexual dysfunction (low libido, vaginal atrophy) | Type 2 diabetes mellitus |
| Insomnia | Cardiovascular disease |
| Low energy | Osteoporosis and fractures |
| Impaired memory and concentration | Impaired cognitive function |

## Management

The optimal management of women with POI should target both cardiovascular and bone health status. Therefore, these women should maintain a healthy lifestyle, which includes following a balanced diet with appropriate intake of calcium and vitamin D, doing aerobic and weight-bearing exercise, giving up smoking, reducing alcohol consumption, and maintaining a normal body weight [1, 26]. These lifestyle interventions are the cornerstone for prevention but also for treatment of T2DM and osteoporosis. Should they develop these diseases, most of them will eventually require pharmacological treatment, therefore appropriate agents should be chosen, taking into consideration their different metabolic, cardiovascular and bone health effects [26].

Of course, POI should be treated as any endocrine deficiency problem and HRT is indicated. More specifically, standard doses of oral (17β-E2 2-4 mg or CEE 0.625-1.25 mg) or transdermal (17β-E2 50-100 μg) estrogens and progestogens (natural progesterone 200 mg or dihydrogesterone 10-20 mg or norethisterone 1-5 mg) are recommended up to the age of normal menopause [1, 3, 27], (Table 2). Women after hysterectomy should receive formulations with estrogens only, while in any woman with an intact uterus progestogen needs to be added. Oral progestogens are administered once or twice daily constantly, resulting in amenorrhea, or periodically 12-14 days per month, resulting in regular monthly bleeding. Transdermal progestogens (norethisterone) are administered twice weekly in a continuous manner, leading to amenorrhea, or in a cyclical manner, for 14 days a month, leading to regular monthly bleeding [3, 27].

HRT presents numerous beneficial effects for these women, including decreased lipid concentrations, improved body fat composition, increased insulin sensitivity and vascular function, as well as decreased CVD risk. Moreover, HRT amelio-

**Table 2** HRT for women with POI (up to the age of 50 years).

| Dosage | Oral estrogens | Transdermal 17ß-E2 |
|---|---|---|
| *Standard dose* | 17ß-E2 2-4 mg or CEE 0.625-1.25 mg | 50-100 μg |

| Estrogens Dose | Natural progesterone | Dihydrogesterone | Norethisterone |
|---|---|---|---|
| *Standard dose* | 200 mg | 10-20 mg | 1-5 mg transdermal 0.25 mg |

*POI: premature ovarian insufficiency; E2: estradiol; CEE: conjugated equine estrogens*

rates BMD and decreases fracture risk in later life [28, 29, 30, 31, 32]. There have been some concerns with HRT regarding breast cancer and venous thromboembolism (VTE) risk, but these derive mainly from studies in older, naturally menopausal women. Indeed, observational data have shown that women with POI present a lower risk of breast cancer compared with controls, and HRT does not appear to increase the risk of breast cancer in women under the age of 50 years. As regards VTE, there is a lack of evidence in women with POI. Findings from studies in older menopausal women should not be directly extrapolated. However, the transdermal route of estradiol administration should be considered in women with POI who are at increased risk of VTE, such as obese ones [33, 34, 35].

Regarding fertility, women with POI can have intermittent ovarian activity and there is a small chance of natural conception (~5%). Therefore, women with POI should be advised to use contraception, if they wish to avoid pregnancy [36]. There are no interventions that have been reliably shown to increase ovarian activity and natural conception rates. Therefore, oocyte donation is, so far, the established option for fertility issues in these women [1, 36, 37, 38]. However, oocyte or embryo cryopreservation should always be advised for women at increased risk of POI, such as before chemotherapy or radiotherapy [10, 11, 38, 39]. Last but not least, gonadectomy should be recommended for all women with detectable Y chromosomal material because of the increased risk of malignancy [1].

## Conclusions

POI is a rather common endocrine disorder and the prevalence of iatrogenic causes, in particular, looks set to rise. Women with POI suffer both short- and long-term health consequences, as a result of estrogen deficiency and oocyte depletion. They should follow a healthy lifestyle and be treated with standard doses of HRT up to the age of normal natural menopause. Oocyte donation is, so far, the only established option for fertility issues in women with POI, but oocyte or embryo cryopreservation should be recommended to all women before any intervention that may affect ovarian tissue.

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