

Samantha F. Butts, MD, MSCE

Chief, Division of Reproductive Endocrinology and Infertility, Penn State Health, Hershey, PA; Vice Chair of Quality and Safety, Department of Obstetrics and Gynecology, Penn State Health, Hershey, PA; Professor, Department of Obstetrics and Gynecology, Penn State College of Medicine, Hershey, PA

The overlooked and undertreated perils of premature ovarian insufficiency

ABSTRACT

Premature ovarian insufficiency (POI) is loss of ovarian function before age 40. Genetic, autoimmune, and iatrogenic causes are well defined, but 90% of cases are idiopathic. POI prevalence is estimated to be between 3% and 4%, with many cases undiagnosed or untreated. Affected individuals experience prolonged estrogen deficiency unless hormone therapy is instituted to restore physiologic levels. Untreated POI is associated with multiple health risks, including premature death due to cardiovascular disease.

KEY POINTS

POI is a pathologic condition—not simply a hastening of natural menopause.

Untreated POI affects fertility, cardiovascular and bone health, sexual function, and quality of life. Women with POI are at increased risk for cardiovascular disease, osteoporosis and related fracture, multimorbidity, and early death.

Menopausal hormone therapy is a core component of POI treatment. Women’s Health Initiative findings do not apply and should not be used to justify withholding hormone therapy.

Women with POI may still become pregnant. If pregnancy is not desired, contraception must be addressed.

PREMATURE OVARIAN INSUFFICIENCY (POI) is a pathologic condition resulting in profound hypoestrogenism that can begin as early as adolescence, depriving affected females of decades of ovarian support for their overall health and well-being. More than a potential fertility problem, POI-related hypoestrogenism has major long-term health consequences, including increased risk for cardiovascular disease, osteoporotic fractures, and premature mortality.

Delay in the diagnosis of POI can occur when amenorrhea, prolonged menstrual irregularity, or vasomotor or urogenital symptoms are not fully evaluated in younger individuals. Physicians should be alert to the possibility of undiagnosed POI and know what to do if the condition is suspected. In December 2024, a consortium of international reproductive medicine specialists published updated evidence-based guidelines for diagnosis and management of POI, including more than 100 best practice recommendations.¹

This article presents the current definition, epidemiology, and prevalence of POI and summarizes the diagnostic and management approach to this serious condition. In general, a team approach to POI—bringing together expertise in reproductive endocrinology and infertility, obstetrics and gynecology, and cardiovascular and musculoskeletal disease—offers the best outcomes for this patient population.

Medical Grand Rounds articles are based on edited transcripts from Medicine Grand Rounds presentations at Cleveland Clinic. They are approved by the author but are not peer-reviewed.

doi:10.3949/ccjm.92gr.25056

PREMATURE OVARIAN INSUFFICIENCY

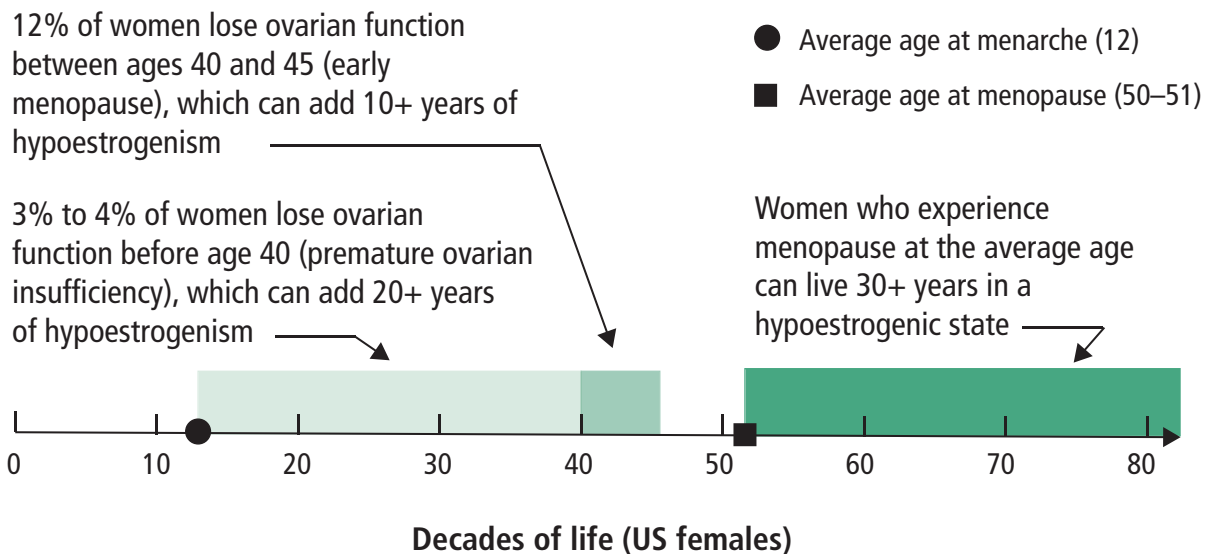


Figure 1. Timing of ovarian senescence has significant implications for managing symptoms and reducing sequelae related to estrogen deficiency. Currently, women can expect to live one-third of their lifetime after menopause, and the health risks they face are important to address. Women who lose ovarian function 10, 20, or more years before the average age at menopause face even more serious threats from long-term hypoestrogenism if left untreated.

Based on information from reference 1.

POI IS NOT MENOPAUSE

Although women with POI share some health risks with women who are naturally menopausal at later ages, the approach to health maintenance in these 2 populations is distinct. Optimal management of women with POI hinges on distinguishing the condition from natural menopause.

Natural menopause, the permanent cessation of menstruation following age-related loss of ovarian activity, is a physiologic process that occurs at an average age of 50 to 51 years (range 46 to 55) in the general female population.^{2,3} In the United States, women experiencing menopause at age 50 will live another 30 years or more in a state of hypoestrogenism. Women experiencing **early menopause** (loss of ovarian function between ages 40 and 45) spend even more years in an estrogen-deficient state.

POI is defined as the loss of ovarian function before age 40.^{1,4-6} It is a pathologic condition that can begin as early as adolescence and should not be mistaken as menopause that occurs earlier than usual. A case in point: despite having decreased ovarian function, women with POI have a 5% to 10% probability of spontaneous pregnancy,⁷ whereas menopausal women cannot achieve pregnancy. If women with

POI do not desire pregnancy, contraception must be addressed.

What is the problem in POI?

Fundamentally, POI is a problem of declining ovarian function due to a decrease in follicle number, an increase in follicle destruction, or poor follicle response to gonadotropins before age 40.⁶ Iatrogenic causes aside, POI can be difficult to detect. Clinical hallmarks are amenorrhea or menstrual irregularity with inappropriately high follicle-stimulating hormone (FSH) levels (ie, FSH values ≥ 20 IU/L) and low estradiol levels. However, ovarian functional decline can be intermittent and unpredictable in POI, with low FSH concentrations and vaginal bleeding.

Nomenclature matters

POI was first described in 1942 by pioneering endocrinologist Fuller Albright, MD, who referred to the syndrome as “primary ovarian insufficiency” to convey that the problem was functional.⁸ Albright’s terminology accurately captures the continuum of ovarian dysfunction displayed in affected women (*insufficiency*) and infers that the cause is within the ovary (*primary*).

Different terms have been used since, such as *premature ovarian failure* and *premature menopause*, which

do not accurately describe the fluctuating basis of the condition and have a negative connotation. In this author's opinion, physicians should be precise when characterizing this condition and sensitive to the ways in which a patient may internalize the gravity of their diagnosis.

POI IS NOT AS RARE AS ONCE THOUGHT

The rise in women desiring pregnancy beyond the third decade of life has led to increased awareness about POI and the realization that the scope of the problem is greater than previously thought. Whereas older epidemiologic studies reported a global POI prevalence of 1%, 2 meta-analyses published in the past 6 years are consistent in estimating a prevalence between 3% and 4%.^{9,10}

Early menopause also is more common than has been reported. In an analysis of pooled prevalence estimates from 31 studies, Golezar et al⁹ calculated a 3.7% prevalence of POI and a 12.2% prevalence of early menopause (ovarian insufficiency before age 45) worldwide. Although women experiencing early menopause are a separate population from women with POI, when considered together, these 2 populations represent a significant proportion of women at risk for complications of long-term estrogen deficiency (Figure 1).¹

POI HAS MAJOR HEALTH IMPLICATIONS

Long-term hypoestrogenism in POI has serious implications for overall female health and well-being (Table 1). Two areas of particular importance for primary care are the impact of untreated POI on risk for cardiovascular disease and low bone mass.

Cardiovascular disease

Although the mechanisms have not been completely elucidated, considerable evidence suggests that estrogen plays a cardioprotective role during the reproductive years of a woman's life, with heart disease risk in women after menopause "catching up" to the risk in men. What does heart disease risk look like if ovarian senescence occurs years before the typical age of natural menopause? The following cohort studies shed light on this question.

- The Adventist Health Study¹¹ followed 6,182 US female patients over a 13-year period and found an ischemic heart disease mortality of 5.5 per 1,000 person-years; those described as experiencing menopause between ages 35 and 40 experience an 80% increased risk of fatal ischemic heart disease

TABLE 1
Health risks associated with undiagnosed or untreated premature ovarian insufficiency

Associated endocrine disorders
Thyroid disease or Hashimoto thyroiditis
Adrenal insufficiency
Long-term health risks
Osteoporosis and fractures
Cardiovascular disease
Reduced life expectancy due to cardiovascular disease

compared with study participants who were 49 to 55 years of age at menopause (relative risk 1.8, 95% confidence interval 1.2–2.7).

- A large study conducted in the Netherlands followed 9,450 postmenopausal women over a 20-year period and found that those who were 52 or older at menopause had an 18% reduction in cardiovascular disease mortality compared with study participants who were age 44 or younger at menopause.¹²
- In a UK study that assessed a composite outcome of incident coronary artery disease, heart failure, ischemic stroke, and 5 other cardiovascular diseases in 14,260 postmenopausal female patients, 6.0% of participants with natural menopause before age 40 (described as "premature menopause") experienced the primary outcome compared with 3.9% of participants without premature menopause.¹³ In this study, the rate of premature menopause was 3.4%, similar to the POI prevalence estimates reported in recent meta-analyses.^{9,10}

Osteoporosis

Estrogen plays a critical role in regulating healthy bone turnover in reproductive-aged women, with peak bone mass achieved between the second and third decades of life.¹⁴ Bone mass begins to decrease with onset of perimenopause, with greater losses linked with lower serum estrogen levels.

Young women with spontaneous POI have been found to have significantly lower bone mineral density scores (lumbar, femoral neck, and total hip) on dual-energy x-ray absorptiometry scans compared with regularly menstruating women of a similar age.^{15,16} Incidence of osteoporotic fractures also is higher. In a study analyzing hip fracture rates in more than 1,000 women with osteoporosis, the rate was 9.4% in women who entered menopause before age 45 vs 3.3% in women who experienced menopause at a typical age.¹⁷

TABLE 2
Contraindications to menopausal hormone therapy

Pregnancy
Unexplained vaginal bleeding
Poorly controlled liver disease
Previous estrogen-sensitive cancer (including breast cancer)
Previous coronary heart disease, stroke, myocardial infarction, or venous thromboembolism
Personal history or inherited high risk of thromboembolic disease

Based on information from reference 19.

A 23-year longitudinal study in a cohort of 6,803 Australian women born between 1946 and 1951 adds further evidence of worse bone health in POI and early menopause. In this cohort, 2.6% of women reported POI and 4.5% reported early menopause (defined as menopause before age 45). By age 68, 49.7% of women with POI or early menopause had a diagnosis of osteoporosis or fracture during follow up vs 36.6% of women with usual-age menopause.¹⁸ This translates to a 37% higher risk of osteoporosis and a 45% higher risk of fracture in the women with POI or early menopause.

Multimorbidity

The recently published Canadian Longitudinal Study on Aging² adds to the sobering evidence of the long-term health impacts of POI. This large prospective study included more than 12,000 postmenopausal women—3% with POI, 11.3% with menopause at age 40 to 45 (early menopause), and 58.7% with menopause at age 46 to 55 (defined as average-age menopause). The mean age was 34.8 years in the POI group and 51 years in the average-age group. The aim of the study was to compare the prevalence of multimorbidity (defined as 2 or more chronic conditions) and severe multimorbidity (3 or more chronic conditions) across the 3 groups.² Multimorbidity rates were 63.8% in the POI group, 51.1% in the early menopause group, and 40.6% in the average-age group. The POI group also had a higher rate of severe multimorbidity than the average-age group (39.2% vs 21.1%); 50% of women in the early menopause group had severe multimorbidity.

As reported in other studies, risk for heart disease and poor bone density were higher in the women with POI than in the women who experienced average-age menopause.² Ischemic heart disease rates were 5.9% in the POI group and 1.8% in the normal menopause

group, while rates of osteoporosis or osteopenia were 21.2% and 14.7%, respectively.

In this cohort, 12,339 individuals had complete menopause data, and their use of menopausal hormone therapy (MHT) was summarized according to menopause status: having ever been on MHT was reported by 53.5% of participants who experienced POI, 40.9% of those who experienced early menopause, and 30.4% of women transitioning to menopause at average age.²

Associated endocrine conditions

Beyond recognizing increased risk of cardiovascular disease and osteoporosis, physicians should be aware that POI also is associated with autoimmune endocrine conditions. Up to 20% of patients with POI are found to have concomitant Hashimoto thyroiditis, and as many as 50% of patients are at risk of developing autoimmune adrenal insufficiency if they have adrenal autoimmunity.⁴ Testing for markers of autoimmune adrenal disease (21-hydroxylase autoantibodies) is recommended for women with POI of unknown cause (ie, no iatrogenic cause identified, genetic testing unrevealing).¹ Such testing is typically done after POI diagnosis and referral to a specialist, as discussed below.

IN POI, HORMONE THERAPY IS PHYSIOLOGIC REPLACEMENT

MHT is a core component of POI management, barring contraindications to its use (Table 2).¹⁹ It includes the administration of estrogen as stand-alone therapy in women without a uterus and in conjunction with progesterone analogs for those who do have a uterus to prevent the development of endometrial cancer. A discussion of the role of testosterone therapy, while of interest to many patients and clinicians, is beyond the scope of this review.

Counseling and individualization of care are essential to the shared decision-making regarding initiation of MHT. Multiple professional organizations that have issued evidence-based guidelines for POI management recommend MHT for patients in whom it is appropriate and safe; the minimum duration of MHT should be until the average age of natural menopause.^{1,5,19}

A closer look at the Canadian Longitudinal Study on Aging² shows that only half of the women with POI were ever on MHT, and the mean duration was only 7.1 years. With a mean age of 34.8 years in the POI group, that translates to a significant shortfall in exogenous estrogen exposure. Further, 80% of those who had ever used hormone therapy discontinued it before study

TABLE 3

Menopausal hormone therapy (MHT) in premature ovarian insufficiency (POI): Principles and recommendations

Systemic MHT is physiologic estrogen replacement in women with POI; oral or transdermal MHT that achieves estrogen replacement levels is recommended as a first-line approach

MHT is indicated to reduce long-term health risks associated with POI and to treat symptoms of estrogen deficiency

MHT is indicated until age 50 to 51 even if estrogen-deficiency symptoms are absent

The need to continue MHT beyond age 50 to 51 should be based on a personalized risk-benefit assessment

Systemic MHT does not provide contraception in women with POI

Women's Health Initiative study results should not be extrapolated to treatment decision-making in women with POI or early menopause because these individuals were not included in the study²²

Based on information from references 1, 5, and 19.

TABLE 4

Premature ovarian insufficiency (POI) causes and risk factors

Classification by cause

Idiopathic (90% of cases)

Genetic

Monosomy X (Turner syndrome)

Fragile X premutation (fragile X mental retardation 1 [*FMR1*]) carrier

Autoimmune

Isolated

In association with polyglandular failure

Iatrogenic

Cancer treatment with chemotherapeutic agents, stem cell transplantation, or pelvic radiation (exposure > 10–12 Gy highest risk)

Bilateral salpingo-oophorectomy

Risk factors for POI and early menopause

Family history (menopause before age 46 in mother, sister, aunt, or grandmother)

Smoking^a

Earlier onset of menopause

Increased prevalence and severity of vasomotor symptoms

^aIn the Canadian Longitudinal Study on Aging,² which examined multimorbidity risk in POI, 15.5% of women in the POI group smoked vs 7.3% in the group who experienced menopause at an average age.

Based on information from references 4 and 5.

initiation. This underutilization of hormone therapy, perhaps due to unfounded safety concerns, represents a missed opportunity to provide evidence-based treatment through at least age 50 to 51.

Regarding potential safety concerns, it is imperative that physicians who encounter women with suspected or diagnosed POI understand that results from the Women's Health Initiative (WHI) are not generalizable to this group. The average age of the study participants in the WHI was approximately 63 years, and the age range was 50 to 79 years.^{20,21} Management with

MHT has a distinct risk-benefit profile in a woman who is 28 years old and could be prematurely deprived of estrogen production for 20 or more years vs a woman who transitions into menopause naturally at age 51. This point is reinforced in a 2024 summary of the WHI study findings by several of the original investigators, who acknowledge that the WHI hormone therapy results “should not be extrapolated to decision-making for women with premature or early onset of menopause (ie, age ≤ 45 years) because these individuals were not studied in the WHI.”²²

TABLE 5
Clinical clues to premature ovarian insufficiency in reproductive-age females

Irregular menstrual cycles (amenorrhea or oligomenorrhea) for ≥ 4 months
Infertility
Vasomotor symptoms
Urogenital atrophy symptoms

Based on information from reference 1.

Optimal management of POI goes beyond hormone replacement to addressing urogenital symptoms, long-term health risks, fertility, sexual well-being, emotional distress, and quality of life.¹ While all the important facets of this symptom spectrum are not addressed in this review, the complexities of management should be individualized to the patient's symptoms, cardiometabolic and general health status, and preferences. For this reason, POI is best managed by specialists with expertise in this condition. However, physicians generally should be familiar with current recommendations for MHT in these patients (Table 3).^{1,5,19,22}

UNCOVERING POI: A ROLE FOR PRIMARY CARE

Timely diagnosis is the first step in the care of female patients with POI, and delays in confirming POI impede opportunities to optimize overall health and well-being. Also, without a diagnosis, physicians cannot factor POI into their risk stratification and reduction approaches to other conditions, eg, in a woman with early signs of cardiovascular disease or a fragility fracture.

Primary care physicians are in a position to expedite diagnosis by being alert to pertinent details in a patient's personal or family history and to complaints and other clinical clues that should raise suspicion about POI and trigger an appropriate evaluation.

Causes and risk factors to bear in mind

Although 90% of cases of POI are idiopathic, there are causes to keep in mind (Table 4).^{2,4,5} Iatrogenic causes of POI are clear and include bilateral salpingo-oophorectomy, gonadotoxic cancer therapy, and other medical or surgical treatments that hasten ovarian senescence before age 40. Genetic and autoimmune causes and associations are also important to test for *after a diagnosis of POI*. In this author's experience, this specialized testing can be performed

and consolidated in collaboration with experienced specialists to ensure accuracy in test performance.

As for risk factors, a positive family history is relevant. A family history of early menopause (before age 46) has been associated with a 6-fold increased likelihood of early menopause.²³ In a cross-sectional study by Cramer et al,²³ women with the following family histories were at higher risk for early menopause: (1) having a sister or multiple family members who experienced menopause before age 46 and (2) having multiple female family members who experienced menopause before age 40.

Cigarette smoking is a risk factor to address at every opportunity, as it is one of the most important behavioral correlates of ovarian aging. Smoking can hasten the onset of menopause by up to 4 years, especially in patients who are heavy smokers.²⁴⁻²⁶ Since oocyte loss is irreversible once it occurs, smoking cessation could only mitigate future oocyte toxicity. Smoking also is linked with increased severity of vasomotor symptoms.^{27,28}

Clinical clues to watch for in young female patients

Irregular and especially absent menstrual cycles for at least 4 months are a possible clue to POI and should be evaluated further (Table 5).¹ In a survey of 48 young women diagnosed with POI, 92% reported that loss of menstrual regularity was their initial symptom.²⁹ More than half of the respondents reported that at least 3 clinician visits occurred before laboratory testing was ordered, and a quarter reported that more than 5 years had elapsed before their POI diagnosis was confirmed.

Many women desiring pregnancy may report inability to conceive. Regardless of the age of the patient, POI should be on the differential diagnosis when amenorrhea is present. It also is important not to overlook symptoms more commonly associated with estrogen deficiency that occurs in perimenopause or menopause. Women with POI are just as likely to experience vasomotor and urogenital symptoms.

Recommended tests if POI is suspected

The recently published international consensus guidelines for POI include diagnostic criteria for the condition; these criteria are summarized in Table 6.¹ When POI is suspected, ordering tests such as FSH and estradiol represents a first diagnostic step. Testing to exclude pregnancy also is indicated. If POI is suspected based on prior clinical history and risk factors and a woman is currently using oral contraceptives, this medication should be discontinued for 1 to 2 weeks before blood is drawn for a more accurate assessment of ovarian

TABLE 6

Approach to premature ovarian insufficiency (POI) diagnosis and evaluation**Criteria for diagnosis of POI^a**

History of bilateral oophorectomy or other iatrogenic cause of POI

OR

≥ 4-month history of spontaneous amenorrhea or irregular menstrual cycles

FSH > 25 IU/L (repeat in 4 to 6 weeks if diagnostic uncertainty)

Estradiol concentration^b

Negative serum human chorionic gonadotropin test

Further testing for POI causes (specialist evaluation)

Genetic (karyotype, fragile X premutation testing)

Autoimmune (adrenal antibodies, thyroid screening)

Other (additional testing individualized)

^aDiagnosis of POI does not require a specialist, but referral is indicated if there is clinical uncertainty. Note that oral contraceptives can skew follicle-stimulating hormone (FSH) and estradiol values and should be stopped for 1 to 2 weeks before hormone testing.

^bEstradiol levels are often ordered in conjunction with FSH concentration to assist with test interpretation. Typically, the combination of low estradiol levels and elevated FSH is consistent with POI.

Based on information from reference 1.

function. If FSH and estradiol levels are diagnostic, no further testing is needed to confirm POI. Repeat FSH testing is indicated otherwise.

Table 6 also lists recommended tests to determine a cause for POI once a diagnosis is confirmed. In the author's experience, patients are best referred to a specialist for genetic, autoimmune, and other specialized testing after POI diagnosis.

Finally, it is important to consider the risk of low bone mass, osteoporosis, and fracture in patients who meet the diagnostic criteria for POI. In this author's practice, it is not uncommon to see a reproductive-age female patient for evaluation and find she has not menstruated for years or has been experiencing symptoms of estrogen deficiency.

In these cases, a patient may have been prematurely estrogen deficient when she should have been building or maintaining bone mass. A baseline dual-energy x-ray absorptiometry scan is prudent and supported by national and international POI guidelines.^{1,5} While there is not a guarantee that payers will routinely cover this testing in the POI population,

there appears to be a growing acceptance that this is a clinical standard, and access is improving.

CONCLUSION

Whether idiopathic or due to iatrogenic, genetic, or autoimmune causes, up to 4% of women worldwide will develop POI, and as such are at risk for its collateral morbidity. Symptoms associated with POI are among the most common presenting complaints for women seeking clinical care including, but not limited to, irregular periods, infertility, sexual dysfunction, and heat intolerance. Timely recognition of POI is essential to mitigate the sequelae of delayed management. Consideration of a broad array of treatment modalities, targeted to the patient and driven by the most appropriate evidence, will promote health, longevity, and quality of life in POI.

DISCLOSURES

The author reports teaching and speaking for the Endocrine Society and Pacific Coast Reproductive Society, serving as Associate Editor for *Fertility and Sterility*, and serving as advisor or review panel participant for Ferring Pharmaceuticals.

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Address: Samantha F. Butts, MD, MSCE, Department of Obstetrics and Gynecology, 500 University Drive, Suite C3608, Hershey, PA 17033; sbutts@pennstatehealth.psu.edu