Premature Ovarian Insufficiency: Etiology, Diagnosis, and Treatment

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At the conclusion of this educational activity, participants should be able to:

1. Discuss potential etiologies of premature ovarian insufficiency (POI).
2. Describe clinical assessment and diagnostic criteria for POI.
3. Discuss strategies for management of symptoms of hypoestrogenism with POI and prevention of long-term health consequences.

Disclosure

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Premature ovarian insufficiency (POI) is a condition marked by impaired ovarian function occurring before the age of 40. POI can have wide-ranging effects on hormone regulation, reproductive potential, sexual health, and overall long-term health, especially bone strength and cardiovascular function. This article provides an overview of the potential etiologies of POI and describes diagnostic criteria and recommended assessment. Current management strategies are discussed, with an emphasis on hormone replacement therapy. Women's health nurse practitioners are well-positioned to facilitate early recognition and diagnosis of POI, provide patient education and counseling for informed decision-making, and collaborate in the development and implementation of individualized care plans to optimize patient outcomes.

Keywords: autoimmune disorders, genetic abnormalities, hormone replacement therapy, premature ovarian insufficiency, primary amenorrhea, secondary amenorrhea

Premature ovarian insufficiency (POI) occurs when the ovaries lose normal function before the age of 40.[1] Also referred to as primary ovarian insufficiency, this condition is distinct from menopause and differs from the previously used term *premature ovarian failure*, which is now less favored due to its implications of irreversible loss of function.[2] POI affects approximately 1–3.5% of women and can have profound and wide-ranging effects on overall health and quality of life.[1]

Because the ovaries play a central role in hormone production, POI leads to decreased estrogen levels, which can disrupt menstrual cycles, impair fertility, and accelerate bone loss, increasing the risk for osteoporosis.[2] Cardiovascular health may also be compromised due to the protective effects of estrogen being diminished.[1,2] Additionally, POI can significantly affect sexual function, leading to vaginal dryness, decreased libido, and discomfort or pain during intercourse, factors that can impact intimate relationships and emotional well-being.[2] Many women also experience psychological effects, including anxiety, depression, and grief related to loss of fertility or altered self-image.[2]

This article reviews the potential etiologies, clinical assessment, diagnostic criteria, and management strategies for POI. Women's health nurse practitioners are in a key position to recognize early signs and symptoms, facilitate timely diagnosis, and support patients through education and counseling. Their role in providing compassionate, patient-centered care is critical to helping individuals navigate both the physical and emotional challenges of POI, ultimately improving long-term health outcomes.

Potential Etiologies

POI presents a diagnostic and treatment challenge as there are several potential etiologies to consider. Genetic abnormalities, iatrogenic factors, autoimmune illness, environmental factors, and idiopathic origin are among the most common causes.[3] Identifying the underlying cause of POI is clinically important, as certain etiologies carry significant implications for the patient and their family.

Genetic Abnormalities

Several genetic abnormalities have been linked to POI. Two genetic abnormalities most commonly correlated with POI are Turner syndrome and fragile X premutation.[1] While Turner syndrome and fragile X premutation are both strongly associated with an increased risk of POI, not all individuals with these genetic conditions will develop POI.[2,4] Turner syndrome is a chromosomal disorder that occurs when a female has only one complete X chromosome and is missing all or part of the second X chromosome.[5] The condition affects approximately 20–50 per 100,000 live female births.[5] The presentation of Turner syndrome can vary significantly depending on the specific karyotype.[5] Turner syndrome can impact

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multiple organ systems and is associated with a variety of medical complications, including short stature, congenital heart defects, renal anomalies, hearing loss, and nonverbal learning disabilities.[5] Historically, pregnancy has been contraindicated in women with Turner syndrome due to elevated risks of maternal mortality, particularly from aortic dissection.[5] However, the 2018 American Heart Association guidelines adopted a more moderate approach, indicating that pregnancy may be safely pursued in selected individuals, even with certain risk factors.[5] Current recommendations advise against pregnancy in women with a history of aortic dissection, an ascending aortic size index (ASI) ≥2.5 cm/m², or an ASI of 2.0–2.5 cm/m² in the presence of additional risk factors.[5]

Females who carry the fragile X premutation defined by an abnormal expansion of the CGG trinucleotide repeat (typically 55–200 repeats) in the *FMR1* gene on the X chromosome are relatively common, with an estimated prevalence of approximately 1 in 150 in the general population.[4,6] While most carriers do not experience intellectual disability, they are at increased risk for a range of health conditions, most notably fragile X-associated primary ovarian insufficiency, which affects up to 20% of female premutation carriers.[4] In addition to reproductive challenges, female carriers may also be at elevated risk for mental health conditions such as anxiety and depression.[4] The severity and presentation of these symptoms can vary widely among individuals, underscoring the importance of individualized care and early genetic counseling. Lastly, it is essential to consider how the *FMR1* premutation can influence family planning decisions, given the risk of transmitting fragile X-associated disorders to offspring.

Iatrogenic Factors

Chemotherapy and radiation can significantly affect ovarian function. The impact is influenced by the patient's age at the time of treatment, the type of chemotherapy and/or radiation location, and the number of treatment cycles received.[7] For example, patients who receive treatment at a younger age tend to have a better chance of preserving some ovarian follicles, which can help maintain ovarian function, while radiation to the brain, whole body, spine, or pelvis significantly increases the risk of POI.[7] In addition to chemotherapy and radiation, gynecologic surgeries involving the ovaries, uterus, or adjacent pelvic structures have a potential impact on ovarian function and reserve, including the risk of POI.[1]

Autoimmune Disorders

Autoimmune disorders can be the origin of POI.[8] Autoimmune disorders are estimated to be responsible for approximately 4–15% of POI cases.[9] Autoimmune oophoritis is an immune-mediated attack on ovarian tissue, leading to inflammation, follicular depletion, and impaired ovarian function.[8] Anti-oocyte antibodies have been detected in approximately 24–73% of patients with confirmed POI. However, reported prevalence rates vary widely across studies, and the accuracy and clinical significance of these findings remain a subject of debate.[8]

Autoimmune oophoritis is frequently observed in patients with autoimmune polyglandular syndromes, particularly type 1 and type 2, where it often presents as part of a broader constellation of endocrine and nonendocrine autoimmune disorders.[8] Both autoimmune oophoritis and POI are also strongly associated with Addison disease and autoimmune thyroid diseases such as Graves disease and Hashimoto thyroiditis.[9] In many cases, autoantibodies targeting steroidogenic enzymes, particularly anti-21-hydroxylase antibodies, are implicated in the pathogenesis. These antibodies can damage both the adrenal cortex, leading to Addison disease, and the ovarian steroid-producing cells, resulting in autoimmune oophoritis. The association with autoimmune thyroid diseases is likely due to a shared autoimmune predisposition, where the immune system aberrantly targets multiple endocrine organs.[9] Timely recognition and management of adrenal insufficiency and thyroid disorders is essential, as both conditions carry the potential for life-threatening complications if left untreated or mismanaged.[8] POI also has established associations with several other autoimmune diseases, both organ-specific and systemic, such as diabetes mellitus, systemic lupus erythematosus, myasthenia gravis, rheumatoid arthritis, Crohn's disease, and multiple sclerosis.[8]

Environmental Factors

Environmental factors such as endocrine disrupting chemicals (EDCs) have been associated with the onset of POI and accelerated ovarian aging through multiple pathways.[10] Common EDCs include phthalates, bisphenols, and phytoestrogens. Individuals encounter EDCs in a variety of ways, ranging from contaminated substances such as air, water, and food to cosmetics and pesticides. EDCs interact with ovarian cell receptors, causing changes in signaling networks and genetic regulation.[10] A recent PubMed review highlights that exposure to EDCs, including phthalates, bisphenol A, perfluoroalkyl and polyfluoroalkyl substances, and polychlorinated biphenyls, is linked to accelerated ovarian aging, diminished ovarian reserve, and earlier menopause.[11] Epidemiologic studies show associations with reduced fertility and POI, while experimental animal research reveals mechanisms such as increased follicular apoptosis and epigenetic changes.[11] Although findings vary and human data remain limited, minimizing EDC exposure is recommended to protect reproductive health.[11]

Idiopathic POI

Finally, patients may meet the clinical and hormonal diagnostic criteria for POI while no causative factor is identified. This occurs when all testing (eg, genetic,

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autoimmune disorder) is normal and there are no identifiable iatrogenic or environmental exposure factors. This accounts for the majority or approximately 75–90% of POI cases.[12] Although idiopathic POI is the most common form, it is often the most distressing for patients. The absence of an identifiable cause can create uncertainty, emotional burden, and significant challenges to both counseling and management.

Assessment and Diagnosis

The clinical presentation of POI is variable. Symptoms may be intermittent as ovarian function fluctuates and can vary in severity depending on the underlying cause. Symptoms often reflect the state of estrogen deficiency. Some individuals may not experience any symptoms other than amenorrhea or irregular menses.[2] Because of the potential long-term health consequences, a thorough assessment is essential. The assessment investigates the potential causes, related medical conditions, psychosocial well-being, and impact of symptoms on quality of life.

Health History

When evaluating for POI, inquire about the patient's pubertal sexual maturation and menstrual history, as well as signs and symptoms of hormonal imbalances, and obtain a complete medical history.[3] In evaluating pubertal sexual maturation, especially in patients with primary amenorrhea, ask about the age at onset of thelarche (breast development) and pubarche (development of pubic and underarm hair). These milestones help assess the progression and timing of puberty.[3] For patients presenting with secondary amenorrhea, obtain a comprehensive menstrual history. This includes documenting the age at menarche, cycle frequency, duration of menstrual flow, the number of pads or tampons used on the heaviest day, and the presence and severity of dysmenorrhea.[3] Symptoms to screen for in individuals being evaluated for menstrual irregularities or suspected hormonal imbalance include acne, hirsutism, weight changes, recent changes in diet or exercise habits, salt cravings, temperature intolerance or fluctuations, fatigue, weakness, nipple discharge, and hair thinning or hair loss.[3] Assess for symptoms associated with estrogen deficiency, such as vasomotor symptoms (hot flashes and night sweats), vaginal dryness or itching, and mood or cognitive changes, including irritability, low mood, or difficulty concentrating.[2,3] In the evaluation of primary amenorrhea, assess for anosmia or hyposmia (lack or decreased sense of smell) to exclude Kallmann syndrome, and obtain a family history of delayed menarche to identify potential constitutional delay of puberty. These details are critical in guiding further diagnostic evaluation and determining appropriate management.[3] A comprehensive health history is essential when evaluating patients with menstrual irregularities or suspected POI. This assessment should include information about allergies, current and past medications, and both medical and surgical histories. Certain medications, such as antipsychotics, hormonal therapies (including contraceptives), and chemotherapeutic agents, can disrupt normal menstrual function. Additionally, medical conditions such as autoimmune disorders and a history of chemotherapy or radiation therapy can significantly impair ovarian function.[3] The obstetric history, including previous pregnancies and outcomes, provides important insights into reproductive health.[2] A surgical history is critical as well, particularly gynecologic procedures involving the ovaries or uterus, as these may directly impact menstrual patterns and fertility potential.[1] Family history of early menopause or other hormonal imbalances should be explored, as these may suggest an underlying genetic or endocrine predisposition.[2]

Physical Examination

In addition to health history, a comprehensive physical examination to assess for anatomical anomalies, Tanner stage, and other pertinent clinical signs is essential.[3] Starting from the top of the body, assess the thyroid gland. Thyroid enlargement or nodules may suggest hormonal dysfunction that could contribute to menstrual irregularities. A breast exam is also essential to determine Tanner staging, which helps assess the patient's stage of pubertal development.[3] Additionally, evaluate for any masses, skin changes, or nipple discharge, which may indicate underlying endocrine or pathologic issues. Assess the skin and hair for signs of hormonal imbalance, particularly acne and hirsutism, which may suggest polycystic ovary syndrome or other causes of androgen excess. Examine the abdomen to assess for masses, tenderness, striae, or pregnancy.[3] Perform a focused genital exam starting with Tanner staging of pubic hair and external genitalia to help determine the degree of sexual maturation. Inspect the clitoris to identify signs of clitoromegaly, which may indicate androgen excess. Evaluation of the vaginal mucosa can provide insight into estrogen status; in estrogen-deficient states (such as POI or menopause), the vaginal epithelium may appear pale, dry, thin, and lacking rugae, while in estrogen-replete states the tissue is typically pink, moist, and rugated.[3] In cases of primary amenorrhea, careful examination of the external genitalia is essential to assess for anatomical anomalies such as vaginal agenesis.[3] These congenital abnormalities can obstruct menstrual flow or prevent normal pubertal development and should be identified early to guide appropriate diagnostic imaging and management.

Laboratory and Diagnostic Tests

If the patient has primary amenorrhea, a pelvic ultrasound is required in the initial workup to assess the reproductive organs.[3] Initial bloodwork testing involves assessing the patient's hormones: follicle stimulating

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hormone (FSH)/luteinizing hormone, estradiol, thyroid-stimulating hormone, prolactin, androgens, and human chorionic gonadotropin to rule out pregnancy.[3] Hormonal therapy, such as birth control, can conceal and bring changes to the menstrual cycle. Therefore, this testing should be completed when the patient is not on hormonal therapy.[1]

Diagnosis Criteria

Lab values indicative of a POI diagnosis include an elevated FSH level of ≥25 IU/L, accompanied by a low estradiol level.[1] Alongside these laboratory findings, patients with POI typically present with primary or secondary amenorrhea and may exhibit signs and symptoms consistent with hypoestrogenism.[1] When the laboratory results correspond with the clinical presentation, a diagnosis of POI can be established.[1]

In cases where diagnostic certainty is lacking, such as when the initial FSH level is inconclusive or the clinical presentation does not align, repeat testing of FSH and estradiol after 4 weeks is recommended.[1] If the second set of results shows elevated FSH and low estradiol, the diagnosis can be confirmed. This approach using updated guidelines streamlines the diagnostic process and allows for earlier diagnosis and prompt initiation of treatment.[1]

Secondary Testing and Risk Assessment After Diagnosis

Once the diagnosis is confirmed, the next step involves additional testing, such as a dual-energy x-ray absorptiometry (DXA) and bloodwork.[1] The DXA is used to determine a baseline bone density.[1] A lipid profile provides a baseline for monitoring cardiovascular health.[1] Additional bloodwork evaluates for potential causes, the patient's ovarian reserve, and nutrient deficiencies. To screen for genetic abnormalities, chromosomal analysis (karyotype) and fragile X premutation testing are advised.[1] For autoimmune disorder evaluation, standard testing includes thyroid function tests as well as screening for adrenal autoantibodies.[3] An anti-Müllerian hormone (AMH) level can be obtained to assess ovarian reserve and potential future fertility.[3] A referral to a reproductive endocrinology and infertility specialist should be considered if the patient has a low AMH and the patient desires fertility preservation. Lastly, vitamin D and calcium levels should be assessed for deficiencies.[1,3]

Management

The goals for treatment of POI include management of symptoms related to hypoestrogenism and prevention of long-term health consequences. A multidisciplinary approach is needed to address associated medical conditions, fertility, and emotional support for patients facing the challenges associated with a diagnosis of POI.[13] Initial treatment decisions are based on individual patient goals and needs, underlying conditions, symptoms, and whether the patient has primary or secondary amenorrhea.

Primary Amenorrhea

Primary amenorrhea is defined as the absence of menstruation under specific clinical conditions that reflect abnormal pubertal development.[3] It may be diagnosed when there is no onset of menstruation and no development of secondary sexual characteristics, such as breast development or pubic hair, by the age of 13. Alternatively, it can be diagnosed if menstruation has not occurred within 3 years following the onset of breast development, which typically marks the beginning of puberty. Lastly, the absence of menstruation by age 15, regardless of whether secondary sexual characteristics are present, also meets the criteria for primary amenorrhea.[3]

The hormonal replacement therapy (HRT) regimen for primary amenorrhea starts with estrogen.[14] Estrogen in the form of a patch or pill is the method used for pubertal induction. The patch is the preferred method because it avoids first-pass hepatic metabolism, which lowers the risk for venous thromboembolism.[14] In addition, the transdermal delivery mirrors endogenous estrogen secretion.[14]

Typically, HRT is initiated with a low dose of estrogen, which is gradually increased over time to reach the full therapeutic level.[14] For POI associated with a known condition, such as Turner syndrome, pubertal induction generally begins around 11 years of age and typically spans 2–3 years to complete.[1,14] The North American Society for Pediatric and Adolescent Gynecology provides an example schedule for pubertal induction in patients with Turner syndrome.[14] If the diagnosis is made at a later age, the pubertal induction process is modified and typically accelerated to achieve appropriate development within a shorter time frame.[1] The therapeutic estrogen dose varies by formulation and includes a 0.1-mg transdermal patch, 1- to 2-mg pill, or 0.1-mg vaginal ring.[15,16]

Progesterone is typically added to the hormone replacement regimen for endometrial protection around the 2-year mark or sooner if breakthrough bleeding occurs.[14] Progesterone can be administered in various forms, including oral medroxyprogesterone acetate (a synthetic progestin), micronized (bioidentical) progesterone, or via a progesterone-releasing intrauterine device.[15] Both medroxyprogesterone acetate and micronized progesterone can be given cyclically or continuously.[15,16] It is suggested that progesterone, such as micronized progesterone, be taken at bedtime due to its potential sedative effects.[13] The dosing regimen varies depending on the type of progesterone used, whether it is administered cyclically or continuously, and the clinical guidelines or references.[3,15,16] Once pubertal induction is complete with the patient having reached a therapeutic dose of estrogen

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and progesterone added to the regimen, additional HRT options become available.

Secondary Amenorrhea

Patients with POI presenting with secondary amenorrhea typically have a history of normal pubertal development and menarche but subsequently experience irregular menstrual cycles or complete cessation of menstruation.[3] In the case of POI, current guidelines define menstrual irregularity as cycles that are at least 3–4 months apart.[3,12]

It is recommended to start estrogen therapy at a moderate dose around half of the full therapeutic dose, such as a 0.05-mg estrogen patch, and titrate efficiently to the therapeutic level. In addition to the estrogen, a form of progesterone should be included in the regimen for endometrial protection in patients who have a uterus.[3] Patients may continue using separate estrogen and progesterone therapies or consider a combined HRT method.[1] Additionally, some patients receiving systemic HRT may require vaginal estrogen to manage genitourinary syndrome of menopause.[1] Vaginal estrogen comes in the form of cream, tablet, suppositories, or vaginal ring.[13] While the rate of spontaneous ovulation is low, one additional aspect to consider is the need for contraception.[3] Studies estimate that approximately 5% of women with POI experience intermittent spontaneous ovulation, corresponding to a similar percentage who may conceive naturally.[3,1] Consequently, effective contraception should be discussed and recommended for individuals with POI who are not attempting pregnancy to prevent unintended conception. This consideration is particularly important given the unpredictable nature of ovarian function in POI and the potential health implications of unplanned pregnancy.[1] The patient may switch to a combined contraceptive method. It is recommended that the combined contraceptive be taken in a continuous or extended cycling regimen.[1] An alternative approach involves the patient continuing the estrogen HRT, while incorporating contraception using a progestin-only method.[3]

Patients with POI are advised to remain on HRT until the average age of menopause, typically 52 years of age.[13] HRT is essential for these patients, as it supports numerous bodily functions, including heart and bone health, cognitive performance and mental well-being, and reproductive health.[13,15]

Nonhormonal Treatment Options

For patients with POI who have contraindications to HRT, nonhormonal treatment options are available to manage symptoms and prevent long-term health complications.[1] Bisphosphonates may be considered for those with osteoporosis or osteopenia and additional fracture risk factors, although they are generally not first-line in younger women who can take estrogen, as HRT provides broader systemic benefits.[17] Available oral bisphosphonate options include alendronate, ibandronate, or risedronate. Intravenous options include zoledronic acid and ibandronate.[17] Treatment should be coordinated with an osteoporosis specialist. Bone mineral density should be monitored with DXA scans every 1–3 years, and adequate calcium and vitamin D intake ensured.[17] Reassessment of the use of bisphosphonates after 3–5 years is recommended due to limited long-term safety data.[17] Although adverse neonatal outcomes like spontaneous abortion and low birth weight have been reported with bisphosphonate exposure before or during pregnancy, current evidence does not confirm a direct causal link. Further research is needed to guide clinical decisions regarding their use in maternal and fetal health.[18]

In addition, nonhormonal medications such as selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, gabapentin, fezolinetant, and oxybutynin may be prescribed to manage vasomotor symptoms, with choices tailored to the patient's individual needs and medical history.[2] The existing data on these nonhormonal methods are primarily derived from studies in older adult populations; therefore, they are not currently recommended for use in younger individuals due to limited evidence on safety and efficacy.[1] While nonhormonal therapies are available to address many menopausal concerns, HRT offers the additional potential benefit of cardiovascular protection.[1]

Ongoing Support for Health

Annual visits provide an important opportunity to monitor bone health and cardiovascular risk factors. Estrogen deficiency symptoms including genitourinary symptoms can be assessed, and adherence to or concerns with HRT can be addressed. Sexual health, fertility and/or contraception needs, and support for psychological health are important components for discussion. Scheduling tests to monitor risk factors is dependent on current health status, relevant symptoms, and previous test results (Box). A multidisciplinary approach should be continued with review of visits with specialists and initiation of any needed referrals for the management of complications and comorbidities.[1,2]

All women with POI should be encouraged to adopt a healthy lifestyle to support their overall health and reduce the risk of complications such as osteoporosis, cognitive impairment, and cardiovascular disease.[2] A balanced diet that includes adequate calcium and vitamin D is essential for bone health, and supplementation may be required if dietary intake is insufficient. Regular weightbearing exercise such as walking, jogging, or resistance training should be promoted to support both bone and heart health. Avoiding tobacco use is critical, as smoking accelerates bone loss and increases cardiovascular risk. Women should also aim to maintain a healthy body weight, as extremes in weight can negatively affect hormonal and metabolic balance. In addition, limiting alcohol intake is advised, since excess alcohol can impair bone health. Lastly, addressing emotional well-being

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Box. Follow-Up and Ongoing Support For Health[1,2]

- Bone health: Assess risk factors. Perform bone density testing every 1–5 years depending on risk factors, previous test results, and clinical judgment.
- Cardiovascular health: Assess risk factors, lipid profile, and hemoglobin A1c based on risk factors, previous test results, and clinical judgment.
- Estrogen deficiency: Assess for symptoms (genitourinary, vasomotor, cognition). Discuss adherence to HRT and any concerns.
- Sexual health: Assess and address any concerns.
- Fertility and contraception: Assess need for and provide contraception. Discuss fertility concerns and make referrals if desired.
- Psychological health: Screen for depression and anxiety. Address quality of life issues.
- Healthy lifestyle: Provide education and encouragement.
- Other health conditions: Manage and refer as needed.
- Other tests: Obtain TSH every 5 years or sooner if there are symptoms or risk factors. Repeat of antibody tests is not indicated unless new signs or symptoms arise.

Abbreviations: HRT, hormone replacement therapy; TSH, thyroid stimulating hormone.

through stress management and access to mental health support is a key component of comprehensive care for women living with POI.[2]

Implications for Practice

For women's health nurse practitioners, a thorough understanding of the clinical presentation, diagnostic evaluation, and management options for POI is crucial. Early recognition and accurate assessment allow nurse practitioners to guide timely interventions that can mitigate the long-term health consequences of POI, such as bone loss, cardiovascular risk, and psychosocial impacts. By providing patient-centered education, counseling, and individualized hormone therapy dosing, nurse practitioners play a vital role in optimizing health outcomes and supporting women through the complexities of this condition. Their expertise ensures that care is holistic, evidence-based, and tailored to each patient's unique needs.

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