The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

# COMMITTEE OPINION

Number 605 • July 2014
Reaffirmed 2018

**Committee on Adolescent Health Care**

*This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.*

# Primary Ovarian Insufficiency in Adolescents and Young Women

**ABSTRACT:** Primary ovarian insufficiency is the depletion or dysfunction of ovarian follicles with cessation of menses before age 40 years. There is no consensus on criteria to identify primary ovarian insufficiency in adolescents, and delay in diagnosis is common. Health care providers who make this clinical diagnosis should be mindful of the sensitive nature of this medical condition. Patients and their families should be counseled on the effect of the patient's condition on future fertility, on the risk of comorbidities associated with primary ovarian insufficiency, and on the condition's potential for genetic inheritance. Psychologic counseling also should be offered because impaired self-esteem and emotional distress have been reported after diagnosis of primary ovarian insufficiency. Once primary ovarian insufficiency is diagnosed, patients should be evaluated at least annually. The goals of hormonal therapy extend beyond simply symptom relief to levels that support bone, cardiovascular, and sexual health. Referrals to a reproductive endocrinology and infertility specialist should be made when desired by the patient and family to further discuss available reproductive treatments.

The number of reproductive years among women varies, depending on steroid production by the ovaries. Primary ovarian insufficiency is the depletion or dysfunction of ovarian follicles with cessation of menses before age 40 years, and it has previously been referred to as premature menopause or primary ovarian failure. "Primary ovarian insufficiency" is the preferred term advocated by the National Institutes of Health because ovarian function is intermittent or unpredictable in many cases. Because 5–10% of women with primary ovarian insufficiency experience spontaneous conception and delivery, primary ovarian insufficiency can be distinguished from natural menopause and also may be described as decreased ovarian reserve (1, 2). This Committee Opinion addresses primary ovarian insufficiency in adolescents and young women.

## Etiology

Follicle depletion or dysfunction in adolescents may be caused by many different factors. It is often caused by chromosomal abnormalities or damage from chemotherapy or radiation therapy. It is also associated with a premutation in the *FMR1* gene for fragile X. Primary ovarian insufficiency may be associated with multiple endocrinopathies, including hypoparathyroidism and hypoadrenalism. Less frequently, it can result from infiltrative or infectious processes (3). Pelvic surgery also may lead to impairment of ovarian function. Approximately 4% of women who have primary ovarian insufficiency will have adrenal or ovarian antibodies, which suggests an autoimmune mechanism for disease (4). In many cases, the etiology remains unknown (1).

### Chromosomal Abnormalities

A common cause of primary ovarian insufficiency in adolescents is gonadal dysgenesis, with or without Turner syndrome (3). When adolescents present with primary amenorrhea and no associated comorbidities, 50% are found to have abnormal karyotypes. Among younger women (aged 30 years or younger) with secondary amenorrhea, 13% also have been noted to have an abnormal karyotype (5). Although pubertal and growth delays are common in this group, many affected females may first be recognized at the time of evaluation for menstrual abnormalities.

### Chemotherapy and Radiation Therapy

The immediate loss of ovarian function after chemotherapy or radiation therapy is termed "acute ovarian failure," which may be transient. With chemotherapy, the age of the patient when she received chemotherapy, types of medication, and number of doses all have an effect on the possibility of gonadotoxicity. Although the highest incidence of acute ovarian failure occurs after the use of alkylating agents or procarbazine, the younger the patient at the time of receiving the chemotherapy, the more likely it is that some follicles will survive (6–8). Whole-body, whole-brain, pelvic, and spinal irradiation also increase the risk of acute ovarian failure (9). Pelvic irradiation (especially doses more than 10 Gy) is a significant risk factor for acute ovarian failure (8). Chemotherapy combined with radiation therapy increases the chance of acute ovarian failure. It should be noted that even females who menstruate after chemotherapy have an increased lifetime risk of primary ovarian insufficiency (9).

### Fragile X Syndrome

Fragile X syndrome is the most common form of hereditable mental retardation. Among females with primary ovarian insufficiency and a normal karyotype, 6% have a premutation in the *FMR1* gene (5). Although the onset of menstruation appears to be normal among premutation carriers in adolescence, approximately 1% of premutation carriers will experience their final menses before age 18 years (10). If a woman has a personal or family history of ovarian failure or an elevated follicle-stimulating hormone (FSH) level before age 40 years without a known cause, fragile X premutation carrier testing should be offered (11).

## Diagnosis

There is no consensus on criteria to identify primary ovarian insufficiency in adolescents, and delay in diagnosis is common. (See Box 1 for a reasonable approach to diagnosis and initial evaluation.) Although some adolescent females will report hot flushes or vaginal symptoms like dryness or dyspareunia, the most common presenting symptom of primary ovarian insufficiency is primary or secondary amenorrhea. Among patients with amenorrhea, the incidence of primary ovarian insufficiency ranges from 2% to 10% (3). Abnormal bleeding patterns also may include oligomenorrhea (bleeding that occurs less frequently than every 35 days), nonstructural causes of abnormal uterine bleeding (eg, ovulatory dysfunction, iatrogenic, or not yet classified), or polymenorrhea (bleeding that occurs more often than every 21 days) (1). Because irregular menstrual cycles are both common during early adolescence and an initial symptom of early primary ovarian insufficiency, diagnosis can be difficult in this population. Although less than 10% of women who present with abnormal menses will ultimately be found to have primary ovarian insufficiency, the condition has such detrimental consequences on bone health that early diagnosis of this condition is important (12). Therefore, in young females it is important to evaluate amenorrhea or a change from regular to irregular menses for 3 or more consecutive months in the absence of hormonal preparations such as oral contraceptives (OCs) for all potential causes, including pregnancy, polycystic ovary syndrome, hypothalamic amenorrhea, thyroid abnormalities, hyperprolactinemia, and primary ovarian insufficiency (1, 12). Inquiries should be made about family medical history because females with a family history of early menopause are at risk of primary ovarian insufficiency (13).

Initial laboratory evaluation for suspected primary ovarian insufficiency includes measurements of basal FSH and basal estradiol levels and tests to rule out causes such as pregnancy, thyroid disease, and hyperprolactinemia. Gonadotropin and estradiol values may be altered by concomitant use of hormonal preparations and thus should only be obtained in patients who are not taking hormonal medications, including OCs. If gonadotropins are elevated into the menopausal range (typically, basal FSH levels will be greater than 30–40 mIU/mL, depending on the laboratory used), a repeat FSH measurement is indicated in 1 month. If the result indicates that FSH is elevated, a diagnosis of primary ovarian insufficiency can be established. Estradiol levels of less than 50 pg/mL indicate hypoestrogenism.

Antimüllerian hormone and inhibin B are being evaluated to determine their value in the diagnosis of primary ovarian insufficiency. With further research, antimüllerian hormone testing may become increasingly valuable in assessing ovarian reserve before and after chemotherapy for young women with cancer, before and after ovarian surgery, and for females at high risk of primary

**Box 1. Diagnosis and Initial Evaluation of Primary Ovarian Insufficiency** ⇦

Diagnosis of primary ovarian insufficiency

- Menstrual irregularity for at least 3 consecutive months
- Follicle-stimulating hormone and estradiol levels (two random tests at least 1 month apart)
- Prolactin and thyroid function test

If diagnosis is confirmed:

- Karyotype
- *FMR1* premutation
- Adrenal antibodies
  - — 21-hydroxylase (CYP21) by immunoprecipitation
  - or
  - — Indirect immunofluorescence
- Pelvic ultrasonography

Data from Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med 2009;360:606–14.

ovarian insufficiency (14). However, there is significant variability in inhibin B levels between menstrual cycles. This marker does not reliably predict a poor response to ovarian stimulation, and thus, inhibin B is not a recommended test.

Surrogate markers of ovarian reserve (presence of regular menses, serial serum estradiol levels, and antral follicle count by transvaginal ultrasonography) are highly variable and are not predictive of future fertility or hormonal production in young women who have undergone treatment for cancer (6, 7), but are currently undergoing investigation. Once a diagnosis of primary ovarian insufficiency is established, further testing, including karyotype, adrenal antibodies, *FMR1* premutation, and pelvic ultrasonography, may be indicated to investigate possible etiologies of primary ovarian insufficiency.

## Treatment

Optimal treatment of an adolescent in whom primary ovarian insufficiency is diagnosed requires special sensitivity to both the physical and emotional needs of young women receiving this diagnosis during a time of significant developmental changes. Patients may be emotionally unprepared and may require more information and understanding to process the immediate and long-term implications of this disorder.

### Hormonal Therapy

For adolescents with primary ovarian insufficiency, the objective of treatment is to replace the hormones that the ovary would be producing before the age of menopause, making the treatment distinctly different from hormonal therapy for menopause that focuses on the treatment of menopausal symptoms. The goals of hormonal therapy extend beyond simply symptom relief to levels that support bone, cardiovascular (CV), and sexual health. Regardless of the etiology, patients with primary ovarian insufficiency are estrogen deficient. Thus, young women with primary ovarian insufficiency may need higher doses of estrogen than menopausal women to ensure adequate replacement and optimal bone health (12). In girls with absent or incomplete breast development, estrogen therapy should be initiated and increased slowly before administration of graduated progesterone dosages until breast development is complete to prevent tubular breast formation. For those patients who have not initiated or completed pubertal growth and sexual maturity, consultation with a specialist in growth and development and hormonal therapy in children is recommended.

Once pubertal development is complete, ongoing hormonal therapy will be necessary for long-term health. Hormonal support involves daily therapy with the goal of maintenance of normal ovarian functioning levels of estradiol. Transdermal, oral, or occasionally transvaginal estradiol in doses of 100 micrograms daily is the therapy of choice to mimic a physiologic dose range and to achieve symptomatic relief. The addition of cyclic progesterone for 10–12 days each month is protective against endometrial hyperplasia and endometrial cancer, risks of unopposed estrogen. Oral estradiol may be used, but it increases the potential for thromboembolism relative to transdermal estradiol due to the first-pass effect on the liver. Oral contraceptives contain higher doses of estrogen than are necessary for hormonal therapy; therefore, they are not recommended as first-line hormonal therapy.

## Fertility and Contraception

Fertility may persist even when few functional follicles are present. Because of occasional spontaneous resumption of ovarian function, there is a 5–10% chance of spontaneous pregnancy despite a diagnosis of primary ovarian insufficiency (10). Unless pregnancy is desired, a discussion of effective contraception should take place. Although OCs are commonly prescribed in this situation, the use of barrier methods or an intrauterine device is encouraged (1). If a patient chooses a nonestrogen method of contraception, estrogen also should be administered to preserve bone mineral density and prevent other adverse effects of hypoestrogenemia. A missed menstrual cycle should warrant a pregnancy test.

## Associated Comorbidities

Primary ovarian insufficiency increases the risk of bone loss, CV disease, and endocrine disorders. Health care providers also should be aware of the potential psychologic effects of primary ovarian insufficiency and should counsel family members and patients on the risk of associated comorbidities.

### Bone Loss

Loss of ovarian function at an early age affects bone architecture at the very time when bone accrual is at its maximum. There are no published data to support specific recommendations for dual-energy X-ray absorptiometry scanning in adolescents with estrogen deficiency. Although some experts suggest monitoring bone density annually in adolescents with estrogen deficiency during early to mid puberty to document peak bone accrual and then every 2 years in late adolescence, others do not because the implications of a low bone mineral density result in this population are unclear given the low risk of fracture and the potential for long-term treatment of low bone mass. To date, long-term use of bisphosphonates is not recommended in the adolescent population because of uncertain adverse effects and safety profiles. Further research in this area is needed.

### Cardiovascular Disease

Individuals with early loss of endogenous estrogen have been shown to have an increased risk of CV mortality (15). Although data in the adolescent population are lacking and there are no standard screening regimens

for CV disease in this population, vigilant monitoring is warranted, and practitioners should help patients optimize CV health. Routine visits should include counseling on tobacco avoidance and appropriate diet and exercise to optimize CV health. Measuring blood pressure at least annually and lipid levels every 5 years is recommended. Patients with Turner syndrome have additional CV risks, including aortic aneurysm. Additional guidelines for patients with Turner syndrome and no obvious CV pathology include either routine cardiac imaging every 5–10 years or focused imaging when transitioning from a pediatric to adult health care provider, before attempting pregnancy, or with the appearance of hypertension to assess for coarctation or aortic stenosis (16). Although early loss of ovarian function has been associated as a risk factor for CV mortality, there are no data indicating that these patients are at an increased risk of CV adverse effects from hormonal therapy (15, 17).

### Endocrine Disorders

Approximately 20% of adults with idiopathic primary ovarian insufficiency will experience hypothyroidism, most commonly Hashimoto thyroiditis (5, 18). Following initial diagnosis of primary ovarian insufficiency, it is appropriate to test thyrotropin levels for the presence of thyroid peroxidase antibodies. Although no recommendations for routine thyroid screening exist in this population, given the high prevalence of this disorder in patients with primary ovarian insufficiency, it is acceptable to test for thyroid disease every 1–2 years. Patients with primary ovarian insufficiency also have a 50% chance of developing adrenal insufficiency if they have adrenal autoimmunity. Patients should be tested for adrenal antibodies and if results are positive, should undergo yearly corticotropin stimulation testing. Data are lacking on the follow-up of patients with negative test results (1). Diabetes mellitus, pernicious anemia, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, and dry eye syndrome also have been associated with primary ovarian insufficiency, and testing should be based on symptomatology. Antiovarian antibodies may be present in these patients, but their specificity and pathogenic usefulness has not been validated (17).

### Patient Counseling

When primary ovarian insufficiency is diagnosed in the adolescent female, the patient and her family are often unprepared for such news with its implications for compromised fertility and impaired self-image and the need for long-term hormonal therapy. It is best to inform the patient and family by having a direct conversation in the office (12). Adolescents may demonstrate myriad emotions ranging from apathy or denial to remorse or sadness, and these emotions may be different from those of their parents or guardians. Practitioners can consider telling the parents separately from their children so that the parents will have an opportunity to understand the diagnosis and adjust their demeanor to be most supportive of their daughters. Parents also can provide valuable insights about their daughters' ability to appreciate the significance of the diagnosis of primary ovarian insufficiency and guide the clinician or team. Health care providers who make this clinical diagnosis should be mindful of the sensitive nature of this medical condition as well as the cultural significance of the diagnosis within the family unit. Use of the term "premature ovarian failure" can be particularly troubling to a young woman and her family (3). "Insufficiency" is the more accepted term in this population and more truly reflects the possibility of intermittent resumption of function. Patients and their families should be counseled on the effect of the patient's condition on future fertility. Referrals to a reproductive endocrinology and infertility specialist should be made when desired by the patient and family to further discuss available reproductive treatments. In vitro fertilization with donor oocytes is often the most appropriate treatment; there are otherwise limited therapeutic options. Although the procedure may not be ideal, it may provide some hope for the patient who is told that her fertility is severely compromised. However, this is not a recommended option for patients with Turner syndrome because of the risk of aortic rupture during pregnancy. Psychologic counseling also should be offered because impaired self-esteem and emotional distress have been reported after diagnosis of primary ovarian insufficiency (19–21). Because many patients will use the Internet to learn more about their diagnoses, referral to appropriate sources for support is an efficient means to enhance patient care (see Resources).

A greater understanding of female reproductive biology and the physiologic effect of primary ovarian insufficiency enables health care providers to offer counseling for these young women. Once primary ovarian insufficiency is diagnosed, patients should be evaluated at least annually. Physicians should address the special needs of this population and counsel family members and patients on the risk of comorbidities associated with primary ovarian insufficiency and the condition's potential for genetic inheritance. Referral to accurate medical information is encouraged.

## Resources

*The following resources are for information purposes only. Referral to these sources and web sites does not imply the endorsement of the American College of Obstetricians and Gynecologists. These resources are not meant to be comprehensive. The exclusion of a source or web site does not reflect the quality of that source or web site. Please note that web sites are subject to change without notice.*

International Premature Ovarian Failure Association
PO Box 23643
Alexandria, VA 22304
(703) 913-4787
http://www.ipofa.org

*Eunice Kennedy Shriver* National Institute of Child Health and Human Development

*Eunice Kennedy Shriver* National Institute of Child Health and Human Development. Primary ovarian insufficiency. Available at: http://poi.nichd.nih.gov. Retrieved February 5, 2014.

National Fragile X Foundation

National Fragile X Foundation. Fragile X-associated disorders: FXPOI. Available at: http://www.fragilex.org/fragile-x-associated-disorders/fxpoi. Retrieved February 5, 2014.

## References


1. Nelson LM. Clinical practice. Primary ovarian insufficiency. N Engl J Med 2009;360:606–14. [PubMed] [Full Text] ⇦
2. Testing and interpreting measures of ovarian reserve: a committee opinion. Practice Committee of the American Society for Reproductive Medicine. Fertil Steril 2012;98:1407–15. [PubMed] [Full Text] ⇦
3. Rebar RW. Premature ovarian "failure" in the adolescent. Ann N Y Acad Sci 2008;1135:138–45. [PubMed] ⇦
4. Rafique S, Sterling EW, Nelson LM. A new approach to primary ovarian insufficiency. Obstet Gynecol Clin North Am 2012;39:567–86. [PubMed] [Full Text] ⇦
5. Nelson LM, Covington SN, Rebar RW. An update: spontaneous premature ovarian failure is not an early menopause. Fertil Steril 2005;83:1327–32. [PubMed] [Full Text] ⇦
6. Wallace WH, Anderson RA, Irvine DS. Fertility preservation for young patients with cancer: who is at risk and what can be offered? [published erratum appears in Lancet Oncol 2005;6:922]. Lancet Oncol 2005;6:209–18. [PubMed] ⇦
7. Johnston RJ, Wallace WH. Normal ovarian function and assessment of ovarian reserve in the survivor of childhood cancer. Pediatr Blood Cancer 2009;53:296–302. [PubMed] ⇦
8. Green DM, Sklar CA, Boice JD Jr, Mulvihill JJ, Whitton JA, Stovall M, et al. Ovarian failure and reproductive outcomes after childhood cancer treatment: results from the Childhood Cancer Survivor Study. J Clin Oncol 2009;27:2374–81. [PubMed] [Full Text] ⇦
9. Duffy C, Allen S. Medical and psychosocial aspects of fertility after cancer. Cancer J 2009;15:27–33. [PubMed] [Full Text] ⇦
10. De Caro JJ, Dominguez C, Sherman SL. Reproductive health of adolescent girls who carry the FMR1 premutation: expected phenotype based on current knowledge of fragile x-associated primary ovarian insufficiency. Ann N Y Acad Sci 2008;1135:99–111. [PubMed] ⇦
11. Carrier screening for fragile X syndrome. Committee Opinion No. 469. American College of Obstetricians and Gynecologists. Obstet Gynecol 2010;116:1008–10. [PubMed] [*Obstetrics & Gynecology*] ⇦
12. Nelson LM. Spontaneous premature ovarian failure: young women, special needs. Menopause Manag 2001;10(4):1–6. [Full Text] ⇦
13. Menstruation in girls and adolescents: using the menstrual cycle as a vital sign. ACOG Committee Opinion No. 349. Obstet Gynecol 2006;108:1323–8. [PubMed] [*Obstetrics & Gynecology*] ⇦
14. Nelson SM. Biomarkers of ovarian response: current and future applications. Fertil Steril 2013;99:963–9. [PubMed] [Full Text] ⇦
15. van der Schouw YT, van der Graaf Y, Steyerberg EW, Eijkemans JC, Banga JD. Age at menopause as a risk factor for cardiovascular mortality. Lancet 1996;347:714–8. [PubMed] ⇦
16. Pinsker JE. Clinical review: Turner syndrome: updating the paradigm of clinical care. J Clin Endocrinol Metab 2012;97:E994–1003. [PubMed] [Full Text] ⇦
17. Rebar RW. Premature ovarian failure. Obstet Gynecol 2009;113:1355–63. [PubMed] [*Obstetrics & Gynecology*] ⇦
18. Kim TJ, Anasti JN, Flack MR, Kimzey LM, Defensor RA, Nelson LM. Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. Obstet Gynecol 1997;89:777–9. [PubMed] [*Obstetrics & Gynecology*] ⇦
19. Liao KL, Wood N, Conway GS. Premature menopause and psychological well-being. J Psychosom Obstet Gynaecol 2000;21:167–74. [PubMed] ⇦
20. Schmidt PJ, Cardoso GM, Ross JL, Haq N, Rubinow DR, Bondy CA. Shyness, social anxiety, and impaired self-esteem in Turner syndrome and premature ovarian failure. JAMA 2006;295:1374–6. [PubMed] [Full Text] ⇦
21. Groff AA, Covington SN, Halverson LR, Fitzgerald OR, Vanderhoof V, Calis K, et al. Assessing the emotional needs of women with spontaneous premature ovarian failure. Fertil Steril 2005;83:1734–41. [PubMed] [Full Text] ⇦




ISSN 1074-861X

Primary ovarian insufficiency in adolescents and young women. Committee Opinion No. 605. American College of Obstetricians and Gynecologists. Obstet Gynecol 2014;123:193–7.