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Hormone Therapy in Primary Ovarian Insufficiency

ABSTRACT: Primary ovarian insufficiency describes a spectrum of declining ovarian function and reduced fecundity due to a premature decrease in initial follicle number, an increase in follicle destruction, or poor follicular response to gonadotropins. The sequelae of primary ovarian insufficiency include vasomotor symptoms, urogenital atrophy, osteoporosis and fracture, cardiovascular disease, and increased all-cause mortality. In women with primary ovarian insufficiency, systemic hormone therapy (HT) is an effective approach to treat the symptoms of hypoestrogenism and mitigate long-term health risks if there are no contraindications to treatment. Hormone therapy is indicated to reduce the risk of osteoporosis, cardiovascular disease, and urogenital atrophy and to improve the quality of life of women with primary ovarian insufficiency. Although exogenous estrogen replacement is recommended for women with primary ovarian insufficiency, data comparing various hormonal regimens for disease prevention, symptom amelioration, and safety are lacking in this population. As a first-line approach, HT (either orally or transdermally) that achieves replacement levels of estrogen is recommended. Combined hormonal contraceptives prevent ovulation and pregnancy more reliably than HT; despite only modest odds of spontaneous pregnancy in women with primary ovarian insufficiency, this is a critical consideration for those who deem pregnancy prevention a priority. Treatment for all women with primary ovarian insufficiency should continue until the average age of natural menopause is reached (age 50–51 years). Finally, considering the challenges that adolescents and young women may face in coping with the physical, reproductive, and social effects of primary ovarian insufficiency, comprehensive longitudinal management of this condition is essential.

Recommendations and Conclusions

The American College of Obstetricians and Gynecologists (the College) makes the following recommendations and conclusions:

- Primary ovarian insufficiency is a pathologic condition that should not be considered a hastening of natural menopause.
- Although women with primary ovarian insufficiency share common health risks with naturally menopausal women, the approach to health maintenance in these women is distinct.
- In women with primary ovarian insufficiency, systemic hormone therapy (HT) is an effective approach

to treat the symptoms of hypoestrogenism and mitigate long-term health risks if there are no contraindications to treatment.

- Hormone therapy is indicated to reduce the risk of osteoporosis, cardiovascular disease, and urogenital atrophy and to improve the quality of life of women with primary ovarian insufficiency.
- In contrast to the treatment of postmenopausal osteopenia or osteoporosis, which focuses on bisphosphonates as first-line therapy, low bone mass in women with primary ovarian insufficiency is managed most appropriately with HT.
- Women with primary ovarian insufficiency may experience hot flushes, night sweats, vaginal dryness,

dyspareunia, and disordered sleep; some symptoms may develop before cycle irregularity. These symptoms routinely respond well to HT as indicated.

- As a first-line approach, HT (either orally or transdermally) that achieves replacement levels of estrogen is recommended. However, serum estradiol level testing is not recommended to monitor the effects of treatment.

- Combined hormonal contraceptives prevent ovulation and pregnancy more reliably than HT; despite only modest odds of spontaneous pregnancy in women with primary ovarian insufficiency, this is a critical consideration for those who deem pregnancy prevention a priority.

- For a woman who prefers noncontraceptive estrogen replacement and wants highly effective contraception, insertion of a levonorgestrel intrauterine device is preferable to oral progestin therapy.

- Treatment for all women with primary ovarian insufficiency should continue until the average age of natural menopause is reached (age 50–51 years).

Primary ovarian insufficiency describes a spectrum of declining ovarian function and reduced fecundity due to a premature decrease in initial follicle number, an increase in follicle destruction, or poor follicular response to gonadotropins (1, 2). At least 90% of cases of primary ovarian insufficiency are idiopathic (1, 3). Only a small number of genetic and molecular derangements have been described that damage human follicle number and function severely enough to result in overt primary ovarian insufficiency (1, 4–7). Among the most notable conditions that result in primary ovarian insufficiency are those in which one X chromosome is damaged (isochromosome X), lost (Turner syndrome and Turner mosaics), or altered (*FMR1* permutation carriers). A number of autoimmune disorders and single-gene defects also are associated with primary ovarian insufficiency. Young women with cancer or other serious illnesses that require chemotherapy or pelvic radiation are at risk of primary ovarian insufficiency because these agents may cause profound and rapid follicular atresia. Detailed information regarding the workup, causes, and diagnosis of primary ovarian insufficiency is reviewed in Committee Opinion No. 605, *Primary Ovarian Insufficiency in Adolescents and Young Women* (3).

Overt ovarian insufficiency refers to women younger than 40 years who have elevated follicle-stimulating hormone levels in the menopausal range (at least 30–40 mIU/mL) and amenorrhea (1, 3, 8). This clinical state, traditionally referred to as "premature menopause" or "premature ovarian failure," affects 1% of women. The term "primary ovarian insufficiency" more accurately captures the nature of ovarian dysfunction displayed in affected women, 50% of whom experience infrequent ovulation and menstrual cycles after diagnosis and 5–10% of whom may achieve spontaneous pregnancies (1).

Regardless of the underlying cause of primary ovarian insufficiency, the consequences of ovarian dysfunction and hypoestrogenism can be dire for affected individuals. The sequelae of primary ovarian insufficiency include vasomotor symptoms, urogenital atrophy, osteoporosis and fracture, cardiovascular disease, and increased all-cause mortality (9–11). In women with primary ovarian insufficiency, systemic HT is an effective approach to treat the symptoms of hypoestrogenism and mitigate long-term health risks if there are no contraindications to treatment. Hormone therapy is indicated to reduce the risk of osteoporosis, cardiovascular disease, and urogenital atrophy and to improve the quality of life of women with primary ovarian insufficiency. The results from the Women's Health Initiative trials related to menopause therapy are not applicable to young women with primary ovarian insufficiency whose exposure to physiologic estrogen has been withdrawn prematurely. When HT is withheld from women with primary ovarian insufficiency because of extrapolation of good epidemiologic evidence from the wrong population, those women may experience many negative health consequences. The focus of this Committee Opinion is to review the medical and psychosocial risks facing women with primary ovarian insufficiency and to discuss the various HT treatment options available.

Symptoms and Health Consequences

Bone Loss and Fracture Risk

Women with primary ovarian insufficiency-related estrogen deficiency are at risk of osteopenia, osteoporosis, and fracture, especially if hypoestrogenism occurs early in life and before accrual of peak bone mass (3, 12–14). A number of large, well-designed prospective studies have provided strong evidence that early age at menopause, especially when occurring at 45 years or younger, is associated with a risk of fracture that is 1.5–3-fold higher than the risk for women who experience menopause after age 50 years (13, 15–18). In a study of more than 1,000 patients, the incidence of hip fracture in women starting menopause at age 40 years was 9.4% compared with 3.3% in those starting menopause at age 48 years (15). In the Rotterdam study, a prospective population-based cohort study that evaluated risk factors for incident fractures among 3,000 men and women, vertebral fracture was 2.5 times more likely to occur in women who experienced menopause before age 45 years compared with those who experienced menopause after age 50 years (18). In studies that have evaluated the role of HT in women at elevated risk of fracture based on menopausal age, significant reductions in fracture risk have been described (13, 17, 18).

Other risk factors for low bone mass in women with primary ovarian insufficiency include delay in primary ovarian insufficiency diagnosis of 1 year or more, vitamin D insufficiency, nonadherence to

prescribed HT, sedentary lifestyle, and lack of calcium supplementation (14). Dual-energy X-ray absorptiometry has been recommended for the evaluation of bone mineral density in women diagnosed with primary ovarian insufficiency, but consensus regarding the frequency of interval surveillance is lacking, especially in adolescents (1, 3, 19). In contrast to the treatment of postmenopausal osteopenia or osteoporosis, which focuses on bisphosphonates as first-line therapy, low bone mass in women with primary ovarian insufficiency is managed most appropriately with HT. Given the extremely long half-life of bisphosphonates, there is concern regarding the safety of this class of drugs in women with primary ovarian insufficiency, who could spontaneously become pregnant or pursue donor egg in vitro fertilization to achieve a pregnancy (20). To date, long-term use of bisphosphonates is not recommended in the adolescent population because of uncertain adverse effects and safety profiles (3).

Cardiovascular Disease Risk

Natural menopause represents an established transition in health risks for women, especially regarding cardiovascular disease (21, 22). Postmenopausal women have less favorable lipid profiles compared with premenopausal women and the risk of metabolic syndrome has been shown to increase after menopausal transition (23, 24). Women who develop primary ovarian insufficiency are also at increased risk of cardiovascular events and cardiovascular mortality compared with women who do not experience early menopause (25–27). In a 20-year follow-up of a 12,000-woman cohort study conducted in the Netherlands, cardiovascular mortality decreased by 2% for every year that menopause was delayed after age 39 years (27). In a subsequent prospective cohort study that monitored more than 6,000 U.S. women for 12 years, patients who reported experiencing menopause between the ages of 35 years and 40 years at study entry had a 50% greater subsequent risk of ischemic heart disease-related death (risk adjusted for diabetes, hypertension, parity, age at first birth, and physical activity) compared with those who experienced menopause between the ages of 49 years and 51 years (25). The association between primary ovarian insufficiency and cardiovascular disease risk may be explained in part by metabolic and endothelial changes that occur with estrogen deprivation. A cohort study observed significant endothelial dysfunction in women with primary ovarian insufficiency compared with age- and body mass index-matched women, demonstrated by diminished flow-mediated brachial artery diameter. After 6 months of HT, the brachial artery diameters of women with primary ovarian insufficiency were comparable with those of the control group (28). In this study and others, HT has been shown to improve endothelial dysfunction and reduce intima media thickness (29), blood pressure, plasma angiotensin, and creatinine (30). Primary ovarian insufficiency also may be related to cardiovascular disease risk and mortality as an indicator of overall aging and age-related morbidity (11, 31).

Epidemiologic evidence supporting the use of HT to prevent cardiovascular events in women with primary ovarian insufficiency is currently lacking. However, there also are no data that indicate that women with primary ovarian insufficiency who are treated with HT experience an increased risk of cardiovascular adverse effects compared with unaffected women using HT or combination hormonal contraceptives (daily combined estrogen–progestin in the form of combination oral contraceptive pills, the contraceptive ring, or transdermal patches) (3, 32).

Vasomotor Symptoms and Quality of Life

Women with primary ovarian insufficiency may experience hot flushes, night sweats, vaginal dryness, dyspareunia, and disordered sleep; some symptoms may develop before cycle irregularity (1). These symptoms routinely respond well to HT as indicated. Some women may be asymptomatic; younger women in particular may not exhibit symptoms.

Cognition, Mood, and Psychosocial Functioning

Evidence regarding cognitive decline in women with primary ovarian insufficiency is limited and mixed. A cohort study reported that *young* (defined as younger than 43 years) surgically menopausal women who were not receiving HT demonstrated signs of cognitive impairment compared with controls (33). These findings contrast with other reports that suggest preserved cognitive function in women with primary ovarian insufficiency who have intact ovaries (34).

Primary ovarian insufficiency has been referred to as "the silent grief" because of the negative self-image and isolation that can develop once a diagnosis is confirmed (35). Women with primary ovarian insufficiency who were surveyed about their diagnosis report significant levels of grief, diminished self-esteem, sadness, and limited access to psychological support to address these feelings (3, 35–39). Poor psychosocial functioning is explained, in small part, by vasomotor symptoms in this population (40). The emotional response to a diagnosis of primary ovarian insufficiency may be more complex and challenging in the adolescent population than for adults. Support from family or mental health professionals is important to facilitate the understanding and acceptance of the diagnosis (1, 3, 40).

Risk of Breast and Endometrial Cancer

Data are insufficient to evaluate the association between HT or combined hormonal contraceptives administered to women with primary ovarian insufficiency and the risk of developing breast cancer. Although a number of epidemiologic studies have examined the association between HT in women who are naturally menopausal at midlife and breast cancer risk, demonstrating a

20–30% increased risk of the disease in these postmenopausal HT users (41, 42), these data are not generalizable to women with primary ovarian insufficiency. Women with primary ovarian insufficiency are much younger at the time of HT initiation and their baseline risk of breast cancer is significantly lower compared with women to whom HT is administered after natural menopause. Short-term exposure to HT in BRCA1 and BRCA2 carriers following risk-reducing bilateral salpingo-oophorectomy has not been associated with an increased risk of developing breast cancer (43). Like women with primary ovarian insufficiency, these women are young and require physiologic replacement of hormones. Although reassuring, these data are not a substitute for epidemiologic studies that specifically evaluate the risk of breast cancer in women with primary ovarian insufficiency who are treated with long-term HT.

Multiple epidemiologic studies have tested the association between combined hormonal contraceptive use in the general population and risk of breast cancer. Overall, the evidence suggests that women who use or have a history of using combined hormonal contraceptives are not at increased risk of breast cancer (44–53). Although this is reassuring, an even more important question for women with primary ovarian insufficiency is whether long-term use of combined hormonal contraceptives beginning at a relatively young age is associated with breast cancer risk. Data regarding risk of breast cancer for long-term users are mixed. In a systemic review of 15 publications addressing this question, five demonstrated an association between oral contraceptive pill use of at least 5–10 years and breast cancer, whereas the remaining 10 demonstrated no such association (44). Meta-analyses have demonstrated no association between long-term oral contraceptive pill use and breast cancer risk when pooling estimates of multiple studies (45, 46). More specifically, studies on the association between long-term combined hormonal contraceptive use initiated by nulliparous women younger than 30–45 years and breast cancer risk have yielded mixed results (47–57); some of the highest-quality studies showed no association (49, 50). Data specifically evaluating the use of combined hormonal contraceptives in women with primary ovarian insufficiency are lacking, so care should be individualized to the needs of each patient. Women and obstetrician–gynecologists and other health care providers should engage in shared decision making to make the best treatment decision after a discussion of risks and benefits of combined hormonal contraceptive use.

Unopposed estrogen replacement therapy is an important risk factor for endometrial hyperplasia (10–50% incidence per year) and cancer (up to a 10-fold increase in absolute risk) and, therefore, is not recommended (41, 58–62). The addition of progestogen therapy (synthetic or natural agonists of the progesterone receptor at appropriate sequential or continuous doses) to estrogen replacement significantly reduces the risk; current combined HT regimens are not associated with an increased risk of endometrial hyperplasia or cancer (41, 63, 64). The current regimens add continuous or sequential progestogen therapy to estrogen replacement (65, 66) (Table 1).

Hormone Therapy Options

Although exogenous estrogen replacement is recommended for women with primary ovarian insufficiency, data comparing various hormonal regimens for disease prevention, symptom amelioration, and safety are lacking in this population. As a first-line approach, HT (either orally or transdermally) that achieves replacement levels of estrogen is recommended (1, 3, 65). However, serum estradiol level testing is not recommended to monitor the effects of treatment. Estrogen replacement can be achieved with the following estradiol preparations: 1–2 mg oral 17β-estradiol daily, 100 micrograms transdermal 17β-estradiol daily, or conjugated equine estrogens 0.625–1.25 mg daily (Table 1) (1, 65, 67). The choice of estrogen therapy should be combined with

Table 1. Bioequivalent Hormonal Dosages for Hormone Therapy for Primary Ovarian Insufficiency*

| Estrogen | Progestogen | |
	Continuous	Sequential
1–2 mg micronized 17β-estradiol (oral)	2.5–5 mg medroxyprogesterone acetate daily (oral)	10 mg medroxyprogesterone acetate daily (oral) for 12 days each month
100 micrograms 17β-estradiol (transdermal)	100 mg micronized progesterone daily (oral)	200 mg micronized progesterone daily (oral) for 12 days each month
0.625–1.25 mg conjugated equine estrogen (oral)		

*Select one of the estrogen options to be combined with one of the progestogen options.

appropriately dosed progestogen therapy (administered continuously or sequentially) to prevent endometrial hyperplasia and cancer. In contrast with continuous progestogen therapy, cyclic administration allows for earlier recognition of a pregnancy. Women with primary ovarian insufficiency may spontaneously ovulate on an infrequent basis, and the absence of a withdrawal bleed should prompt the patient to test for pregnancy.

Another common approach is the use of combined hormonal contraceptives, which may allow for ease of administration and less patient stigma compared with a HT regimen. However, the dose of estrogen and progestin in combined hormonal contraceptives is not replacement dosage; these hormonal preparations are significantly more potent than the aforementioned HT options (65). To date, no well-powered randomized trials exist comparing HT with combined hormonal contraceptives in women with primary ovarian insufficiency to determine cardiovascular risk (either coronary artery disease prevention or risk of venous thromboembolism), quality-of-life measures (eg, vasomotor symptoms, bleeding profile, sexual dysfunction, patient satisfaction), or bone health. Because the replacement doses of estrogen provided in HT are less potent than the estrogen in combined hormonal contraceptives, HT may have a lower risk of venous thromboembolism. To further reduce the risk of venous thromboembolism with HT, some experts recommend treatment by the transdermal route, eliminating the "first-pass" effect on the liver (68, 69).

Combined hormonal contraceptives prevent ovulation and pregnancy more reliably than HT; despite only modest odds of spontaneous pregnancy in women with primary ovarian insufficiency, this is a critical consideration for those who deem pregnancy prevention a priority. For a woman who prefers noncontraceptive estrogen replacement and wants highly effective contraception, insertion of a levonorgestrel intrauterine device is preferable to oral progestin therapy (62, 70). Barrier methods of contraception also may be used. Treatment for all women with primary ovarian insufficiency should continue until the average age of natural menopause is reached (age 50–51 years) (2). Treatment may continue past age 50–51 years if a woman has clinical symptoms or indications. Regardless of age, the decision to continue HT should be individualized and based on a woman's symptoms and the risk–benefit ratio.

Conclusion

Primary ovarian insufficiency is a life-altering diagnosis that presents numerous medical and psychosocial challenges for affected women. Although additional research is needed to define optimal treatments that balance benefits and risks, HT is the central element of the long-term clinical management of these patients. Primary ovarian insufficiency is a pathologic condition that should not be considered a hastening of natural menopause. Although women with primary ovarian insufficiency share common health risks with naturally menopausal women, the approach to health maintenance in these women is distinct. The approach to HT for primary ovarian insufficiency is full replacement doses of hormone for long-term treatment. Finally, considering the challenges that adolescents and young women may face in coping with the physical, reproductive, and social effects of primary ovarian insufficiency, comprehensive longitudinal management of this condition is essential.

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