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Review

A practical guide for managing young women with primary ovarian insufficiency

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Abstract

Primary ovarian insufficiency (POI) is a condition characterized by sex-steroid deficiency, amenorrhea, infertility, and elevated gonadotropins in women younger than 40 years of age. Most affected women produce estrogen intermittently and may ovulate despite the presence of high gonadotropin concentrations. POI is a heterogeneous disorder and may occur as a result of decreased initial follicle number, ovarian follicle dysfunction or ovarian follicle depletion. In most cases, the etiology cannot be identified. Spontaneous POI is associated with increased risk for hypothyroidism, Addison's disease and diabetes mellitus. POI increases the risk for osteoporosis and cardiovascular disease. Women with POI need exogenous sex steroids to compensate for the decreased production by their ovaries. Thus, premenopausal hormone therapy is required at least until these women reach the age of natural menopause.

Keywords: primary ovarian insufficiency; management; hormone replacement therapy; infertility

Introduction

Primary ovarian insufficiency (POI), also referred to as premature ovarian failure or premature menopause, is a condition characterized by sex - steroid deficiency, amenorrhea, infertility, and elevated gonadotropins in women younger than 40 years of age[1]. The prevalence of POI increases with increasing age, reaching approximately 1% of women by age 40 years[2]. POI occurs in 10% to 28% of women with primary amenorrhea and 4% to 18% of women with secondary amenorrhea[3]. Young women with POI produce estrogen intermittently and may ovulate despite the presence of high gonadotropin concentrations. Pregnancies have occurred

Table 1. Etiology of POI

Idiopathic or karyotypically normal spontaneous primary ovarian insufficiency
Ovarian insufficiency due to chemotherapy, radiation
Ovarian insufficiency due to ovarian surgery
Ovarian insufficiency due to chromosomal abnormalities (X-chromosome defects (i.e. FMR1 premutations); autosomal chromosome defects)
Ovarian insufficiency due to gonadotropin-receptor abnormalities
Ovarian insufficiency due to enzyme deficiencies affecting ovarian function
Galactosemia (*GALT* gene mutations)
Blepharophimosis, ptosis, and epicanthus in versus syndrome type 1 (autosomal dominant syndrome, in which primary ovarian insufficiency is the predominant syndrome)
Perrault's syndrome (familial autosomal recessive primary ovarian insufficiency in association with deafness)

in 5% to 10% of women after the diagnosis of POI.

Young women find the diagnosis of POI particularly traumatic and frequently need extensive emotional and psychological support. Although most of these women will, in fact, be infertile, it is important to emphasize that POI can be transient and that spontaneous pregnancies have occurred even years after diagnosis[3].

Etiology

POI is a heterogeneous disorder and may occur as a result of decreased initial follicle number, ovarian follicle dysfunction or ovarian follicle depletion (Table 1). In most cases, the etiology cannot be identified. The incidence of familial cases, which suggest a genetic component, varies in several studies, from 30% to 12.7%[4,5]. A large number of genes have been screened for their potential to cause POI[3]. POI affects 15% to 22% of women who carry the FMR1 premutation (fragile X), whereas the premutation is found in 4%-5% of women with POI[6,7]. Fragile X syndrome is the most common cause of hereditable mental retardation[6,7].

How to diagnose primary ovarian insufficiency

POI is defined by the presence of at least 3-4 months of amenorrhea and at least two serum follicle stimulating hormone (FSH) concentrations measuring greater than 40 IU/L (obtained at least 1 month apart)[1]. POI may present as either primary amenorrhea (absence of menses in a girl who has reached the age of 16) or secondary amenorrhea (cessation of menses in a woman previously menstruating for 6 months or more). Questions that should be asked about the medical history are shown in Table 2.

Primary amenorrhea is not associated with vasomotor symptoms. Signs of primary amenorrhea may include urogenital atrophy and incomplete development of secondary sex characteristics. In patients with primary amenorrhea, stature, signs of Turner's syndrome, and other features of gonadal dysgenesis should be examined. In patients with primary amenorrhea, particular attention should be paid to breast and pubic hair development according to Tanner stages. Short stature, stigmata of Turner syndrome, and other dysmorphic features of gonadal dysgenesis should be considered. A karyotype should be per-

Table 2. Questions about the medical history in young women with POI
Family history of POI
History of chemotherapy or pelvic irradiation
History of pelvic surgery
Personal or family history of autoimmune diseases
Family history of mental retardation

Table 3. Diagnosis of POI in women with menstrual disturbances
Menstrual disturbances for at least 3-4 months
FSH: High (two measurements at least 1 month apart)
Estradiol: Low
PRL: Normal
TSH: Normal or high (1/3 of women with POI have hypothyroidism)

formed in all patients experiencing primary ovarian insufficiency. Women with ovarian insufficiency and a karyotype containing a Y chromosome should undergo bilateral gonadectomy because of substantial risk for gonadal germ cell neoplasia.

In the majority of patients, ovarian failure develops after the establishment of regular menses (secondary amenorrhea). In these cases, symptoms may include hot flushes, night sweats, sleep disturbances, sexual dysfunction and dyspareunia, fatigue, problems with concentration and memory, and mood changes. The development of secondary sex characteristics is normal in women with secondary amenorrhea. Signs of secondary amenorrhea may include urogenital atrophy.

Laboratory testing for the diagnosis of POI is shown in Table 3. Once the diagnosis of POI is made, further testing should include adrenal antibodies, FMR1 premutation and pelvic ultrasonography. A discussion about the consequences of fragile X premutations should be made before the test is performed. Women with FMR1 premutation should be referred for genetic counseling[7]. Baseline bone mineral density (BMD) testing should be performed in all women with POI[3,8]. Mammography should be performed annually after age 45 years in accordance with accepted guidelines[9]. Additional mammography screening in premenopausal women younger than 45 years who are receiving physiologic hormone therapy is not warranted, unless it is clinically indicated[9]. Ovarian antibody testing is not indicated[10]. Other tests should be performed as clinically indicated[8].

Antimullerian hormone testing may be performed for ovarian reserve assessment in girls with mosaic Turner syndrome, in young women with cancer before and after cancer therapy and in young women before and after pelvic surgery[8].

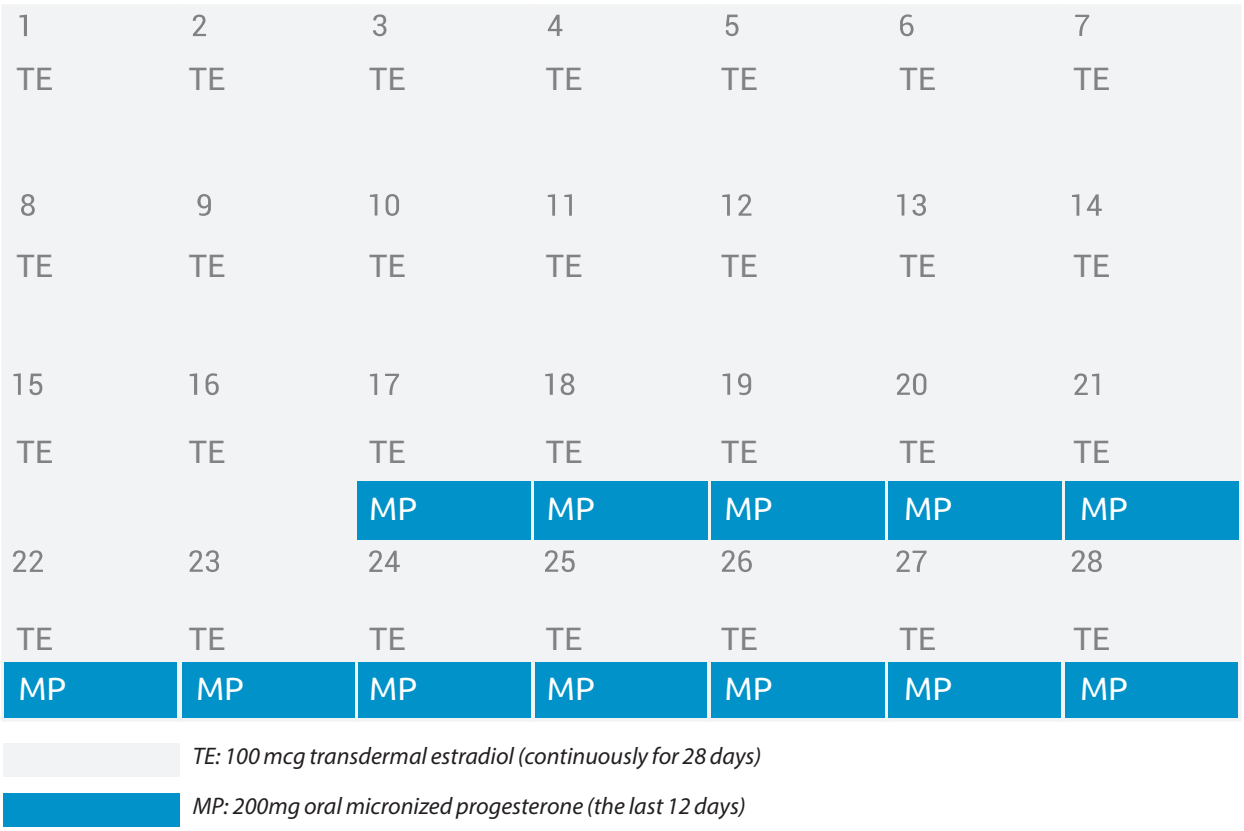

Figure 1: Cyclic hormone replacement therapy for young women with POI

Associated endocrine disorders and long term consequences

Spontaneous POI is associated with an increased risk for hypothyroidism, Addison's disease and diabetes mellitus[11]. Women with POI have significantly decreased sexual function scores, as evaluated by the Derogatis Interview for Sexual Function Self - Report, compared with control women[12].

POI increases the risk for osteoporosis[13] and cardiovascular disease[14,15]. Importantly, epidemiologic studies suggest that POI, either spontaneous or following bilateral oophorectomy performed before the age of 45 years, is associated with significantly decreased life expectancy[16,17].

What is the appropriate treatment plan?

A. Hormone replacement therapy

Women with POI need exogenous sex steroids to compensate for the decreased production by their ovaries. Practically, there is no alternative to hormone replacement in women with POI. For young women with POI, hormone therapy is "true replacement" of ovarian hormones. In these young women, hormone replacement therapy until the age of natural menopause may be necessary for relief of menopausal symptoms (i.e., vasomotor symptoms and urogenital atrophy) and prevention of long - term consequences of sex - steroid deficiency, such as osteoporosis and possibly cardiovascular disease.

Optimal hormone therapy depends on whether the patient has primary or secondary amenorrhea. Young women with primary amenorrhea in whom secondary sex characteristics have failed to develop initially should be given very low doses of estrogen in an attempt to mimic the gradual pubertal maturation process. Women with secondary amenorrhea

who have been estrogen deficient for 12 months or longer also should be given low - dose estrogen replacement initially to avoid adverse effects such as mastalgia and nausea.

Because women with POI can have spontaneous pregnancies, cyclic regimens of hormone therapy that produce regular, predictable menstrual flow patterns (Figure 1), mimicking the menses of age - matched women with normal ovarian function should be used, instead of continuous combined hormone therapy that results in the absence of menses[1]. Consequently, if these young patients miss an expected menses, they should be tested for pregnancy and instructed to discontinue the hormone therapy. An estrogen dose equivalent to 100 mcg transdermal estradiol (i.e., a higher dose than the standard dose given to older women experiencing natural menopause) is needed to achieve adequate estrogen replacement in young women and prevent bone loss[18]. The parenteral route should be preferred in order to decrease the risk of venous thromboembolism[15]. A progestogen should be given for 12 to 14 days per calendar month to prevent endometrial hyperplasia (i.e., oral micronized progesterone, 200 mg). Estrogens given in usual replacement doses do not suppress spontaneous follicular activity or ovulation.

B. Fertility treatment

Women with POI have normal fertility before the disorder develops[1,3]. Spontaneous pregnancies have occurred in 5% to 10% of women after the diagnosis of POI[1]. At present, it is not possible to predict which patient will conceive and pregnancies have occurred even in women with no follicles observed on ovarian biopsy or with undetectable AMH levels. Women with POI on hormone replacement therapy, who miss an expected menses, should be tested for pregnancy and, if positive, the hormone therapy should be promptly discontinued.

Fertility preservation may be considered in women who will undergo cancer treatment[8]. However, fertility preservation is not an option for women with spontaneous POI, around the time of diagnosis. For women with POI desiring pregnancy, assisted reproduction with oocyte donation is the method of choice[8].

Follow up of therapeutic outcomes

Initially, after the young woman begins hormone replacement therapy, a brief follow - up visit 6 weeks later may be useful to discuss patient concerns about hormone replacement therapy and to evaluate the patient for symptom relief, adverse effects, and patterns of withdrawal bleeding. Particular attention should be paid in counseling about exercise and adequate calcium and vitamin D intake[1].

Additional follow - up should be determined based on the patient's initial response to therapy and the need for any modification of the regimen. The persistence of hot flushes may require the increase in the estrogen dose. However, oral estrogens produce a marked dose - dependent increase in sex - hormone binding globulin (SHBG) levels; switching to parenteral therapy may alleviate menopausal symptoms by decreasing SHBG concentrations and, thus, increasing bioavailable estrogen. On the other hand, the presence of breast tenderness or nausea may require the decrease in the estrogen dose. Endometrial biopsy should be considered in women with POI taking cyclic hormone therapy, if vaginal bleeding occurs at any time other than the expected time of withdrawal bleeding or when heavier or more prolonged withdrawal bleeding occurs. Women with POI should also be evaluated continuously for the presence of signs and symptoms of associated autoimmune endocrine disorders, such as hypothyroidism, adrenal insufficiency, and diabetes mellitus. At present there are no guidelines for follow-up bone mineral density testing. However, in women with significant bone loss, repeat testing should be performed as clinically indicated. Other bone - protecting agents, such as bisphosphonates and human parathyroid hormone, such be used with caution in POI women with osteoporosis. As previously mentioned, women with POI have a 5% - 10% chance for a spontaneous pregnancy. Bisphosphonates have long - term skeletal retention, and these agents can be released from the skeleton several years later. Bi-

sphosphonates have a category C rating for safety in pregnancy and should not be used in any woman with POI desiring pregnancy.

Conclusions

POI is a condition characterized by sex - steroid deficiency, amenorrhea, infertility, and elevated gonadotropins in women younger than 40 years of age. It affects 1% of women by age 40 and 0.1% by age 30. Women with POI sustain sex - steroid deficiency for more years than do naturally menopausal women. This deficiency results in a significantly higher risk for osteoporosis and cardiovascular disease. The goal of therapy is to provide a hormone replacement regimen that maintains sex steroid status as effectively as the normally functioning ovary. This usually requires the administration of estrogen at a higher dose than the standard dose given to older women experiencing natural menopause. Because women with POI can have spontaneous pregnancies, hormone therapy should produce regular, predictable menstrual flow patterns. Patients who miss an expected menses should be tested for pregnancy and, if positive, the hormone therapy should be promptly discontinued.

Annual follow - up should include assessment of adherence with the prescribed hormone therapy regimen and evaluation for signs and symptoms of associated endocrine disorders.

Conflict of interest

All authors declare no conflict of interest.

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