Premature ovarian failure: diagnosis and treatment

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Summary

Premature ovarian failure (POF), also known as primary ovarian insufficiency, is diagnosed in the event when primary or secondary amenorrhea and hypoestrogenism with high levels of gonadotropins occur in women before the age of 40. POF, caused by genetic, autoimmune and environmental factors, leads to a decrease in numbers of primordial follicles, accelerated atresia, and impaired follicular function. The diagnosis of POF is an indication for hormonal replacement therapy (HRT), which should be continued until the mean age of menopause in a given population. HRT reduces the intensity of vasomotor symptoms and has a beneficial effect on the central nervous, skeletal, cardiovascular, and urinary-reproductive systems.

Key words: Premature ovarian failure; Menopause; Hormonal replacement therapy.

Introduction

Premature ovarian failure (POF), also known as primary ovarian insufficiency, is diagnosed in the event when primary or secondary amenorrhea and hypoestrogenism with high levels of gonadotropins occur in women before the age of 40. It has been estimated that by the ages of 40, 30, and 20 approximately, one in 100, one in 1000, and one in 10,000 women, respectively, will have suffered from POF [1].

Etiology of POF

POF caused by genetic, autoimmune, and environmental factors, leads to a decrease in numbers of primordial follicles, accelerated atresia, and impaired follicular function. In case of spontaneous POF in women with normal karyotype, the loss of ovarian function is usually idiopathic (90% of the affected females). In the remaining cases, POF occurs due to genetic background: chromosomal aberrations (Turner's syndrome, deletions and translocations of chromosome X, trisomy X, fragile X syndrome), single gene mutations (congenital glycosylation defects, galactosemia, blepharophimosis-ptosis-epicanthus inversus syndrome), type Ia pseudohypoparathyroidism, mutations of the follicle stimulating hormone (FSH) receptor, the luteinizing hormone (LH) receptor, and bone morphogenetic protein 15 [2, 3], or autoimmune background: antibodies against the pellucid zone, a-enolase, 21-hydroxylase, and 17a-hydroxylase, P450scc [1, 4-9].

Furthermore, POF may be the consequence of surgical interventions in the lesser pelvis, radiotherapy and chemotherapy, viral infections, and environmental factors. It is believed that any intervention in the lesser pelvis may increase the risk of POF as a result of changes in ovarian vascularization and inflammatory lesions. POF resulting from the excision of endometrial ovarian cysts, serous cysts or electrocoagulation of the ovarian surface in the course of polycystic ovary syndrome, has also been described. The risk is the highest in case of repeated surgeries of the ovaries. The incidence of POF after laparoscopic excision of bilateral endometrial cysts has been estimated to be 2.4% [10]. The POF ratio is higher also in women after hysterectomy as a result of changes in ovarian vascularization. As far as radiotherapy is concerned, POF is diagnosed in women who received a dose of 20 Gy [1], while the risk of POF after chemotherapy increases with patient age and dose, being the highest for alkylating agents and taxanes [1]. One month of chemotherapy is believed to shorten the reproductive period by 1.5 years [11]. POF may also be caused by some viral infections: parotitis, varicella, and cytomegalovirus [1], while the cause and effect connection with tuberculosis, malaria, and dysentery has not been extensively documented [3, 12]. Environmental factors that play a role in the etiology of POF include tobacco smoking (accelerates menopause by approximately 1.8 years), heavy metals, organic solvents, pesticides, and industrial chemicals.

POF diagnosis

As far as hormonal tests are concerned, apart from measuring FSH, LH, and 17b-estradiol concentration levels, it is recommended to assess the levels of prolactin (PRL), thyroid stimulating hormone (TSH), inhibin B and anti-Müllerian hormone (AMH). FSH result over 30 mIU/ml is diagnostic of primary ovarian failure. The diagnosis can be made if a two-fold increase in the FSH levels is noted twice every four weeks. A result over 15 mIU/ml is an indication for repeated testing and additional 17b-estradiol measurement. 17b-estradiol concentration over 50 pg/ml and/or LH levels higher than FSH signifies the presence of at least a few normal ovarian follicles. In women with POF, a decrease in the inhibin B levels usually precedes the increase of FSH concentration. Anti-Müllerian hormone is a more sensitive predictive marker of ovarian reserve than FSH. The presence of ovarian follicles on ultrasound is found in

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even 30% of women with spontaneous POF [14]. In 20% of them, the ovulation has been noted within four months of the observation and their chances for future pregnancy range from 5% to 10% [3].

Among all genetic tests, karyotype evaluation is recommended in all women with primary amenorrhea, as well as tests for fragile X mental retardation 1 (FMR1) gene in case of family history of POF, fragile X syndrome or mental retardation [13].

All women with spontaneous POF are recommended to undergo tests for anti-ovarian, anti-thyroid and anti-adrenal cortex antibodies. Hypothyroidism (25%), Addison's disease (3%), and type I diabetes (2.5%) are common comorbid conditions for POF [22]. The presence of antibodies is especially prognostic in relation to adrenal cortex and correlates with future insufficiency of that organ. Thus, each woman found to have anti-adrenal antibodies is advised to undergo the corticotropin-releasing hormone (CRH, corticoliberin) test.

Laparoscopic ovarian biopsy is not recommended in POF women with normal karyotype. The result of the biopsy has no influence of the pregnancy prognosis (absence of follicles in the biopsy does not exclude their presence) and the procedure further diminishes the ovarian reserve. In some cases, ovarian biopsy allows to uncover the causes undermining POF. The presence of connective tissue but absence of ovarian follicles are found in case of gonadal dysgenesis, while autoimmune background will be demonstrated by the presence of perifollicular infiltrations consisting of lymphocytes.

Prognosis

The presence of ovarian follicles on ultrasound offers some chances for future pregnancy (5-10%) [3]. Other markers of good prognosis include unstable FSH levels and autoimmune and/or chemotherapy-related POF [24]. Primary amenorrhea remains to be the most significant adverse prognostic factor [15].

Management

Hormone therapy

The diagnosis of POF is an indication for hormone replacement therapy (HRT) that should be continued until a given population reaches menopausal age [16]. HRT reduces the intensity of vasomotor symptoms and has a beneficial effect on the central nervous, skeletal, cardiovascular, and urinary-reproductive systems. HRT has been confirmed to reduce the risk of changes connected with dementia, depressions, impaired cognitive functions and changes in the blood supply of certain parts of the brain. Such management improves bone density, lipid profile, the condition of the skin, and mucosa. 17b-estradiol (50 mg - injected or two mg - orally) and micronized progesterone (100 mg), dydrogesterone (ten mg) or norethisterone are used in sequential therapy. Androgen substitution is recommended in case of intensified symptoms of testosterone deficiency (absent libido) [13]. Unlike in women after menopause, no negative consequences or risks connected with HRT were found in POF cases.

Contraceptives

Hormonal contraceptives are not recommended due to changes that occur in the central nervous, cardiovascular, and urinary-reproductive systems. They are also believed to be ineffective because of high gonadotropin levels in POF women [23]. Barrier methods are preferable in POF.

Infertility treatment

Oocyte donation and *in vitro* fertilization is the method of choice in the infertility treatment of POF. That course of management is possible in all women with normal uterus and has a higher success rate than the standard *in vitro* procedure [25]. Other ways of management have been described in women who do not accept such management, among others didehydroepiandrosterone (DHEA) administration (50 mg/day for two to six months until conception) [17], pituitary gland suppression with estrogens, and ovulation induction with exogenous gonadotropins [18, 19]. Additionally, corticosteroid administration is recommended in autoimmune-related POF (dexamethasone one mg for three months) [20]. Recent years have brought reports on ovarian tissue or whole ovary transplants in women with POF [21].

Conclusions

POF may be caused by genetic and autoimmune factors, surgical interventions in the lesser pelvis, radiotherapy and chemotherapy, viral infections, and environmental stimuli. The diagnosis of POF is an indication for HRT that should be continued until a given population reaches menopausal age. Oocyte donation and *in vitro* fertilization is the method of choice in the infertility treatment of POF. Barrier methods are preferable contraceptives in POF.

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