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Primary Ovarian Failure

Primer Over Yetersizliği

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Abstract

Primary ovarian failure (POF) is a common cause of infertility in women. It is characterized by amenorrhea, hypoestrogenism and elevated gonadotropin levels in women younger than 40 years of age. Primary causes of POF are the X chromosome abnormalities (monosomy, trisomy, translocation, deletion) or genetic defects that can occur as a result of autosomal gene mutations. Autoimmune ovarian damage may be seen alone or may be associated with some autoimmune diseases or syndromes; but the specificity and sensitivity of ovarian antibodies is still under debate. Bilateral oophorectomy, chemotherapy, radiotherapy and infections cause the secondary POF. Symptoms of POF include irritability, nervousness, loss of libido, depression, dry skin, vaginal dryness and frequent infections. POF is diagnosed with FSH levels higher than 40 IU/L and estradiol levels below 50 pmol/L in women younger than 40 years of age. For the patients who desire pregnancy, consecutive estrogen-progesterone replacement therapy is the first step treatment, and oocyte donation may be advised thereafter. Suitable estrogen-progesterone treatment improves quality of life, and protects patients from complications such as osteoporosis, cardiovascular disease and stroke. Pregnancy has been obtained with assisted conception held by donated oocytes in women with POF. Cryopreservation of oocytes, embryos and ovarian tissue is used to preserve ovarian reserve in women undergoing cancer treatments. *(The Medical Bulletin of Haseki 2015; 53: 10-5)*

Key Words: Primary ovarian failure, ovarian follicle dysfunction, infertility, hormone replacement therapy

Özet

Primer over yetersizliği (POY) kadınlarda infertilitenin yaygın bir sebebidir ve 40 yaşın altındaki kadınlarda amenore, östrojen eksikliği ve artmış gonadotropin seviyeleri ile karakterizedir. POY'un primer nedeni X kromozom anomalileri (monozomi, trizomi, translokasyon, delesyon) ya da otozomal genlerdeki mutasyonlar sonucu oluşabilen genetik defektlerdir. Otoimmün over hasarı tek başına ya da bazı otoimmün hastalık veya sendromlarla birlikte görülebilir; fakat overyan antikorların spesifitesi ve sensitivitesi hala kuşkuludur. Bilateral ooferektomi, kemoterapi, radyoterapi ve infeksiyonlar sekonder POY nedenleridir. POY semptomları irritabilite, sinirlilik, libido azalması, depresyon, cilt kuruluğu, vajinal kuruluk ve enfeksiyon sıklığında artıştır. POY tanısı 40 yaşından küçük bir kadında FSH'nin 40 IU/L'den yüksek, estradiolün 50 pmol/L'den düşük olması ile konur. Gebelik isteyen hastalarda ardışık östrojen, progesteron replasman tedavisi ilk basamak tedavidir, sonrasında oosit donasyonu tavsiye edilebilir. Uygun estrojen-progesteron tedavisi yaşam kalitesini arttırır, osteoporoz, kardiyovasküler hastalık ve inme gibi komplikasyonlardan hastaları korur. Bağışlanan oositlerle gerçekleştirilen yardımla konsepsiyon ile POY'lu kadınlarda gebelik elde edildiği kanıtlanmıştır. Embriyo, oosit ve over dokusunun dondurularak saklanması kanser tedavisi gören kadınlarda over rezervini korumak için kullanılmıştır. *(Haseki Tıp Bülteni 2015; 53: 10-5)*

Anahtar Sözcükler: Primer over yetersizliği, overyan follikül disfonksiyonu, infertilite, hormon replasman tedavisi

Primary Ovarian Failure

Menstruation, a monthly occurrence following ovulation, is imperative for female health and reproductivity. Genital tract maturation, adequate bone density and sex steroids necessary for health depend on healthy ovaries. Reproductivity and overall health may be impaired in women with irregular menstruation (1). Menopause occurs as a result of depletion of functional primordial follicles and is described as permanent ending of menstruation (2). Defining a certain age of menopause for the world as a whole is not possible. Several studies have reported menopause ages of 50±4 (3), although this figure varies by country. Menopausal age described for Turkey is 46-47 (4). Menopause onset before the age of forty is described as premature menopause.

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There are three diagnostic criteria for primary ovarian failure (POF): amenorrhea longer than 4 months, age less than 40 years and serum FSH levels above 40 mIU/ml in two occasions with at least one month interval between them (5). Primary ovarian failure is a difficult condition for a young woman to acknowledge as her physical and mental health, sexual life, reproductive capacity and social life will be affected. Compared to the women in the same age group, such women are at higher risk for cardiovascular disease, stroke and osteoporosis. Sex hormone deficiency will also have negative impacts on the urogynecological system. The prevalence of primary ovarian failure differs by ethnicity (0.1-1.4%). The incidence in the general population varies from 0.3 to 1.1% (6). In a study, the prevalence of POF was 10-18% in the primary amenorrhea group and 4-18% in the secondary amenorrhea group (7).

Etiology

Although the cause remains unidentified in most of the cases with primary ovarian failure, the disorder develops through two mechanisms: follicle dysfunction and follicle absence. In follicle dysfunction, ovaries do contain follicles but these do not function normally as a result of diverse pathologic events. Follicle absence, on the other hand, is associated with insufficient intrauterine primordial follicle count or rapid depletion of follicles due to several genetic and environmental factors (8-11). Table 1 lists POF causes by these mechanisms.

A single X chromosome is sufficient for ovarian differentiation (12). However, in cases without two intact X chromosome as in individuals with Turner's syndrome (45,X0), ovarian follicles degenerate with delivery. The second X chromosome ensures continued ovary functioning (13). Absence of a second X chromosome leads to ovarian dysgenesis in almost all cases and to primary amenorrhea and, rarely, secondary amenorrhea (14). The most common chromosome abnormality leading to POF is the absence of X chromosome (15). Menstruation may continue for a couple of years in mosaic cases of Turner's syndrome (45,X/46,XX) (16).

Fragile X syndrome is a clinical condition resulting from increased repeated formation of triple nucleotide sequences at the first exon of the FMR1 gene (Xq27.3). Fragile X syndrome occurs when the number of repeated triple nucleotide sequences exceeds 200 and no transcription occurs at the FMR1 gene and, as a consequence, no FMR1 protein is expressed (17). Healthy individuals have less than 60 repeated sequences of this gene loculation. Fragile X premutation develops when the number of repeated sequence is between 60 and 200 and is a FMR1 protein-expressing condition (18). Individuals who are carriers of premutation have less than expected oocytes in the ovaries at the time of birth (19). Women who develop premature ovarian failure are 10-fold more likely to carry fragile X premutation compared to the overall population. A woman with sporadic POF is 2-5% more likely to have fragile X premutation. It is identified in 13-15% of individuals with familial POF (19-21).

Mutations in autosomal gene have also been found to be associated with POF. Studies on mutations in receptors and gonadotropins have revealed that these very rare conditions could also lead to POF. Point mutation, which causes inactivation at the FSH receptor, has autosomal recessive contribution and is responsible for the POF cases first identified in Finland (22). Mutation at the short arm of the second chromosome results in the synthesis of alanine instead of valine amino acid. In individuals with this mutation, the ovaries are hypoplasic and contain less primordial follicles histologically, whereas complete ovarian dysgenesis and streak ovary syndrome are never observed. In individuals with FSH receptor mutation, secondary amenorrhea develops over the years following normal puberty (23).

Autocrine- and paracrine-regulating mechanisms at follicular microenvironments such as the hypothalamic-pituitary-ovarian system are also known to be involved during the continued folliculogenesis. Most of the regulating factors released from the oocyte and granulosa cells belong

Table 1. Disorders leading to Primary Ovarian Failure
Mechanism and Cause
Ovarian follicle dysfunction
Signal defect
FSH-Receptor mutation
LH- Receptor mutation
Pseudohypoparathyroidism type 1 a
Enzyme defect
Isolated 17α hydroxylase deficiency
Aromatase deficiency
Autoimmunity
Autoimmune lymphocytic oophoritis
Polyglandular autoimmune syndrome
Autoimmune polyendocrinopathy- candidiasis- ectodermal dystrophy
Insufficient follicle count
Luteinizing graafian follicles
Ovarian follicle absence
Initial follicle count insufficiency
Blepharophimosis- ptosis-epicanthus inversus syndrome
46, XY gonadal dysgenesis
Spontaneous accelerated follicle loss
Turner's syndrome
Trisomy or polysomy X
Xp or Xq macrodeletions
Autosomal or X translocations
POF: Primary ovarian failure

to the Transforming Growth Factor (TGF) super-family (24). This family includes activin/inhibin, Bone Morphogenetic Protein (BMP) and Growth Differentiation Factor subgroups. By controlling FSH via the negative feedback mechanism, inhibin ensures completion of folliculogenesis. In premenopausal women, serum inhibin levels start to elevate before the onset of menopausal symptoms. Inhibin, which reflects the decreased ovarian follicle capacity, is therefore a good indicator (25). In a study with 43 POF cases, gene mutation of inhibin, a glycoprotein, at the alpha subunit was shown in 3 women (7%), but in only one woman (0.7%) in the control group of 150 subjects (26).

Cases of spontaneous 46,XX POF may by the component of a syndrome. Mutation at the ATM gene (ataxia-telangiectasia mutated), which is responsible for ataxia-telangiectasias syndrome characterized by cerebellar ataxia, telangiectasias, immune defects, cancer predisposition and premature ageing, may result in ovarian failure (2).

Blepharophimosis-ptosis-epicanthus inversus syndrome (BPES) develops as a result of mutation at the type 1 FOXL2 (forkhead box L2) gene and may be a cause of POF (27). FOXL2 gene has an important role in early ovarian differentiation and in maintaining ovarian function (28).

Galactosemia affects one in every 60000 neonates and exhibits autosomal recessive involvement. With a clinically heterogeneous presentation, galactosemia results from complete or partial deficiency of galactose 1-phosphate uridyl transferase (GALT). Excessive amounts of galactose 1-phosphate (Gal 1-P) accumulate in the plasma of such individuals. Although the mechanism that leads to POF in galactosemia in not known, apoptosis secondary to accumulation of Gal 1-P or other galactose metabolites at the oocyte or ovarian stromal cells may be the underlying cause (29).

Primary ovarian failure polyglandular syndrome (hypothyroidism, adrenal insufficiency and hypoparathyroidism) may co-exist with autoimmune conditions including dry eye syndrome, myastenia gravis, rheumatoid arthritis, diabetes mellitus or systemic lupus erythematosus (8,30,31). The incidence of anti-ovarian antibodies differs significantly among patients with primary ovarian failure (0-67%). Establishing their roles and clinical relevance is challenging due to very variable ELISA tests and because anti-ovarian antibodies may be present only temporarily, and there is a weak correlation between antibody values and the severity of the condition. IgG-type steroid cell antibodies have been found as bound to the hilar, granulosa and theca cells of the ovary. These antibodies, however, are present in Addison's disease rather than isolated POF patients. Development of POF in 10-15 years has been reported in 42.8% of Addison's disease patients who were carriers of steroid cell antibodies (32). Anti-ovarian antibody measurement is not recommended in patients with POF due to the poor specificity of the assay (33).

Primary ovarian failure ovarian may develop as a result of surgical interventions, viral infections or exposure to environmental toxic agents, although the leading causes of acquired conditions are chemotherapy and radiotherapy. Agents used to treat autoimmune diseases such as systemic lupus erythematosus and rheumatoid arthritis and those that are used to prevent rejection after organ transplantation result in gonadal damage. The type of cancer, intensity of treatment and patient's age during treatment determine the risk of (34).

Chemotherapy-associated ovarian damage occurs due to disturbed follicular maturation or primordial follicle depletion or both (35,36). Alkylating agents used for the treatment of Hodgkin's disease or autoimmune diseases are the chemotherapeutics which are most commonly associated with gonadal damage (35,37,38). These agents do not need cell proliferation to exert cytotoxic effect and may destroy resting oocyte and primordial follicle's pregranulosa cells (36). Anti-metabolites used for the treatment of breast cancer exert their activity on split cells and thus cause less damage on the ovaries. Methotrexate is used at high doses for the treatment of osteosarcoma and has recently found increasing use in ectopic pregnancies. Although there is some evidence suggesting that methotrexate affects gonadal functions, the agent is considered to have no effect on ovary functions (39). While there are studies indicating that gonadotropin-releasing hormone agonists co-administered with chemotherapy may protect oocyte functions (40-42), this treatment needs to be investigated by extensive randomized studies.

Ovaries are highly susceptible to radiation. Patient age, the extent, dose and type of the radiotherapy administered are important prognostic factors in POF development. Single-dose radiotherapy causes more damage on the oocytes than radiotherapy in divided doses. While abdominal and pelvic irradiation present the highest risk for the ovaries, even scattered radiation in therapies where the ovaries are out of the radiation scope may result in significant ovarian damage (37).

Clinical and Laboratory Assessments

Primary ovarian failure is a clinical condition characterized by secondary amenorrhea before 40 years of age due to absence of menarche associated with primary ovarian defect (primary amenorrhea) or premature depletion of ovarian follicles or their remission during folliculogenesis. In primary ovarian failure, disturbance of regular menstruation bleedings is the foremost symptom. Absence of menstruation in a 15-year-old female is defined as primary amenorrhea, while interrupted menstruation for 4 months or longer in a woman with regular menstruation is defined as secondary amenorrhea. Once pregnancy is ruled out, a detailed history of past infections should be taken. Poorly-controlled diabetes mellitus, malnutrition, thyroid dysfunction, androgen excess (polycystic ovary syndrome), hypothalamic dysfunction or hyperprolactinemia may also be a cause for secondary amenorrhea (43).

Regardless, any adolescent or young woman with menstruation intervals longer than 90 days or with less than 9 cycles of menstruation should undergo diagnostic tests. These tests include karyotype, FMR1 premutation and hormone analyses. About half of the patients with primary amenorrhea while the majority of the women with secondary amenorrhea have abnormal karyotype (44). From the biochemical perspective, high serum levels of gonadotropin (LH, FSH) (hypergonadotrophic amenorrhea) and low serum levels of gonadal hormone (estrogen and inhibin) assist diagnosis. FSH levels are markedly higher than LH. FSH levels above 40 IU/L in two occasions with an interval of at least one month represent a conclusive evidence for diagnosis (45). Ovarian autoantibodies are identified in a small number of POF patients. Today, data derived from ovarian antibody screening have lost their value because such data do not provide guidance regarding patient management or clinical course to be taken (33).

Ultrasonographical assessment of the ovaries should target elucidating ovarian morphology and any evidence of follicular activity. Ovaries smaller than normal are often observed with ultrasound imaging. 'Streak over' pattern is observed in patients with gonadal dysgenesis accompanied by primary amenorrhea. Primary follicles could be observed with laparoscopy and ovarian biopsy in patients with ovarian failure with observed hypoplastic ovary (0.20 ml-0.30 ml) (46).

It is known that ovary functions may return to normal and ovulation may take place intermittently in patients with primary ovarian failure. Due to this intermittent correction of ovarian functions, pregnancy may occur in 10% of patients at the early stage of the disease (47,48) and in 2% of those with Turner's syndrome (49,50).

Adrenal failure develops in 50% of women with adrenal antibodies. Such patients should be examined with corticotrophin stimulation test once yearly (51). All patients with primary ovarian failure should be informed of adrenal failure symptoms and should be assessed for adrenal function in case any of the symptoms develop (2).

Thyroid autoimmunity (most commonly Hashimoto's thyroiditis) co-exists in 14-27% of the cases at the time of primary adrenal failure diagnosis. Patients positive for thyroid peroxidase antibody should also have thyrotropin levels measured (52).

Treatment

Being diagnosed with primary ovarian failure is a devastating situation for a young woman. Patients assume a nervous and irritable attitude towards the clinician during the acute phase shortly after the diagnosis. Patients should stay in touch with a psychologist to receive effective emotional support throughout this period and should be given adequate information on the disease and prognosis using a delicate and empathetic approach. It is often overlooked that this new condition which the patient has to confront will have continued psychological outcomes in the long term: lack of self-confidence and depressive mood observed in these patients are not the mere consequence of estrogen deficiency (1).

Menopause has adverse impacts on cognitive functions (53), and surgical menopause has been associated with disturbances in cognitive functions (54) and memory (55).

Patients complain from hot flashes, nocturnal sweating, irritability, vaginal dryness and difficulty in concentrating during the acute phase. Women who enter premature menopause are at reduced risk of breast cancer and thrombosis. More importantly, however, these women who will suffer from estrogen deficiency for a significantly extended time in their lives will become susceptible to osteoporosis and cardiovascular disease. Early-onset endothelial dysfunction associated with sex hormone deficiency is the underlying cause of the increased risk of cardiovascular disease. Risk of age-related cardiovascular mortality is doubled in women with POF (56).

Gonadal steroids play an important role in continued bone integrity and in maintaining bone mass both in women and men. Females who suffer from the deficiency of these hormones during adolescence and young adulthood will never be able to reach optimum bone density (57). Although all bone compartments are affected from estrogen deficiency, a more pronounced loss occurs in the trabecular bones compared to cortical bones (58). Conn et al. have demonstrated reduced vertebral bone mass by 21% in women with POF compared to an age-matched population with regular menstruation (59). There is a direct proportion between bone mineral loss and the duration of amenorrhea and the degree of estrogen deficiency (60).

The basis of the management of patients with primary ovarian failure is hormone replacement therapy. This therapy not only eliminates the symptoms of estrogen deficiency symptoms during the acute phase, but it also protects the patients against the risk of osteoporosis and cardiovascular disease. Despite the absence of randomized, controlled studies on hormone replacement therapy in patients with primary ovarian failure, many authors agree that these patients should be treated with estrogen and progesterone replacement till the average menopause age (61). Average serum estradiol level throughout the menstrual cycle in a woman with normal menstrual cycles is 100 pg/ml (62). Although there are no studies comparing different hormonal therapies in women with primary ovarian failure, estradiol at 100 mcg/day administered transdermally gives comparable serum estradiol levels and corrects the symptoms. Transdermal estradiol is minimally efficient on hemostatic factors and previous studies have demonstrated smaller risk for venous thromboembolism compared to treatment with oral estrogen (63-65). Treatment with medroxyprogesterone acetate at 10 mg/day for 12 days every month is the preferred progesterone therapy. This approach stimulates secretory endometrium and protects against endometrial cancer (66,67). Oral contraceptives are not recommended for the first line treatment because they contain more steroid hormone than physiologically needed (2).

The American Society for Reproductive Medicine and the International Menopause Society recommends estrogen replacement therapy in patients with POF (68,69).

Promising results are being obtained in several malignant diseases, particularly in hematological malignancies prevalent during adolescence and breast cancer during early adulthood. Extended life expectancy puts these patients at risk for the expected consequences of chemotherapy and radiotherapy. Cases of pregnancy achieved by frozen storage of oocyte and ovarian tissues have been reported among these patients (70-74).

A longer period in menopause becomes inevitable with extended life expectancy. Because this duration is longer in patients with primary ovarian failure, the consequences of sexual hormone deficiency is more common. In addition, early onset of menopause has negative psychological impacts on the individual. Incomplete reproduction in most of these patients also contributes to these effects. Patients should be provided with psychological support at each visit and should be given detailed information on the prognosis.

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