Thai Journal of Obstetrics and Gynaecology
June 2002, Vol. 14, pp. 169-175

REVIEW

Premature ovarian failure

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Premature ovarian failure (POF) is cessation of ovarian function before the age of 40. [1] It affects 1% of women by age 40 years and 0.1% by age 30 years.[2] It is characterized by amenorrhea , infertility, sex steroid deficiency and elevated gonadotropins. Although the cause of POF remains elusive in most cases, elucidation of the multiple pathogenetic mechanisms has greatly improved the management of this complex endocrine disorder. Furthermore, POF is associated with substantial morbidity and mortality, and from diagnosis to treatment it represents a challenge for the clinician. This paper gives an overview of the etiology, diagnosis and management of POF.

Embryology

In the embryo, germ cells first appear in the urogenital ridge. These germ cells then migrate to the primitive ovary. Once within the ovary, the germ cells multiply to form 3.5 million potential oocytes in each ovary. Most germ cells are destroyed by the body through apoptosis.[3] Before birth, two-thirds of the 7 million eggs are destroyed, presumably as part of quality control mechanism. Between infancy and the age of 40 years, eggs are gradually reduced from approximately 1 million to 10,000 in each ovary. Around the age of 40 years, the process of egg destruction is accelerated and few are left by the age of 50 years. (Figure 1) If there is an abnormality of the X chromosome, such as in Turner's syndrome when one X chromosome is missing, then germ cell production is normal but the first phase of egg destruction is accelerated leaving very few eggs available at birth.[4]

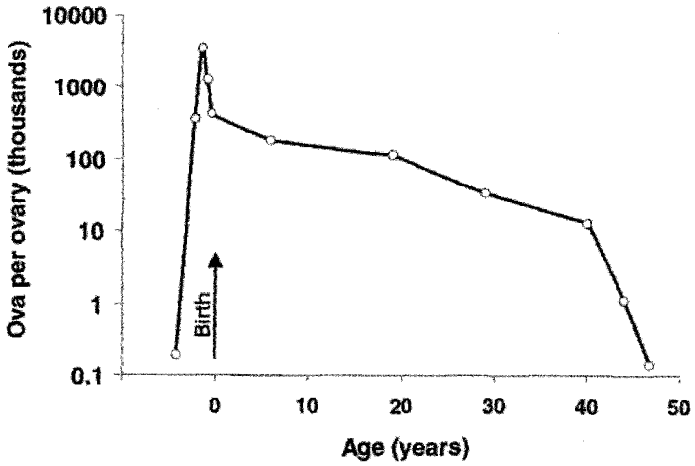

Fig. 1. The number of germ cells in ovary over life.[5]

Etiology

The cause of premature ovarian failure is unknown in the majority of women in whom the diagnosis is made.[5] POF patients can be divided into two distinct categories: patients with follicle depletion and patients with follicle dysfunction. (Table 1)

Table 1. Classification of POF [6]

Ovarian follicle depletion	
Deficient initial follicle number	
Pure gonadal dysgenesis	
Thymic aplasia/hypoplasia	
Idiopathic	
Accelerated follicle atresia	
X-chromosome related : Turner's syndrome, X mosaics, X deletions	
Galactosemia	
Iatrogenic : Chemotherapy, Radiation, Surgery	
Viral agents	
Autoimmunity	
Oocyte-specific cell-cycle regulation defect	
Idiopathic	
Ovarian follicle dysfunction	
Enzyme deficiencies :	17a-Hydroxylase, 17-20 Desmolase, Cholesterol desmolase, Galactose-1-phosphate uridyltransferase
Autoimmunity	
Lymphocytic oophoritis :	Gonadotropin receptor blocking Igs, Antibodies to gonadotropins
Signal defects :	Abnormal gonadotropin, Abnormal gonadotropin receptor, Abnormal G protein
Iatrogenic	
Idiopathic (resistant ovary syndrome)	

Follicle depletion

An initial deficiency in primordial follicles or an accelerated rate of follicular atresia would result in premature depletion of the initial follicle endowment.

Deficiency in primordial follicles

The mechanism regulating germ cell migration, proliferation of oogonia, and initiation of meiosis to form primordial follicles remains obscure. The problems of these complex processes could result in POF by reducing the initial follicle pool.

Accelerated follicle atresia

X-chromosome abnormalities

X chromosome mosaicism (45,XO/46,XX; 46,XX/47,XXX) is the most common chromosomal abnormality in women with POF.[7] Chromosomal abnormalities are detected in 40% to 50% of women with primary amenorrhea.[8] On the basis of cytogenetic and clinical studies from patients with partial deletions of the X chromosome, a "critical region" for normal ovarian function has been proposed for Xq13-q26.[9] Additional reports have suggested that a gene (*POF1*) localized to Xq21.3-q27[10] or within Xq26.1-q27 may be important in defining ovarian function. A second gene

(*POF2*) of paternal origin was discovered using molecular techniques located more proximal to the Xq locus at Xq13.3-q21.1.[11]

In some instances, POF appears in several female members of the same family where no cytogenetic defect can be identified.[12] From the published pedigrees, it is clear that familial POF has several modes of inheritance - autosomal dominant, autosomal recessive and X linked inheritance have been reported.[13-15]

POF is also present in families with rare inherited conditions such as galactosaemia, fragile X syndrome and blepharophimosis. An increase in the familial incidence of POF have been found in fragile X premutations, suggesting that the *FMR1* gene (Xq27.3) may have a role in ovarian function. [16] Based on the recent study, approximately 21% of premutation carriers have POF.[17]

Galactosemia

Galactosemia is a rare autosomal recessive disorder due to a deficiency in the enzyme galactose-1-phosphate uridyltransferase (GALT). These patients develop hepato-cellular, ocular, renal, and neurologic damage as a result of the accumulation of galactose and its metabolites. Premature ovarian failure develops in most patients with galactosemia.[18]

Iatrogenic

POF is a result of chemotherapy or radiotherapy. The risk for ovarian failure depends on the age of the patient at treatment, drug type, dose, and duration of treatment. Patients undergoing chemotherapy with alkylating agents may experience transient ovarian failure. In general, younger women are more resistant to the ovarian effects of chemotherapeutic agents than are older women.[19] Despite the development of amenorrhea and elevated gonadotropins, in some younger patients, ovarian function returns.[20]

Radiation-induced ovarian failure also depends on the age of the patient and the dose received. An important factor in the development of ovarian failure is the position of the ovaries in relation to the radiotherapeutic field.[21] Surgical transposition of the ovaries out of the irradiation field can be performed to reduce the probability of ovarian failure.[22]

Pelvic surgery, such as, ovary cyst removal or hysterectomy, might damage the ovary, probably by affecting the blood supply or causing inflammation in the area. The risk of ovary failure through pelvic surgery is unknown and thought to be very small indeed for most routine operations. Surgery on more distant organs, such as the appendix, is not reported to damage the ovary - even though related infections might cause infertility through the formation of adhesions between the fallopian tubes and surrounding structures.

Infectious Agents

Mumps oophoritis has been implicated as a rare cause of POF.[23] Patients with mumps oophoritis should be reassured that in most cases following recovery of the mumps, normal ovarian function is expected to resume.

Ovarian follicular dysfunction

Some patients with POF have normal-appearing oocytes and follicles, but they fail to function properly despite an adequate level of gonadotropins. Thus, the presence of oocytes does not ensure normal ovarian function. Although most causes of follicle POF are unclear, in a small subset of patients, ovarian dysfunction can be attributed to specific causes.

Enzyme deficiencies

Enzyme deficiencies including cholesterol desmolase, 17alpha-hydroxylase, and 17-20 desmolase impair estrogen synthesis and cause amenorrhea and failure to develop secondary sex characteristics despite the presence of developing follicles.[24] Cholesterol desmolase deficiency results in no steroid hormone synthesis, and patients with this deficiency rarely survive to maturity. Patients with 17alpha-hydroxylase deficiency, which impairs both adrenal and gonadal steroidogenesis, have hypertension, hypokalemia, and ovarian failure. Patients with isolated 17-20 desmolase deficiency have ovarian failure in the presence of normal adrenal function.[24]

Auto-immunity

POF may be associated with autoimmune endocrine disorders such as autoimmune adrenal failure (Addison's disease), diabetes mellitus, and hypothyroidism, with the last condition being the most common.[25] Autoimmunity is a recognized mechanism of ovarian failure.[26] Autoimmune oophoritis may be either cellularly or humorally mediated and seems to be a dominant cause of reversible premature ovarian failure.[6]

Autoimmune lymphocytic oophoritis

Autoimmune lymphocytic oophoritis was initially described in association with Addision's disease, however, isolated cases of lymphocytic oophoritis have also been reported.[27] It is characterized by inflammatory infiltration of the theca interna of developing follicles and sparing of primordial follicles.

Signal defects (Gonadotropin and gonadotropin receptor abnormalities)

Stimulation of the G-protein– coupled gonadotropin receptors induces second messengers that initiate specific cellular functions. Defects in the gonadotropins or their receptors could result in ovarian failure, such as, mutation of the gene for the beta subunit of FSH[28], gene for the FSH receptor [29,30] and gene for LH receptor [31,32].

Clinical presentation

Signs and Symptoms of Spontaneous Premature Ovarian Failure

POF may present as either primary or secondary amenorrhea.[6] Women with chromosomal defects are more likely to present with primary amenorrhea, although individuals with mosaicism may have some functional gonadal tissue giving rise to various degrees of sexual development and transient menstrual cyclicity. The age of presentation of POF in many cases depends on the timing and rapidity of follicular atresia. In the majority of patients, ovarian failure develops after the establishment of regular menses.[7] There is no characteristic menstrual history preceding POF. Approximately 50% of patients have a history of oligomenorrhea or dysfunctional uterine bleeding (prodromal POF), 25% have amenorrhea acutely, some postpartum, and others after stopping oral contraceptives.[6]

Primary amenorrhea is not associated with symptoms of estrogen deficiency. Symptoms in most cases (more than 75%) of secondary amenorrhea may include hot flushes, night sweats, fatigue, and mood changes.[8] Prodromal POF may present with hot flashes even when patients are menstruating regularly. Incomplete development of secondary sex characteristics may occur in women with primary amenorrhea, whereas these characteristics are usually normal in women with secondary amenorrhea.

Diagnosis

Diagnosis is based on a history of oligomenorrhea or amenorrhea and serum levels of FSH above 40 IU/l preferable combined with serum estradiol levels < 100 pg/l.

History and physical examination

In most patients with POF, ovarian failure is idiopathic. However, a specific disease process may be recognized in a few patients. A complete history should be taken regarding prior ovarian surgery, chemotherapy or radiation. History of autoimmune disorders, especially symptoms of adrenal failure (Addison's disease), include anorexia, weight loss, abdominal pain, weakness, salt craving, and increased skin pigmentation, should be obtained.[6] Findings associated with autoimmune disorders should be also evaluated, such as premature graying of the hair (autoimmune hypothyroidism) and vitiligo (autoimmune adrenal failure). In patients with primary amenorrhea, history of secondary sex characteristics, such as, breast and pubic hair development should be obtained. Short stature, stigmata of Turner's syndrome, and other dysmorphic features of gonadal dysgenesis should be sought. Ideally, a pelvic examination should be performed, however, this is not always clinically appropriate. In the majority of cases, physical examination is completely normal.

Laboratory evaluation

A karyotype should be performed in all patients

experiencing premature ovarian failure. Patients with ovarian failure and a karyotype containing a Y chromosome should undergo bilateral gonadectomy because there is a substantial risk for gonadal germ cell neoplasia.[33]

Ovarian biopsy and antiovarian antibody testing are investigative procedures with no proven clinical benefit in POF.[6] As clinically indicated, the work-up should include tests for the diagnosis of other possible concurrent autoimmune disorders such as hypothyroidism, diabetes mellitus, and Addison's disease. The most useful evaluation for women with spontaneous POF who have a normal karyotype includes an assay for serum thyroid-stimulating hormone (TSH) and fasting plasma glucose. Testing for adrenal insufficiency with corticotropin stimulation can be performed as clinically indicated.[25] The erythrocyte sedimentation rate (ESR) and assays for antinuclear antibodies and rheumatoid factor should be performed only as clinically indicated.

In conclusion, a diagnostic evaluation within the framework of POF can be limited or extensive. Diagnostic laparoscopy and vaginal utrasonography have no place in the diagnostic work-up of POF. Measuring bone mineral density is essential and all other tests should be considered according to the individual circumstances and preferences of the patient.

Prognosis

Normal menopause is an irreversible condition, whereas premature ovarian failure is characterized by intermittent ovarian function in one-half of young women. Affected women produce estrogen intermittently and may ovulate despite the presence of high gonadotropin levels.[34] Pregnancies have occurred after the diagnosis of premature ovarian failure, even in women with no follicles observed on ovarian biopsy.[8] Around 5-10% of all POF patients become pregnant spontaneously at some time after diagnosis. However, randomized controlled trials have shown that no treatment can increase the chances of pregnancy.[35] Oocyte donation still is the only available treatment for infertility due to ovarian failure.

POF patients may develop osteoporosis. Pathological bone mineral density (BMD) was found in 50% of POF patients not using HRT and atraumatic fractures were found in 5% of them.[36,37]

Management

Young women find the diagnosis of premature ovarian failure particularly traumatic and need a great deal of personal and emotional support.[33] In autoimmune POF, corticosteroid treatment has no proven benefit on the basis of prospective controlled studies. In fact, major complications can occur, such as iatrogenic Cushing's syndrome, osteonecrosis, and corticosteroid-induced osteoporosis.[38]

Hormonal replacement therapy

The initial concern of patients with POF is the need for estrogen and progesterone replacement therapy to relieve symptoms of estrogen deficiency, to maintain bone density, and to reduce the risk of cardiovascular disease.

Despite a standard regimen for hormone replacement therapy, two thirds of young patients have a significantly reduced BMD that may be associated with increased risk for hip fracture. Forty-seven percent of these women have been found to have significantly reduced BMD within 1.5 years of their diagnosis.[39]

Practical Guide for Hormone Replacement Regimens for Young Women with POF[38]

Optimal hormone replacement therapy depends on whether the patient has primary or secondary amenorrhea. In the patient with the latter condition, the duration of estrogen deficiency is the important factor. Young women with primary amenorrhea in whom secondary sex characteristics have failed to develop should initially be exposed to very low-dose estrogen in an attempt to mimic a gradual pubertal maturation process. A therapeutic example would be 0.3 mg of conjugated equine estrogens (CEE) unopposed daily for 6 months, with incremental doses at 6 monthly intervals until the required maintenance dose is achieved. This method seems to result in optimal breast development as well as allowing time for the young woman to adjust psychologically to her maturational

changes. Cyclical progestin therapy, 12 to 14 days per month, should be instituted toward the end of the second year.

Women with secondary amenorrhea who have been estrogen-deficient for 12 months or more should also initially be given low-dose estrogen replacement to avoid unwanted side effects such as mastalgia and nausea; however, they can be titrated up to the maintenance dose over a 6-month period, and progestin therapy can be instituted concomitantly. Women with a brief history of amenorrhea are less likely to experience unwanted side effects with hormone replacement if given a reduced dose for the first month of therapy and then a full dose from the second month onward.

Infertility-related therapy

Young women with POF desiring fertility should be informed that there is a 5% to 10% chance for spontaneous pregnancy.[8] Hormone replacement therapy does not prevent conception. Patients who do not want to get pregnant should be offered a low-dose oral contraceptive pills (20-30 µg of ethinyl estradiol)

Ovulation induction in these patients using clomiphene citrate, human menopausal gonadotropins, and a combination of gonadotropin-releasing hormone analogue with purified urinary FSH have not resulted in greater ovulation rates than those seen in untreated patients. [40-42]

Oocyte donation

Oocyte donation is the only proven therapy for patients with POF who desire pregnancy.[43] These patients may feel an urgency to proceed to oocyte donation. They should be informed that, in some cases, spontaneous pregnancy may occur[44] and that, if they choose to wait for a while before proceeding, oocyte donation is as successful in older women as it is in younger women.[43]

Follow-Up

Young women with POF should be monitored annually regarding their compliance with hormone replacement therapy. These patients should be followed up for the presence of signs and symptoms of associated autoimmune endocrine disorders, such as hypothyroidism, adrenal insufficiency, and diabetes mellitus. Serum TSH and fasting plasma glucose are recommended for yearly screening. Additional testing should be performed as clinically indicated.[25]

Conclusion

POF is not an uncommon disorder. The early loss of ovarian function has significant psychosocial consequences and major health implications. Women with POF have a nearly twofold age-specific increase in mortality rate and hence require thorough assessment, hormonal replacement therapy, and long-term surveillance to monitor therapy and minimize health risks including autoimmune disease in later life. Hormone replacement therapy remains the cornerstone of treatment, and the best chance of achieving a pregnancy is through oocyte donation.

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