Premature Ovarian Failure : An Overview

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Abstract

Premature ovarian failure (POF) is a syndrome characterized by cessation of follicular-ovulatory function in women under the age of 40. Except for genetic disorders and exposure to high dose radiation or chemotherapy, the precise phenomena underlying the pathogenesis of POF are largely unknown. Although POF was once thought to be permanent, a substantial number of patients experience spontaneous remissions. Hormone replacement therapy remains the cornerstone of treatment, and the best chance of achieving a pregnancy is through oocyte donation. An understanding of basic ovarian embryology and physiology will allow clinicians to develop new innovative therapies for patients with POF.

Keywords: premature ovarian failure, premature menopause, hormone replacement therapy, oocyte donation

1. Introduction

Premature ovarian failure (POF) is a condition causing amenorrhea, hypoestrogenism and elevated gonadotropins with the cessation of ovulatory and endocrine functions of the ovary in women younger than 40 years. The age-specific incidence of POF is found to be 1 in 100 by age 40 and 1 in 1,000 by age 30[1]. Early loss of ovarian function has both significant psychosocial sequelae and major health implications[2]. It has been observed that POF is associated with a nearly two-fold age-specific increase in mortality rate[3].

The diagnosis of POF patients is made on the basis of the presence of at least 4 months of amenorrhea and two serum follicle-stimulating hormone (FSH) values >40 mIU/ml, measured

at least 1 month apart, in women <40 years of age[4]. Several studies have shown that POF, unlike natural menopause, is not necessarily permanent; and the possibility for the menstrual cycle to resume and pregnancy to occur are not absolutely excluded[5]. Despite the occurrence of amenorrhea and elevation of FSH levels, ovaries of the POF subjects harbor residual oocytes, albeit in significantly diminished numbers. These residual follicles do have the possibility to exhibit episodic function, as opposed to the virtually inert oocyte-granulosa units seen in age-appropriate menopause[6]. Nearly 50% of these patients with ovarian follicle function have been reported to exhibit estradiol (E_2) levels of >50 pg/ml, with 20% ovulating as defined by luteal phase serum progesterone levels of >3 ng/ml[7]. Young women with POF may thus produce estrogen intermittently and may even exhibit sporadic ovulatory cycles[7]. In fact, histologic evaluation of the ovary allowed differentiation of cases without follicles, and therefore irreversible, from those with follicles, which do have theoretical chances to restore ovarian function[8]. Ultrasonography showed the presence of ovarian follicles in over 40% of women with POF, while another 20% of cases, despite the presence of follicles, were falsely diagnosed as afollicular[9]. These follicles were usually arrested before the antral phase of follicle development and resisted gonadotropin stimulation [resistant ovary syndrome (ROS), also known as Savage's syndrome]. Indeed, pregnancies have been reported after a diagnosis of ovarian failure[10].

The concept of premature ovarian failure in this respect does not mean complete cessation of ovarian function, but rather cessation of proper ovarian function. In light of the transient or intermittent nature of this condition and because residual ovarian function may remain despite elevated serum gonadotropins, 'premature ovarian dysfunction' or 'premature ovarian insufficiency' would be a more accurate phrase to describe this specific condition[11,12].

2. POF: broad classification and etiology

The precise etiology and intricate mechanism elementary to the development of POF remain obscure. However, the heterogeneity of patients with POF suggests for a wide spectrum of pathogenic mechanisms[13]. Amidst such diversity, simply on the basis of ovarian follicular status, most authorities subdivide the patients under two distinct categories:

1. Patients with follicle depletion (afollicular), and
2. Patients with follicle dysfunction (follicular).

3. Follicle Depletion

Some patients may present with afollicular type of POF where follicles are depleted prematurely. This premature attrition of follicles can be due either to rapid depletion of follicles or to a normal depletion rate involving an inadequate number of follicles[14]. The exact cause of premature loss of follicles is unknown, however, theoretically two mechanisms have been envisioned that may contribute to the untimely exhaustion of ovarian reserve in POF patients –

1. Failure of the ovaries to receive the appropriate complement of oogonia. This may entail migratory failure of the germ cells, or defective mitotic activity of oogonia.
2. Exaggerated attrition of the normally acquired complement of oocytes.

Deficient Initial Follicle Number

The mechanisms regulating germ cell migration, proliferation of oogonia and initiation of meiosis to form primordial follicles remain obscure. A perturbation in any of these complex processes could result in POF by reducing the size of the initial follicle pool.

The ovaries devoid of follicles in the familial 46,XX gonadal dysgenesis may result from an autosomal/somatic mutation in the genes that control germ cell migration or mitotic oogonial proliferation. Recently, 2 different genetic mutations were discovered in murine models of germ cell deficiency. One line had mutant *c-kit* gene at the W locus[15], and the second was created by an insertional transgenetic mutation of chromosome 11 A2-3[16]. Further study of these mutant murine models may elucidate a genetic cause for afollicular POF.

In the primate, the fetal thymus plays a role in establishing the normal endowment of primordial follicles[17]. Interestingly, human conditions with thymic hypoplasia or aplasia have been associated with POF[18].

Accelerated Follicle Atresia

Chromosomal anomalies

Chromosomal abnormalities are detected in 40-50% of women with primary amenorrhea[19]. It has been found that POF is frequently linked to X-chromosome abnormalities[20]. Although it is most commonly associated with X-monosomy[21], a substantial number of cases have X-chromosome re-arrangements including inversions and more than 100 postpubertal women with X/autosomal balanced translocations. The X chromosome has been identified to bear sequences critical to ovarian function. Abnormalities of the short arm of the X chromosome

(Xp) generally do not affect ovarian function, whereas deletions or translocations of the long arm, the Xq region, do[22]. This zone has been called the 'Xq critical region' for the maintenance of ovarian function and normal reproductive lifespan[23]. Recent studies suggest that two genes (*POF1* and *POF2*), important for ovarian function, are localised to Xq21.3-q27 and Xq13.3-q21.1, respectively[24]. Also, at least eight different genes in Xq21 are involved in ovarian function[25]. In addition, an increase in the familial incidence of premature menopause was found in women with Fragile-X syndrome (FXS) permutations[26], thus indicating that the Fragile-X Mental Retardation 1 (*FMR1*) gene (Xq27.3) may influence ovarian function[27]. Conway *et al*. (1997)[28] found in their study population that FXS premutations occur at least ten times more frequently in women with POF than in the general population. According to Sherman (2000)[29], FXS premutation carriers are at an increased risk for POF, with an incidence rate of 16-21%.There are two major models that have been accounted for X-chromosome involvement in POF[30]. In one, a number of X-linked genes function directly in ovarian development, and interruption of any of them somehow provokes POF. Such a model has been demonstrated for the major autosomal locus on chromosome 3, which is implicated in POF with blepharophimosis/ptosis/epicanthus inversus syndrome[31]. The alternative model suggests that some translocations, whether or not they interrupt a gene, can adversely affect X-chromosome dynamics during follicle formation or maintenance.

The presence of an X chromosome in excess or its absence may be associated with accelerated follicular atresia[32]. Fetuses with a single X chromosome, as in Turner's syndrome (45,XO), develop normal ovaries with the normal complement of primordial follicles[33], but later, there occurs a rapid loss of oocytes[34] leading to the development of abnormal gonads with an increased fibrous content, the classic description of the streak gonad. In this case, chromosomal pairing in early meiotic prophase is defective and may be responsible for the accelerated oocyte deaths.

Galactosemia

An increased incidence of POF has been demonstrated in galactosemia, an autosomal recessive disorder, which in its classical form, is characterised by the deficiency of galactose-1-phosphate uridyltransferase (GALT)[35]. This defect causes hepatocellular damage, renal tubular damage, cataracts and mental retardation. The block in normal galactose metabolism owing to GALT deficiency results in the accumulation of the metabolic precursors, galactose and galactose-1-phosphate, as well as products of alternate pathways such as galactitol, which are responsible for the outcome of hypergonadotropic hypogonadism in female patients. According to one study, 81% of the 47 affected female patients developed ovarian failure, with primary amenorrhea noted in 8, and the majority experienced POF shortly after

puberty[36]. It has been presumed that the ovarian failure is the result of a direct toxic effect of galactose and its metabolites on primordial follicles. Suggestions have been made that ovarian accumulation of galactose-1-phosphate results in the degradation of uridine nucleotides and thereby induces atretic cell death[37]. Experimental studies on rats have shown that female rat fetuses exposed to high maternal galactose levels during gestation had a significantly decreased number of oocytes[38]. These evidences imply that ovarian failure in galactosemia may be due to accelerated follicle atresia by apoptosis after birth. Galactose may play a role in follicular atresia by causing an accumulation of methylglyoxal through slowing of the glutathione redox cycle. This slowing of the redox cycle in turn promotes apoptosis[39]. It may also be due to defective gonadotropin function due to abnormalities in their carbohydrate composition and reduced bioactivity, and/or the neutral isoelectric point in FSH isoforms[40].

Iatrogenic causes

POF may also result from chemo- and radiotherapy, and the likelihood of developing the disorder depends on age at treatment, drug type, dose and duration of treatment.

Chemotherapy: Ovarian dysfunction is a common consequence of chemotherapy. The histologic appearance of the ovaries after chemotherapeutic treatment revealed abundant primordial follicles with maturation arrest beyond the primary follicle stage[41]. Treatment with MOPP (Mustine, Oncovine, Procarbazin, and Prednisone) or with MVPP (Mustine, Vinblastine, Procarbazin, and Prednisone) resulted in 15-62% secondary ovarian failure[42]. There are two phases in the ovarian response to the insults by the alkylating agents (e.g. busulfan, cyclophosphamide). Initially, there is an acute phase causing amenorrhea due to atresia in follicles with actively proliferating granulosa cells[43]. Subsequently, there is a phase of follicle depletion due to the long-term effects of these agents. Granulosa cells are suspected to be the primary ovarian target cells for cyclophosphamide-associated gonadal damage, possibly leading to early depletion of follicles and POF[44].

Radiotherapy: Radiation-induced ovarian failure is dependent on the age of the patient and the dose received. An ovarian radiation dose of $\geq$600 cGy produces permanent ovarian failure in virtually all individuals >40 years of age[45]. Ovaries severely damaged by radiation show loss of primordial and developing follicles, fibrosis and hyalinisation of the stroma, vascular sclerosis of hilar cells, and occasional formation of decidua-like tissue in the superficial cortex[46]. Thus, it is recommended to perform oophoropexy and shielding of the ovaries during radiation. Of clinical note, pregnancies conceived after irradiation, like in chemotherapy, are not at increased risk of congenital anomalies[47].

Environmental Causes

Environmental toxins resulting in oocyte destruction might cause ovarian failure. Cigarette smoke is an acute ovarian toxicant, and on average, smokers experience an earlier menopause than nonsmokers[48,49]. Polycyclic aromatic hydrocarbons, the major elements of cigarette smoke, have been shown to alter oocyte meiosis in a dose-dependent manner and destroy oocytes in mice[50].

Infections

Viral or other infectious agents may play a role in some cases of ovarian failure. Mumps oophoritis, which occurs in 5% of women with mumps[51], is most frequently associated with premature menopause. There is evidence that the ovary is most sensitive to damage by the mumps virus during the fetal and pubertal periods[52]. There are also anecdotal reports of viral and microbial infection such as varicella, shigella, malaria being followed by POF[53].

4. Follicle Dysfunction

As stated earlier, some patients with POF have normal-appearing oocytes and follicles, yet they fail to function properly in the presence of adequate levels of gonadotropins. Thus, the mere presence of oocytes does not ensure normal ovarian function. The causes of this form of POF are mostly unclear. Perhaps, follicle dysfunction represents a transition phase in the process of development of afollicular form, however, in a small subset of patients, ovarian dysfunction can be attributed to specific causes.

Enzyme Deficiencies/ Metabolic Disorders

Several specific enzyme defects can disrupt estrogen synthesis, resulting in pubertal delay, primary amenorrhea and elevated gonadotropin levels despite the existence of normal-appearing primordial follicles in the ovary. Defects in the cholesterol desmolase, 17α-hydroxylase, 17-20 desmolase and aromatase enzymes can cause these clinical and histologic abnormalities[54]. Impaired steroidogenesis with loss of negative feedback resulting in an elevation in the endogenous FSH level has been implicated as the pathogenic mechanism; the higher levels of FSH, by recruiting larger cohorts of follicles, result in an accelerated exhaustion of the oocyte repertoire[55]. Although these patients present with POF, they exhibit no clinical manifestations of adrenal insufficiency.

Interestingly, fertilisable eggs could be retrieved after ovulation induction for *in vitro* fertilisation in patients with either 17α-hydroxylase deficiency or 17-20 desmolase deficiency despite undetectable peripheral estradiol levels[56].

Deficiency of GALT, as discussed earlier, induces POF by an as yet undefined mechanism. Studies suggest that GALT deficiency may cause POF by follicle dysfunction, abnormal

gonadotropin bioactivity, or accelerated oogonial atresia. Several studies have shown a direct effect of galactose or its metabolites on the parenchyma of the ovary, which may explain the ovarian failure[38, 57].

Galactosemia

It needs yet to be substantiated if follicular resistance to gonadotropins is a step in the progression of the disease to its irreversible form, but there is a report that a galactosemic patient with POF had normal-appearing primordial follicles that were resistant to gonadotropins [58].

There is at present no authenticated explanation that may account for follicular refractoriness in galactosemic subjects. However, it has been suggested that galactosemia may alter the carbohydrate residues (galactose and galactosamine) on gonadotropin molecules and render them biologically inactive. Prestoz *et al*. (1997)[59] found that the terminal disaccharides on the FSH molecule, galactose and sialic acid, were partially deficient in galactosemic patients. The resultant isoforms of FSH were shown to have a higher binding affinity to the FSH receptor but little ability to activate it via cAMP. The investigators proposed that an increase in these isoforms could cause defects in gonadotropin signaling and possibly act as anti-hormones, producing antagonistic effects at the FSH receptor levels. Other investigators, in contrary, have found normal biologic activity of the gonadotropins from galactosemic patients.

Signal Defects

The failure of normal-appearing follicles to respond to elevated gonadotropin levels could also, theoretically, be caused by the production of abnormal gonadotropins, abnormal or down-regulated gonadotropin receptors, or a defective second messenger system. Several inherited defects of gonadotropin synthesis and secretion causing hypogonadism have been described[60]. These include mutations of the autosomally-inherited GnRH receptor gene, X-linked *KAL* gene and *DAX-1* genes. The *KAL* mutation, which results in Kallman's syndrome, and the *DAX-1* mutation, which results in X-linked adrenal hypoplasia, cause a deficiency of GnRH. In addition, the *DAX-1* mutation results in defective pituitary production of gonadotropins. Mutations of the β-subunit of FSH cause primary amenorrhea with poorly developed secondary sex characteristics and infertility[60], whereas mutations of the β-subunit of luteinizing hormone (LH) have only been reported in a male with delayed puberty[61].

Recent reports have demonstrated abnormal FSH and LH receptors in several kindreds of familial POF. Mutations in the FSH receptor gene result in hypergonadotropic primary or early secondary amenorrhea and anovulation, with variable development of secondary sex

characteristics. Women heterozygous for the gene have normal fertility. Ovarian biopsy specimens from these patients revealed the presence of primordial follicles in all cases[62, 63].

Mutations of the LH receptor gene also cause primary or secondary amenorrhea and anovulation, yet they allow normal development of secondary sex characteristics. Ovarian biopsies in these patients revealed primordial, preantral and antral follicles, whereas no preovulatory follicles, corpora lutea, or corpora albicans were seen[64, 65].

As more women with POF undergo genetic studies, it is anticipated that multiple subgroups, each with a different biologic basis for POF, will be identified; and that would be consistent with a heterogenous condition with multiple causes.

5. Immunological aspects of POF

A spectrum of autoimmune disorders has been recognised in patients with POF[66], with an incidence range of 0-57%[67]. Early reports emphasised the association between POF and Addison's disease[68]. Subsequently, it has been observed that other autoimmune manifestations, such as thyroid diseases (9%), polyglandular syndromes (3%), idiopathic Addison's disease (2%), rheumatoid arthritis (1%) and in less than 1% systemic lupus erythematosus, vitiligo, myasthenia gravis, pernicious anemia, hypoparathyroidism, insulin-dependent diabetes mellitus and Crohn's disease[67], could be correlated with POF. POF also frequently occurs in patients having type I or type II polyglandular autoimmune disease[69]. It has been found that about 24% of the women with idiopathic Addison's disease had amenorrhea and 10% have POF[68]. On the other hand, patients with POF without other clinical autoimmune disease had, in about 30% of the cases, circulating organ-specific auto-antibodies to the ovary, oocytes, enzymes related to hormone production (thyroid peroxidase and 3β-hydroxysteroid dehydrogenase (3β-HSD), FSH receptors and deoxyribonucleic acid (DNA) synthesis in granulosa cells[70].

6. Therapeutic management of POF

Despite elevated levels of gonadotropins, approximately 50% women with POF harbor some, albeit few, functional oocyte-granulosa units. Multiple therapeutic approaches have therefore been advocated to restore ovarian function and achieve pregnancy. It is, however, important to note that women with POF do exhibit intermittent ovarian function[7] with 5-10% chance of spontaneous pregnancy[53], and to date, controlled trials with no therapeutic strategy, except oocyte donation, could demonstrate any success in excess over the placebo treatments[71]. Hormone replacement therapy (HRT) is routinely used in POF women[72]. Attempts at ovulation induction in these patients using clomiphene citrate, human menopausal

gonadotropins and a combination of GnRH-analog with purified urinary FSH[73] resulted in no greater ovulation rates than those seen in untreated patients.

For women with POF desiring fertility, induction of pregnancy with donor oocyte remains a viable option[74]. But patients with chemotherapy- or radiation-induced POF have a lower pregnancy rate from donor oocytes[75]. A possible modality for preservation of fertility potential in the "at risk" progeny may be offered through ovarian cryopreservation; however, the technique at present remains experimental and only scanty reports of success in achieving pregnancy following transplantation of the preserved tissue are available[76].

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