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Review Article

Understanding Basic Concepts of Premature Ovarian Failure

Mona Sharma[1]* and Ashutosh Halder[2]

[1]*Additional Professor, Department of Reproductive Biology, AIIMS, New Delhi, India*
[2]*Professor and Head, Department of Reproductive Biology, AIIMS, New Delhi, India*

***Corresponding Author:** Mona Sharma, Additional Professor, Department of Reproductive Biology, AIIMS, New Delhi, India.

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Abstract

Premature ovarian failure (POF) is a condition characterized by hypergonadotropic hypoestrogenic amenorrhea in women under the age of 40 years. Most cases of POF remain idiopathic despite of various etiologies described. Women with POF often complain of menstrual problems, infertility and menopausal symptoms. This review highlights the basic concepts needed to understand etiopathogenesis, clinical and therapeutic aspects of POF.

***Keywords**: Reproductive Health; Ovarian Failure; FSH; Oocyte Atresia*

Introduction

Reproductive health includes not only the attainment and maintenance of good health but also prevention and treatment of ill health. According to International Conference for Population and Development (ICPD) held in 1994 at Cairo, "Reproductive health is a state of complete physical, social and mental well-being and not merely the absence of disease or infirmity, in all matters relating to the reproductive system and to its functions and processes. Reproductive health therefore implies that people are able to have the capability to reproduce and the freedom to decide if, when and how often to do so" [1]. Fertility thus is a key component of reproductive health. Infertility has become a global health issue. "Prevalence of infertility in women is percentage of women in reproductive age group (15 - 49 years) at risk of becoming pregnant (not pregnant, sexually active, not using contraception and not lactating) who report trying for a pregnancy for two years or more" [1]. Prevalence of infertility in female is estimated to be 15% in India [2]. Female infertility contributes to 37% of infertile couples [3]. Infertility arising due to decreasing ovarian function is called premature ovarian failure (POF) and constitutes roughly 1% cases of infertility in females [4]. POF is a condition characterized by cessation of ovarian function in women before the age of 40 years [5]. The characteristic features of the disease are amenorrhea (for more than 6 months), high serum follicle stimulating hormone levels (FSH > 40 IU/L) and low estrogen levels (E2 < 10 pg/ml) on two different occasions at 4 - 6 months apart. The decreasing levels of inhibin B and anti-mullerian hormone (AMH) are also used for diagnostic purpose. Women with POF more commonly present with secondary amenorrhea but may present with primary amenorrhea in its most severe form. The disorder affects 1 in 100 women by the age of 40 years, 1 in 1000 women by the age of 30 years and 1 in 10,000 women by the age of 20 years [4]. POF has two important consequences, hypoestrogenism and infertility. Symptoms of low estrogen levels include hot flushes, night sweats, fatigue, and mood changes. Another irreversible consequence is infertility due to the decreased oocyte reserve as a result of either early loss of ovarian follicles or their insufficient number at the time of birth. Moreover, when the disease is diagnosed clinically, the fertility potential is already lost or has decreased to minimum.

The proposed etiological factors of POF are environment factors (viruses, chemical agents, radiations), metabolic diseases (galactosemia), autoimmune disorders (Addison's disease, Hashimoto's disease) or iatrogenic factors such as chemotherapy, radiotherapy and any surgical damage to the ovaries [6]. POF can be syndromic when occurs in combination with various other disorders such as Turner syndrome which is characterized by complete or partial absence of one X chromosome. The other form of POF is non-syndromic when it occurs as an isolated disorder. This review further highlights the etiopathogenesis, clinical and therapeutic aspects of POF.

Terminologies used and diagnostic criteria

Primary ovarian insufficiency, premature ovarian insufficiency and premature ovarian failure are often used interchangeably in literature for a spectrum of disorder characterized by hypergonadotropic amenorrhea. It was described first in 1942 as "Primary Ovarian Insufficiency" (POI) [7]. According to European Society of Human Reproduction and Embryology (ESHRE) Guidelines 2016, the condition is termed as "Premature Ovarian Insufficiency" in a woman < 40 years with oligomenorrhea or amenorrhea for at least 4 months having FSH > 25 IU/L on two occasions at least 4 months apart. Markedly low or undetectable serum levels of AMH confirm the diagnosis. POI is not a complete failure in ovarian function unlike menopause as spontaneous ovulations are encountered in this condition [8]. American College of Obstetrics and Gynecology (ACOG) gave its committee opinion in 2017 and identified this condition as "Primary Ovarian Insufficiency". Irrespective of various terminologies used, the clinical spectrum is classified into three stages: occult, biochemical and overt. The overt stage indicates complete failure of ovarian function and is often termed as POF [9] The three stages can be differentiated based on clinical and laboratory findings (Table 1). Diagnosing POF based on radiological imaging is not essential. Thin endometrial echo (< 4 mm), small ovarian volume and low antral follicle count (AFC < 5) confirm the diagnosis.

Clinical State	Fertility	FSH levels	Menstruation
Normal	Normal	Upto 10 IU/L	Regular
Occult	Reduced	Upto 10 IU/L	Regular
Biochemical	Reduced	10 - 40 IU/L	Regular/Oligomenorrhea
Overt (POF)	Reduced	> 40 IU/L	Oligomenorrhea/Amenorrhea

Table 1: *Stages of primary ovarian insufficiency.*

Mode of onset

The understanding of mechanisms causing ovarian dysfunction depends on its mode of onset-either spontaneous or as a consequence of iatrogenic insult to ovary (chemotherapy, radiotherapy, surgery etc.). In both conditions, the result is accelerated loss of ovarian reserve and deficiency of circulating sex hormones. Spontaneous POF is insidious in onset and diagnosis is often delayed. Whereas induced/iatrogenic POF can be anticipated in advance and preventive measures of long term health risks due to hypoestrogenism can be initiated earlier.

Etiologies

Oocyte undergoes growth arrest twice in its lifecycle: first at prophase I, second at metaphase II. Prophase I arrest gets released before ovulation with oocyte maturation and Metaphase II arrest is released after ovulation and during fertilization by sperm factors [10]. The process of oocyte atresia begins before birth and it continues throughout reproductive years until menopause. But if it reaches before 40 years of age, it is considered premature. Among women<40 years of age, incidence increases with advancing age. Various mechanisms influence the magnitude of follicular atresia from in-utero time until menopause. Premature follicular depletion can also be due to inher-

ently smaller ovarian reserve. POF may occur as a result of wide spectrum of disorders leading to accelerated oocyte depletion [11]. Few of these causes are discussed below.

Genetic

Genes primarily regulate the primordial follicle pool, rate of oocyte apoptosis and follicular atresia. Genetic aberrations or mutations lead to decreased gene dosage, impairment of cell cycle or oocyte meiotic resumption. This may lead to decreased primordial follicle pool and increased follicular atresia due to apoptosis or failed follicular maturation.

Genetic etiology accounts for 20 - 25% cases of POF [11]. Despite of various etiologies described, 70% - 90% cases of POF remain idiopathic and may involve a substantial genetic contribution [12]. In around 12% cases of idiopathic POF, X-chromosomal aberrations have been recognized as the genetic etiology [13-15]. The aberrations include either whole or partial X-chromosome deletions, duplications, or translocations. Several candidate genes have been found which may be associated with POF but mutations causing POF have been studied in less number of studies. The prevalence of such defects needs to be determined. Long arm/q arm of X-chromosome regulates germ cell development and survival [16]. Turner syndrome with loss of X-chromosome is the most common genetic etiology associated with POF. Loss of q arm manifests with gonadal dysfunction [17]. Oocyte specific genes that take part in folliculogenesis and ovarian function are candidate genes implicated in POF. Multiple diagnostic methods such as microarray based genomic hybridization, next generation sequencing have been used extensively to identify genetic aberrations associated with POF. Even simpler cost effective techniques such as single strand conformation polymorphism has shown effective outcome [18].

Genes such as fork head box L2 (FOXL2), nuclear receptor subfamily five group a member 1 (NR5A1), newborn ovary homebox (NOBOX), factor in germline alpha (FIGLA), bone morphogenetic factor 15 (BMP15), GDF9 and inhibin alpha (INHA) promote folliculogenesis. Mutations in these genes have been associated with POF [19]. Another novel gene-parathyroid hormone responsive B1 (PTHB1) was found to be associated with POF. The role of PTHB1 was not known in POF but association of its variants has been seen in Bardet-Biedl syndrome which can sometime be associated with POF. Therefore, PTHB1 can be a novel gene for POF [20]. Similarly, association of ADAMTS19 was shown in another study [21]. This gene is a metalloprotease which gets upregulated during gonadal differentiation. Other potential genes proposed to be associated with POF are MCM8, BRSK1 etc [22]. But, their functional characterization is needed to develop insight into the disease pathogenesis. The most promising association of POF has been proved withFMR1 premutations based on targeted gene approach [23]. In the presence of these premutations, the relative risk of POF is 16% [24].

Studies in animal models have proved the importance of androgen receptors in POF. Androgen receptor knockout mice models are associated with POF phenotype. Mutational analysis of whole androgen receptor gene has found 4 novel mutations in POF by PCR and sequencing [25]. The strong association of one of the inhibin gene-INHA has been observed in POF by sequencing [26]. The other candidate gene approach found association of GDF9 [27]. Screening of FOXL2 gene could not show strong association in POF in Indian population [28].

X-chromosome and ovarian function

POF is proposed to be genetically heterogenous. Multiple genes and signaling pathways regulate ovarian function. Various genes in the "critical region" of X-chromosome that extends along Xq13-Xq26 are implicated in folliculogenesis and oocyte development [29]. Novel gene mutations have been found in this region. Cytogenetic studies have identified that aberrations in long arm of X-chromosome were involved in ovulation defects. X-chromosome rearrangements were observed in POF patients. Several new genes have been identified in distal portion of Xq26 which are proposed to be associated with POF. These genes are HS6ST2, E2F and GPC3 [30]. Their involvement in pathogenesis of POF is yet to be demonstrated. Till now, role of 2 X-linked genes responsible for POF have been confirmed. These are

FRAXA and POF1B. But, their association accounts for only a small proportion of POF cases (6.5% FRAXA, 1% POF1B) and are not the only factors leading to ovarian dysgenesis.

X-chromosome aberrations such as deletions, duplications and translocations have been detected in two main loci-POF1 and POF2. POF1 region, present between Xq26.2-q28 (OMIM: 311360) has shown the presence of deletions in POF patients [5,29]. The most important candidate gene in POF1 region is FMR1 (Fragile site mental retardation 1 gene). Other identified POF1 genes are HS6ST2, TFDP3 and GPC3 gene [30]. Another POF locus is POF2 which extends from Xq13.3-q22 (OMIM: 300511). The candidate genes of this region are DIAPH2, DACH2 andPOF1B.

Diaphanous 2 drosophila homologue (DIAPH2) gene (OMIM: 300108)

DIAPH2 gene is located at Xq22, spans about 1MB and consists of 27 exons. This gene is the human homologue of *Drosophila melanogaster* diaphanous gene [38]. The protein DIA encoded by this gene is a member of FH1/FH2-formin protein family. These proteins regulate cytokinesis and other actin mediated morphogenetic processes required in early developmental stages [31]. The gene is also expressed in ovary and is proposed to be involved in oogenesis by affecting cell divisions [14]. Mutations in this gene lead to POF by affecting cell division.

Daschshund homolog 2 (DACH2) gene (OMIM: 300608)

DACH2 comprises of 11 exons and spans about 700 kb. The gene is present at Xq21.3. In drosophila, dac is a transcriptional co-factor participating in a nuclear complex consisting of sine oculis (so), eyes absent (eya) and dachshund (dac). The drosophila eya gene is reported to be essential in oogenesis, for the correct differentiation of somatic follicle cells into polar cells. It is proposed to be important for development of mammalian gonads, and its alteration in humans may be a risk factor for POF [31].

Premature ovarian failure 1 B (POF1B) Gene (OMIM: 300603)

POF1B gene is located proximal to the centromere present at Xq21. The gene comprises of 17 exons and spans about 100 kb and is present only in vertebrates. POF1 B is highly expressed in polarised epithelial tissues. The gene is also considered to have a function in early ovarian development. It is found to be interrupted by the breakpoint of X chromosome. It is a good candidate gene for POF and its aberrations have been associated with POF [31].

Fragile-site-mental-retardation 1 (FMR1) gene (OMIM:309550)

FMR1 gene consists of 17 exons, spans 38 kb and is located at Xq27.3. Alternate splicing of terminal exons produces a number of FMR1 protein isoforms [32]. FMR1-mRNA is highly expressed in male gonads, in the fetal and adult brain [33]. FMR1 protein is expressed in germ cells of fetal ovary and also in the granulosa cells of maturing ovarian follicles [34]. The mutated FMR1-mRNA when accumulated, has long-term toxic effect on the ovary leading to follicle atresia.

Dysfunction of FMR1 gene causes Fragile X syndrome, also called as Martin-Bell syndrome. The genetic cause of the disease is expansion of CGG trinucleotide repeats to more than 200 units in the 5‟untranslated region of exon1. If the repeats are in range of 55 - 199, it is termed as premutation. FMR1 premutations are present in about 11% familial and 13% sporadic cases of POF. Although a recent study suggests that only 2% of POF cases have FMR1 premutations [35].

Transcription factor DP family, member 3 (TFDP3) gene (OMIM:300772)

TFDP3 consists of 1 exon and is located at Xq26.2. TFDP1, TFDP2 and TFDP3 are members of the DP protein family. They bind E2Fs to form heterodimers which are essential for high affinity DNA binding and efficient transcriptional activity. The E2F transcription factors are involved in the regulation of a variety of life processes like cell cycling, cell growth, apoptosis, cell differentiation and development. These transcriptional factors are also expressed in ovarian and breast cancers. TFDP3 shares a homology with the other two members. It also interacts with E2F transcription factors. Unlike TFDP1 and TFDP2, TFDP3 inhibits E2F-mediated transcriptional activation, thereby inhibiting cell differentiation and cell growth [36]. No role of this gene in the etiology of POF has been studied so far.

Glypican 3 (GPC3) gene (OMIM:300037)

GPC3, a member of the glypican family, is an 8 exon gene present at Xq26. It spans about 500 kb encoding 70kDa core protein. The molecule of GPC3 links to the cellular membrane through a glycosyl-phosphotidylinositol anchor [37]. It plays an important role in regulating cellular growth and apoptosis by interacting with various growth factors like Wnt, FGF2 and BMPs [38]. It is expressed ubiquitously in the embryo but its expression is restricted to colon and ovary in adults [30]. Inherited as X linked recessive, GPC3 gene mutations are responsible for Simpson dysmorphia syndrome [39]. This syndrome is characterized by large protruding jaw, widened nasal bridge, enlarged tongue, short hands and fingers. GPC3 expression is increased in hepatocellular carcinoma (HCC). It plays an important role in cell proliferation and metastasis in HCC. It is considered as a biomarker for HCC and can be a potential target molecule for HCC gene therapy. But GPC3 mutations are not associated with any adverse effects on ovarian physiology as shown by various case reports [40].

Heparan sulfate 6-o sulfotransferase 2 (HS6ST2) gene (OMIM:300545)

HS6ST2 gene is present at Xq26.2 (132626010….132961395, GRCh38.p7 assembly, 342386 bp). The gene has 6 exons. The gene encodes an enzyme heparan sulfate 6-sulfotransferase (HS6ST) which catalyses the transfer of sulphate from 3‟- phosphoadenosine5‟-phosphosulphate to position 6 of the N-sulphoglucosamine residue of heparan sulfate (HS).

HSPGs are present on the cell surface, extracellular matrix and basement membranes. They are known to interact with proteins such as heparin-binding growth factors, extracellular matrix components, selectins, protease inhibitors, and lipoprotein proteases, thereby regulating cell proliferation, differentiation, adhesion, migration, and morphological regulation during development. HSs are present in ooplasm and are found to be important for sperm nuclear decondensation thus playing an important role in fertilization [41]. An enzyme similar to HS6ST has been found in drosophila oocyte having an important role in establishing the oocyte and embryonic polarity. Although parallel role in human oocyte has been proposed but very few studies are done to elucidate role of HS6ST2 in POF [42].

Autoimmunity

Ovary can be the target of autoimmune attack causing ovarian dysfunction and eventually failure. Most common autoimmune condition associated with POF is Grave's disease that is seen in 20-30% of cases, next two common conditions are Addison's disease and type 1 diabetes mellitus occurring in 3% and 2.5% cases of POF respectively [43].

Screening with antithyroid peroxidase, antithyroglobulin antibody and antiadrenal antibody estimation is recommended. End organ functions should be checked in these patients by investigating thyroid function tests and cortisol levels. Normal baseline cortisol levels are suggestive of normal adrenal function. Autoimmune involvement can also be polyglandular. More than 20% women with POF have more than one autoimmune condition [44]. Though the clear diagnosis of autoimmune POF is based on identification of organ specific antibodies but other laboratory investigations can also be suggestive of presence or absence of autoimmune pathology. Various studies have shown poor diagnostic and prognostic relevance of antiovarian antibodies. This is due to different lab protocols followed and pres-

ence of multiple ovarian components as antigens. The importance of presence of ovarian autoimmune cause is also hampered by the fact that POF is the end stage disease which is usually diagnosed at the time when all the follicular supply is exhausted and possibly the target antigens for autoimmune attack on ovary. Therefore, these are not essential to evaluate in POF.

Infections

Association of POF with underlying infections as causative etiology has been proposed but true incidence of post-infectious ovarian failure is lacking. Mumps oophoritis occurs in 2 - 8% of women with POF [45]. In most cases, normal ovarian function is attained once infection gets over. Clear history related to symptoms should be asked to identify the exposure to infectious agents. However, screening for infections in POF is not indicated in absence of risk factors or history indicating exposure.

Metabolic

A number of enzymatic pathway disorders have been associated with follicular dysgenesis. Galactosemia due to deficiency of galactose 1-phosphate uridylyl transferase deficiency was first identified to be associated with POF. Others are 17 hydroxylase deficiency causing decrease in cortisol, androstenedione, testosterone and estrogen deficiency. Aromatase deficiency prevents conversion of testosterone to estrogen.

Idiopathic

Despite many etiological factors described, 70 - 90% cases of POF remain idiopathic. Few commonly done investigations are needed not only to unmask a possible underlying etiology but also to look for associated risks such as risk of aortic aneurysms in Turner syndrome and adrenal insufficiency in POF with autoimmune thyroid disorders.

Novel associations in POF

Ovarian development is regulated by miRNAs mediated expression of genes taking part in folliculogenesis and ovulation. Role of miRNAs in immune modulation have also been confirmed. miRNAs transfer themselves in other tissues by means of extracellular vesicles such as exosomes. NOBOX (Newborne Ovary Homeobox gene) is one of the gene implicated in POF and is found to be regulated by miR-196a [46,47].

Mitochondria is the major energy source needed for folliculogenesis or oogenesis. Altered mitochondrial function/oxidative phosphorylation has caused abnormalities in oocyte maturation, fertilization and embryo development [48]. Reduced mitochondrial DNA content has been correlated with ovarian aging [49]. L-carnitine is one of the mitochondrial shuttle proteins that transfer long chain fatty acids into mitochondrial matrix for oxidative phosphorylation. This function has been found to be crucial for oocyte maturation but the role of l-carnitine and shuttle proteins has not been studied in POF as yet [50].

Inflammatory aging has been found to be associated with pathogenesis of POF recently [51]. Blood levels of proinflammatory cytokines such as tumor necrosis factor alpha (TNF- α) and interleukin-2 (IL-2) found to be increased in POF patients **[52].** *In vitro* studies have shown TNF- α induced degenerative and apoptotic changes in oocytes [53].

Clinical presentation

Women with POF may present with wide symptomatology that vary from manifestations of estrogen deficiency to features suggestive of underlying etiology. In most cases, the first symptom is menstrual irregularity that eventually sets in amenorrhea. About 10% of women

present with primary amenorrhea and majority of women with POF present with secondary amenorrhea [54]. Loss of regular menstruation in a normal non- pregnant woman indicates further investigation. Women may also present with menopausal symptoms such as hot flushes, dyspareunia, vaginal dryness, decreased libido and sleep disturbances. Women with primary amenorrhea may never present with menopausal symptoms. At times the disease is diagnosed during clinical evaluation of infertility. Women with underlying autoimmune disorders may also present with hyperpigmentation of skin, alopecia or goiter.

Long-term sequelae

Cardiovascular

Estrogen maintains cholesterol metabolism thereby preventing atherosclerotic plaque formation and coronary diseases. Untreated cardiovascular complications increase morbidity in women with POF due to endothelial dysfunction leading to atherosclerosis. Hormonal therapy is recommended in these patients.

Bone health

Women with POF are prone for decrease in bone mineral density and risk for fractures due to decreasing levels of estrogen. Hormonal therapy is recommended in POF patients to prevent these risks [55].

Cognitive decline

Premature deficit in estrogen leads to neurocognitive decline as suggested by increase occurrence of Alzheimer's disease in these patients [56].

Infertility

Loss in reproductive potential in POF is an irreversible consequence as the spontaneous resumption of ovarian function is highly unlikely at this stage.

Menopausal

Women with POF are susceptible to menopausal symptoms such as hot flushes, night sweats, sleep disturbances, mood fluctuations, decreased libido, vaginal dryness, dyspareunia etc. These symptoms are due to premature decline in oocyte number and dysfunction of remaining follicles resulting in decreased levels of estrogen and ovarian testosterone.

Initial evaluation of POF patients

Relevant clinical information is needed to diagnose the causative factor in POF. A detailed menstrual and obstetric history may indicate primary/secondary amenorrhoea and primary/secondary infertility respectively. Menopausal symptoms will indicate estrogen deficiency. Family history of early menopause, autoimmune disorders, or mental retardation in males indicates familial POF, autoimmune POF or fragile X syndrome respectively as the etiological factors. Prior pelvic surgery, irradiation, chemotherapy; infections (mumps, tuberculosis, varicella); liver disorders, diabetes, will rule out iatrogenic, infectious or non-endocrine causes of POF respectively. Similarly clinical symptoms indicative of autoimmune hypothyroidism such as cold intolerance, constipation, dry skin, weight gain, hoarseness, swelling in neck, premature graying of hair, slow heart rate or hyperthyroidism such as irritability, tremors, heat intolerance, moist skin, bulging of eyes, palpitations need to be noted. Physical examination findings suggestive of Turner syndrome such as short stature, webbed neck, short metacarpals, wide carrying angles; narrowing of eye opening, drooping of eyelids for blephrophimosis syndrome; exophthalmos,

bradycardia/tachycardia, premature graying of hair, vitiligo for autoimmune thyroid dysfunction and butterfly pattern facial rash (malar rash), patchy hair loss (alopecia areata) should be noted to rule out lupus [42].

Associated ovarian pathological changes give definitive evaluation of ovarian reserve. Two types of pathological changes can be found in POF: small ovaries with deprived of follicles, and normal-sized ovaries with few mature follicles. The main underlying pathogenic feature is oocyte apoptotic changes where they are undergoing atresia at an accelerated rate. Apoptosis is programmed cell death mediated by intracellular or extracellular signalling pathways and both the increased or decreased rate of apoptosis are associated with disorders [57-59]. There are various methods to study cellular apoptotic changes. Multiple studies have shown the apoptotic pathological changes in preeclamptic placenta and ovaries of women with POF [60-63].

Preventive and therapeutic options

Syndromic POF in women with Turner syndrome, familial or chemotherapy induced POF can be managed by counseling the patient for oocyte cryopreservation. Cryopreservation has been tried in male cancer patients also and is considered a useful technique for fertility preservation although effects of cryoinjuries have been reported [64,65]. Careful counseling remains the core of treatment plan in women with POF since POF has been associated with psychological distress. Sequelae of hypogonadism need continuous evaluation and medical treatment. Estrogen deficiency causing bone loss and predisposition to coronary heart disease should be alarmed to the patient. Appropriate management with estrogen/progestin therapy ameliorates the menopausal symptoms.

American college of obstetrician and gynecologists (ACOG) recommends hormone replacement therapy (HRT) as an effective way to treat low estrogen effects in POF.

Oral administration of estradiol (1 - 2 mg daily) or conjugated equine estrogens (0.625 - 1.25 mg daily) or transdermal estrogen regimens (0.1 mg daily) can achieve physiological estrogen levels [66]. In addition, cyclic progesterone can be given to maintain endometrium. In few situations use of HRT is contraindicated such as in women with a history of breast and ovarian cancer, in breast-feeding mothers as it can lead to neonatal jaundice and neonatal breast enlargement, patients with cardiovascular diseases [67].

Conclusion

POF is a heterogeneous disorder with multiple etiologies. Early diagnosis of POF based on medical history and examination will help in predicting the likelihood of early menopause and allow these women to opt for embryo preservation techniques or planning early pregnancy. Moreover, POF has cumulative negative reproductive effects over time. So, it is utmost important to make a timely diagnosis and planning management strategies to avoid negative effects on reproductive efficiency of women with POF.

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