

Review Article

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Early menopause: A hazard to a woman's health

Claudio Hernández-Angeles & Camil Castelo-Branco*

*Gynecobstetrics number 4 "Luis Castelazo Ayala" Hospital. Mexican Social Security Institute, Mexico & *Clínica Institute of Gynecology, Obstetrics and Neonatology, Hospital Clínic- August Pi i Sunyer Biomedical Research Institute (IDIBAPS), Faculty of Medicine-University of Barcelona, Barcelona, Spain*

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Early menopause or premature ovarian insufficiency (POI) is a common cause of infertility in women and affects about one per cent of young women. This disorder has significant psychological sequelae and major health implications. Its relevance has increased in recent years due to the fact that age of motherhood is being delayed in developed countries, with the risk of having either primary ovarian insufficiency or less possibilities of pregnancy. The main characteristics are absence of ovulation, amenorrhoea and high levels of serum gonadotrophins (hypergonadotropic hypogonadism). Although the aetiology remains uncertain in most cases, several rare specific causes have been elucidated. Potential causes for POI are iatrogenic (ovarian surgery, radiotherapy or chemotherapy), environmental factors, viral infections, metabolic and autoimmune diseases, and genetic alterations. Because of the association with other autoimmune diseases, close follow up is recommended in patients with POI. The traditional indicators to evaluate ovarian ageing are age, serum hormonal levels, anti-Mullerian hormone, antral follicle count, and ultrasonography of ovaries. Hormone replacement therapy remains the mainstay of treatment, and the best chance of achieving a pregnancy is through oocyte donation. This article aims to present an overview of potential causes, clinical manifestations, and treatment options of POI.

Key words Early menopause - hypergonadotropic - hypogonadism - ovarian dysfunction - ovarian failure - ovarian physiology - premature ovarian failure

INTRODUCTION

The women fertility reduces in parallel with the ageing¹. Premature ovarian insufficiency (POI), commonly referred to as premature ovarian failure (POF) is a disorder characterized by dysfunction of the ovary before 40 years of age. The main characteristics include absence of ovulation, amenorrhoea and high levels of serum gonadotrophins (hypergonadotropic hypogonadism, HH). POF is not uncommon; its

incidence is estimated to be as high as 1 in 100 by the age of 40, and 1 in 1000 by the age of 30 years^{1,2}.

As early as in 1930s, physicians noted abnormally elevated urinary gonadotropin levels in "premature menopause". In 1950, Atria³ observed 20 patients with "precocious menopause" and defined the basic clinical features of POI, including amenorrhoea before the age of 40, clinical manifestations of hypoestrogenism, an association with viral sickness, and the efficacy of hormonal treatment.

Ovarian ageing resulting in ovarian failure and menopause is a continuous⁴. Menopause generally occurs around 51 yr of age, with an age range varying between 40 and 60 yr^{1,2,5}. The World Health Organization (WHO) defines menopause as the permanent cessation of menstruation due to the loss of ovarian follicular activity⁵. The final menstrual period is retrospectively assigned after 12 months of amenorrhoea. During the Stages of Reproductive Aging Workshop (STRAW) the criteria were formulated to distinguish the various stages of reproductive ageing, based on menstrual cycle pattern and follicle stimulating hormone (FSH) levels: (i) the (early, broad and late) reproductive stage, (ii) the (early and late) menopausal transition, and (iii) the (early and late) postmenopause. Cycles in the early menopausal transition are characterized by elevated but variable early follicular phase FSH levels and low anti-Müllerian hormone (AMH) levels and antral follicle count (AFC)⁶. Menstrual cycles in the late menopausal transition are described by increased variability in cycle length, extreme variations in hormonal levels, and increased prevalence of anovulation⁶.

POI is defined as the occurrence of amenorrhoea (for 4 months or more) before the age of 40 in women, accompanied with an increase of serum FSH to menopausal level (usually over 40 IU/l, obtained at least 1 month apart) and estradiol levels less than 50 pg/ml (which signifies hypoestrogenism)⁷. Another indicator is the AMH, whose serum levels can help assess the state of follicular senescence, which is a possible predictor of risk for POI⁸. However, there are presently no single screening test that can predict a woman's reproductive lifespan. Serum hormonal levels, AMH, AFC and ultrasonography of ovaries, together with age are traditional signs to evaluate ovarian ageing⁹. The conception of ovarian reserve is the assessment of the reproductive ability as a function of the number and quality of residual oocytes. Decreased or diminished ovarian reserve (DOR) describes patients of reproductive age having regular menses whose response to ovarian stimulation or fertility is reduced compared with women of similar age. DOR is different from menopause or POI¹⁰.

As yet, there are no well-established diagnostic criteria but differential diagnosis is needed to discount pregnancy, and other underlying conditions causing secondary amenorrhoea such as polycystic ovary syndrome (PCOS), hypothalamic disease, or uncontrolled diabetes mellitus¹¹. Potential causes for POF are iatrogenic (ovarian surgery, radiotherapy or

chemotherapy), environmental factors, viral infections, metabolic and autoimmune diseases, and genetic alterations, although its origin is idiopathic, and probably genetic in most cases¹² (Table). This article provides an overview of potential aetiologies, clinical manifestations, and treatment modalities of POI.

ANATOMY AND PHYSIOLOGY

Determination of follicle number

The stock of primordial follicles (oocytes surrounded by granulosa cells) in the ovaries, established before birth, has to supply the reproductive needs of a woman for the lifetime. The number of primordial follicles having potential to develop into a fertilizable oocyte is one component of the ovarian reserve¹³. At about 20 wk of foetal life, a maximum number of about 7 million germ cells is reached^{14,15}. At birth and at menarche, about 1,000,000 and 3,00,000 are left, respectively, of which only 400-500 follicles will develop fully and ovulate over the next 35-40 years. At a mean age of 37-38 yr, only about 25,000 resting follicles are present in the ovaries. Menstrual cycles become irregular at about age 45, which is on average six years at the (pre) menopause⁶.

It is uncertain why so many germ cells are lost during the development of the primordial follicle pool. Once shaped, primordial follicles are recruited throughout life to enter folliculogenesis. The ovarian reserve can be influenced at multiple points during development and folliculogenesis: (i) primordial germ cell migration and proliferation; (ii) oocyte entry into meiosis I, synapsis, recombination and arrest in dictyate

Table. Aetiological factors of premature ovarian failure

1. Genetic	X-chromosomal abnormalities, mutations
2. Metabolic	Galactosemia, 17-OH deficiency
3. Iatrogenic	Surgical procedures, chemotherapy, radiotherapy
4. Autoimmune	Autoimmune oophoritis
5. Infectious	Mumps, HIV
6. Environmental/lifestyle	Cigarette smoking
7. Idiopathic	

stage; (iii) transition from oocyte clusters to primordial follicles; (iv) primordial follicle activation; and (v) deficiencies in folliculogenesis or ovulation. The first three phases occur at the foetal and therefore, are not likely to be relevant in clinical treatment of infertility. The current and long-held dogma has been that the number of primordial follicles at birth represents the total ovarian reserve for the entire length of reproductive life; however, contradictory information suggest that oocyte “stem cells” continuously contribute to the ovarian reserve^{13,16}. The remarkably good result of *in vitro* fertilization (IVF) in (pre)menopausal women when employing oocytes of young donors further highlights that the oocyte rather than the endometrium determines the age-dependent fertility loss¹⁷.

Only in the case of fecundation is the second division completed and therefore, all stages are under the influence of certain signals, and the entire process may last for many decades. It is suggested that oocyte derived factors, such as growth differentiation factor 9 (GDF9) or bone morphogenetic protein 15 (BMP15) may be effective in regulating folliculogenesis¹⁸.

Endocrinological factors in ovarian ageing

From the time of puberty onward, the GnRH (gonadotropin releasing hormone) pulse generator communicates with the pituitary gland through the pulsatile secretion of GnRH, which in turn communicates with the ovaries through the secretion of FSH and luteinizing hormone (LH). At each level of this communication system, multiple neuro endocrine molecules orchestrate precise positive and negative feedback loops, to ensure regular opportunities for fertilization^{19,20}. Glutamate and norepinephrine generate major excitatory signals, while γ -amino butyric acid (GABA) and endogenous opioids generate inhibitory signals¹⁹. Recently discovered factors, such as the RF-amide peptide superfamily [kisspeptins, 26/43RFa, gonadotropin-inhibiting hormone (GnIH), RF-releasing peptides (RFRP)] also play a role¹⁹.

Reproductive ageing is considered as a dysregulation of the GnRH pulse generator by a progressive lack of neurochemical control from other brain centers^{15,20}. One of the first signals of this change is the monotropic increase of FSH during the early follicular phase, which produces the acceleration of follicle depletion¹⁵. Then, the interruption in the development of dominant follicles or withdrawal of estrogen without corpus luteum function causes extended cycles and anovulatory haemorrhages¹⁹.

FSH acts on granulosa cells through its receptor (FSHr) to upregulate Cyp19a1 (commonly named as aromatase) and hydroxysteroid (17- β) dehydrogenase 1 to stimulate estradiol production. FSH is critical for protection of follicular atresia, improvement of granulosa cell proliferation, and stimulates the upregulation of luteinizing hormone receptors (LHR) in these cells. Furthermore, an additional growth hormone, insuline-like growth factor 1 (IGF1), increases granulosa cell responsiveness to FSH¹³. As a result of the decreasing cohort of antral follicles, first inhibin B secretion reduces, then estradiol, and finally inhibin A secretion. This results in variations in the feedback mechanisms. The endocrine control of luteal phase does not significantly change with advancing age. In case ovulation still happens, the secretion of estradiol, progesterone, and inhibin A from the corpus luteum appear unchanged^{19,21}.

Genetic causes

Genetic causes are considered as major factor in determining age at menopause in general population, and are described in 7 per cent of POF occurrence^{12,22}. The chromosomal and genetic aberrations mostly involve X-chromosome, yet findings of autosomal involvement are reported²². Even though a large number of related genes have been found, with some understanding of their pathogenesis, the precise genetic mechanisms are often uncertain²³.

Sex chromosome abnormalities

Aneuploidies: In various reports, chromosomal abnormalities, namely aneuploidies and rearrangements have been established as the most common causes of POI, corroborating the importance of cytogenetic testing and genetic advising²⁴. Loss of one X-chromosome as X monosomy [Turner syndrome (TS)], in which most women present with gonadal dysgenesis with primary amenorrhoea and loss of ovarian reserve before puberty. Employing fluorescent *in situ* hybridization (FISH) and several specific marker to the short arm of X-chromosome including DXS1058, DXS6810, DXS1302 and ZXDB, deletion of Xp11.2-p22.1 was submitted as a critical zone linked to TS and POI²⁴. In addition, X-mosaicisms (45,XO, 45,XO/46,XX, 46,XX/47,XXX) are currently the most common chromosomal defect with incidences ranging from 5 to 40 per cent. Women in this group can present menstruation during several years before

developing a complete POI^{12,25}. The wide variation in the occurrence of chromosomal disorders possibly represents patient referral bias.

One candidate gene for gonadal dysgenesis in these patients is *USP9X* (ubiquitin-specific protease 9), which escapes the X-inactivation process and is located on chromosome Xp11.4, a critical region for ovarian development¹¹. Other candidate genes include *ZFX* (zinc finger protein, X-linked) and *BMP15* (bone morphogenetic protein 15). As for other aneuploidies, POI may be related with trisomy X (47,XXX) and tetrasomy (48,XXXX).

Mutations: The *FMRI* (Fragile X mental retardation 1) premutation of CGG replicates with incidence of 1:800 in males and 1:100-200 in women, is accepted as the most important gene associated with POI^{26,27}; is located on Xq27.3²³ and produces an autosomal dominant genetic disorder called fragile X syndrome, distinguished by mental retardation and other symptom such as hyperactivity or attention and emotional problems^{12,27}. Premutation alleles befall in 7 per cent of sporadic POI and 21 per cent in familial POI, considerably higher than in general population²⁸. A critical region from Xq13.3 to Xq27 has been characterized for ovarian development and function^{29,30}. Powell *et al*³¹, employing molecular techniques, found a second gene (*POF-2*) of paternal origin situated more proximal to the Xq locus at Xq13.3-q21.1. Region Xq 21.3-Xq27 is considered premature ovarian failure 1 (*POF-1*). Other potential POF genes located on X-long arm are Diaphanous homolog 2 (*DIAH2*) related with cytoskeleton and implicated in oogenesis and Dachshund homolog 2 (*DACH2*)³². The surveillance suggested that transcendent genes for normal ovarian function are situated on both arms of the X-chromosome. Autosomal genes whose mutations cause some of the syndromes associated with the development of POF are : *FSHR*, *GNAS*, *FOXL2*, *GALT*, *AIRE*, *STAR*, *CYP17A1*, *CYP19A1*, *eIF2B*, *NOG*, *ATM*, *POLG*, *PMM1*, *BMPRI1B* and *GJA4*¹².

Metabolic disorders

Classical galactosaemia is triggered by mutation in the galactose-1-phosphate uridyl- transferase (*GALT*) gene located on chromosome 9p13³³ and is a complex, life-threatening disease occurring during the first week of life and comprises various clinical abnormalities which, in the absence of a galactose-restricted diet, result to liver failure in the second half of the first week of life and death by acute liver and kidney

failure within a few days³⁴. In some cases presenting with a milder phenotype, the diagnosis will be made later in childhood when mental retardation, cataract and hepatomegalia will be detected. In other cases, galactosaemia might be completely asymptomatic, when a sufficient residual *GALT* activity is still continued.

Clinically, patients present with hypergonadotrophic hypogonadism in a context of either primary amenorrhoea with pubertal retardation or secondary amenorrhoea which may start at any age and progress to POI. However, the ovarian dysfunction may present transiently as a gonadotrophin-resistant syndrome described by an alternation of periods with hypergonadotrophic failure and ovulatory cycles³⁵. The mutations that completely eliminate *GALT* activity, such as the homozygous Q188 mutation, are responsible for a poor prognosis, whereas mutations which allow a remaining *GALT* activity are less like to induce long-term complications³⁶.

Mechanisms and timing of follicle development disruption are still not clear. It has been hypothesized that the accumulation of galactose and its toxic products of metabolism (galactose-1-phosphate and galactitol) after birth (since toxic metabolites in foetus should be cleared rapidly by maternal enzymes) leads to direct ovarian impairment³⁶. Glycosylation defects have been hypothesized to account for some of the neurological long-term complications of galactosaemia³⁶.

Chemotherapy irradiation and environmental toxins

Chemotherapy and radiotherapy remain the cornerstone of cancer treatment. The efficacy of chemotherapeutic agents depends upon their ability to destroy rapidly dividing cells. These produce DNA defects as well as oxidative damage in somatic and germ cells. Persistent unrepaired DNA double-strand breaks activate apoptotic death in oocytes³⁷. The clinical impact of chemotherapeutic drugs on the ovary is variable ranging from no effect to complete ovarian atrophy. The degree of damage is dependent upon the type of the chemotherapeutic agent used, dose given, age of the patient and her baseline ovarian reserve. The prepubertal ovary is less susceptible to damage by chemotherapeutic agents while older women have a lower ovarian reserve and therefore, are more susceptible to POF³⁸.

Alkylating agent cyclophosphamide is a non-cell cycle-specific drug that is cytotoxic even to

resting cells, and results in up to 40 per cent risk of ovarian failure at childbearing age³⁸. Alkylating agents are reported to be of high risk of gonadotoxicity, while vinca alkaloids, anthracyclic antibiotics, and antimetabolites are of relatively low risk. Histological examination of ovaries in females after treatment with chemotherapeutic drugs showed blood vessel damage, cortical fibrosis and reduced follicle numbers²².

Human oocyte is susceptible to damage after radiation, with an estimated median lethal dose (LD₅₀) of >2Gy. Damage to the ovary by radiotherapy is due to the age of the patient and dose of the ovarian exposure. The effective sterilizing dose (ESD) is the dose of fractionated radiotherapy at which POI occurs immediately after treatment in 97.5 per cent of patients. ESD reduces with rising age, being 20.3 Gy at birth, 18.4 Gy at 10 yr, 16.5 at 20 yr, and 14.3 Gy at 30 yr, with only 6 Gy being required to cause POI in women over 40 yr old³⁹.

All women who desire to preserve fertility should be advised and informed about currently available fertility preservation options by fertility specialists. Recommendations should be individualized and should not violate the ethical principles. Gonadotropin-releasing hormone agonist (GnRHa) is often used in combination with chemotherapy causing suppression of the gonadotropin levels to prepubertal levels and reduces utero-ovarian perfusion⁴⁰, these actions are believed to protect the follicles from apoptosis.

Chen *et al*⁴¹ concluded that the use of GnRHa should be proposed in women of reproductive age receiving chemotherapy and should be given before or during treatment. GnRHa should begin at least 10 days before the beginning of chemotherapy because of the initial flare-up effect and should continue till two weeks after the end of chemotherapy⁴². Currently, ovarian tissue cryopreservation, embryo cryopreservation, oocyte cryopreservation and *in vitro* maturation are considered and these can be recommended in selected patients and should be offered only by centres with the necessary laboratory and surgical capability⁴³. After POI prevention contraception should be considered in sexually active women⁴⁴.

Environmental toxins resulting in oocyte damage might cause POI. Smoking is the most widely studied toxin that alters ovarian function by accelerating follicular atrophy and atresia through increased apoptosis in primordial germ cells⁴⁵. Polycyclic aromatic hydrocarbons (PaHs), toxic

chemicals in tobacco, induce aromatic hydrocarbon receptor (Ahr)-driven expression of Bax in oocytes, followed by apoptosis²². Endocrine disruptors, heavy metals, solvents, insecticides, plastics and industrial chemicals, were associated with adverse reproductive outcomes and ovarian failure in animals. However, the underlying mechanisms were not yet fully clarified and contradictory results were found in human²³.

Immunology of POI

Autoimmune disease is characterized by autoreactive T-cells and the presence of organ and non-organ-specific autoantibodies^{46,47}. There are three different situations of autoimmune ovarian insufficiencies: associated with adrenal autoimmunity, non-adrenal autoimmunity and isolated idiopathic POI⁴⁸.

Initial data estimated that 10 per cent of patients with Addison's disease would develop POI 5-14 years before adrenal disorder. Addison's disease infrequently develops in isolation, with the majority of patients having other associated endocrine disorders. The strongest association of POI is with autoimmune Addison's disease in the context of two types of autoimmune polyendocrine syndromes (APS)^{46,47}. Type 1 [autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)] characterized as hypoparathyroidism, adrenal failure, and chronic mucocutaneous candidiasis occurs in young children. POI in the form of primary amenorrhoea develops in 60 per cent of type I patients and type II (a polygenic syndrome with autoimmune Addison's disease with adrenal insufficiency and other autoimmune illness without hypoparathyroidism)^{46,48} occurs in a much broader age range (third to fourth decade) and the incidence of POI is variable.

POI may also be associated with localized or systemic non-adrenal disorders^{49,50}. Between 10 and 30 per cent of women with POI have a simultaneous autoimmune disease, the most commonly reported being hypothyroidism^{49,50}, and the most clinically important hypoadrenalism; as well concurrent with hypoparathyroidism⁵¹, hypophysitis, type 1 diabetes mellitus, and non-endocrine autoimmune haemolytic anaemia, pernicious anaemia, vitiligo, alopecia areata, celiac disease, inflammatory bowel diseases, primary biliary cirrhosis, glomerulonephritis, multiple sclerosis, Sjogren's syndrome⁵² and myasthenia gravis⁴⁸ have been reported.

Antiovarian antibodies

A plausible hypothesis for autoimmune oophoritis is a selective involvement of developing follicles, sparing primordial follicle in early phase, with increased ovarian size with luteinized cyst⁵³. This autoimmune disease is described by serum ovarian autoantibodies detected mainly by indirect immunofluorescence⁵³ and enzyme-linked immunosorbent assay (ELISA). Antigens involved in autoimmune oophoritis, such as zona pellucida/oocyte⁵⁴, granulosa cells, theca cells⁵², corpus luteum and steroidogenic enzymes: 17 α -hydroxylase (17 α -OH), cytochrome P450 side-chain cleavage enzyme (p450 scc) and 21-hydroxylase^{47,53} have been reported as the markers of ovarian autoimmunity.

Infections

Mumps oophoritis has been considered to be a cause of POI. True incidence of post-oophoritis ovarian failure is uncertain. In the majority of affected women, return ovarian function occurs following recovery^{55,56}. HIV infection or the corresponding antiretroviral treatment may impair ovarian functions and fertility, and end in POI⁵⁷. There are also anecdotal reports of viral and microbial infection, such as varicella, cytomegalovirus, malaria being followed by POI^{56,58}. The true frequency of ovarian failure due to viral illness is uncertain.

TREATMENT AND PROGNOSIS

After corroborating the diagnosis of POI, karyotyping and analysis of *FMRI* premutation should be done to exclude major genetic causes. It is widely accepted that the mainstay of treatment of POI is hormone replacement therapy (HRT), at least until the average age of natural menopause. These women have an increased risk of premature death, mainly from cardiovascular disease, and POI has a potentially devastating influence on bone, with a decreasing bone mineral density, osteoporosis, and increased risk of fracture. Other reasons of morbidity comprise dementia, cognitive decrease and Parkinsonism⁵⁹.

Induction of puberty is mandatory in young women with pre-pubertal POI, to enable the pubertal growth spurt as well as for development of secondary sexual characteristics, but uterine morphology is often insufficient with failure to accomplish normal volume and configuration, and often a low success rate on oocyte donation programmes⁶⁰. An extensive variety of treatment modalities are reported in post-pubertal

young women, but, there is no clear evidence of best practice⁶¹. Physiological Sexual Steroids Replacement (pSSR) appears to recover uterine morphology and parameters of uterine function; however, both, age at POI and underlying aetiology seem to play a role in the success of the medication.

Pregnancies have been shown to occur in women with POI⁶². Ovulation was reported in 20 per cent of patients with POI who were observed successively over a 4-6-month period, but forecasting the probability of spontaneous remission in a specific individual is currently not feasible. Assisted reproductive technique with oocyte donation and *in vitro* fertilization should be recommended. Besides medical treatment, professional and family support is essential as POI can also adversely affect emotional health, provoke stress, loss of self-esteem, social isolation, increased shyness and anxiety.

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Reprint requests: Dr Camil Castelo-Branco, Institut Clinic of Gynecology, Obstetrics & Neonatology, Hospital Clinic c/ Villarroel 170 08036- Barcelona, Spain
e-mail: castelobranco@ub.edu