Chapter 6

Premature Ovarian Insufficiency

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Abstract

Premature ovarian insufficiency (POI) is a heterogeneous disorder, affecting approximately 1% of women before the age of 40. Heterogeneity of POI is reflected by various causes. The known causes are genetic defects, autoimmune ovarian damage, metabolic, iatrogenic following surgery, cancer therapy, and environmental factors. However, in most cases, the cause remains unknown (idiopathic POI). The main symptom is the absence of regular menstrual cycles, and the diagnosis is confirmed by the raised gonadotropins and low estradiol. The disorder usually leads to infertility and has long-term comorbidities such as cardiovascular diseases, osteoporosis, and cognitive impairments. Management includes the use of hormone replacement therapy till the age of natural menopause. In women having fertility issues, the spontaneous conception varies between 5 and 10%, and in vitro fertilization with donor oocytes remains the treatment of choice. Moreover, fertility preservation options can be offered to some patients with cancer and those at risk of early menopause, such as those with familial cases of POI. Further research is clearly needed, to identify new mechanisms which may improve the prediction of the early onset of the disease.

Keywords: premature ovarian insufficiency, irregular menstrual cycle, estrogen deficiency, hormone replacement therapy, infertility treatment

1. Introduction

Premature ovarian insufficiency (POI) is a heterogeneous condition defined by the presence of menopausal-level serum gonadotropins in repeated blood tests with menstrual disturbance (oligomenorrhea or amenorrhea) in adolescent girls or women under 40 years of age [1]. Several different terms have been used to describe this condition, such as premature menopause, premature ovarian insufficiency (POI), or premature ovarian failure (POF). Confusion exists concerning nomenclature, namely, the use of POF or POI. The term POI has

been adopted recently by the European Society of Human Reproduction and Embryology (ESHRE) consensus instead of "failure" [2]. Because it was found to more accurately describe the fluctuating nature of the condition. The POF is best considered as the only final stage of POI [3, 4]. The incidence of spontaneous POI has been estimated to affect 1 in 100 women before 40 years of age and 1 in 1000 women before 30 years of age [1, 5]. Although the incidence of spontaneous POI appears to have remained stable, of increasing concern is the rising incidence of iatrogenic POI [6]. Improved survival following malignant diseases has led to increasing numbers of women experiencing the long-term effects of cancer treatments. A recent cohort study estimated the incidence of POI, both spontaneous and iatrogenic, at 7.4% [7]. The risk of POI varies by ethnicity, ranging from 0.1% in Japanese to 1% in Caucasian and 1.4% in African American and Hispanic groups [8]. Environmental factors such as cigarette smoking and poverty were associated with an increased risk of idiopathic POI. In contrast, certain factors related to ovulation, such as late menarche, irregular menstruation, and longer breastfeeding seem to reduce the risk of POI [9]. The familial form of POI is rare, representing 4–31% of all cases of POI [10–12]. Morris DH et al. (2011) reported that women were around six times more likely to have early menopause if their mother (odd ratio [OR], 6.2; $p < 0.001$) or older sister (OR, 5.5; $p < 0.001$) also experienced early menopause [13].

2. Objective

In this comprehensive review, we aim to provide an overview of the current knowledge of the identifiable causes leading to POI development and the recent advances in the management of its consequences in terms of long-term complications as well as in terms of infertility concerns.

3. Methods

Literature search strategy: Using the MEDLINE database and Google Scholar, we conducted a comprehensive literature search to identify relevant publications on menstrual cycle disorders associated with premature ovarian insufficiency. The keyword combinations include "premature ovarian insufficiency," "primary ovarian failure," "hypergonadotropic amenorrhea," "hypergonadotropic hypogonadism," and "early menopause."

Selection criteria: The search was restricted to articles that were published up to May 2018 in English language and that assessed at least one of the following aspects of the condition: "epidemiology," "diagnosis," "etiology," "long-term consequences," "hormonal replacement therapy," "infertility management," and "prediction."

Data synthesis and analysis: The conclusions and the interpretation of the findings were based on our personal experience. In addition, we provided some clinical recommendations and guidelines about the management of patients experiencing premature or early menopause based on the expertise of prestigious scientific societies such as the European Society for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM). Statistical testing was not conducted.

4. Diagnosis

Current studies have failed to determine specific biomarkers or signs/symptoms of POI that will accurately predict when menopause will occur. Some women with POI may not experience any specific symptoms particularly in the idiopathic form of the largest etiology, which may delay the establishment of the diagnosis.

One study reported that over 50% of patients with POI had seen at least three clinicians before the diagnosis was made, and in 25% the diagnosis took more than 5 years [14]. Before puberty, the clinical picture is characterized by absent menarche, and pubertal delay results in absent sexual maturation. After puberty, the typical disorder is characterized by the loss of menstrual regularity (oligomenorrhea or amenorrhea) in young women for 3 or more consecutive months and often associated with symptoms of estrogen deficiency such as vasomotor symptoms which are similar to those observed with the onset of menopause, such as hot flushes, insomnia, nervousness, irritability, loss of libido, vaginal dryness, dyspareunia, etc. Female infertility is a common concern, as only 5–10% of the patients will conceive spontaneously [15]. POI may be part of other syndromic features: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, blepharophimosis-ptosis-epicanthus inversus syndrome, carbohydrate-deficient glycoprotein syndromes, galactosemia, Turner syndrome, and PHP I [16].

Additionally, patients can experience long-term consequences of hypoestrogenism, including low bone density (osteoporosis) [17], cardiovascular diseases [18], and neurocognitive disorders [19]. For the biochemical confirmation, follicle-stimulating hormone (FSH) levels are used as the gold standard in establishing a diagnosis of POI. Two serum FSH levels in the menopausal range should be obtained at least a month apart (**BOX 1**) [27]. However, there is a lack of consensus on adequate cutoff levels used to define hypergonadotropism. No follicles were found in ovarian biopsies when FSH levels are above 33 and 40 mIU/ml in women with primary and secondary amenorrhea, respectively [20]. Some women with POI express FSH levels lower than these proposed cutoff values, particularly women with autoantibodies. La Marca et al. (2009) found that women with POI due to steroidogenic cell autoimmunity had significantly lower FSH levels (n = 26, median 37 mIU/ml) compared with idiopathic POI (median 99 mIU/ml) (P = 0.001) [21]. Furthermore, estradiol (E2) levels are typically low, with a level of 50 pg/ml in women with absent or nonfunctioning follicles [22]. Antimullerian hormone (AMH) is currently the most convenient predictor of ovarian reserve. Very low AMH levels seem to play a role in predicting age at menopause [23, 24].

Younger than 40 years of age

Oligo/amenorrhea for at least 4 months

Two FSH levels in the menopausal range, obtained at least a month apart

Data from [27].

Box 1. Criteria to establish the diagnosis of premature ovarian insufficiency.

Test	Implications	
	Positive test	**Negative test**
Genetic/Chromosomal		
Karyotyping (for diagnosis of Turner syndrome)	Refer to endocrinologist, cardiologist and geneticist	A second analysis of the karyotype in epithelial cells (in case of high clinical suspicion)
Test for Y-chromosomal material	Discuss gonadectomy with the patient	
Fra-X	Refer to geneticist	
Autosomal genetic testing[1]		
Antibodies2		
ACA/21OH antibodies	Refer to endocrinologist	Re-test in case of clinical signs
TPO-Ab	Test TSH every year	or symptoms

[1]not at present indicated in women with POI, unless there is evidence suggesting a specific mutation (e.g. BPES).
[2]POI of unknown cause or if an immune disorder is suspected.
Data from [25].

Table 1. Summary of diagnostic workup.

The differential diagnosis is based on the exclusion of other causes of primary and secondary amenorrhea, for example, pregnancy, polycystic ovarian syndrome, hypothalamic-pituitary disease (pituitary tumors, hyperprolactinemia, Kallmann syndrome), hypothalamic amenorrhea (induced by stress, intensive exercise, anorexia, weight loss, fasting, and severe diseases), endocrine disorders (hyperthyroidism, hypothyroidism, and Cushing syndrome), and vaginal/uterus anatomical abnormalities, such as Rokitansky syndrome or Asherman syndrome. Once the diagnosis has been confirmed, second-line investigations to look for an underlying cause should be considered which may have implications for the individualization of the management **Table 1** [25].

5. Etiology

Three potential mechanisms can be associated with POI, that is, a congenital decrease in primordial follicles, accelerated follicular atresia, and an inability to recruit primordial follicles [26]. The known causes of POI are wide ranging and can be divided into spontaneous and iatrogenic categories.

5.1. Spontaneous POI

Most cases of spontaneous POI are idiopathic despite the diagnostic advances [27] but may be also due to genetic causes, autoimmune disorders, metabolic dysfunction, enzyme deficiencies, toxins, or infections [27–29].

5.1.1. Genetic causes of POI

The normal ovarian function requires the presence of many intact genes functionally normally and in a coordinated fashion. Chromosomal abnormalities are found in around 10–12% of women with POI, of which the majority is X chromosomal abnormalities [30]. An increasing number of studies have documented autosomal involvement. The incidence of chromosomal abnormalities is higher in women with primary amenorrhea (21%) than in those presenting with secondary amenorrhea (11%) [31].

5.1.1.1. X Chromosome defects

Both the short and long arms of the X chromosome appear to play important roles.

X Chromosome defects usually involve either complete deletion of one X (Turner syndrome) or partial deletions, duplications, and balanced translocations between the X and autosomal chromosomes. Females lacking an X chromosome as well as those showing an extra X chromosome are predisposed to developing POI. Monosomy X (45X), known as Turner syndrome, is due to the loss of the second sex chromosome and affects 1 in 2500 live-born female infants and has a frequency of 4–5% in POI [32]. In phenotypic women, Turner syndrome is associated with short stature, gonadal dysgenesis, and primary amenorrhea. In women with Tuner syndrome, oocyte loss usually begins early in childhood as a result of accelerated follicle atresia [33]. The vast majority of pregnancies with this karyotype end in spontaneous miscarriage, and it is argued that the surviving individuals most likely carry some degree of mosaicism [34]. In mosaic Turner syndrome (45X/46XX), patients have a milder phenotype and may present later with secondary amenorrhea and hypergonadotropic hypogonadism. Trisomy X (47XXX) is caused by nondisjunction of the X chromosome during meiosis. It is the most common form of aneuploidy, occurring in 1:900 women. About 1.5–3.8% patients with POI had the triple X [30, 35] and may manifest in many mosaic forms, that is, 45X/47XXX, 46XX/47XXX, or 47XXX/48XXXX [36]. The presence of three X chromosomes presumably leads to meiotic disturbance and, secondarily, ovarian failure. X Chromosome deletions associated with POI are more common than translocations. At present, the microdeletions are not normally identified by conventional karyotyping and so often go unrecognized. Krauss et al. reported in 1987 a family in which one woman and two girls, with early menopause, had a deletion of the long arm of the X chromosome (Xq21–Xq27) [37]. Cytogenetic and molecular analyses of POI women carrying a balanced X-autosome translocation allowed the identification of a "critical region" for the ovarian development and function on the long arm of the X chromosome from Xq13.3 to q27. Various deletions or translocations occurring within this region and also on the short arm of the X chromosome have been associated with POI [38, 39]. POI can also be associated with the Xq isochromosome which occurs when the centromere splits abnormally in the transverse plane instead of the longitudinal plane. The resulting chromosome pair contains structurally identical arms with identical genes. The isochromosome for the long arm (q) is the most common X structural abnormality. These patients present with streak gonads and Turner-like characteristics which are rare causes of POI [40].

5.1.1.2. Single-gene defects

The fragile X syndrome is an X-linked dominant genetic disorder that is a leading cause of mental retardation and autism. Women exhibiting extended repeats of the CGG trinucleotide sequence may be classified as having the permutation (55–199 repeats) or the full condition (>200 repeats). There is an association, although nonlinear, between the number of repeats and the severity of the condition. The fragile site of the X chromosome contains a (CGG) repeat in the 5′ region of the gene. In normal variants, the trinucleotide repeat ranges from 6 to 55 repeats.

The syndrome occurs when the number of the repeats exceeds 200, being denominated as full mutation alleles. The fragile X mental retardation 1 (FMR1) gene premutation, mapped at position Xq27.3 on the X chromosome, is the most frequently identified single-gene mutation associated with POI outside the Xq POI critical region. It has been shown that females carrying a premutation have up to 23% rate of POI and experience menopause 5 years earlier than average [41]. The FMR1 premutation has been identified in 11% of familial POI and 3% of sporadic cases [42–44], and therefore, screening for the FMR1 premutation is usually recommended in women diagnosed with POI to identify those patients and family members who may be at risk of having children with fragile X syndrome. Those with identified premutation should be referred for family genetic counseling. *The bone morphogenetic protein 15 gene (*BMP15) *is a member of transforming growth factor beta (TGF-ß) superfamily and is located on the short arm of the X chromosome (Xp11.2) within the Xp POI critical region* [45, 46]. It is an *oocyte-specific folliculogenesis growth differentiation factor (GDF) and appears to have a vital role in folliculogenesis and granulosa cell growth.*

Approximately 1.5–12% of POI is associated with *BMP15* gene mutation [47–50].

Fragile site, folic acid type, rare (*FRAXE*)/fragile site mental retardation 2 gene (*FMR2*) has been described in patients who have the cytogenetic changes of fragile X syndrome but who are *FMR1* mutation negative. It was found at Xq28 and found to be folate sensitive [51].

5.1.1.3. Autosomal genetic defects

While several genes relevant to ovarian function lie on the X chromosome, autosomal genes also appear to be involved in the development of POI [26].

In recent years, attention has focused on genes that are known to play a role in folliculogenesis and ovarian function. Oocyte-specific gene expression is necessary for primordial follicle formation and their subsequent differentiation into primary follicles. A number of autosomal genes have been suggested as a causative factor of POI. For some of these genes, mutations are identified, while others are listed as candidate genes with a need for further investigation. The genes with identified mutations that could result in POI are genes involved in folliculogenesis (NR5A1, NOBOX, FIGLA, and FOXL2), folliculogenesis growth factors (GDF9 and inhibin A), sex hormone function (*CYP17A1, CYP19*, FSH/luteinizing hormone (LH) receptors, and *NR5A1*) [26, 38], or genes identified in syndromes often associated with POI such as Bloom syndrome BLM 15q26.1 [52], Ataxia telangiectasia,

A-T. ATM 11q22-q23 [53], Werner syndrome WRN 8p12 [54], and Rothmund-Thomson syndrome RTS 8q24.3 [55]. Given that the conventional approaches have had limited success in finding causative genes, further research and new techniques on the genetic background of POI including genome-wide analysis in affected families may change this recommendation in the near future.

5.1.2. Autoimmune causes of POI

Anti-ovarian antibodies are reported in POI by several studies, but their specificity and pathogenic role are questionable. Autoimmune diseases are estimated to be involved in the pathogenesis of up to 5% of POI cases. Adrenal autoimmunity is thought to account for 60–80% of autoimmune POI [56], and there is a strong association between the presence of adrenal antibodies and a diagnosis of autoimmune lymphocytic oophoritis [57]. The evidence of oophoritis is rare (<3%) in POI in the absence of adrenal involvement [16]. The presence of many other autoantibodies has been investigated such as ovarian and other steroidogenic cell autoantibodies; however, reliable markers to diagnose non-adrenal autoimmunity are yet to be identified [56]. POI can be associated with endocrine (thyroid, hypoparathyroid, diabetes mellitus, and hypophysitis) and non-endocrine diseases (chronic candidiasis, idiopathic thrombocytopenic purpura, vitiligo, alopecia, autoimmune hemolytic anemia, pernicious anemia, systemic lupus erythematosus (SLE), rheumatoid arthritis, Crohn's disease, Sjogren syndrome, primary biliary cirrhosis, and chronic active hepatitis) (**Table 2**) [16, 58, 59]. POI may be part of the autoimmune polyglandular syndromes (APS) when accompanied by other autoimmune endocrinopathies. POI is more common with APS types I and III than with APS type II [60].

5.1.3. Metabolic causes of POI

A number of inherited enzymatic pathway disorders have been associated with ovarian follicular dysfunction leading to POI such as galactose-1-phosphate uridylyltransferase deficiency (galactosemia) [61], 19, carbohydrate-deficient glycoprotein deficiency [62], 17α-hydroxylase/17,20 desmolase deficiency [63], and aromatase mutations [64] where there is biochemical damage of the ovary and autoimmune regulator which triggers autoimmune damage. However, the strength of evidence linking each anomaly with POI is variable.

Endocrine	Hypo/hyperthyroidism, Hypoparathyroidism, Diabetes mellitus type II, Hypophysitis, Addison's disease.
Non-endocrine	Idiopathic thrombocytemic purpura, Chronic candidiasis, Vitiligo, Alopecia, Hemolytic or Pernicious anemia,
	Systemic lupus erythematodes, Rheumatoid arthritis, Cirrhosis, Sjogren's sy, Primary biliary cirrhosis, Chronic hepatitis etc.

Data from [16, 58, 59].

Table 2. Endocrine and non-endocrine diseases associated with premature ovarian failure.

5.2. Induced POI

The induced POI may result from damage to the ovaries, such as that caused by iatrogenic agents like chemotherapy, radiotherapy, pelvic surgery, and also environmental toxic agents.

5.2.1. Cancer therapy

There is an overall increase in cancer prevalence followed by an increase in long-term survival of the affected patients these days compared to the past. The 5-year survival rate for childhood, adolescent, and young adult cancer currently exceeds 80% [65]. Medical treatment for neoplastic conditions can be associated with POI. Chemotherapy and radiotherapy are well-documented causes of POI.

Chemotherapy induces apoptosis of mature ovarian follicles, and histological studies have shown fibrosis, vascular damage, and reduced follicle numbers. The gonadotoxic effect of chemotherapy is drug and dose dependent [66]. Alkylating agents have been shown to be gonadotoxic [67]. The prepubertal ovary is relatively resistant to this form of gonadotoxicity [67]. The risk of developing POI after radiotherapy is dependent on the radiation therapy field (abdominal pelvic, total body irradiation) and on dose and age [68–70]. Transposition of the ovaries in young women requiring pelvic irradiation helps in preserving their ovarian function.

5.2.2. Pelvic surgery

Aside from surgical menopause due to bilateral oophorectomy, limited evidence suggests that pelvic surgery is maybe associated with POI such as hysterectomy [71], tubal sterilization [72], or both ovarian surgery for endometrioma and endometriosis [73] presumably due to damage to ovarian blood vessels as a result of the surgical procedure. Research has now also linked ovarian drilling for polycystic ovary syndrome and removal of endometriotic cysts to an earlier age at menopause [74, 75].

5.2.3. Toxins

The increasing prevalence of POI in recent years might be also due to an increase in presently unidentified environmental toxic agents. However, studies examining the cause and effect of the chemical substances and POI in humans are rare.

Chang et al. (2007) found that cigarette smoking was associated with an increased risk of POI (OR = 1.82 [1.03–3.23]) [76]. Many other endocrine-disrupting substances have been also suggested to be ovotoxic and influencing the age of menopause such as 2-bromopropane [76], vinylcyclohexene diepoxide (VCD) [77], polycyclic aromatic hydrocarbons (PAHs) [77], etc., but they are not readily considered as diagnosable causes of POI. Further research is warranted to clarify in which toxicants affect human reproduction and how insufficiency with FSH values is found in the menopausal range [78].

5.2.4. Infections

It has been indicated that many viral infections can be followed by POI, but only mumps oophoritis has been directly linked to POI, explaining 3–7% of POI cases [79]. Other potential

causes of POI include tuberculosis, malaria, varicella, and *Shigella* [80]. More recently, there has been suggestion that human immunodeficiency virus (HIV) infection (or antiviral therapy) can lead to POI. However, a recent systematic review revealed nonconclusive evidence due to a significant methodological limitation with available data [81].

6. Management

Patients must be provided with adequate information (education, understanding, and counseling). Management should address the following aspects: psychology support, ovarian hormone replacement for the prevention of long-term complications, and therapy for fertility.

6.1. Psychologic support

The diagnosis of POI is an extremely devastating psychologic disturbance [35]. Some will experience a range of emotions such as high levels of depression and low levels of self-esteem with negative effects on sexuality [82], and providers should offer support regarding infertility, altered self-image, and sexual dysfunction. Patients may benefit from referral to a psychologist and support groups [83].

6.2. Hormone replacement therapy

Hormone replacement therapy (HRT) remains the cornerstone of treatment for relief of menopausal symptoms (including vasomotor instability, sexual dysfunction, mood, fatigue, and skin issues) and prevention of long-term morbidity and earlier mortality related to prolonged estrogen deficiency [84]. The results of Women's Health Initiative (WHI) study should not be applied to young women with POI [85, 86]. In contrast with women older than 50s, POI is a pathologic condition in which young women have low serum E2 levels compared with their peers. For young women with E2 deficiency, hormone therapy is indeed a "replacement," whereas in women with normal menopause, hormone therapy is hormone "extension." Physiological replacement of ovarian steroid hormones until the age of 50 years (the average age of natural menopause) is generally accepted as routine, unless a specific contraindication exists, such as an estrogen-dependent malignancy. At present, very little evidence exists regarding the optimum method of hormone replacement, and options include both the combined oral contraceptive pill (COC) and hormone replacement. Data regarding the optimal estradiol levels in POI are lacking; however, the average serum estradiol level during the menstrual cycle in normal women is approximately 100 pg/ml [87]. Transdermal and transvaginal replacement of 100 μg/day of estradiol achieves physiologic blood levels in this range and provides adequate symptomatic relief. The transdermal route has the advantage of avoidance of first-pass hepatic metabolism and appears to be free of an excess risk of thrombosis compared with oral estrogen [88–90]. To reduce the risk of endometrial hyperplasia, 5–10 mg of medroxyprogesterone acetate should be given for 12 days of the month, provided that the uterus is present and intact [90, 91]. However, the optimum type of progestogen is unclear. With the use of this regimen, most of women will develop monthly withdrawal bleeding, which

may be psychologically important to the patient. The COC is also commonly used as hormone replacement in POI. However, they should not be recommended as first-line hormone replacement. Indeed, they result in supraphysiological doses of sex steroid hormones and are associated with an increased risk of thromboembolic events related to the first-pass effect on the liver [27]. Androgen replacement could be carefully considered for women who have persistent fatigue and low libido despite optimized estrogen replacement [92]. Transdermal testosterone administration and dehydroepiandrosterone treatment are two of the options for androgen replacement in these women [93]. Importantly, this should be performed with great caution and for relatively short periods until more data are available. When there has been no spontaneous start to puberty or progression of breast development, many options for HRT are suggested for puberty induction. However, systemic administration of increasing doses of estradiol, preferably by transdermal application, is the only form of therapy to achieve natural levels of estradiol in blood and mimic normal estradiol physiology in adolescence and adulthood [94, 95]. Patients who do not want to get pregnant should be offered contraception due to the 5–10% chance of spontaneous conception. Women with untreated POI are at increased risk of developing long-term comorbidities such as cardiovascular disease [96], metabolic syndrome [97], osteoporosis, dementia, cognitive impairment, Parkinsonism, reduced sexual function, and psychological well-being. Untreated POI can induce specific increase in mortality rate due to complications of the prolonged estrogen deficiency compared to those with a menopause after the age of 50 years [98]. The main reason for shortened life expectancy in women with POI is cardiovascular disease. The Framingham study was one of the first to show a higher incidence of cardiovascular disease among postmenopausal women than age-matched women who were premenopausal [99]. A number of studies have subsequently demonstrated higher rates of coronary artery disease, higher rates of heart failure, and higher rates of mortality in women reaching menopause before 40–45 years of age, and it has been demonstrated that this impairment was reversed by estrogen replacement [100]. Compared with control women, women with premature ovarian insufficiency have reduced bone mineral density. The prevalence of osteoporosis in POI appears to be in the range of 8–14% [101]. Multiple studies have shown that the lower bone mineral density (BMD) seen in women with POI is associated with significantly higher overall fracture risk, and this has been associated with the presence, degree, and duration of estrogen deficiency. Studies on fracture risk in early menopause compared to natural menopause have demonstrated that fracture rates are reduced among women with POI or early menopause who are treated with the use of HRT [101–103]. Early data demonstrate an increased risk of cognitive impairment [104]. Some studies suggest that estrogen is neuroprotective. The Mayo Clinic Cohort Study of Oophorectomy and Aging demonstrated that women who underwent either unilateral or bilateral oophorectomy before the onset of the menopause had an increased risk of cognitive impairment or dementia [105] and Parkinsonism [104] compared to controls and that this risk increased with younger age at oophorectomy. They also demonstrated a protective role for estrogen replacement in women with bilateral oophorectomy when taken until at least 50 years of age. A similar finding was noted in a Danish cohort study, revealing an increased risk of dementia in women undergoing oophorectomy prior to the age of 50 years, with a similar trend of increasing risk with earlier age at oophorectomy [106].

6.3. Fertility

6.3.1. Spontaneous conception and POI

For many women with POI, infertility is the most devastating aspect of the diagnosis.

Fertility of women with POI is severely diminished, but unlike menopause, POI may be accompanied with spontaneous ovarian activity and natural pregnancies in approximately 5–10% [107]. Currently, no fertility treatment has been found to effectively increase fertility in women with POI including estrogens [108–110], 5-dehydroepiandrosterone (DHEA) [111], corticosteroids [112], and azathioprine [113].

6.3.2. Assisted reproductive technology (ART) and POI

6.3.2.1. Oocyte donation

The only proven therapy for obtaining a pregnancy in patients with POI is fertilization of a donor oocyte. At present IVF with donor oocytes confers the highest chance of pregnancy for women with POI with high success rates of around 40–50% per cycle.

The pregnancy rate from oocyte donation is not greatly affected by the recipient's age [114, 115].

6.3.2.2. Fertility management of the Turner syndrome

There are special considerations regarding oocyte donation in women with Turner syndrome. If pregnancy is desired, hormone replacement therapy can be initiated to increase uterine size, followed by assisted reproductive technology, namely, in vitro fertilization with an oocyte donor. However, coexisting cardiac abnormalities associated with Turner syndrome may increase the risk of pregnancy for the mother, and therefore this type of approach to achieve pregnancy is strongly discouraged [116, 117]. Should a Y chromosome be identified with or without an SRY gene mutation, the patient should be counseled about the risk of development of a gonadal tumor, and gonadectomy should be advised [118, 119].

6.3.2.3. Fertility preservation and POI

Fertility preservation may also be considered for women at risk of POI; in young women who require cancer treatments, including chemotherapy, radiotherapy, and surgery; or for those who have a strong family history of POI. Options for fertility preservation include ovarian transposition, oocyte or embryo cryopreservation, and ovarian tissue cryopreservation. Ovarian transposition remains the standard of care for women undergoing pelvic radiation, although it has been suggested that it may be combined with ovarian tissue cryopreservation. Embryo cryopreservation remains the most successful technique, with success rates approaching that of fresh embryo transfer [120, 121]. Live birth rates of approximately 30% per embryo transfer have been reported, depending on the age of the patient [120]. The success of oocyte cryopreservation has also improved significantly in recent years, and birth rates similar to that of fresh oocytes have been reported [122]. Oocyte cryopreservation is a potential option

for women without a partner. Since the initial report of successful pregnancy following ovarian tissue cryopreservation and subsequent transplant in 2000 [123], there has been increasing success with the technique [124, 125].

7. Prediction and genetic counseling

Contrary to the induced POI occurring in cancer survivors, the spontaneous POI particularly the idiopathic form is still difficult to be predicted in the general population. Low circulating AMH level is currently thought to be the most reliable measure of reduced ovarian reserve and may play a role in predicting age at menopause [23]. Sowers et al. (2008) have shown that AMH starts declining 5 years before the final menstrual period. All these observations suggest a potential role for AMH in screening women at high risk for POI and in well woman screening programs [24]. Autoantibody screening, for anti-adrenal, anti-ovarian, and antithyroid antibodies, is also recommended [25]. Genetic counseling is nowadays recommended for several reasons, when a genetic form of POI is suspected or identified. The prevalence of familial POI has been reported to be between 4 and 31% of cases in various series [126–129]. The early diagnosis of familial POI will provide the opportunity to predict the likelihood of early menopause and allow other reproductive choices to be made, such as freezing embryos or having children earlier. Karyotyping and screening for the FMR1 gene permutation are especially important in younger patients with or without mental retardation or when a female is born from a family with female members affected with POI. The review of McConkie-Rosell states that approximately 13–24% of women who are fragile X premutation carriers (identified through families with fragile X syndrome) have POI [130].

8. Future

Continued advances in DNA sequencing techniques will facilitate finding additional genes responsible for POI in other portions of the genome. Besides, the future holds the possibility of restoring ovarian function with ovarian or oogonial stem cell (OSC) therapy which may open the door to novel fertility preservation strategies for women with both age-related and POI [131]. More recently, Kawamura et al. (2013) have successfully promoted follicle growth, retrieved mature oocytes, and performed IVF. Following embryo transfer, a healthy baby was delivered [132]. This in vitro activation (IVA) approach has been reproduced by a group in Zhengzhou University, China, with two cases [133]. Up to the summer of 2018, there were more than one dozen of successful cases.

9. Summary

The POI represents a continuum of declining ovarian function with intermittent ovulation in women below the age of 40 years resulting usually in an earlier than average menopause. Its incidence is gradually increasing secondary to the improved survival of young women with

cancer. In most cases, the etiology is unknown, but known causes include genetic disorders, particularly involving the X chromosome, associations with autoimmune diseases, cancer therapy, pelvic surgery, and also environmental toxic agents. A timely diagnosis of POI is the main challenge. The typical disorder is characterized by the loss of regular menstrual cycles, and the diagnosis is confirmed by the detection of menopausal-level serum gonadotropins in repeated blood tests. Second-line investigations should be directed by specific clinical indications. Regardless of the etiology, patients with POI are estrogen deficient. The aims of HRT extend beyond simply symptom relief to levels that support cardiovascular, bone, and cognitive health. Only 5–10% of women with POI may conceive spontaneously. Currently, there are no proven treatments to improve ovarian function, and only the use of donor eggs with IVF confers the highest chance of pregnancy. However, in women with Turner syndrome, this approach is strongly discouraged. To date, the prediction of POI is difficult in the general population. However, in women at risk of POI particularly those who have a strong family history of POI, or require cancer treatments, a screening program will provide the opportunity to predict the likelihood of early onset menopause and to consider fertility preservation as well. Further research is needed particularly in idiopathic POI to identify mechanisms and specific molecular defects which may offer a better opportunity for early therapeutic interventions.

Conflicts of interest

There are no conflicts of interest.

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