Genetic aspects of premature ovarian failure: A literature review

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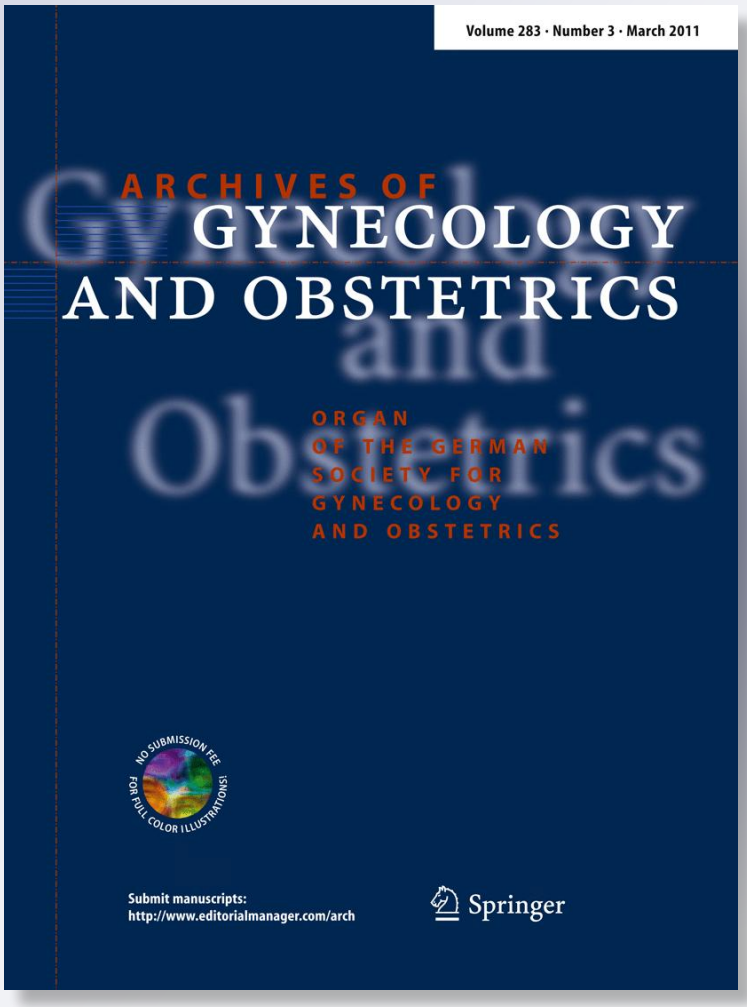

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REPRODUCTIVE MEDICINE

Genetic aspects of premature ovarian failure: a literature review

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Abstract
Background The diagnosis of premature ovarian failure (POF) is based on the finding of amenorrhea before the age of 40 years associated with follicle-stimulating hormone levels in the menopausal range. It is a heterogeneous disorder affecting approximately 1% of women <40 years, 1:10,000 women by age 20 years and 1:1,000 women by age 30 years. POF is generally characterized by low levels of gonadal hormones (estrogens and inhibins) and high levels of gonadotropins (LH and FSH) (hypergonadotropic amenorrhea).
Methods Review of significant articles regarding genetic causes that are associated with POF.
Results Heterogeneity of POF is reflected by a variety of possible causes, including autoimmunity, toxics, drugs, as well as genetic defects. Changes at a single autosomal locus and many X-linked loci have been implicated in women with POF. X chromosome abnormalities (e.g., Turner syndrome) represent the major cause of primary amenorrhea associated with ovarian dysgenesis. Many genes have been involved in POF development, among them *BMP15*, *FMR1*, *FMR2*, *LHR*, *FSHR*, *INHA*, *FOXL2*, *FOXO3*, *ERα*, *SF1*, *ERβ* and *CYP19A1* genes.
Conclusion Despite the description of several candidate genes, the cause of POF remains undetermined in the vast majority of cases.

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Introduction

Premature ovarian failure (POF) (MIM—311360), or premature ovarian insufficiency, is an early ovarian dysfunction clinically defined as the cessation of ovarian function with elevated gonadotrophin and low estrogen level before or at the age of 40 years [1]. This condition is characterized by the presence of primary or secondary amenorrhea for at least 4 months, hypoestrogenism and elevated serum gonadotropin concentrations. The diagnosis is confirmed by two blood tests at least 1 month apart to measure FSH [2–4].

POF incidence in patients with 46, XX karyotype was estimated in around 1:1,000 women under 30 years old, 1:250 around 35 years old and 1:100 at 40 years old [5].

Multiple causes of POF can be defined and result in follicle reduction and/or defects in the follicular development stimulus mechanism [5]. Ovarian dysfunction can be secondary to autoimmune diseases, infections (e.g., mumps), chemotherapy and radiation treatment and metabolic diseases (e.g., galactosemia), but for most of the cases, the etiology is idiopathic and probably genetic [6]. The genetic basis to the disease is supported by the occurrence of families with several affected women [3, 7–9].

Regarding the genetic causes of POF, they can be chromosomal or caused by single genes, involving the X chromosome or autosomes [10]. The X chromosome abnormalities represent 13% of the cases, followed by the *FMR1* premutation that represents 6% of the cases [11, 12]. Besides, there are many reports of mutations and polymorphisms in genes related to the sporadic form of

the disease that will be discussed in details in this manuscript.

The X chromosome defects

Defects involving large aberrations on the X chromosome have been associated with POF including complete deletion of one X (Turner syndrome), trisomy X, partial deletions or X/autosome translocations [10].

Turner syndrome

The Turner syndrome has an incidence of 1 in 2,500 females and is characterized cytogenetically by X chromosome monosomy (45,X). In about 60% of cases, however, in addition to the 45,X cell line, another cell line is observed that has the complete chromosome number but presents one structurally abnormal X or Y chromosome [13, 14]. Clinically, the syndrome is characterized by gonadal dysgenesis with primary amenorrhea, sexual infantilism, webbing of the neck, cubitus valgus and short stature in phenotypic women [14]. Ovarian failure in TS is due to accelerated follicular atresia, usually manifesting in childhood but sometimes later in life [15]. Infertility in 45,X patients is caused by oocyte loss in the early stages of the meiotic prophase, before the pachytene meiotic stage, resulting in ovarian dysgenesis and streak ovaries. Ogata and Matsuo [16] argued that ovarian failure in X monosomies could be caused by non-specific pairing errors at meiosis that increase the probability of germ cell atresia—the extent of ovarian failure correlates with the extent of pairing failure.

Trisomy X

Trisomy X (47,XXX) is a sex chromosome aneuploidy condition and occurs in approximately 1 in 1,000 female births; however, it is estimated that only approximately 10% of cases are diagnosed. Although non-mosaic 47,XXX karyotypes are the most frequent, mosaicism occurs in approximately 10% of cases and in many combinations such as 46,XX/47,XXX or 47,XXX/48,XXXX, or in combinations including Turner syndrome cell lines such as 45,X/47,XXX or 45,X/46,XX/47,XXX [17]. Clinical characteristics include epicanthal folds, hypertelorism, upslanting palpebral fissures, clinodactyly, overlapping digits, pes planus and pectus excavatum. Hypotonia and joint hyperextensibility may also be present [18]. Although major medical problems are not present in most cases, some medical problems may be associated with trisomy X as genitourinary abnormalities, ranging from unilateral kidney and renal dysplasia to ovarian malformations [19]. Pubertal onset and sexual development are usually normal in trisomy X; however, there have been cases of ovarian or uterine dysgenesis described in children and young adults with trisomy X [17].

There are multiple case reports of women with trisomy X found to have POF, with endocrine findings of hypergonadotropic hypogonadism. The ages of these cases have ranged from 19 to 40 years [20]. Studies on the prevalence of POF in adolescents or adults with trisomy X have not yet been performed. One study that performed genetic screening on women presenting with POF identified trisomy X in 3% of cases [21]. In trisomy X, a large percentage of the reported cases of POF have also been associated with autoimmune diseases, including autoimmune thyroid disorder [21].

The X chromosomes rearrangements

There is a ''critical region'' for ovarian development and function on the long arm of the X chromosome that ranges from Xq13.3 to q27. Alternative mechanisms proposed for the explanation of the ovarian defect account for the size of the critical Xq region. They include the direct disruption of relevant loci or a 'position effect' caused by the rearrangements on contiguous genes. The 'position effect' is a mechanism involving the deletion or translocation of regulatory domains to different position on the genome that might cause changes in gene transcription [22]. However, it has been stated that deletions of the short arm of the X chromosome usually result in primary amenorrhea, whereas deletions of the long arm of the X chromosome result in either primary or secondary ovarian failure [23]. Consequently, both the short and long arm of the X chromosome seem to contain important genes for ovarian function.

Genes involved in premature ovarian failure

Many genes have been involved in POF development. The genes responsible for the most number of cases are described on Table 1 according to chromosomal disposition.

BMP15 (bone morphogenetic protein 15)

BMP15, located at Xp11.2, is a member of the large superfamily of the transforming growth factor b (TGFb) proteins involved in diverse cellular processes during embryonic development and tissue formation [24]. Studies

Table 1 The genes involved in POF development

	Gene	Chromosomelocation
X linked genes	*BMP15*	Xp11.2
	FMR1	Xq27.3
	FMR2	Xq28
Autosomal genes	*LHR*	2p21
	FSHR	2p21
	INHA	2q33-q36
	FOXL2	3q23
	FOXO3	6q21
	ERα	6q25
	SF1	11q13
	ERβ	14q23.2
	CYP19A1	15q21.1

in mouse showed that both *Bmp15* and *Gdf9* are specifically expressed in the oocyte; this expression begins in the one-layer primary oocyte and remains at high levels throughout the course of follicular maturation and ovulation [25]. Mutations in *Gdf9* and *Bmp15* were identified in mouse and sheep strains showing altered ovulation [26]. In humans, *BMP15* was reported to carry causative mutations in two sisters, who were affected with primary amenorrhea and who carried a mutation inherited from the father [27]. The human mutation was shown to act as dominant negative and to decrease in vitro growth of granulosa cells after stimulation with wild-type *BMP15*. In humans, *BMP15* maps to Xp11.22, proximal to, but not within, the Turner syndrome candidate region defined by deletion analysis [28]. Accordingly, its presumed role in ovarian function seems to be more relevant to follicular maturation or in determining the ovulation quota than for establishing the final number of ovarian follicles as is expected to occur in Turner syndrome [29]. Tiotiu et al. [30] found nine variants of the *BMP15* gene including six missense substitutions and one insertion of three nucleotides in patients with POF. One variant (A180T) was identified among two POF cases and also in two controls, and could be considered a rare polymorphism. Zhang et al. [31] and Ledig et al. [32] failed to find association of *BMP15* and POF. The contribution of *BMP15* in the pathogenesis of POF is yet uncertain.

FMR1 (fragile X mental retardation 1)

It has been estimated that around 21% of the familial cases of POF are associated with the premutation of *FMR1*, located at the X chromosome (Xq27.3) [33, 34]. The gene has an expansible region composed of repeats of a CGG nucleotide in the 5′UTR position. According to the number of CGG repeats, three allelic classes can be defined: normal alleles (from 6 to 55 CGG repeats), premutated alleles (from 55 to 200 CGG repeats) and full mutation (>200 CGG repeats) (Fig. 1).

The consequence of the full mutation is the fragile X syndrome, the most common inherited cause of mental retardation. The premutation can suffer an expansion to a full mutation and this phenomenon is believed to occur during meiosis in the oocytes and depends on the repeat

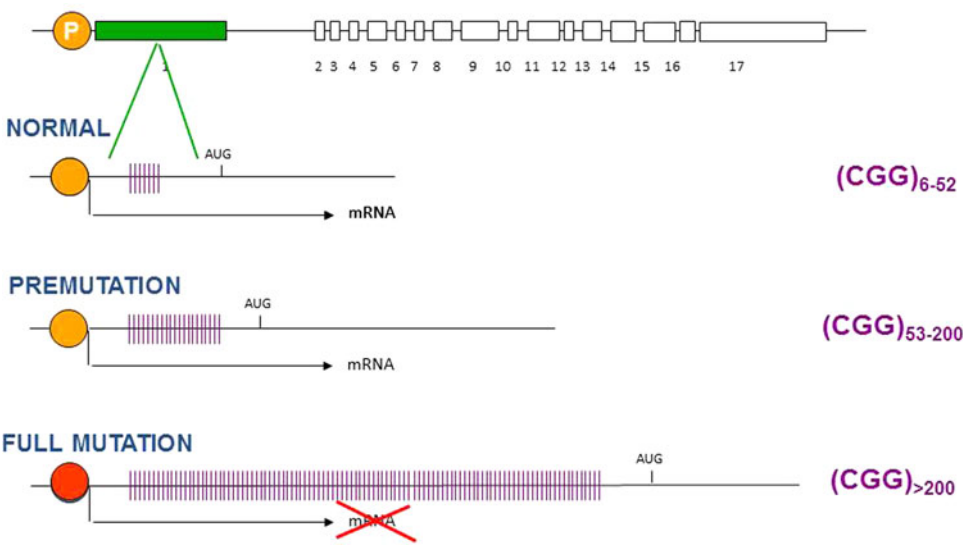

Fig. 1 Variation in the repeat number of *FMR1* alleles in normal, permutated and full mutated patients

size carried by the mother [35]. The mother of the fragile X syndrome child is in most of the cases a premutation carrier [35] and can transmit the mutation to 50% of their offspring.

There are many discussions on how premutation can cause ovarian dysfunction and POF. The hypotheses are that the ovarian dysfunction is due to a diminished ovarian pool or due to an accelerated rate of atresia [36]. Expression studies showed that FMRP protein is highly expressed on germinative fetal cells from ovary. This elevated expression can lead to exacerbate oocyte development, resulting in the decrease of the initial pool of oocytes. Alternatively, Allen et al. [36] proposed that the mRNA produced by the mutated alleles can have a "toxic effect" during the reproductive life that may lead to an elevated follicle atresia. The toxic effect is attributed to the gain of function of mRNA, which, in high levels, kidnaps one or more mRNA-binding proteins, depleting the stock of cellular proteins that fail to perform other cellular functions. The kidnapping of proteins also triggers the accumulation or abnormal processing of proteins by proteosomal degradation pathway, leading to formation of cellular inclusions [37].

FMR1 premutation occurs approximately in 1:800 men and 1:100–200 women. The phenotype of premutation is quite variable and generally not associated with mental retardation. However, POF incidence in female premutation carriers can vary from 20 to 28% [38–40]. Among women with normal alleles, the incidence of POF is around 0.1–1% [3]. Sullivan et al. [41] observed that *FMR1* premutation carriers have a frequency 13 times higher and a 5 years younger mean age of menopause when compared with control individuals.

It was observed that premutation carriers also are susceptible to diseases associated with menopause such as thyroid diseases, hypertension, seizures, osteoporosis, fibromyalgia and peripheral neuropathy [36]. Besides, carriers of premutation older than 50 years can also develop FXTAS (fragile X tremor ataxia syndrome), a neurodegenerative disorder associated with the high level of *FMR1* mRNA produced [37, 38].

FMR2 (fragile X E mental retardation syndrome)

FMR2 gene is located at Xq28, 600 kb distal from *FMR1* and like this gene has a trinucleotide repeat within exon 1. There are also full mutated and premutated alleles. Thus, the mechanism generating disease is similar to *FMR1* cited above [42].

Besides, deletions in *FMR2* have been described in women with POF. Murray et al. [42] found three women, with POF and *FMR2* deletions, two of them located near putative transcription site of *FMR2*. It is plausible that deletions in this area lead to either terminating transcription or forces the use of an alternative start site, generating aberrant *FMR2* transcripts [42].

LHR (luteinizing hormone receptor)

For the correct biological menstrual activity, two gonadotropic hormones are needed: follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [43]. LH belongs to the family of glycoprotein hormones. Structurally, LH is a heterodimer consisting of two dissimilar subunits: the α-subunit and the hormone-specific β-subunit. It plays an important role in the maintenance of progesterone production by the corpus luteum in the development of follicular growth, stimulation of steroidogenesis and oocyte maturation. It also promotes ovulation and luteinization of the ovarian follicle, which stimulates the production of androgens that serve as substrate to follicular estradiol synthesis in the ovary. Abnormal LH secretion induces anovulation, luteal insufficiency and premature oocyte maturation, leading to menstrual disorders, polycystic ovary syndrome (PCOS), recurrent miscarriage and infertility [43].

G1502A, a common genetic variant in exon 3 of the LH β-subunit gene, located at 2p21, resulted in the amino acid substitution of serine for glycine at position 102, and this substitution may have a potent effect on LH function. Because glycine and valine are important components in the formation of hydrophobic regions in a protein and serine has a polar side chain, the replacement of glycine by serine at position 102 introduces a hydrophilic force in the molecule. This could affect the normal conformation and function of LH and thus contribute to menstrual disorders [44].

FSHR (follicle-stimulating hormone receptor)

During adult life, until menopause, LH together with FSH regulates the production of the steroid sex hormones estradiol and progesterone by theca cells that surround growing follicles in the ovary [45].

The FSH receptor has been considered an important candidate to POF. Defects on this receptor can diminish the ability of the receptor either to bind FSH or to activate signal transduction pathways, impairing its function. Diverse mutation and polymorphisms have been described in women with POF [46].

A homozygous missense mutation, C566T, in the *FSHR* gene, located at 2p21, has been linked to POF in six Finnish families [47]. However, Sunblad et al. [46] and Vilodre et al. [48], failed to find association of the polymorphism in Argentinian and Brazilian patients, respectively.

Female mice carrying mutated *Fshr* gene, called follitropin receptor knockout (FORKO), display similar phenotype and are sterile because of a folliculogenesis block at a primary stage. In these mice, the intra-ovarian injection of an adenovirus expressing human *FSHR* gene is able to restore FSH responsiveness and reinitiate ovarian folliculogenesis as well as resume estrogen production in female FORKO mice [49].

INHA (inhibin, alpha)

The inhibins are dimeric glycoproteins predominantly produced in the gonads [50]. Inhibin has two subunits α and β that form, respectively, inhibin A and B, which act at different times of the menstrual cycle. The levels of inhibin A, codified by *INHA* gene in 2q33–q36, increase in the middle of the cycle, indicating the production and secretion by the preovulatory follicle, and increase again in the luteal phase indicative of production by the corpus luteum. The levels of inhibin B, codified by *INHB* gene, increase in the middle of the follicular phase [51, 52]. They act by inhibiting the hypothalamic–pituitary–gonadal axis in regulating the secretion of FSH in the normal menstrual cycle process that allows scheduled ovulation of one mature follicle [53].

Two previous studies [54, 55] suggested the involvement of the *INHA* gene in the etiology of POF. However, it remains unclear on the relationship between polymorphisms of the *INHA* gene and reduced expression of inhibin [56]. Recent studies [55, 57–59] in populations of New Zealand, Slovenia, India and Italy have observed significant differences in the frequency of alleles of *INHA* gene promoter with POF between groups and controls, and concluded that such variations were related to the manifestation of POF.

Several studies suggest that decreased levels of inhibin during peri-menopause, associated with the concomitant increased levels of activin A, may be responsible for the high FSH level characteristic of the aging of the reproductive function. Whereas the reduction in the rate of inhibin/activin observed during menopause occurred probably due to compromised synthesis of inhibin [60], ovarian failure might be thought to result from mutations in the *INHA* gene, causing decreased inhibin concentration and consequently increasing the concentration of FSH.

FOXL2 (forkhead box L2) and *SF1* (splicing factor 1)

FOXL2, located at 3q23, is a winged-helix/forkhead (FH) domain transcription factor, and mutations in the *FOXL2* gene are responsible for blepharophimosis–ptosis–epicanthus inversus syndrome (BPES) (OMIM no. 110100) type I, in which affected women exhibit POF. In situ hybridization and immunohistochemistry studies confirm that *FOXL2* is mainly localized to undifferentiated granulosa cells in the ovary [61]. In *Foxl2* knockout murine ovaries, failure of granulosa cell differentiation leads to premature activation of primordial follicles and consequent follicular depletion and atresia [62]. Earlier reports indicated that disruption of *FOXL2* in mice leads to a block in ovarian follicle development due to the failure of somatic cell development around growing oocytes [63].

SF1, located at 11q13, is an orphan nuclear hormone receptor, also known as *NR5A1*, and is essential for gonadal development. Mice with granulosa cell-specific conditional knockout of *Sf1* are sterile, have fewer follicles, lack corpora lutea and have hemorrhagic cysts. These characteristics indicate the essential role of *SF1* in the ovary, which is possibly in estrogen production [64]. Granulosa cells of small and preovulatory rodent ovarian follicles express *Sf1*, and this expression is modulated by gonadotropins. Therefore, *SF1* is likely to be a crucial factor for regulating the expression of enzymes involved in ovarian steroidogenesis. Consequently, any conditions that affect the transcriptional activities of *SF1* could disturb steroid hormone synthesis [65].

Park et al. [65] found that endogenous *FOXL2* and *SF1* proteins interact in a human granulosa cell line, and that *FOXL2* negatively regulates the transcriptional activity of *SF1* on the steroidogenic enzyme, CYP17. Interestingly, the *FOXL2* mutants identified in POF patients with BPES type I failed to repress *SF1*-mediated *CYP17* gene induction. The authors identified a novel regulatory role for *FOXL2* that provided a possible mechanism by which mutations in *FOXL2* disrupted normal ovarian follicle development.

FOXO3a (forkhead box O3)

The *FOXO3a* gene, located at 6q21, belongs to the forkhead gene family, which also consists of *FOXL2* and *FOXO1A* genes. As transcription regulators, or switches that turn other genes on and off, forkhead genes are believed to control processes related to aging, cancer and diabetes. *FOXO3a* expression occurs in the ovary and plays roles in ovarian development and function [66].

It was observed that in knockout mice with *Foxo3a* are sterile. Further study revealed that within the ovaries of mice lacking the *FOXO3a* gene, the follicles that contain eggs had been activated earlier and much more widely than in females with normal *FOXO3a* genes. When a follicle is activated, it begins to mature. Once activated, a follicle has a finite lifespan. So, the premature activation of follicles results in the early death of most eggs in mice that lack the *FOXO3a* gene [67].

It appears that abnormal *FOXO3a* gene function leads to misregulation of follicle activation, causing POF in mice. Watkins et al. [66] observed eight variations in *FOXO3a* in women with POF. Two variations seem to be more relevant (C1262T and G1517A), once those result in amino acid changes and consequent changes in protein conformation. However, more studies are necessary to confirm the relevance of these findings for POF determination.

ER (estrogen receptor)

Considering that initial follicular pool size and rate of follicular depletion are associated with the age of menopause, genetic variants in sex hormone receptor genes could affect the risk of POF [68].

Depending on the estrous/menstrual cycle stage in females, ovarian-derived estradiol exerts either a negative or a positive effect on the hypothalamic axis to regulate the synthesis and secretion of pituitary gonadotropins, LH, regulating folliculogenesis and FSH, acting on follicular development [69]. Estrogen acts through estrogen receptor which has two subtypes in human tissues: ERα [70] and ERβ [71], coded respectively by *ESRI*, located on 6q25.1 and *ESR2* located on 14q23.2.

Polymorphisms at these genes have been associated with altered hormonal profiles [72] and with reproductive patterns of women, as the onset of natural menopause [73] and the age of menarche [74]. The *ESRI* contains two single polymorphism (SNPs) at *Pvu*II (−397 T/C) and *Xba*I (−351 A/G) restriction sites and a polymorphism of repeat TA in the promoter of *ERα* gene [68]. There was also an association of TA repeat polymorphism at the gene promoter associated with POF. Syrrou et al. [75] observed that there was an extremely low number repeat size of (TA)*n* in women with POF than in the general population. In addition, Bretherick et al. [9] found an inverse correlation, where the long (TA) repeat allele was associated with POF.

It has been suggested that (TA)*n* repeat could affect gene expression. The *ESR1* gene promoter has a very complex genomic organization containing multiple promoter regions with alternative splice sites. The (TA)*n* repeat length could affect alternative promoter usage, resulting in unsuitable ERα expression in certain tissues [9].

Kim et al. [76] studied the effect of polymorphism interactions between *CYP19A1* (cytochrome P450, family 19, subfamily A, polypeptide 1, located at 15q21.1) and *ESR1* on the development of POF. The authors found a significant association with POF and the combined genetic effect between the *CYP19A1* (rs10046, C/T) and the *ESR1* (rs1569788, C/T) polymorphisms (odds ratio 12.67, 95% confidence interval: 1.61–99.71). A statistically significant association was also observed between POF and the *CYP19A1* (rs10046) polymorphism under a dominant model (odds ratio: 2.51, 95% confidence interval: 1.33–4.76), suggesting that epistasis between *ESR1* and *CYP19A1* may be involved in the regulation of folliculogenesis.

Perspectives

Being diagnosed with POF can be an unexpected and upsetting diagnosis, and women often express anger, depression, anxiety, loss and sadness that is often underestimated. This is even more upsetting if the woman or couple do not have children [77].

Infertility is a significant issue for most women undergoing POF, and although many women will ovulate at sometime following the diagnosis of POF, this cannot be predicted with any reliability. However, ovulation and successful pregnancy can occur in around 5–10% of patients [78]. A number of treatment regimens have been evaluated with the aim of restoring fertility; however, treatments with clomiphene, gonadotropins, GnRH agonists or immunosuppression do not significantly improve the chance of conception and are not used [78]. The only reliable fertility treatment is the use of donor eggs, which is an assisted reproductive procedure.

In most of the cases, there is a period of increase in FSH before POF is established. At this time, cryopreservation of ovarian tissue or oocytes for later in vitro growth and maturation may be possible [79]. However, given that women who present with symptoms of POF will most likely have follicles that are of lower quality [77], this would require that only women who were aware of future impending ovarian failure would be able to use this technology. At present, in vitro maturation of immature follicles is possible, but in vitro growth and maturation of stored ovarian tissue is not reliably achievable in humans [77].

Given the lack of any preceding signs or symptoms of impending POF, women with a family history of POF should pass through family planning counseling. The opportunity to collect and store oocytes or ovarian tissue may also need to be considered. The early detection and identification of specific molecular defects would provide a better opportunity for early intervention and also provide a focus on potential targets for therapeutic intervention [77].

Conclusion

In conclusion, women with POF are not necessarily sterile. Resumption of ovarian activity (be it intermittent) occurs in approximately 10% of these women [80]. However, the

chance of spontaneous conception is <5%, and about 90% were nulliparous at the time of diagnosis [10]. In recent years, the candidate gene approach has helped to identify genes and pathways involved in POF. Therefore, the pathogenic mechanism still remains unknown in most of the cases. However, when a genetic alteration is found in a woman, it can be useful for family counseling because it can predict the female relatives who are at higher risk for POF and fertility loss in young age. Genetic counseling for female infertility should be considered when screening women with idiopathic POF, at least for the most prevalent genetic alterations as X chromosome abnormalities and *FMR1* premutation. Professional help should be offered to help patients cope with the emotional sequelae of POF.

Conflict of interest We declare that we have no conflict of interest.

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