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Francisco Barbosa Soares Barros da Silva  
Premature ovarian insufficiency –  
clinical orientations for genetic  
testing and genetic counselling

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# **Premature ovarian insufficiency – clinical orientations for genetic testing and genetic counselling**

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## Abstract

Premature ovarian insufficiency (POI) is a heterogeneous disorder diagnosed in women before 40 years old and describes a wide range of impaired ovarian function, from diminished ovarian reserve to premature ovarian failure. Genetic etiology accounts for 20-25% of patients. The evidence that POI can be isolated (non-syndromic) or part of a pleiotropic genetic syndrome highlights its high heterogeneous etiology. Chromosomal abnormalities as a cause of POI have a prevalence of 10-13%, being 45,X complement the most common cytogenetic cause of primary amenorrhea and mosaicism with a 45,X cell line more frequently associated with secondary amenorrhea. Other X chromosome aberrations include deletions, duplications, balanced and unbalanced X-autosome rearrangements involving the critical region for the POI phenotype (Xq13-Xq21 to Xq23-Xq27).

The identification of two or more pathogenic variants in distinct genes argues in favor of a polygenic origin for POI. Hundreds of pathogenic variants (including mitochondrial) have been involved in POI etiology mainly with key roles in biological processes in the ovary, such as meiosis and DNA damage repair mechanisms, homologous recombination, follicular development, granulosa cell differentiation and proliferation, and ovulation.

The most common single gene cause for premature ovarian insufficiency is the premutation for *FMRI* gene (associated with fragile X syndrome) with alleles ranging from about 55 to about 200 CGG trinucleotide repeats. POI occurs in 20% of women with this premutation. As females with premutation or full mutation alleles are also at risk of having affected children, their genetic counselling should include the indication for prenatal diagnosis or preimplantation genetic testing after intracytoplasmic sperm injection and trophoctoderm biopsy.

In conclusion, in clinical practice high-resolution karyotype and *FMRI* gene molecular study should be performed as first-tier tests in the assessment of POI. Additionally, array Comparative Genomic Hybridization (array-CGH) or specific next generation sequencing (NGS) panels should be considered to identify chromosomal deletions/duplications under karyotype resolution or other pathogenic variants in specific genes associated with POI. This is particularly important in patients with first or second-degree relatives also affected with POI, improving their reproductive and genetic counselling.

### **Keywords**

Premature ovarian insufficiency, *FMRI* gene premutation, karyotype, Next Generation Sequencing, array Comparative Genomic Hybridization, reproductive counselling.

## 1. Introduction

Natural menopause is commonly defined as the time when a woman has experienced 12 consecutive months of amenorrhea without an obvious cause [1]. A collaborative study reported that the average age at natural menopause across 21 studies from 10 countries ranged from 47 to 53 years, varying across ethnic groups from 48 years for women of South Asian background to 50 years for Caucasian women living in Australia and Europe, and 52 years for Japanese women [2]. These results are primarily obtained from women living in high-income countries, hence the average age at menopause for women in low- and middle-income countries may lie outside this range.

Premature ovarian insufficiency (POI), also known as primary ovarian insufficiency, is a heterogeneous disorder diagnosed in women before the age of 40 years old and describes a wide range of impaired ovarian function. It starts with diminished ovarian reserve and finally reaches premature ovarian failure [3]. Menopause before the age of 40 is also commonly referred to as premature menopause. Menopause that occurs between 40 and 45 years is termed early menopause [4].

The designation premature ovarian failure or premature menopause should be considered as only the final stage of premature ovarian insufficiency [5]. The incidence of premature menopause is about 1:10,000 in women by the age of 20 years, 1:1,000 in women under 30 years and 1:100 in women under 40 years [6].

### 1.1 Non-Genetic etiology

Although most POI cases are considered idiopathic, several risk factors have been described. Iatrogenic factors such as pelvic surgery, impairing ovary vascularization, or ovarian surgery, with or without oophorectomy, chemotherapy or radiotherapy for cancer are unquestionable etiologies.

Early menarche, nulliparity or low parity, cigarette smoking and being underweight are also strong risk factors associated with premature menopause [4]. Among the lifestyle factors studied, cigarette smoking has been the most consistently linked to earlier age at natural menopause [4]. Smoking is associated with earlier menopause [7], and it has been shown that women who smoke stop menstruating 1 to 2 years earlier than comparable non-smokers [8]. Current smokers were at twice the risk of premature menopause and had an 80% increased risk of early menopause compared with never smokers [9]. Interestingly, smokers who had quit for more than 10 years had a similar risk as never smokers, highlighting the clear benefits of early smoking cessation

(preferably before the age of 30 years) for decreasing the risk of premature or early menopause [9]. Some studies have shown a dose–response effect on atrophy of ovarian follicles, in that heavy smokers have an earlier natural menopause than light smokers [8].

## 1.2 Genetic etiology

Genetic causes account for approximately 20-25% of patients with POI [5].

In spite of the great quantity of genetic studies identifying new genetic variants associated with premature ovarian insufficiency, these results are very often conflicting and of uncertain clinical value namely because many of these genetic variants are of unknown significance. The complexity of interpretation and appreciation of these findings further supports the purpose of this review of establishing practical clinical orientations about etiological genetic research of premature ovarian insufficiency and consequent genetic counselling.

It is possible to estimate what proportion of the etiology can be ascribed to genetic factors as opposed to environmental factors (heritability). Estimates of the heritability of a condition or trait provide an indication of the relative importance of genetic factors in its causation, so that the greater the value for the heritability the greater the role of genetic factors. The reported heritability estimate of 0,52 for age at natural menopause [10] suggests that genetic effects explain at least half of the inter-individual variation in age at natural menopause [4].

Since genetic factors explain a substantial proportion of the variability in age at natural menopause, family history may be an important predictor of age at menopause. Early menopause in a mother, sister, aunt or grandmother was associated with six-fold increased odds of early menopause and eight-fold increased risk of premature menopause [11].

Twin registries in the United Kingdom and Australia indicate that twins have a significantly higher prevalence of premature ovarian insufficiency than the general population, with a 3-fold greater prevalence [12]. Although the prevalence of POI in monozygotic (identical) and dizygotic (non-identical) twins are similar, ages at menopause were more concordant among monozygotic than among dizygotic twins. If one twin experienced menopause before age 40, her identical sister was almost seven times as likely to do so at the same age, confirming that the risk of POI has a strong heritable component [4].

Genetic anomalies in syndromic and non-syndromic forms of the disease, such as chromosomal abnormalities and point mutations in coding regions of POI genes (autosomal and X-linked genes), have been described [13]. Up to 90% of non-syndromic premature ovarian insufficiency cases are estimated to be idiopathic, with about 30% having an affected first degree relative, supporting a potential underlying genetic etiological basis [14].

Besides the variability of the genetic factors associated with POI and the remarkable differences in frequency among different ethnic groups, several genes come out as POI candidates. However, only a small part of them has been established as causative factor and gene-gene and protein-protein interactions are not yet entirely clear [15].

Presence of premature ovarian insufficiency as one component of a pleiotropic genetic disorder (pleiotropism: several different effects from a single gene) is also well recognized [5]. The evidence that POI can be isolated (non-syndromic) or part of a pleiotropic genetic syndrome highlights its high heterogeneous etiology. To date, what we know is just the tip of the iceberg of POI genetic etiology, despite the fact that causative lists are expanding.

Chromosomal abnormalities have been recognized as a cause of POI. Percentages vary widely among reported series but a prevalence of 10-13% seems reasonable [5]. The most common cytogenetic cause of POI is Turner syndrome, often but not universally associated with X monosomy (45,X), which leads to ovarian dysgenesis and accelerated follicular atresia [5]. Despite being the most common cytogenetic cause of primary amenorrhea the karyotype 45,X is a very rare finding in women with the onset of premature ovarian insufficiency. Actually, X monosomy without mosaicism is much more typically found in primary amenorrhea but a small number of 45,X women have menstruations (3% of 45,X patients actually menstruated) [16]. Mosaicism 45,X/46,XX and other forms of mosaicism are associated with secondary amenorrhea. The relative proportion of normal (46,XX) and 45,X cells will significantly influence the clinical expressivity of Turner syndrome and POI. The variable clinical expressivity can also be justified by non-identified (hidden) mosaicism, which could be the main explanation for the rare cases of ovarian activity and for the much rarer cases of pregnancy in women with Turner syndrome.

Other X chromosome aberrations include deletions and duplications, and balanced and unbalanced X-autosome rearrangements. A region of the long arm of the X

chromosome that seems critical for the POI phenotype extends from Xq13-Xq21 to Xq23-Xq27.

Hundreds of genes have been involved in premature ovarian insufficiency etiology by their participation in key biological processes in the ovary, such as meiosis and DNA damage repair, homologous recombination, follicular development, granulosa cell differentiation and proliferation, and ovulation. For instance, *MCM8* gene pathogenic variants (formerly designated as mutations) are involved in the POI phenotype, playing an important role in chromosomal stability, homologous recombination during meiosis and DNA break repair [17]. It has been shown that several transcription factors (e.g. *NOBOX* and *FOXL2*) play key roles during female gonadal development and pathogenic variants in these genes lead to POI [18] as also some meiotic genes have been considered important in determining the oocyte pool [13]. Pathogenic variants have been described in a number of genes with pleiotropic syndromic phenotypes that include POI (e.g. *NOBOX* and *GDF9*, respectively involved in the first stages of folliculogenesis and granulosa cell differentiation and proliferation) [19].

The identification of at least two pathogenic variants in distinct genes argues in favor of a polygenic origin for POI [13]. A high-resolution copy-number variations (CNV) analysis of the X chromosome in fertile females and in women affected with POI also supports its polygenic etiology [20]. The authors observed a 2,5-fold enrichment for rare CNVs comprising ovary-expressed genes and genes implicated in autoimmune response, inflammatory processes and apoptotic signaling in the affected women. Autoimmunity may lead to increased cell death in the ovary and result in follicle depletion, causing premature ovarian insufficiency [17]. It is possible that differences observed between CNVs on the X chromosome in POI and fertile women are the consequence of deficiencies in DNA repair [20]. A subset of women with idiopathic POI may have chromosomal instability due to defects in DNA repair, demonstrating the sensitivity of gonads to DNA injuries and oocyte depletion as a secondary cellular defense against damaged cells [21].

Mitochondrial inheritance is exclusively maternal and is considered to be a key determinant of female reproductive aging and infertility [22]. Mitochondrial pathogenic variants have also been associated with POI. Defects in the *POLG* gene, which encodes polymerase gamma, responsible for mitochondrial DNA synthesis, have been reported in women with POI [23]. The association of nuclear and mitochondrial genes responsible for mitochondria function with female oogenesis and fertility is not surprising as the

number of mitochondria increases at least 1000-fold in human oocytes [24, 25]. Mitochondria are essential for multiple processes during oogenesis, such as ATP production, apoptosis and calcium homeostasis [26].

Distinct from non-syndromic premature ovarian insufficiency, pleiotropic Mendelian disorders may manifest POI as part of their phenotypic spectrum. Indeed, the most common single gene explanation for premature ovarian insufficiency is represented by such a disorder - premutation for fragile X syndrome [5].

Fragile X syndrome is caused by the deficiency or absence of FMRP (fragile X mental retardation protein), a widely expressed RNA-binding protein that also regulates translation. The FMRP protein is expressed in neurons and granulosa cells [27]. Theoretically, the deficiency or absence of FMRP can occur through any type of deletion or inactivation mutation, but in more than 99% of cases there is an expansion of a segment of CGG repeats in the 5' untranslated region of the *FMR1* gene that leads to DNA hypermethylation and inhibition of transcription [28].

Fragile X syndrome is the most common single gene cause of intellectual disability and autism [29]. Clinical features include mental retardation, characteristic facial features with large ears and prominent jaw, connective tissue findings (joint hypermobility), large testes after puberty and behavioral abnormalities. Fragile X syndrome occurs in males when CGG repeats number is above 200. Around 70% of females with more than 200 CGG repeats show intellectual disability [30]. The incidence of fragile X syndrome is approximately 1:4,000 in males and 1:8,000 in females [31]. The *FMR1* gene has four types of alleles: normal, intermediate, premutation and full mutation. Normal alleles have a range from about 5 to about 44 repeats. The most common repeat length is 29 or 30 CGG repeats. Normal alleles have no meiotic or mitotic instability (in stable, normal alleles, the CGG region is interrupted by a AGG triplet after every 9 or 10 CGG repeats; the AGG triplets are thought to anchor the region during replication and prevent strand slippage) [28]. Intermediate alleles range from about 45 to about 54 repeats and can be considered normal given that such alleles are not associated with fragile X syndrome and have not been observed to expand to a full mutation in one generation [28]. However, a grey-zone allele of 52 repeats was reported to expand to a premutation allele of 56 repeats in one generation, which subsequently expanded to a full mutation allele in the next generation [32]. Premutation alleles range from about 55 to about 200 CGG repeats. These alleles are long repeat tracks that are unstably transmitted from patient to child. Expansions from the premutation size range to the full mutation typically occur

during maternal transmission. In fact, with extremely rare exceptions, the patient of origin of the expansion to the full mutation is female [28]. The smallest *FMRI* premutation allele reported to expand to a full mutation in a single generation had 56 repeats [32]. Most individuals with the premutation do not show fragile X syndrome-related features; however, some with high repeat sizes (above 100 repeats) have been identified with learning difficulties, emotional problems or even intellectual disability [33]. Full mutations have more than 200-300 CGG repeats, typically several hundred to several thousand repeats. There is usually broad somatic variation within each patient. Hypermethylation is typically present on most or all copies, with the exception of DNA extracted from chorionic villus sampling (CVS) [28].

Premature ovarian insufficiency occurs in 20% of women with alleles in the premutation range of *FMRI* gene (usually more than 80 CGG repeats) [34, 35]. Another study also demonstrated that 72% of the women with POI had a repeat size length of 80-100 CGG triplets [29], similar to findings from previous studies that identified women with 80-100 repeats to be at the highest risk for POI compared to repeat lengths of 59-79 or above 100 [36, 37].

A meta-analysis study confirmed this significant association between the *FMRI* premutation and an increased risk for every stage of POI (from diminished ovarian reserve to premature ovarian failure). However, it didn't find a correlation between the *FMRI* CGG intermediate repeat length and the severity of idiopathic POI [3]. Moreover, a large population-based study found no association between the length of CGG repeats in the normal allele and the risk of early menopause and also didn't find an association with age at menopause [7]. Therefore, there is no evidence to support an association between high normal and intermediate range *FMRI* alleles with a risk of premature ovarian insufficiency. Interestingly, ovarian function remains normal in women with full mutation range repeat alleles.

## **2. Discussion and conclusion**

New strategies with next generation sequencing (NGS) using panel specific genes, whole exome sequencing (WES: sequencing all the protein coding genes) or whole genome sequencing (WGS: sequencing the complete DNA of a genome) will certainly revolutionize this field and give more precise insight into the complex gene network involved in POI. Discovering the molecular basis and pathogenesis of POI is useful to understand the ovarian physiology and improve genetic and fertility counselling. Once

new pathogenic variants are found, they can help predict menopause age and may help women plan their fertility [15]. However, given that a huge number of genetic variants of unknown significance will emerge, the genotype-phenotype correlation and the corresponding causative relevance and clinical appreciation will be important challenges, namely because of additional difficulties represented by incomplete penetrance and variable clinical expressivity.

The prevalence of chromosomal abnormalities as a cause of POI is about 10-13%. Mosaicism 45,X/46,XX is a frequent finding, being the variation in the severity (expressivity) of POI influenced by the relative proportion of X monosomic (45,X) and normal (46,XX) cells. Therefore, performing karyotype for the clinical evaluation of POI is important because karyotype is still the best genetic testing for the detection of chromosomal mosaicisms. In addition, it is also important for large X chromosome aberrations, such as deletions and duplications, and balanced and unbalanced X-autosome rearrangements, involving the region of the long arm of the X chromosome from Xq13-Xq21 to Xq23-Xq27 that seems critical for the POI phenotype. In this context, array Comparative Genomic Hybridization (array-CGH) could be used after a normal karyotype result to identify microscopically undetectable chromosomal deletions or duplications, mainly in patients with first or second-degree relatives also affected with POI.

The importance of the molecular analysis of the *FMRI* gene is based on the significant association between the premutation allele and an increased risk for every stage of POI, from diminished ovarian reserve to premature menopause. In fact, POI occurs in 20% of women with alleles in the premutation range of the *FMRI* gene, being the risk greater when the CGG trinucleotide sequence length of the premutation allele is between 80 and 100 repeats. All at-risk family members of known carriers should be offered testing to determine their status [28]. All the daughters of a man who carries a premutation will inherit the premutation. In the next generation, male offspring of these women are at risk of inheriting either the premutation or a full mutation. Premutation alleles are meiotic and mitotically unstable and therefore this results in a high risk of expansion (increase in size length of CGG repeats) from premutation to a full mutation allele during maternal transmission (actually, with extremely rare exceptions, the parent of origin of the expansion to the full mutation is female). As females with premutation or full mutation alleles are also at risk of having affected children, their genetic counselling should include the indication for prenatal diagnosis for all pregnancies.

Because methylation is not fully established at the time of chorionic villus sampling (CVS), the appearance of full mutations examined by a methylation-specific method may vary in CVS as compared with blood and amniocytes [28]. In the minor fraction of CVS cases with a result that is ambiguous between a large premutation and a small full mutation by size criteria alone, a follow-up amniocentesis may be required. Additionally, mosaicism between trophoblasts and somatic cells is theoretically possible. For this reason, when CVS results indicate a premutation, follow-up amniocentesis has been suggested to rule out mosaicism for a full mutation [28].

Preimplantation genetic testing for monogenic diseases (PGT-M) after in vitro fertilization with intracytoplasmic sperm injection (ICSI) and trophectoderm biopsy could also be done. Not allowing the direct detection of the premutation or the full mutation, PGT-M is done by identification of linked polymorphic markers closely associated with the *FMRI* gene, thus being essential that the parents are informative for these polymorphic markers.

The advanced maternal age as a consequence of a voluntary progressive delay in the childbearing decision makes it even more important to identify a premutation carrier of the *FMRI* gene in an early phase of the reproductive lifespan. The reproductive and genetic counselling of women with or at risk of premature ovarian insufficiency for having a premutation allele must include clear and complete information about the risks of an irreversible premature ovarian failure and about the possibilities and limits of a close monitorization of ovarian reserve. This knowledge can influence women's decisions about the timing of procreation, eventually leading to no further delay of an ongoing procreative project and even increasing the pregnancy likelihood through the practice of assisted reproductive technologies, and also about considering oocyte or embryo cryopreservation for potential fertility preservation. This rigorous and in time reproductive counselling may prevent that the options for having children become limited to egg donation, donor embryo or adoption.

In conclusion, there is potential for WES or WGS to become an "all-in-one" test for assessment of premature ovarian insufficiency. Nevertheless, as this still remains way off from coming into routine practice, high-resolution karyotype and *FMRI* gene molecular study should be performed as first-tier tests in the assessment of POI. Additionally, specific NGS panels and array-CGH should be considered after normal results for *FMRI* gene and karyotype, mainly in familial cases of premature ovarian insufficiency. The application of these clinical orientations for genetic testing will

contribute for a better understanding of the disease and will improve reproductive and genetic counselling.

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# EUROPEAN JOURNAL OF OBSTETRICS & GYNECOLOGY AND REPRODUCTIVE BIOLOGY

## AUTHOR INFORMATION PACK

### TABLE OF CONTENTS

• Description	p.1
• Audience	p.1
• Impact Factor	p.1
• Abstracting and Indexing	p.2
• Editorial Board	p.2
• Guide for Authors	p.4



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### DESCRIPTION

The *European Journal of Obstetrics & Gynecology and Reproductive Biology* has an open access mirror journal [European Journal of Obstetrics & Gynecology and Reproductive Biology: X](#), sharing the same aims and scope, editorial team, submission system and rigorous peer review. The *European Journal of Obstetrics & Gynecology and Reproductive Biology* is the leading general clinical journal covering the continent. It publishes peer reviewed original research articles, as well as a wide range of news, book reviews, biographical, historical and educational articles and a lively correspondence section. Fields covered include **obstetrics, prenatal diagnosis, maternal-fetal medicine, perinatology**, general **gynecology, gynecologic oncology, uro-gynecology, reproductive medicine, infertility, reproductive endocrinology, sexual medicine** and **reproductive ethics**. The *European Journal of Obstetrics & Gynecology and Reproductive Biology* provides a forum for scientific and clinical professional communication in **obstetrics** and **gynecology** throughout Europe and the world.

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(2) Brown SS, ed. Prenatal Care. Reaching Mothers, reaching infants. Washington: National Academy Press, 1998.

(3)[dataset] [3] Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. <http://dx.doi.org/10.17632/xwj98nb39r.1>.

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