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Premature ovarian insufficiency: Genetic causes and treatment options. A literature review

© Valentina M. Denisova[1], Maria I. Yarmolinskaya[2, 3], Karina A. Zakurayeva[2]

[1] NGC Next Generation Clinic, Saint Petersburg, Russia;
[2] The Research Institute of Obstetrics, Gynecology, and Reproductology named after D.O. Ott, Saint Petersburg, Russia;
[3] North-Western State Medical University named after I.I. Mechnikov, Saint Petersburg, Russia

Premature ovarian insufficiency is a syndrome characterized by hypergonadotropic ovarian insufficiency and the reduction of ovarian function before age 40. This leads to reproductive failures, metabolic changes, and a decrease in quality of life. Currently, occult and initial forms of premature ovarian insufficiency, which have their own diagnostic features and management tactics, can be figured out. The frequency of this syndrome is between 1.1 and 3.7% and the tendency for incidence to increase can be seen. This article is a literature review of the data available in the PubMed database (2005–2020), with international clinical guidelines taken into consideration. The genetic causes of premature ovarian insufficiency, clinical signs of this pathology and treatments options for such patients are included into the review. In addition, some features of assisted reproductive technology within this group are described.

Keywords: premature ovarian insufficiency; genetic causes; poor response.

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Преждевременная недостаточность яичников: генетические причины и тактика ведения пациенток (обзор литературы)

© В.М. Денисова[1], М.И. Ярмолинская[2, 3], К.А. Закураева[2]

[1] NGC Next Generation Clinic (Василеостровская клиника репродукции), Санкт-Петербург, Россия;
[2] Научно-исследовательский институт акушерства, гинекологии и репродуктологии им. Д.О. Отта, Санкт-Петербург, Россия;
[3] Северо-Западный государственный медицинский университет им. И.И. Мечникова, Санкт-Петербург, Россия

Преждевременная недостаточность яичников — синдром, характеризующийся гипергонадотропной недостаточностью яичников и снижением их функции в возрасте до 40 лет, приводящий к нарушению репродуктивной функции, метаболическим изменениям, снижению качества жизни женщин. В настоящее время также выделяют оккультную и начальную формы преждевременной недостаточности яичников, характеризуемые определенными особенностями диагностики и тактики ведения. Частота встречаемости синдрома составляет от 1,1 до 3,7 %, наблюдается тенденция к росту данной патологии. Работа представляет собой литературный обзор данных с 2005 по 2020 г., доступных в базе данных PubMed, а учтены также международные клинические рекомендации. В обзоре рассмотрены генетические причины преждевременной недостаточности яичников, аспекты клинических проявлений данной патологии, а также тактика ведения больных. Описаны нюансы программ вспомогательных репродуктивных технологий у пациенток с преждевременной недостаточностью яичников.

Ключевые слова: преждевременная недостаточность яичников; генетические причины; бедный ответ.

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Premature ovarian failure or, more correctly, premature ovarian insufficiency (POI) is a syndrome characterized by hypergonadotropic insufficiency of the ovaries and a decrease in their function before age 40 years. The age limit of 40 years is adopted because of its reflection in two standard deviations from the average age of natural menopause. According to a 2005 study, the prevalence of this disease is approximately 1.1% in the general population [1] and up to 3.7% in some European countries [2].

A woman has approximately 700 thousand to 1 million oocytes inside primordial follicles since birth. The duration of the conservation of this pool determines the duration of the reproductive period of a particular woman. POI is caused by the loss of these follicles with subsequent infertility and the ovaries loss their ability to produce estrogen. The causes of POI may be associated with a decrease in the number of primordial follicles due to increased atresia, destruction, or deviations in recruitment and maturation of primordial follicles [3].

The factors underlying the pathogenesis of POI can be spontaneous or induced [4]. Spontaneous factors include idiopathic, genetic, and immunological (autoimmune) factors, largely associated with genetic and infectious elements. Induced factors include surgical interventions on the ovaries, chemotherapy and radiation therapy, exposure to gonadotoxic agents, as well as uterine artery embolization.

Genetic causes of POI

Conditionally, genetic causes of premature ovarian failure can be divided into several groups [5], namely, genes affecting ovarian development, division and repair of DNA, development of follicles and hormonal signals, metabolism, immunological regulation of genes without an explicit mechanism of action, and chromosomal causes.

Genes affecting ovarian development

Several genes that influence ovarian development are involved in gonadogenesis. These include *NR5A1* (steroidogenic factor 1) and encoding steroidogenic factor 1, which is a nuclear receptor that regulates the development of the adrenal and reproductive systems. Mutations in the *NR5A1* gene can cause several ovarian abnormalities, including gonadal dysgenesis and premature ovarian failure. A cohort study revealed that *NR5A1* gene mutations are rare, and only four missense variants were found in three patients with idiopathic POI [6], but none of them caused clinically significant functional impairment. In that study, the average mutation rate was 1.6%, which is consistent with data from another cohort study [7], but this figure was significantly lower than that in other studies, probably due to the smaller sample size [8].

NR5A1 is a key gene required for gonadal function, and its variants are associated with various phenotypes of reproductive development disorders and are detected in 0.26%–8% of patients with POI.

NR5A1 mutations can be conditionally divided into rare and common ones. Common forms impair insignificantly the protein function, which leads to less pronounced clinical manifestations, or serve as a risk factor for POI, which may contribute to the preservation of fertility in young women with NR5A1 variants [9].

FOXL2, a forkhead transcription factor, is another gene required for gametogenesis. It is expressed in humans during the development of eyelids and follicles; its mutations have been described in Blepharophimosis, ptosis, and epicanthus inversus syndrome (BPES) syndrome [10]. BPES represents an autosomal dominant condition characterized by certain eyelid malformations that may be associated or not associated with premature ovarian failure (BPES type I and BPES type II, respectively) [11, 12]. Protein FOXL2 is required not only during intrauterine development but also for postnatal maintenance of ovarian function, namely, to prevent ovarian inversion, which was demonstrated in an experimental model in female mice with the *FOXL2* gene knockdown [13]. *FOXL2* is studied well in humans, mice, and goats; it is expressed during prenatal development and adolescence and is localized in the granulosa cells of small and medium follicles, specifically, in the cumulus cells of the preovulatory follicle. *FOXL2*-impaired mice have eyelid and forehead dysmorphisms, and they are atokous. However, ovaries carrying *FOXL2* mutations have varied phenotypes. Some patients with *FOXL2* mutations showed a maturation block similar to that in mice (which was demonstrated on the model according to histological examination data); in other women, histological examination of ovarian biopsy samples did not reveal abnormalities, but there were disorders in the ratio of primordial and primary follicles and a tendency to the formation of ovarian cysts [14]. Patients with BPES and the *FOXL2* mutation may have ovaries with a streak of follicles that may lead to scarring. Thus, it becomes clear that different ovarian phenotypes and follicular defects are possible in patients with *FOXL2* mutations.

Bone morphogenetic protein receptor type 1B (BMPR1B) is a receptor for growth differentiation factors (GDFs) such as GDF5 and is important for gonadal and skeletal development. Mutations in the *BMPR1B* gene can cause chondrodysplasia with the absence or underdevelopment of the ovaries [5]. Bone morphogenetic protein 15 (BMP15) and GDF9 are significant in the development of primordial follicles, ovulation, corpus luteum formation, granulosa cell proliferation, and oocyte maturation through paracrine/autocrine signaling pathways.

Genes affecting DNA division and repair

Since primordial germ cells are rapidly divided to form a pool of primordial follicles and then enter meiosis with a long stop in prophase I, genes involved in cell division

are important for ovarian function. Meiotic genes play different roles, such as ensuring correct separation of chromosomes, organization of cleavage spindle fibers, and physical separation of chromosomes or homologous recombination.

Cohesins are required for cohesion (bonding in the centromere region) of sister chromatids during cell division. Cohesin is a protein complex that is actively involved in DNA repair by homologous recombination as well as in cohesion and segregation of chromosomes during cell division.

Mutations in stromal antigen 3 (*STAG3*), which encodes one of the cohesins, are involved in prophase I of meiosis and, as previously reported, can cause premature ovarian failure [15]. Two homozygous variants (c.877_885del, p.293_295del and c.891_893dupTGA, p.297_298ins Asp) in the *STAG3* gene were found in two Chinese sisters with POI and a family history of this pathology in five generations. However, how these *STAG3* variants can lead to POI and infertility is not completely clear [16].

Premature ovarian failure protein 1B (POF1B) is a myosin-like protein that interacts with non-muscle actin filaments and can participate in meiotic division. *POF1B* is located on the long arm of the X chromosome in a region critical for ovarian function, and mutations in *POF1B* can cause POI [17].

During meiosis, homologous recombination occurs between paired chromosomes and requires a synaptonemal complex (a protein complex that forms between homologous chromosomes and holds them by crossing over, that is, the exchange of sections of genetic information). Impairment of this complex leads to infertility in mice, and mutations in the subunit of the synaptonemal complex central element protein 1 complex can cause premature ovarian failure in women [18, 19]. Other components of the synaptonemal complex are considered possible candidates for POI and have been shown to lead to infertility in mouse models [20–22].

Other genes required for homologous recombination, such as helicase for meiosis 1 *(HFM1*) and proteasome 26S subunit ATPase 3 interacting protein (*PSMC3IP*), can also cause POI in humans in case of mutations [23, 24].

Mutations in the nucleoporin 107 *(NUP107*) gene, which encodes the nuclear pore complex, can cause POI in women with XX karyotype [25]. The main role of the pore complex is the transfer of macromolecules between the nucleus and cytoplasm. The complex of nuclear pores allows the implementation of the selective transport of regulatory factors into the nucleus, as well as the transport of specific RNA molecules from the nucleus, thus promoting specific gene expression and signal transduction. The exact role of *NUP107* is still unknown, but studies on insects have shown that gene regulation, in particular in *Drosophila melanogaster*, is required for the progression of mitosis and meiosis [25]. For example, in *Drosophila*, Seh1, a component of the NUP107–160 complex, binds to Mio, a protein required for nuclear architecture and the meiosis process [26]. Changes in *Seh1* (SEH1-like nucleoporin) lead to abnormalities in the mitotic division of germ cells and errors in meiosis [26].

Many candidate genes are involved in meiosis and alter the number of follicles or affect negatively the survival of oocytes in mice. Disorders in cell division due to abnormalities in the aforementioned genes possibly lead to abnormalities in oocytes, which then undergo apoptosis during maturation. The need for a precise division also implies efficient DNA repair mechanisms.

The first gene associated with DNA repair and POI was ataxia telangiectasia mutated (*ATM*) [27]. ATM is a serine/threonine kinase belonging to the PI3/PI4 family of kinases, required for the cellular response to DNA damage. ATM is involved in ovarian functioning, and its deficiency can lead to POI. Deletion of the *ATM* locus in mice enhances the degradation of primordial follicles in prophase I of meiosis during oogenesis, which subsequently leads to a deficiency of primordial and maturing follicles [28]. In their study, Liu et al. demonstrated using whole-exome sequencing that patients with secondary amenorrhea and POI can be carriers of the c.2367C>G *ATM* variant [29].

Other genetic causes associated with genes involved in DNA repair and associated with an increased risk of cancer, premature aging, and POI include mutation in nibrin (*NBN*), Bloom syndrome caused by a mutation in *BLM*, Werner syndrome due to mutation in WRN RecQ-like helicase (*WRN*), Fanconi anemia caused by a mutation in genes such as Fanconi anemia complementation group A (*FANCA*), Fanconi anemia complementation group C (*FANCC*), and Fanconi anemia complementation group G (*FANCG*), as well as Rothmund Thomson syndrome caused by a mutation in ATP-dependent DNA helicase Q4 (*RECQL4*) [5].

Several other genes involved in DNA repair are also associated with the onset of POI. Minichromosome maintenance complex component 8 (*MCM8*) and minichromosome maintenance complex component 9 (*MCM9*) encode proteins required for homologous DNA recombination in the event of damage. The absence of MCM8 and MCM9 proteins contributes to errors in the meiosis process in mice, for example, arrest of prophase I, arrest of primary follicle development, and frequent development of tumors in *MCM8*$^{-/-}$mice, as well as complete absence of oocytes in *MCM9*$^{-/-}$mice [30].

Mutations in *MCM8* cause POI in hypothyroidism [31], and mutations in *MCM9* lead to POI associated with short stature [32], isolated POI [33], or POI associated with colorectal cancer [34]. A recent study detected a significant number of potentially dangerous and novel variants of

MCM8 and *MCM9* mutations that cause POI [35]. Mutations in the *CSB-PGBD3* gene, which encodes a protein involved in the transcriptional repair of paired DNA, also lead to POI [36].

During embryonic development, massive apoptosis of germ cells leads to the elimination of cells that are incapable of replication. Moreover, during normal ovulatory cycles, only one dominant follicle progresses, while the rest are subject to atresia. Therefore, genes involved in apoptosis are also candidates for POI formation. Nanos homolog 3 (*NANOS3*) has a direct effect on the suppression of apoptosis in migrating primordial germ cells, and mutations in *NANOS3* are associated with POI [37, 38]. Progesterone has an antiapoptotic effect on ovarian cells, and mutations or translocations in the membrane component of membrane-associated progesterone receptor component 1 (*PGRMC1)* progesterone receptor have also been revealed in patients with POI [39]. The potential role of apoptosis in POI has been demonstrated in mouse models, for example, in mice knockout for the *BCL2* gene (apoptosis regulator BCL-2) [40].

Genes affecting follicular development and hormonal signals

With the development of next-generation sequencing (NGS) technology, information on the molecular basis of idiopathic POI has increased significantly. Several new pathogenic variants of previously well-studied genes, such as *FSHR*, *GDF9*, *BMP15*, *FIGLA,* and *NOBOX*, have been identified using sequencing technology. These genes were the first to be described in POI pathogenesis because of their role in the development and/or functioning of the ovaries. They can be conditionally divided into functional subgroups, namely, (1) development of germ cells, 2) oogenesis and folliculogenesis, (3) steroidogenesis, and 4) hormonal signals [41]. During embryonic development, numerous germ cells are eliminated by apoptosis and mutations in genes involved in this process, for example, *NANOS3* [37], and eukaryotic translation initiation factor 4E nuclear import factor 1 (*EIF4ENIF1*) [42], which can lead to phenotypic manifestations of POI.

Moreover, the development of POI can be influenced by various factors involved in the recruitment, development, and maturation of follicles and oocytes. These include growth factors such as BMPs, GDFs, and neurotrophic factors (such as nerve growth factor, brain neurotrophic factor, and glial cell-derived neurotrophic factor).

Growth factors of the TGFβ family and *BMP15* and *GDF9* play a fundamental role in ovarian function [42].

BMP15 is a specific oocyte growth/differentiation factor encoded at the Xp locus, which is required for ovarian reserve determination. The biological properties of *BMP15* include promotion of follicular growth and maturation, regulation of sensitivity of granulosa cells to follicle-stimulating hormone (FSH) and determining the follicle pool, and prevention of granulosa cell apoptosis. *BMP15* mutations presumably cause X-linked dominant POI [44]. In 2019, the results of a comparative analysis of the frequency of occurrence of *BMP15* alleles in patients with POI and women without POI were published. The study group included 119 women with POI (they were distributed into two subgroups, namely, those with FSH levels >25 mIU/ml and those with FSH levels of 10–25 mIU/ml). The control group included 88 women aged >50 years without POI. Analysis of *BMP15* genotypes and alleles showed that CT and TT BMP15:c.852 C>T genotypes were found more often in the study group [45].

Other members of the BMP family, such as BMP4 and BMP7, are significant in the hormonal control of folliculogenesis and may be associated with the development of POI.

Another candidate gene is *GDF9*. The GDF9 protein is required for folliculogenesis in the ovaries, mutations in the gene lead to POI, and secondary amenorrhea, first described for the autosomal dominant mode of inheritance [46–48]. Nevertheless, heterozygous *GDF9*$^{+/-}$ mice are fertile, and only female *GDF9*-null mice are infertile due to a block of primary stages of follicular development [5, 41].

The nobox oogenesis homeobox (*NOBOX*) gene is an oocyte-specific gene that acts as a regulator of the transcription of ovarian genes, including *GDF9* and *BMP15*. Mutations in the *NOBOX* gene can lead to POI [49]. All *NOBOX* mutations were found in a heterozygous state [50]. If the clinical manifestations of *NOBOX* mutations were compared in female patients and knockout mice, then the clinical manifestations were less severe and more variable in patients, which may be due to the heterozygous carriage of mutations, than in mice [51].

Mutations causing POI have been detected in spermatogenesis and oogenesis-specific basic helix-loop-helix-containing protein 1 (*SOHLH1*), which encodes a transcription factor involved in folliculogenesis at early stages [51]. SOHLH1 is expressed only at the early stages of folliculogenesis, its expression is absent in secondary follicles, and patients with *SOHLH1* mutations are characterized by a small ovarian volume, which suggests a possible role of this protein in the development of ovaries and germ cells as well as in folliculogenesis [51, 52].

Since follicular development is largely mediated by hormones, many of the genes involved in POI pathogenesis are related to the regulation of hormonal signals. FSH is the key hormone responsible for the growth and development of follicles. FSH consists of two subunits: the α-subunit, which is similar to luteinizing hormone and human chorionic gonadotropin, and a specific β-subunit. Mutations in FSH subunit β (*FSH*β), which encodes the

β-subunit, cause FSH deficiency and amenorrhea [5]. FSH receptor (*FSHR*) mutations are associated with various manifestations of POI. *FSHR* is one of the POI genes in which the relationship between specific mutations and their specific phenotypic consequences is manifested [5]. For example, a homozygous variant of the inactivating mutation p.A189V, one of the most common mutations in the Finnish population, causes primary amenorrhea, hypergonadotropic hypogonadism, and hypoplastic ovaries with impaired follicular growth [53]. With this mutation, patients do not have a functional response to the administration of large doses of FSH, which reflects the absence of signals from FSHR [54]. Patients with POI and lack of response to high doses of FSH and with the p.P519T mutation, which also blocks FSHR function, have also been described. The literature presents data on two patients with a heterozygous *FSHR* mutation (p.I160T/R573C and p.D224V/L601V), which was associated only with a partial loss of FSHR function [55]. These mutations are also associated with a specific phenotype characterized by normal development at puberty, primary or secondary amenorrhea, and normal ovarian size. FSH levels in these women were very high, despite the normal size of the ovaries and the presence of antral follicles. The development of follicles remains normal until the stage of small antral follicles and is disturbed at later stages [5]. Understanding the residual function of FSHR variants provides a presentation of the phenotype.

Functional *FSHR* polymorphisms can lead to FSH dysfunction, a decrease in ovarian function, and induce the development of POI. Polymorphisms rs6165 and rs6166 are the two most common FSHR missense mutations that replace G with A at two loci and thus affect the binding of FSH to its receptor. To assess the potential relationships between FSHR and POI polymorphisms in humans, 14 studies of rs6165 polymorphism (590 cases and 1170 controls) and 13 studies of rs6166 polymorphism (640 cases and 1333 controls) were included in the meta-analysis. No significant relationship was found between the two studied polymorphisms and POI. However, with further analysis, depending on ethnicity, the rs6166 polymorphism was found to be important in the formation of POI for Asian women [56].

Another noteworthy gene is the factor in the germline alpha (*FIGLA*). This gene encodes a protein that is involved in postnatal oocyte-specific gene expression. The protein is a major helix–loop–helix transcription factor that regulates several oocyte-specific genes, including genes involved in folliculogenesis and genes that code for the *zona pellucida*. Mutations in this gene cause POI [57].

FIGLA expression was detected in ovarian and oocyte follicles in metaphase II. This suggests that this gene regulates oogenesis until the oocytes mature [59]. FIGLA binds to the transcription factor E12 (TCF3) to form a dimer that binds to the E-box ZP2, which actively participates in oocyte survival [59]. The study determined the relationship between the *FIGLA* gene and the variants and incidence of POI in the Indian population. Alleles c.427GYC and c.557CYT increase the risk of POI in Indian women. A study also revealed the involvement of c.252CYT and c.427GYC in the pathogenesis of POI [60].

Our proper understanding of the structure and function of primary follicles is predominantly based on studies in mice. FIGLA-deficient mice lose all primordial follicles immediately after birth. Expression of *ZP1, ZP2*, and *ZP3* genes is absent in *FIGLA*-knockout mice. In genetically engineered mice that do not produce ZP1 or ZP3, the pellucid zone is either abnormal or is absent, resulting in infertility. These factors indicate that FIGLA is an important regulator of reproductive function [59, 61, 62].

In another study, recessive inheritance of *FIGLA* mutations has been implicated in POI pathogenesis. Patients with a homozygous mutation had primary amenorrhea, and patients with a heterozygous mutation had secondary amenorrhea. *FIGLA* haploinsufficiency is assumed to be able to cause a milder form of POI than mutations of the homozygous *FIGLA* allele [63].

Steroidogenesis is another key hormonal process that must be intact for the ovaries to function properly. Steroidogenesis represents the process of synthesis of steroid hormones (progesterone, androgens, estrogens, mineralocorticoids, and glucocorticoids) in the adrenal glands, gonads, and several other tissues. In women, estrogen biosynthesis starts in the mitochondria of theca cells, where cholesterol is converted to pregnenolone by the cytochrome P450 (CYP11) enzyme. Pregnenolone is then converted to androgens by the cytochrome P450 family 17 (CYP17 enzyme). Granulosa cells convert androgens to estrogens through CYP19. Estrogens have various functions in the female reproductive system, including uterine and mammary gland growth, stimulation of endometrial growth, as well as simulation of the ovulatory cycle, for example, by inhibiting FSH to prevent multiple follicles from ovulating or by activating luteinizing hormone [5]. All genes involved in steroidogenesis are candidates for POI, and mutations in some of them are already associated with POI in patients. The steroidogenic acute regulatory (STAR) protein is responsible for the transport of cholesterol into the mitochondria for its conversion into steroids. Mutations in the *STAR* gene cause congenital adrenal lipoid hyperplasia. In severe cases, the absence of steroids leads to adrenal crises with early neonatal death. In less severe forms, *STAR* mutations lead to nonclassical lipoid congenital adrenal hyperplasia. Since the ovaries do not express STAR until puberty, they are not involved in the pathological process, but after puberty,

lipids accumulate, and POI may develop in such women [5, 41].

Direct mutations in cytochrome P450 family 17 subfamily A member 1 (*CYP17A1*) and cytochrome P450 family 19 subfamily A member 1 (*CYP19A1*) genes coding for enzymes for hydroxylation of pregnenolone/progesterone and estrogen aromatization, respectively, cause POI of varying severity [5].

Genes affecting oocyte metabolism

Many of the genes that lead to POI are involved in mitochondrial metabolism or functioning. The need for copies of these genes to function may be caused by a high ovarian requirement for energy, potential oxidative stress, or ovarian damage due to errors in metabolic or mitochondrial functions. Several researchers have demonstrated that women with POI have increased levels of markers of oxidative stress [5].

Compared with most somatic cells, which can contain 1,000 to 10,000 copies of mitochondrial DNA (mtDNA) [64], human oocytes contain approximately 100,000 copies of mtDNA. A large number of mtDNA copies are probably required for oocytes to maintain embryonic development after fertilization and before implantation [65]. The level of mtDNA in patients with POI or in the group with "poor" response to ovarian stimulation is significantly reduced [66]. Moreover, the reduced content of mtDNA copies in the blood may reflect an overall intensified aging process, not only the aging process of the ovaries [65].

The literature describes several genes encoding mitochondrial proteins and those associated with POI in the presence of mutations in them. Patients with mutations in genes encoding mtDNA polymerase-γ (mitochondrial DNA polymerase catalytic subunit, *POLG*) have clinical manifestations of progressive external ophthalmoplegia, which includes symptoms of blindness and myopathy and often an ovarian failure or a combination of Parkinsonism and POI [67, 68]. *POLG* is required for the efficient and accurate functioning of mtDNA, and patients with mutations in this gene have mtDNA depletions and/or deletions. In female patients with mutations in *C10orf2* (T7 helicase-related protein with intramitochondrial nucleoid localization) have depletions or deletions of mtDNA and POI with hearing loss [69].

C10orf2 is a mitochondrial helicase responsible for unwinding mtDNA before its replication. An efficient mitochondrial translation is also required for normal functioning of the ovaries, which has been demonstrated in patients with POI and mutations in genes involved in the synthesis of mitochondrial transport RNAs (tRNA), such as leucyl-tRNA synthetase 2 (*LARS2,* mitochondrial), histidyl-tRNA synthetase 2 (*HARS2*, mitochondrial), and alanyl-tRNA synthetase 2 (*AARS2*, mitochondrial). In cases of *LARS2* and *HARS2* mutations, POI is associated with hearing loss and Perrault syndrome. In the presence of the *AARS2* mutation, POI is associated with the onset of encephalopathy in adolescence [5].

Another cause of Perrault syndrome is hydroxysteroid 17-beta dehydrogenase 4 (*HSD17B4*) mutation [70], although most female patients with mutations in this gene have the most outstanding phenotype and do not survive until puberty. This gene encodes a multifunctional enzyme involved in fatty acid oxidation and steroid metabolism, which further disrupts cell metabolism and ovarian function.

Proper metabolism of galactose is also required for ovarian function, as has been established in patients with galactose-1-phosphate uridylyltransferase (*GALT*) mutations with galactosemia, and 80%–90% of these women have POI. Without proper metabolism, galactose accumulates at a toxic level and increases follicular atresia. More than 150 mutations in this gene that can potentially affect ovarian functioning have been identified [5].

Congenital disorders of glycosylation (CDG) represent a group of rare congenital autosomal recessive diseases that interfere with the synthesis of glycoproteins caused by mutations in phosphomannomutase 2 (*PMM2*) (*CDG1*), a gene that encodes the enzyme phosphomannomutase required for the conversion of mannose-6-phosphate to mannose-1-phosphate. Patients with mutations in the *PMM2* gene exhibit neurological symptoms of varying severity [71], while female patients may have signs of POI without neurological disorders, which were described in a clinical case of sisters with POI [72].

Genes affecting immune regulation

Autoimmune diseases such as systemic lupus erythematosus, Hashimoto thyroiditis, and Addison's disease are often concomitant with POI. The autoimmune mechanism is supposed to explain up to 30% of POI cases. Autoimmune oophoritis is characterized by mononuclear infiltration of theca cells of growing follicles, while lymphocytic infiltration is uncommon for follicles in the early stages of development. These infiltrates can include plasma, B, and T cells [73]. Autoimmune POI is often associated with autoimmune Addison's disease, and in typical cases, antibodies to steroidogenic enzymes such as 21-hydroxylase and 17-hydroxylase are revealed in women with this pathology [5].

Autoimmune diseases are often hereditary in nature. In the case of type 1 autoimmune polyendocrine syndrome (APS-1), in which the adrenal glands, thyroid gland, and gonads are affected from childhood, disorders occur in the autoimmune regulator (*AIRE*) gene. *AIRE* encodes an autoimmune regulator, and POI is common in women with a mutation in the *AIRE* gene [74]. AIRE is a protein that is active predominantly in the thymus and plays a role in the recognition of the body's proteins and foreign proteins by

the cells of the immune system [75]. APS2, an adolescent form of the protein that includes adrenal insufficiency, in which POI is often registered, is also associated with several identified susceptibility loci, but not of a monogenic nature [76].

Genes without a clear mechanism of action

Many other genes are involved in the pathogenesis of POI; their role in the disease is still not completely clear. One of the most common genetic causes is the premutation of the fragile gene.

X chromosomes of fragile X mental retardation 1 (fragile X mental retardation protein 1 [*FMR1J*) explain up to 13% of familial cases and 3% of sporadic cases. The normal *FMR1* allele contains 5–44 CGG repeats within the 5'-untranslated region of this gene. Expansion of triplet repeats up to 55–199 is considered a "premutation," while ≥200 repeats are considered a complete mutation leading to mental retardation due to the transcriptional silence of this gene (Martin–Bell syndrome in boys) [77]. In 20% of women carrying the premutation form of this gene, clinical manifestations of POI are noted with a frequency of significantly higher than 1% in the general population.

Premutation of *FMR1* leads to secondary amenorrhea and POI in women aged >30, although earlier onset is also noted [78]. Nonlinear interactions between repeat length and ovarian dysfunction have been established, with repeat lengths from 60 to 100 most commonly leading to POI. Premutation of *FMR1* causes an earlier onset of menopause in general; therefore, POI is not manifested in some carriers, their starting point is age 40, and menopause starts approximately 5 years earlier [5].

This is also evidence of the occult form of POI in carriers of *FMR1* premutation aged 18–40 years with a retained regular menstrual cycle, but with an increased level of FSH and a decreased levels of inhibin B and antiMüllerian hormone [5]. *FMR1* encodes a protein that binds to RNA and polysomes and can be involved in the transport of messenger RNA (mRNA) from the nucleus to the cytoplasm [79]. In individuals with *FMR1* premutation, the levels of FMR1 mRNA are increased, while the levels of the FMR1 protein are decreased, which suggests the effect of the repeat length on translation efficiency [80]. Ovarian failure may be caused by mRNA toxicity to granulosa cells, but the exact mechanism by which premutation and impaired expression of FMR1 leads to disease must be determined. Interestingly, a deletion near the trinucleotide region of repeats in fragile X mental retardation protein 2 *(FMR2)* (*AFF2*) is more common among women with POI than in the general population (1.5 versus 0.04 %) and may also be involved in the disease pathogenesis, but the mechanism is not fully understood [5].

Chromosomal causes

Not only individual genes are involved in the development of POI, but also chromosomal abnormalities. Chromosomal abnormalities occur with a frequency of 10%–13% in women with POI. Quantitative defects include monosomy of the X chromosome, trisomy of the X chromosome, X autosomal translocations, and minor or major rearrangements. An evaluation of the karyotype to detect quantitative abnormalities can be performed using cytogenetic analysis, and the NGS method has recently become a powerful tool, which is used to estimate the copy number for diagnostics of POI and other endocrine pathologies [48]. Turner syndrome is registered when a patient has only one X chromosome (45X), and its incidence is 1 per 2500 women. Most pregnancies with fetuses with this karyotype are terminated spontaneously, and more often, female fetuses that survive have a mosaic shape. The phenotype of girls born with a 45X karyotype or 45X/46XX mosaicism usually includes growth retardation; abnormalities of the cardiovascular, lymphatic, and urinary systems; and other phenotypic features such as syndactyly and rapid apoptosis of fetal oocytes. The presence of two X chromosomes is required to support the development of the ovary. The disease development may be associated with an insufficient number of X-chromosome products to maintain the normal functioning of the ovary, or oocytes may degrade since they cannot undergo meiosis division due to a lack of a homologous pair of the X chromosome [4, 40].

POI can also be associated with partial chromosomal abnormalities, such as terminal deletions with breaks in the proximal Xp and/or proximal Xq regions, such as Xq13 or Xp11. The decisive regions for the normal development of the ovaries are Xq13–27 and Xp13–11. These regions can be disrupted by deletions or translocations that involve the *POF1B* and *FMR1* genes, leading to POI [5].

Breast cancer type 1 and 2 (*BRCA1*/2). *BRCA1* and *BRCA2* play important roles in DNA repair, cell cycle regulation, and maintenance of genome stability. Double-stranded DNA breaks are induced in oocytes during meiotic recombination and, as a consequence, can accumulate in oocytes during normal metabolic processes or when DNA is exposed to damaging agents [81, 82].

The reduced ability to repair double-stranded DNA breaks in *BRCA* mutations can increase oocyte apoptosis, decrease the number of primordial follicles innate originally in the ovaries at birth, and accelerate potentially the depletion of primordial follicles at reproductive age [83].

Preclinical data obtained from studies in mice demonstrated a reduced number of primordial follicles and a less pronounced response to stimulation of ovulation in individuals with the mutation compared with wild-type mice [84].

Another study analyzed the premature aging of the ovaries in carriers of the *BRCA* mutation, including healthy

carriers of the *BRCA* mutation, who underwent prophylactic oophorectomy, and persons who were not carriers of the *BRCA* mutation (control group) who underwent ovarian resection due to benign diseases of the same age. Biomarkers of ovarian aging were analyzed, namely, levels of anti-Müllerian hormone, fibroblast growth factor-23, interleukin-1, Klotho (a transmembrane protein, its count decreases with age) in the blood, mRNA of protein kinase B and anti-Müllerian hormone in ovarian tissues, as well as the number of follicles in the volume of the ovarian tissue. The study showed that young carriers of the *BRCA* mutation have less ovarian reserve [85]. Other studies have revealed that women with early menopause have been carriers of the *BRCA* mutation [86–88].

Research supports a relationship between *BRCA* mutation and accelerated aging of the gonads. A more detailed study of the mechanisms of POI occurrence in patients with the *BRCA* mutation and an assessment of the prevalence of non-cancerous diseases in the group with *BRCA* mutation carriers is required, since these data may be of great importance for determining the management approach for such patients.

New genes identified using NGS technology

In addition to the already well-known genes, approximately 15 genes have been described to cause POI in humans and, as shown in animal models, affect ovarian development and meiosis [41]. These genes include the BMP2 receptor gene (*BMPR2*), Gap-binding protein alpha 4 (GJA4)/connexin-37 (CX37), KHdomain-containing RNA-binding signal transduction-associated protein 1 (KHDRBS1), autophagy protein 7 (ATG7) and autophagy protein 9 (ATG9), notch receptor 2 (NOTCH2), H subunit of RNA polymerase III (POLR3H), accessory protein involved in DNA repair (SPIDR/KIAA0146), MutS homolog 4 (MSH4) and MutS homolog 5 (MSH5), Fanconi anemia complementation group MM (FANCM), basonuclin 1 (BNC1), WD repeat protein 62 (WDR62), BRCA2, tumor protein p63 (TP63), C subunit of RNA polymerase II (POLR2C), and mitochondrial ribosomal protein S22 (MRPS22).

Clinical manifestations

According to the ESHRE guideline [1], POI has three forms, namely, initial, occult, and classical. Most often, secondary amenorrhea or oligomenorrhea, as well as reproductive disorders and symptoms of estrogen deficiency, become one of the first clinical manifestations of POI. Obviously, in clinical practice, female patients with a "latent" or occult form of POI are of great interest. For the first time, this variant of ovarian insufficiency was described as a triad of signs, namely, regular menstruation, infertility, and high blood levels of FSH. Such patients cannot be identified until pregnancy is planned, which causes certain difficulties [89].

Most clinical guidelines indicate the need to measure the blood level of FSH twice with an interval of 4–6 weeks. According to the ESHRE guideline, the diagnostic level of FSH is ≥25 IU/L [1]. In addition to determining the level of FSH in the blood, the ESHRE guideline recommends karyotyping and testing for *FMR1* premutation for all patients with non-atrogenic POI.

Among the important aspects of the consequences for the general somatic health of a POI woman, the influence of the hypoestrogenic status on the cardiovascular system and bone tissue, metabolic changes, as well as psychoemotional and sexual disorders should be noted [3].

Any female patient with POI should be informed about the low chances of spontaneous pregnancy as well as the lack of methods with proven efficiency to enhance ovarian function and increase the possibility of spontaneous conception [1]. Assisted reproductive technologies (ART) using donor oocytes are the method of choice for the implementation of reproductive function. However, therapies suggesting platelet-rich plasma, stem cells, and primordial follicle activation should be evaluated to confirm their efficacy and safety. In addition, women should be offered methods for preserving fertility (cryopreservation of oocytes, embryos, ovarian tissue, and in vitro maturation) before ovarian surgery and gonadotoxic treatment [89].

The choice of approach for the implementation of reproductive function in patients with "latent" or occult POI gained a high research interest within ART programs. Currently, the terminology is changing from the previously accepted "poor ovarian response" to the concept of low prognosis for ovarian stimulation. Patients with a low prognosis are classified into POSEIDON groups depending on the markers of ovarian reserve (anti-Müllerian hormone level, number of antral follicles, or both), woman's age, and number of oocytes obtained in previous cycles of standard ovarian stimulation (if this information is available). The classification is mainly aimed at individualization of the approach to stimulation of patients in ART programs to obtain a euploid embryo with the maximum potential for implantation and pregnancy onset [90, 91]. Depending on the group, various ways to optimize the ovarian response to stimulation can be used, from increasing the dose of FSH and/or adding luteinizing hormone in protocols with gonadotropin-releasing hormone antagonists when performing ovarian stimulation in groups 1 and 2 [92, 93] to more complex management of groups 3 and 4 with the potential prescription of adjuvants (which is currently required to determine further the real efficacy and safety), choice of a long protocol of ovarian stimulation, double stimulation for the accumulation of oocytes or embryos, and preimplantation genetic testing for aneuploidy (PGT-A) [94].

The approach to the management of patients with POI should be multidisciplinary; it is necessary to inform the woman about the effect of this condition on metabolic processes and cardiovascular system; therefore, lifestyle modification and smoking cessation should be recommended. To prevent hypoestrogenic consequences, estrogen–gestagenic therapy should be prescribed, and the condition of the bone tissue should be monitored [1, 3].

POI is an extremely heterogeneous disease caused by mutations in more than 75 genes, which are mainly associated with meiosis and DNA repair. The relationship of some genes to POI etiology has not yet been proven; therefore, functional studies or additional reports are required to confirm the causation of POI by mutations in certain genes. Although the genetic etiology has been studied by several groups and NGS techniques helped reveal new genes and new causes of POI, most cases still have no clear genetic definition. In the next few years, a new genetic etiology of POI phenotypes will be formed. Further research using whole-exome and whole-genome sequencing will provide new insights into the etiology of POI.

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AUTHORS INFO

***Valentina M. Denisova**, MD, Cand. Sci. (Med.);
address: 2 building 3 Petrovsky Prospekt,
Saint Petersburg, 197110, Russia;
ORCID: https://orcid.org/0000-0001-6469-9111;
Scopus Author ID: 57218170473; eLibrary SPIN: 7291-3857;
e-mail: valyik@mail.ru

Maria I. Yarmolinskaya, MD, Dr. Sci. (Med.), Professor,
Professor of the Russian Academy of Sciences;
ORCID: https://orcid.org/0000-0002-6551-4147;
Researcher ID: P-2183-2014; Scopus Author ID: 7801562649;
eLibrary SPIN: 3686-3605; e-mail: m.yarmolinskaya@gmail.com

Karina A. Zakurayeva, Resident Physician;
ORCID: https://orcid.org/0000-0002-8128-306X;
eLibrary SPIN: 5215-7869; e-mail: kareen07kbr@gmail.com

ОБ АВТОРАХ

***Валентина Михайловна Денисова**, канд. мед. наук;
адрес: Россия, 197110, Санкт-Петербург,
Петровский пр., д. 2, стр. 3;
ORCID: https://orcid.org/0000-0001-6469-9111;
Scopus Author ID: 57218170473; eLibrary SPIN: 7291-3857;
e-mail: valyik@mail.ru

Мария Игоревна Ярмолинская, д-р мед. наук,
профессор, профессор РАН;
ORCID: https://orcid.org/0000-0002-6551-4147;
Researcher ID: P-2183-2014; Scopus Author ID: 7801562649;
eLibrary SPIN: 3686-3605; e-mail: m.yarmolinskaya@gmail.com

Карина Анзоровна Закураева, клинический ординатор;
ORCID: https://orcid.org/0000-0002-8128-306X;
eLibrary SPIN: 5215-7869; e-mail: kareen07kbr@gmail.com