PREMATURE OVARIAN FAILURE

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Annotation

POF is a fairly common problem. The age of cessation of ovarian function and the onset of menopause is influenced by a number of factors that can be divided into two groups: modifiable (medical, social, and environmental factors) and non-modifiable (genetic). Heredity is a powerful predictor of accelerated depletion of the follicular apparatus and the onset of early menopause.

Conclusion: In general, the number of patients with POI caused by autoimmune damage is small (4%), but this group of patients should be clearly identified: they are the ones at risk of developing a potentially life-threatening condition - 1-CAI

Keywords: premature ovarian failure, ethiology,diagnose and treat.

Аннотация

ПНЯ — довольно распространенная проблема. На возраст прекращения функции яичников и наступление менопаузы влияет ряд факторов, которые можно разделить на две группы: модифицируемые (медицинские, социальные и факторы окружающей среды) и немодифицируемые (генетические). Наследственность — мощный предиктор ускоренного истощения фолликулярного аппарата и наступления ранней менопаузы.

Заключение: В целом число пациенток с ПНЯ, вызванным аутоиммунным поражением, невелико (4%), однако эту группу пациенток следует четко выделить: именно они входят в группу риска по развитию потенциально опасного для жизни состояния — 1-ПНЯ

Ключевые слова: преждевременная недостаточность яичников, этиология, диагностика и лечение.

Annotatsiya

ETY juda keng tarqalgan muammo. Tuxumdonlar faoliyatining to'xtash yoshi va menopauzaning boshlanishi ikki guruhga bo'linadigan bir qator omillarga ta'sir qiladi: o'zgartiriladigan (tibbiy, ijtimoiy va ekologik omillar) va o'zgartirilmaydigan (genetik). Irsiyat follikulyar apparatlarning tez sur'atda yo'qolishi va erta menopauza boshlanishining kuchli prognozidir.

Xulosa: Umuman olganda, autoimmun zarar tufayli yuzaga kelgan ETY bilan og'rigan bemorlarning soni kam (4%), ammo bemorlarning ushbu guruhini aniq aniqlash kerak: ular potentsial hayot uchun xavfli holatni rivojlanish xavfi ostida bo'lganlar - 1-CAI

Kalit so'zlar: erta tuxumdon yetishmovchiligi, etiologiya, tashxis va davolash.

Generally accepted terminology and standardized diagnostic criteria allow specialists to achieve mutual understanding in diagnosing and treating the disease. The term that most accurately reflects the essence of the problem is "premature ovarian failure" (p rematu re ova rian failu re - POF), proposed by French specialists. Previously, such options as "premature menopause", "hypergonadotropic amenorrhea", "hypergonadotropic hypogonadism" were discussed. Until recently, POF was considered an irreversible condition. G. Jones (1969) described 3 patients with secondary hypergonadotropic amenorrhea and intact follicular apparatus, who very rarely had spontaneous menstruation [3]. In the 1980s, it was proposed to distinguish between the "resistant ovary syndrome" (Savage syndrome; the eponym comes from the surname of one of the patients), in which spontaneous restoration of ovulation occurs, and the "depleted ovary syndrome" — in which their function is irreversibly terminated [4]. In modern literature, they are considered synonyms that define different phases of POF development. With POF, not only spontaneous restoration of ovulation is possible, but also the onset of pregnancy in 5-10% of women, sometimes many years after the manifestation of the disease [5]. It is impossible to determine the cut-off point at which prolonged hypergonadotropic amenorrhea becomes irreversible.

POF is a fairly common problem. In the population of Eastern European women, the proportion of women with POF is 1.0% (95% CI 0.7-1.4), almost the same - 1.1% in the general population of the USA [7]. POF is noticeably more common among African American women - 1.4% (95% CI 1.0-2.1) and women of the Hispanic ethnic group - 1.4% (95% CI 0.8-2.5). In the Asian ethnic group, premature cessation of ovarian function is significantly less common: among Chinese women - 0.5% (95% CI 0.1-1.9) and extremely rare among Japanese women - 0.1% (95% CI 0.02-1.1) [7]. In women under 20 years of age, the prevalence of POI is 1:10,000 women, under 30 years of age 1:1,000, under 40 years of age 1:100 women, with sporadic forms predominating. Familial forms account for no more than 4-20% of POI cases. The leading symptom of POI is hypergonadotropic amenorrhea, which is nonspecific and can be observed in primary ovarian failure of any etiology: gonadal dysgenesis, POI, or as a result of the onset of menopause. There are fundamental differences between natural menopause and POI: according to the WHO definition (1999), menopause is a stable cessation of menstruation due to the loss of follicular activity of the ovaries [8], the onset of which is determined only retrospectively one year after the last menstruation. The annual waiting period is determined based on the results of epidemiological studies - the probability of resumption of menstruation after 12 months of amenorrhea is extremely low. The average age of menopause in the European ethnic group is 50-51 years, the physiological period of menopause in the absolute majority (98%) of women is within 45-55 years [9]. Early or late cessation of ovarian function

is generally atypical for the population of healthy women, and may be a symptom or consequence of a disease.

The age of cessation of ovarian function and the onset of menopause is influenced by a number of factors that can be divided into two groups: modifiable (medical, social, and environmental factors) and non-modifiable (genetic). Heredity is a powerful predictor of accelerated depletion of the follicular apparatus and the onset of early menopause. In a population-based study conducted in 1995 in the United States (n=10,606), the family history of 344 women who experienced menopause before age 45 was compared with the history of women who experienced menopause on time [10]. The onset of early menopause in their first- and second-degree relatives was reported by 129 (37.5%) women in the main group and only 9% of women in the control group (odds ratio - OR 6.1; 95% CI 3.9-9.4). With depletion of the follicular apparatus at the age under 40 years, the influence of heredity increases: OR 8.4; 95% CI 2.5-31.2, similarly, the probability of early cessation of ovarian function increases with the accumulation of several cases of early menopause in the family: OR 12.4; 95% CI 4.4-34.2. Twin studies confirm the presence of a genetic component; moreover, according to the data of national twin registries of Australia and Great Britain (832 pairs of mono- and dizygotic), the prevalence of POI among twins is 3-5 times higher than in the population [11]. POI and physiological menopause are fundamentally different conditions, and, despite the fact that the features of the clinical picture of the syndrome have been repeatedly discussed in the literature, its diagnosis presents considerable difficulties for the physician. This is due to the nonspecificity of the symptoms and variability of the clinical picture of POI.

Etiology of POI is a clinical syndrome that unites a heterogeneous group of diseases in which ovarian failure can be caused by various reasons, with a high probability of hereditary factors. In idiopathic, autoimmune and genetically determined origin of POI, familial and sporadic forms are distinguished. Familial forms account for 4-31% of POI cases. Significant variability is the result of data inaccuracy: a careful assessment of the probands' anamnesis reveals that familial aggregation of POI is much less common. In a Dutch study by Y.M. van Kasteren [12], 63 patients with idiopathic POI were examined. The frequency of the familial form was 12.7%. The risk of developing POI in other relatives with the familial form of the syndrome varies from 100% (complete penetrance) to 1% (as in sporadic cases). As a rule, the etiology of the disease remains unknown - idiopathic POI dominates in the morbidity structure. Sporadic development of idiopathic POI is observed in 81-87.3% of cases, familial aggregation - in 12.7-19% [12, 13]. Genetic factors are assumed in the aggregation of 2 or more cases of POI in a family [12]. Hereditary diseases are divided into 3 types: - chromosomal diseases, which are caused by the absence, excess or disruption of the structure of chromosomes, which significantly disrupts the function of many genes

(Shereshevsky-Turner syndrome); - monogenic diseases caused by a mutation of a single gene. These diseases are characterized by Mendelian inheritance - autosomal dominant, autosomal recessive and X-linked; - polygenic diseases, which are caused by the interaction of several genes and external factors. In POF, a normal karyotype (46, XX) is quite often present, karyotype anomalies are detected only in 2.4-13% of women under 30 years of age. The most typical are monosomy (X0), deletions and translocations of the X chromosome, which allows for spontaneous puberty in 3-7% of patients with Turner syndrome. Cases of spontaneous pregnancy in Turner syndrome are extremely rare. A typical variant of gonad formation for patients with Turner syndrome during the period of intrauterine development is as follows: the laying of germ cells occurs normally, accelerated depletion of the follicular pool begins from the 20th week, and according to one hypothesis, follicles are already absent in the ovaries by birth, according to another, atresia is completed by the beginning of the puberty period, and the ovaries are strands (streak). It is obvious that 2 full-fledged X chromosomes are necessary for the development and functioning of the ovaries. Critical regions for the formation of POF are located in the region of the short arm of the X chromosome Xp 11.2-22.1 [14], and in 2 regions of the long arm POF1 in the region Xq26-q28 [15] and POF2 in Xq13-q21 [16]. Almost 50% of cases of primary amenorrhea are the result of karyotype abnormalities; when POF manifests itself at the age of 30-39 years as secondary amenorrhea, karyotype abnormalities are extremely rare [17]. Familial cases of POF in patients with a normal karyotype suggest their monogenic nature (caused by a mutation of one gene). The genes of interest are autosomal, involved in the regulation of differentiation and function of the gonads: the autoimmune regulator gene (AIRE), the FSH receptor gene (FSHR), the inhibin A gene (INHA), the bone morphogenetic protein 15 gene (BMP15), the forkhead transcription factor gene (FOXL2), the galactose-1-phosphate uridyltransferase gene (GALT), the family of genes associated with leukodystrophy and ovarian failure (EIF2B). When analyzing pedigrees, the most common is the autosomal dominant sex-linked type of inheritance or X-linked with incomplete penetrance, the autosomal recessive type of inheritance is less typical [12, 13]. The boundary between normal gene variability and mutation is quite transparent. A striking example of the conventionality of the boundaries between the norm and pathology is the variability of the number of trinucleotide repeats (CGG) of the FMR1 gene, located on the long arm of the X chromosome in the Xq27.3 region. The expansion of trinucleotide repeats (CGG) of the FMR1 gene has become a classic example of this phenomenon and the reason for introducing the concept of "premutation".

In approximately 4% of women with the 46, XX karyotype, POI is a consequence of autoimmune destruction of tissues involved in steroidogenesis [14, 15]. Autoimmune lymphocytic ovarian oophoritis, which leads to impaired steroidogenesis

in the ovaries, is quite clearly associated with adrenal insufficiency of autoimmune genesis (Addison's disease, primary chronic adrenal insufficiency - 1-CAI) [16, 17]. In general, the number of patients with POI caused by autoimmune damage is small (4%), but this group of patients should be clearly identified: they are the ones at risk of developing a potentially life-threatening condition - 1-CAI [17, 18, 19]. With a combination of POI and 1-CAI of autoimmune genesis, the manifestation of the autoimmune disease in 9 out of 10 cases begins with ovarian insufficiency [39]. In clinical practice, the possibility of clarifying the autoimmune nature of POF for prognostic purposes is of undoubted interest: the development of POF as an independent pathology or its development within the framework of APS. The autoimmune nature of the disease can be established by identifying organ-specific autoantibodies1, using the indirect immunofluorescence method. Specific markers for detecting antibodies to ovarian steroidogenesis enzymes are currently absent [19, 20]. Determination of antibodies to adrenal steroidogenesis enzymes allows not only to identify women with subclinical forms of 1-CNI before the development of acute adrenal insufficiency, but also to identify those who have a high risk of developing it in the near future [21, 22]. In 2% of patients with premature ovarian failure, there is asymptomatic 1-CNI with a real risk of developing acute adrenal insufficiency. The lack of adequate therapy for 1-CNN during pregnancy is associated with a high probability of severe complications in the fetus and mother (prenatal death of the fetus and acute adrenal insufficiency in the mother in the postpartum period) [22]. Timely detection of 1-CNN is of fundamental importance when using assisted reproductive technologies.

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