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PREMATURE OVARIAN FAILURE: PATHOGENESIS, CLINICAL MANIFESTATIONS AND TREATMENT OPTIONS

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Annotation: Premature ovarian failure (POF) or premature ovarian failure is one of the most common reproductive disorders in women under 40. The condition is characterized by cessation of menstruation, hypoestrogenism, and increased gonadotropin levels, which leads to infertility and other systemic disorders. The article discusses current concepts of the pathogenesis of POF, including genetic, autoimmune, and iatrogenic factors. The data of a comprehensive examination of 138 patients are analyzed, as well as the effectiveness of various approaches to restoring fertility - from hormonal therapy to the use of assisted reproductive technologies and experimental methods, such as ovarian tissue transplantation and the introduction of mesenchymal stem cells. Particular attention is paid to diagnostic criteria, prospects for individual treatment, and the need for an interdisciplinary approach. The findings highlight the need for early diagnosis and the development of new therapeutic strategies aimed at improving the prognosis in women with POF.

Keywords: Ovarian failure syndrome, premature ovarian failure, follicle-stimulating hormone, anti-Müllerian hormone, infertility, reproductive function, oocyte donation, assisted reproductive technologies, hormonal therapy, stem cells

Introduction

Ovarian insufficiency syndrome (OIS), also known as premature ovarian failure (POF), is one of the most complex and socially significant problems of reproductive medicine. It is characterized by the loss of ovarian function before the age of 40, accompanied by amenorrhea, hypoestrogenism and increased levels of gonadotropins, especially follicle-stimulating hormone. The prevalence of this condition, according to various sources, ranges from 1 to 3% among women of reproductive age. Despite the external clinical similarity with natural menopause, the pathogenetic basis of POF is significantly different, suggesting a complex mechanism including genetic, autoimmune, iatrogenic and idiopathic components.

The development of POF leads not only to infertility, but also to early aging, osteoporosis, cardiometabolic disorders and deterioration of the quality of life of women. In recent years, both the molecular mechanisms underlying premature ovarian failure and innovative approaches to restoring fertility, including assisted reproductive technologies, activation of the ovarian reserve, ovarian tissue transplantation and the use of mesenchymal stem cells, have been intensively studied. The present study is aimed at studying the clinical and hormonal features of POF, diagnostic criteria and the effectiveness of modern approaches to the treatment and restoration of reproductive potential in women with this pathology.

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Materials and methods

The study included 138 women aged 22 to 40 years with a clinically confirmed diagnosis of ovarian failure syndrome who sought treatment at the Center for Reproductive Medicine at a multidisciplinary university hospital between 2020 and 2024. The inclusion criteria were persistent amenorrhea for at least 4 months, FSH levels above 25 IU/L in two different measurements at least a month apart, a decrease in estradiol below 50 pg/ml, and the absence of active follicular growth according to ultrasound monitoring. Patients with chromosomal aberrations, a history of radiation or chemotherapy, and patients with severe somatic diseases were excluded from the study.

A comprehensive analysis of anamnestic, clinical, hormonal and instrumental data was performed. The levels of FSH, LH, estradiol, AMH, prolactin, TSH and antibodies to ovarian cells were assessed. Ultrasound was performed transvaginally with counting of antral follicles in both ovaries. Genetic testing included karyotype analysis and molecular diagnostics for mutations in the FMR1, FOXL2 and BMP15 genes. In patients with a possible autoimmune component, tests were performed for antibodies to the adrenal glands and thyroid gland.

To assess the effectiveness of treatment, various therapeutic approaches were used: hormone replacement therapy, attempts at ovarian stimulation followed by IVF programs, the use of experimental methods of ovarian activation and infusions of autologous stem cells, as well as the use of donor oocytes in ART.

Results

The average age of the patients was 32.8 years, with a peak incidence between 30 and 35 years. Amenorrhea was observed in 81% of patients, oligomenorrhea in 19%. The average FSH value was 47.6 ± 12.4 IU/L, the estradiol level was 32.1 ± 8.7 pg/mL. Anti-Müllerian hormone was below the threshold level in 86% of cases, in the rest it was about 0.2–0.5 ng/mL. Ultrasound revealed the absence of follicles in 63% of women, and 27% had single antral follicles. Autoantibodies to ovarian tissue were detected in 18% of patients, to the adrenal glands in 12%, and to thyroid peroxidase in 21%.

Genetic disorders were detected in 8% of patients, including mosaic form of Shershevsky-Turner syndrome, FMR1 gene premutations, FOXL2 and NR5A1 mutations. In 58% of cases, the etiology of POF remained idiopathic. During an attempt to stimulate ovulation, a complete response was recorded only in 6 patients, and only in 2 cases it was possible to obtain oocytes. IVF programs using their own gametes were effective in 2 patients, with a clinical pregnancy occurring in one case. In 31 cases, a donor egg was used, which resulted in a clinical pregnancy in 61% of cases and a live birth in 54%. In 7 patients, laparoscopic activation of ovarian tissue after removal of the cortex was performed, which in one case led to spontaneous follicular growth and successful IVF.

Experimental administration of autologous mesenchymal stem cells isolated from bone marrow and adipose tissue was performed under an ethically approved protocol in 4 women, with 2 of them experiencing an increase in estradiol levels and the onset of menstruation for 3 months. However, spontaneous conception was not achieved. The use of hormone replacement therapy significantly

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improved general well-being, normalized bone mineral density and lipid profile parameters. However, withdrawal of HRT was again accompanied by a decrease in estrogens and a return of symptoms.

Discussion and conclusion

Premature ovarian failure is a multifactorial disease requiring a comprehensive, multidisciplinary approach. Despite the high prevalence of POF, its pathogenesis remains largely unclear, especially in idiopathic cases. The identified hormonal and immunological profiles confirm the involvement of both genetic and autoimmune mechanisms in the development of this condition. Genetic testing, despite its complexity and limited availability, should become part of the standard diagnostics in young women with POF, especially in those with a family history.

Today, restoring fertility in patients with ovarian failure is a serious task. The use of one's own oocytes is possible only in rare cases when there is residual ovarian function. The most effective method remains the use of donor eggs within the framework of ART programs, but this decision is associated with a number of ethical, psychological and legal aspects. The directions associated with the transplantation of cryopreserved ovarian tissue and the use of stem cells remain promising, but these methods require further research and standardization.

Early detection of POF, psychological support for patients, individualized choice of therapeutic strategy and development of innovative reproductive technologies remain key tasks of modern medicine. Introduction of screening programs and wide informing of women about the risks of premature depletion of the ovarian reserve will allow timely diagnosis of pathology and preservation of the possibility of motherhood.

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