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CAUSES, DIAGNOSTICS AND PSYCHOLOGICAL IMPACT OF PREMATURE OVARIAN INSUFFICIENCY- REVIEW OF LITERATURE

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ABSTRACT

Premature ovarian insufficiency (POI) before the age of 35 occurs in 1 in 250 women. It can develop on a genetic basis, but also may be a consequence of iatrogenic interventions, such as surgery, radiation or chemotherapy. The patients with impaired ovarian endocrine function may experience disruptive menopausal symptoms. Estrogens deficiency consequences include increased risk of osteoporotic fractures and cardiovascular events. Lack of folliculogenesis and ovulation results in infertility. Detailed review of the literature was conducted to summarize current knowledge about causes, diagnostics, psychological impact and novel therapeutic methods in POI. Review of the literature was conducted by searching the PubMed database and Google Scholar. Checking the literature was carried out by the following keywords: 'premature ovarian insufficiency', 'POI', 'etiology', 'symptomatology', 'treatment', 'pathogenesis', 'genes', 'mutations', 'psychological effects', 'oncofertility'. The multifactorial aetiology of POI, including genetic, autoimmune, iatrogenic, and environmental factors,

highlights the complexity of this condition and the need for a multidisciplinary approach to diagnosis and treatment. Progress in molecular methods of genetic diagnostics, such as whole-genome sequencing, may help identify causative mutations in a larger proportion of idiopathic cases. Hormonal replacement therapy is the gold standard for alleviating menopausal symptoms, maintaining bone density, and reducing cardiovascular risk. The psychological impact of POI cannot be underestimated, with many patients experiencing significant emotional distress and dissatisfaction with the manner in which their diagnosis is delivered. Healthcare providers must prioritize sensitive and informative communication, while also referring patients to appropriate sources of emotional support.

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Introduction.

Premature ovarian insufficiency (POI), previously known as a premature ovarian failure (POF) is a clinical and pathophysiological term, which refers to lack of endocrine and reproductive functions of female gonads. Clinical presentation of patients is similar to physiological state of menopause, but POI applies to patients under 40 years old. Incidence of POI according to the most up to date statistics is 1:250 cases at the age of 35 and 1:100 cases at the age of 40 years [1]. Differences in incidence ratio depends on ethnicity. Regarding to Study of Women's Health Across the Nation (SWAN) prevalence of POI is 0,5% of Chinese, 1% among Caucasian, 1,4% of African American, and 1,4% of Hispanic women. In general, this condition occurs in 1-3,7% of women under 40 years of age [2][3].

POI manifests with menopausal symptoms, such as oligomenorrhoea or amenorrhoea, hot flushes, vaginal dryness, dyspareunia, decreased sexual desire, heart palpitations, mood swings, insomnia, cognitive decline and fatigue. Moreover, patients experience broad spectrum of problems with fertility. The basic mechanisms of this symptoms include hypergonadotropic hypogonadism associated with high serum follicle-stimulating hormone (FSH) and luteinising hormone (LH) level with low serum 17-beta-estradiol level. As an effect of decreased ovarian sex-steroids production, the hypothalamus-hypopituitary-ovarian axis is overstimulated in mechanism of positive feedback loop. Long-term estrogens deficiency may result in increased cardiovascular risk and decreased bones density, leading to severe osteoporotic fractures. In addition, accelerated follicle depletion in POI results in infertility.

European Society of Human Reproduction and Embryology (ESHRE) guidelines indicates that POI diagnosis may be based on measurements of serum FSH and LH levels two times in 4-weeks interval. Levels of gonadotropins above 25 mIU/l in patients with oligo- or amenorrhoea, which persists at least 4 months, will confirm diagnosis [4].

POI should be considered as a spectrum, including biochemical phenotype with increased level of FSH, infertility, decreased ovarian reserve and eumenorrhoea, or full phenotype, when biochemical indicators are accompanied by absence of normal menstrual bleeding [5].

Mechanisms and causes of premenopausal ovarian insufficiency are investigated by researchers for decades. Simultaneously with molecular and advanced genetic methods development, knowledge about POI is increasing rapidly. Despite that, conclusive aetiology remains unknown in over 70% of cases [6].

The purpose of this review is to establish current, the most up-to-date knowledge about aetiology, diagnostic tools, and treatment methods in premature ovarian insufficiency. It also assumes checking literature for latest findings about genetic causes and experimental treatment method, such as stem cells

(SCs). Moreover, assessment of reports about e-cigarettes impact on ovarian function was performed, as they usage became warning phenomenon among young population.

Material and methods.

Review of the literature was conducted by searching the PubMed database and Google Scholar. Checking the literature was carried out by the following keywords: 'premature ovarian insufficiency', 'POI', 'etiology', 'symptomatology', 'treatment', 'pathogenesis', 'genes', 'mutations', 'psychological effects', 'oncofertility', 'stem cells'. This analysis excluded articles published before 2005. Eligibility criterium was full-text articles published in English or Polish language.

Results.

Aetiology.

Causes of POI may be divided into few groups: genetic, autoimmune, toxic, infectious, induced by chemotherapy, radiation therapy, surgery and other factors, such as weight, socioeconomic status or parity. Unfortunately, in more than 70% of POI cases the etiology remains unknown [7].

Genetic defects are the most numerous group of factors and include both chromosomal defects and single gene mutations affecting folliculogenesis, steroidogenesis or gonadotropin receptors functions. Turner syndrome (monosomy of X chromosome), which occurs in 1 per 2500 live births dominates in the first group and it is the most common genetic cause of POI [8]. Although ovaries in Turner syndrome in most cases are replaced by connective tissue, pregnancy in women with Turner syndrome is possible with either autologous, especially in mosaic karyotype, or donated oocytes.

Structural defects of X chromosome, such as deletions, inversions, duplications or translations may also contribute to POI development. Other well-known cause is fragile X syndrome, which is one of the most common causes o mental disability worldwide. Female carriers of fragile X syndrome permutation (FMR1 gene) have an earlier menopause compared with control group, while their neurodevelopmental growth remains unaffected. The age of menopause is dependent on the permutation repeat length. Fragile X Mental Retardation 1 gene mutation is detected in 2-5% cases of POI and in 14% of familial POI cases [9].

Due to the substantial prevalence of Turner syndrome and fragile X permutations, its testing is recommended for women with non-iatrogenic POI.

Association with impaired folliculogenesis or ovarian failure has been described in literature for over 80 of genes and the list is not closed yet [10]. Isolated POI may be a result of AFF2, BMP15, CSB-PGBD3, CYP17A1, EIF4ENIF1, FSHR, HFM1, MCM8, MCM9, NANOS3, NOBOX, PGRMC1, POF1B, SOHLH1, STAG3 and SYCE1 genes mutations. These genes are responsible for proper meiosis process, apoptosis, steroidogenesis or DNA repair. POI may also be a part of more complex clinical entities or diseases, such as leukodystrophy (AARS2 gene), ataxia teleangiectasia (ATM gene), Bloom syndrome (BLM gene), Perrault syndrome (CLPP gene), ovarioleukodystrophy (group of EIF2B genes), Fanconi anemia (group of FANC genes), Werner syndrome (WRN gene), Nijmegen breakage syndrome (NBN gene) or Rothmund-Thomson syndrome (RECQL4 gene) [11]. Moreover, ovarian failure is characteristic part of clinical presentation in women with galactosemia. It is worth mentioning that mutation of LMNA gene, which directly causes cardiomyopathy, may also contribute to ovarian failure.

Coexistence of both characteristic ophtalmological phenotype and premature ovarian insufficiency in women with blepharophimosis, ptosis, epicanthus inversus syndrome type 1 (BPES) is another example, that multidisciplinary cooperation is required to proper diagnostics and treatment of young women. They struggle with infertility and menopausal symptoms, but also symptoms from other body systems. BPES syndrome is a result of located on the long arm of third chromosome FOXL2 gene mutation. FOXL2 gene product is essential for proper development of orbital muscles and palpebras, but it also regulates function of granulosa cells and takes part in folliculogenesis [12]. Moreover, FOXL2 has a direct effect on anty-mullerian hormone (AMH) production [13].

Recently conduced research revealed new genes, which may be associated with ovarian function and signal pathways regulation. Findings of Hsieh TB et al, demonstrate that the loss of calponin 2 encoded by the Cnn2 gene impairs ovarian folliculogenesis with premature depletion of ovarian follicles [14].

Mentioned new findings may contribute to further investigations on the pathogenesis of POI as well as development of new therapeutic methods. It is estimated that whole-genome sequencing would help identify almost 30-35% causes in idiopathic cases [6].

Heterogenous aetiology of POI include also autoimmune response defects, which may occur in 5-17% of POI cases [7]. Presence of lymphocytic oophoritis associated with other autoimmune disorders and steroidogenic cell autoantibodies indicates autoimmune basis. Mechanisms of autoimmune oophoritis remains unknown, but it is possible, that this phenomenon is caused by molecular mimicry of various pathogens and ovarian tissue antigens. Clinical manifestations include enlarged and cystic ovaries, which are gradually destructed in the course of the disease and at the end become atrophic. Depletion of the follicles is also observed. Other characteristic features of autoimmune oophoritis, which differs it from other causes of POI is normal serum inhibin B and LH concentration level. These findings lead to conclusion, that only theca cells are destructed by autoimmune process [15].

It was documented, that approximately 10% of female patients affected by Addison's disease develop POI. On the other hand, the risk of adrenal insufficiency development in women with POI is 300 times higher in comparison with general population [16]. Testing for antiadrenal and 21-hydroxylase autoantibodies may help to identify women with autoimmune POI. Ovarian insufficiency may also present as a part of autoimmune polyglandular syndrome 1 (APS-1) resulting from AIRE gene mutation. In APS-2, it coexists with thyroid diseases, diabetes mellitus, myasthenia gravis or celiac disease. Nevertheless, the most common autoimmune disorder, which may be present with POI is hypothyroidism. Screening for thyroid disease by identifying abnormalities in thyrotropin (TSH) serum level or presence of antithyroid antibodies is very helpful in this population of patients.

It is worth mentioning, that the presence of the autoimmune disorder is not determining the presence of autoimmune aetiology of POI.

In the era of rapidly growing incidence of neoplastic diseases among young population, oncological patients remain the special group of patients with ovarian insufficiency. Advanced chemotherapy and radiotherapy or surgical treatment, which allows longer survival or even complete healing, concomitantly affects quality of life and fertility. From chemotherapeutic drugs, alkylating agents such as cyclophosphamide or melphalan are characterised by the highest ovarian toxicity. Therapy with procarbazine, dacarbazine or doxorubicin also affects ovarian function and future fertility. Relatively safe for reproductive system functions are antimetabolites (methotrexate, fluorouracil) and vinca alkaloids (vinblastine, vincristine) [17].

Significance of tobacco smoke toxins in POI is also worth mentioning. The well-known consequence of smoking is early menopause in cigarette smokers in comparison to nonsmokers. Moreover, it is well documented that conventional cigarettes cause disruption in hypothalamic-pituitary-gonadal axis, alteration of FSH and LH levels, reduction of ovarian reserve, negative impact on oocyte morphology and increased risk of anovulation.

Electronic cigarettes usage among young, reproductive age population is nowadays very worrisome phenomenon. Devices, which were considered as a "safer" substitute for conventional cigarettes, may cause serious health consequentions. They contain nicotine and more than 80 ingredients including flavouring compounds, heavy metals, carbonyls such as formaldehyde or phenols in liquids and aerosols [18]. Despite of circulatory and respiratory system effects, e-cigarettes may have an impact on male and female reproductive system as well. Nicotine disruptive role on ovarian function is similar to conventional cigarettes described above. In animal studies, increased apoptotic cell numbers and inflammation levels in the ovaries was well established [19]. The exposure to formaldehyde resulted in dramatic decrease in follicle number in rat ovaries [20]. More studies in humans are required to establish a negative role of e-cigarettes on female gonads, but for now, this alarming phenomenon can not be underrated.

Treatment.

Hormone replacement therapy.

According to current knowledge, POI has been reported to reduce quality of life and life expectancy, so it is essential to start proper hormone replacement therapy (HRT). It can alleviate both vasomotor and genitourinary symptoms [21]. Other multiple health risk, such as decreased bone density with increased risk of life-threatening fractures and increased cardiovascular risk are also addressed by using appropriate hormone therapy. It is recommended to use HRT formulations, that mimic normal

ovarian hormone production. Therapy should be continued until the normal age of natural menopause [22]. 17-beta-estradiol (1-2 mg daily) in oral form is preferred. For patients with POI associated with some additional conditions, such as obesity or hypertension, transdermal estradiol is recommended [21]. To avoid increased risk of endometrial hyperplasia and cancer, estrogen should be combined with oral micronized progesteron (100-200 mg daily, but only for 12-14 days per month). Alternatively medroxyprogesterone acetate (2,5-5 mg daily) may be used. Exclusion criteria for hormonal therapy include estrogen-dependent malignancy, uterine bleeding of unknown orifice, and history of thromboembolism. Data from randomized, placebo-controlled trial indicates that also testosterone replacement may be beneficial and enhance effects of estrogen therapy on sexual function in women with POI caused by oophorectomy [23].

Findings of latest studies revealed, that physiologic hormone replacement (100-150 ug/d transdermal E2 plus cyclic progestin) was superior to oral combined contraception in increasing lumbar spine bone marrow density [24]. It is essential to provide women with information, that adequate calcium and vitamin D intake with regular physical activity may contribute to maintain proper bone density. Desired vitamin D level is >30 ng/mL. Recommended dose of cholecalciferol is 1000-2000 IU per day. Women with POI should take 1200 mg of elemental calcium daily [25].

The current knowledge about negative impact of estrogen deficiency on cardiovascular system is well established [26]. Women with POI have a higher risk of ischaemic heart disease, cardiovascular and overall mortality compared with age-matched healthy women. Along with life-style modifications, treatment with the use of HRT improves endothelial function and decreases cardiovascular risk.

Multiple observational studies indicate that women with early ovarian insufficiency have increased risk of impaired cognitive function, developing dementia and Parkinson's disease. It is another argument, that hormone replacement therapy should be considered to reduce the risk of cognitive impairment, at least to the natural age of menopause [27].

Fertility.

Chances for spontaneous pregnancy for women with POI without treatment are very low (5-10%) [28]. Ovulation induction in these women is ineffective and should not be recommended. Donation of oocytes followed by in vitro- fertilisation is gold standard and the best option for women with POI, who struggle with infertility. Second approach is informing the patient about adoption possibilities. However, patients often desire genetic offspring, so stem cells (SCs) with their regenerative potential may be promising therapeutic option in this indication. The postulated mechanisms of SCs involve paracrine, proangiogenetic, anti-apoptotic, anti-fibrotic and immunomodulation effects. Animal studies findings indicate, that mesenchymal stem cells may differentiate into granulosa cells and potentially restore endocrine function and folliculogenesis in rodents [29][30]. Another type of stem cells, called embryonic and derived from the inner cell mass of the blastocysts, can restore hormone secretion and reproductive function in a chemotherapy-induced POI mouse model.[31] Promising studies were conducted in humans and reported live births after bone marrow-derived mesenchymal stem cell transplantations [32][33][34]. Interesting findings were described by Zafardoust S et al.in 2020. Autologous Menstrual Blood Mesenchymal Stem Cells (MenSCs) injection in 15 women with POI resulted in pregnancy in 7 of them [35]. Significant progress in understanding SCs mechanisms and potential therapeutic application has been made, but more advanced human studies are necessary to establish their future role in POI. At this moment, over 12 different clinical trials of stem cell therapy for treating POI are conducted [36].

Intraovarian Injection of Platelets Rich Plasma has been documented as a novel, promising approach for treating POI. Prospective study by Y. Cakiroglu et al., reported a pregnancy rate of 20,5% in women treated with intraovarian injection of autologous platelet rich plasma before IVF attempt [37].

Ovarian Tissue Cryopreservation (OTC) and Autotransplantation remains one of the best protocols for patients with cancer, who want to protect their fertility before gonadotoxic or surgical treatment. Data from the meta-analysis indicate, that over 40% of patients successfully delivered at least one child after OTC with autotransplantation [38].

Psychological effects management.

The latest guidelines underline, that health professionals should consider POI in terms of the mental, emotional and psychosexual health. Firstly, hormonal imbalance itself has a disruptive effect on a patients well-being.

Secondly, POI diagnosis is associated with negative stereotypes regarding to the process of menopause and the stigma of infertility. Women with POI may experience feeling of loss of their possibility to fulfil as a mother and loss of femininity. These factors have an additional effect on self-esteem, body-image and the ability to form long-term, intimate relationships [39]. Due to psychological distress, the process of providing information and diagnosis should be careful and gentle. A cross-sectional study conducted by Groff A.et al, revealed that over 70% of women with POI were unsatisfied or very unsatisfied with the manner in which they were informed about the diagnosis. 84% of women felt they were unprepared to receive the diagnosis from an emotional perspective. Feelings associated with first hearing about diagnosis reported by study group include: confusion, depression, anxiety, emptiness, loss, shock, anger, denial, relief and curiosity. Moreover, a large number of women complained that they have trouble finding reliable information about disease. Only 8% reported being referred to sources of emotional support (psychologist, support group) [40]. The recommended approach to inform patients about diagnosis was described by Buckman [41]. It includes establishing patients knowledge about disease, finding out how much the patient wants to know, sharing the information and responding to the patient's feelings, as well as planning future treatment and management. It is suggested, that "warning shot" (for example statement "I have some bad news for you") before receiving information may be helpful for a patient to deal with difficult diagnosis.

Discussion.

Premature ovarian insufficiency remains a significant challenge for women of reproductive age, with wide-ranging impacts on physical and mental health, fertility, and overall quality of life. The multifactorial etiology of POI, encompassing genetic, autoimmune, iatrogenic, and environmental factors, highlights the complexity of this condition and the need for a multidisciplinary approach to diagnosis and management.

Advances in genetic testing, such as whole-genome sequencing, hold promise for identifying causative mutations in a larger proportion of idiopathic cases. Hormone replacement therapy remains the cornerstone of treatment for alleviating menopausal symptoms, maintaining bone density, and mitigating cardiovascular risk. However, research into novel therapeutic approaches, such as stem cell therapy and intraovarian injection of platelet-rich plasma, offers hope for restoring ovarian function and fertility in affected women.

The psychological impact of POI cannot be overlooked, with many women experiencing significant emotional distress and dissatisfaction with the manner in which their diagnosis is delivered. Healthcare providers must prioritize sensitive and informative communication, while also connecting patients with appropriate sources of emotional support.

Conclusions.

POI presents a complex and multifaceted challenge that requires ongoing research, clinical innovation, and patient-centered care. By advancing our understanding of the underlying mechanisms, developing targeted therapies, and providing comprehensive support to affected women, we can work towards improving outcomes and quality of life for those living with this condition.

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Declaration of Interest Statement.

The authors declare that they have no conflict of interest.

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