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UDC: 612.621:618.11-02]:612.017
DOI: 10.2298/VSP1311051D

Premature ovarian failure: immunological aspects and therapeutic strategies

Prevremeno otkazivanje funkcije jajnika: imunološki aspekti i terapijske strategije

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Key words:
ovarian failure, premature; autoimmunity; drug therapy.

Ključne reči:
jajnik, prevremeno otkazivanje funkcije; autoimunitet; lečenje lekovima.

Introduction

Premature ovarian failure (POF) is one of the most enigmatic and challenging conditions in reproductive medicine, that requires multidisciplinary approach and management. POF generally describes a syndrome consisting of amenorrhea, sex steroid deficiency, and elevated levels of gonadotropins in a woman aged more than two standard deviations below the mean age at menopause estimated for the reference population [1]. Infertility and psychological stress are common consequences of this entity, the prevalence of which is 0.9–3%. It is estimated to affect about 1% of women younger than 40, 0.1% of under 30 and 0.01% of women under the age of 20 [2, 3]. POF, premature ovarian insufficiency (POI), premature menopause, premature dysfunction (POD), or hypergonadotropic hypogonadism is one of the most enigmatic disorders. This condition is not irreversible and permanent due to the presence of residual oocytes capable of recruitment and fertilization. Therefore a more appropriate term for this condition might be POD, sygnifying a premature decline, rather than a failure in ovarian function, below the limit associated with fertility and steroidogenesis [4].

Classically, ovarian failure can be considered under the headings of genetic (X-chromosome anomalies; specific genetic mutations referred to oocyte, enzymes, or hormone receptors), autoimmune and environmental causes (viral infection, chemotherapy, radiotherapy, and pelvic surgery). In most cases, however, no precise cause can be identified, and these forms are referred to as idiopathic [5]. Numerous evidence, including association with multiple autoimmune endocrine disorders, clinical reversibility, transitory estrogen deficiency, histological and immunological features and the demonstration of circulating ovarian antibodies in serum samples from women with POF, have suggested its immunological origin. Between 10 and 30% of women with POF have a concurrent autoimmune disease, the most commonly reported being hypothyroidism, and the most clinically important hypoadrenalism, as well as association with myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Crohn's disease has been reported. For many women in whom the cause of ovarian failure is unknown, autoimmunity may be the pathogenic mechanism, as a primary or secondary immune dysfunction process against the ovaries [6, 7].

Autoimmune involvement in premature ovarian failure

The main function of the immune system is to distinguish between self and non-self. Malfunction of down-regulating controlling mechanisms may result in an excessive autoimmune response against self, i.e. an autoimmune disease [8]. Premature ovarian failure can occur as a result of primitive reduced pool of oocytes accelerated follicular atresia; or impaired folliculogenesis. An exaggerated autoimmune reaction involved in atretic acceleration, oocyte wastage or impaired folliculogenesis first described an association between an autoimmune adrenal deficiency and POF [9]. Autoimmune attack might be general or in most instances, partial, reversible, and responsible for, in many cases, fluctu-

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ating course of POF [6, 10]. However, the reality of such autoimmune process, its exact role in ovarian failure, the antigen determinant(s) of ovarian antibodies and cellular immunity, and the efficiency of immunosuppressive therapy should be further clarified.

Physiological role of the immune system in ovarian function

Unlike the testis, the ovary is not an immunologically privileged site. Several immune cells are recruited by the ovaries during the menstrual cycle such as macrophages, lymphocytes and polymorphonuclear granulocytes. These cells are able to secrete cytokynes, which participate in the paracrine regulation of follicular development, ovulation and luteal function. Cytokines modulate gonadotropin-mediated control of ovarian function and generally act in an inhibitory fashion. Tumor necrosis factor-α (TNF-α) secreted by ovarian macrophages is an inhibitor of steroidogenesis, and with proinflammatory cytokine, interleukine 2 (IL-2) decreases corpus luteum function and acts in a cytotoxic manner [11]. Ovulation has been considered an inflammatory process including both leukocytes and cytokines. Therefore, it is logical to consider that abnormalities of this process could perturb ovarian function and be involved in POF by accelerating follicular atresia or by disturbing folliculogenesis.

Clinical aspects of premature ovarian failure

It has long been recognized that POF could be associated with nearly all organ-specific autoimmune diseases, as well as with several autoimmune diseases in the same patients, referred to as autoimmune polyglandular syndrome (APS) [6, 7, 12]. APS-I, also called autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) is a rare autosomal recessive disease caused by mutation in the autoimmune regulator (AIRE) gene, and without any association with a specific human leukocyte antigen (HLA) haplotype [13, 14]. It mainly affects children, and is associated with mucocutaneous candidiasis, ectodermal defects, hypoparathyroidism, Addison's disease, and POF that occurs in 40-60% of cases [14, 15]. APS-II, also called Schmidt-Carpenter syndrome, an autosomal dominant disease, linked to chromosome 6, and associated with HLA B8DR3DR4, comprises Addison's disease, insulin-dependent-diabetes, hypothyroidism and POF with the prevalence of which is 10-25% [7, 16]. APS-III is quite similar to APS-II, except there is no adrenal deficiency, but other autoimmune diseases, such as anemia perniciosa or vitiligo are often associated [17].

Because of a particular association with Addison's' disease, three different situations have to be distinguished: POF associated with adrenal autoimmunity; POF associated with non-adrenal immunity (most frequently associated with thyroid autoimmunity); and isolated, idiopathic POF, the latter which cannot exclude an autoimmune mechanism, possible provoced by environmental factors [18]. Transitory estrogen deficiency, higher anti-Mullerian hormone and inhibin levels (useful ovarian peptides in the assessment of follicular reserve); higher spontaneous recovery of ovarian cycles; and/or spontaneous pregnancy, under hormone replacement therapy (HRT), or without any treatment, suggest a partial, reversible autoimmune attack, particularly in idiopathic POF with a variable degree of ovarian function preservation [5, 19, 20]. Cases of POF associated with antiadrenal autoimmunity represent a homogeneous and well-characterized subgroup of ovarian failure, whereas in other forms of this disease, there is a large diversity in clinical, immunological and histological features.

Immunological features of autoimmune premature ovarian failure

The detection of autoantibodies directed against various ovarian targets strongly supports the hypothesis of an autoimmune aetiology of POF. Different autoantibodies were found in different clinical features of autoimmune POF. POF patients associated with adrenal autoimmunity commonly presented with autoantibodies that recognize several types of steroid-producing cells of the adrenal cortex, testis, placenta and ovary, therefore called steroid cell antibodies (SCA), with the prevalence of which is ~ 60% in APS-I patients; 25–40% in APS-II patients; and almost 78–100% in patients with both Addison's disease and POF [6, 10, 21]. These findings support the idea of a shared autoimmune response in ovarian and adrenal autoimmunity. In POF patients not associated with adrenal autoimmunity, as well as in isolated, or idiopathic POF, the prevalence of SCA remains < 10%. In those patients other autoantibodies could be found, divided into non-ovarian, and ovarian autoantibodies. Thyroid autoimmunity is the most prevalent (25–60%) associated endocrine autoimmune abnormality reported in POF patients without an adrenal autoimmune involvement, and with the presence of high levels of non-ovarian, thyroid peroxidase antibodies, leading to clinical/subclinical hypothyroidism development [1, 22, 23]. Antiovarian autoantibodies (AOA) are usually considered to be a suitable, and independent marker of autoimmune ovarian disease, although their specificity and pathogenic role is questionable. Evidenced data that AOA have been detected in ~ 30–60% of POF patients (particularly idiopathic POF patient), often appearing before the onset of clinical symptoms, with a possibility of prediction future ovarian failure in women with unexplained infertility, support its possible role as a marker either, of a primary, or secondary immune dysfunction process against the ovaries [15, 19, 24, 25]. There are several other autoantibodies towards specific ovarian targets potentially mediated autoimmune damage in POF: 3β-hydroxysteroid dehydrogenase autoantibodies, particularly found in isolated idiopathic POF; gonadotropin receptors autoantibodies; zona pellucida autoantibodies; as well as anti-oocyte cytoplasm antibodies towards maternal antigen that embryos require (MATER) [6, 13, 19].

Recently, authors pointed to the concept of functional autoantibodies (stimulating and/or suppressive) control in autoimmune diseases, particularly those comprising "sister-organs", such as the ovary, thyroid and adrenal glands [26]. Abnormalities of the cellular immunity, i.e. T lymphocytes

(especially effector helper, CD4-positive T cells), macrophages and dendritic cells, also play an important role in autoimmune reactions, particularly in the development of autoimmune lesions, described also in POF, and thus support the autoimmune mechanism of this disease [27, 28].

Histological findings in premature ovarian failure

In those cases where POF is associated with adrenal autoimmunity, histological examination almost always confirms the presence of ovarian follicles with characteristic signs of an autoimmune oophoritis: follicles are infiltrated by inflammatory cells, including lymphocytes, plasma cells, and macrophages; the steroid producing cells being the main target of the immune attack. Only a few patients whose POF is not associated with adrenal autoimmunity presented with typical oophoritis. The rarity of inflammatory infiltrates in these patients does not exclude the possibility of an autoimmune mechanism. Follicular depletion might be the final stage of primary or secondary autoimmune process directed against ovarian structures. However, systematic histological screening of POF revealed detectable follicles varying from few to numerous in 40% of cases [6, 14]. Hypothetically, autoantibodies to the ovary may have been present in the ovary without reaching detectable levels in the serum or inducing local inflammation.

Management of premature ovarian failure

POF is a delicate condition and a difficult diagnosis for women to accept. Women with POF have unique needs that require special attention. The loss of reproductive capabilities requires multidisciplinary management which includes the provision of proper counseling, nutrition supplement advice, HRT, possible immunosuppressive therapy, and reproductive health care, including contraception and fertility issues [29]. Although in most of the cases POF is idiopathic there is the need for further tests, looking for a specific aetiology, such as autoimmune, and genetic studies, the latter especially important in familial POF. The strong association of POF with APS makes screening for this condition essential [24, 30]. In idiopathic POF full attention must given to the investigation of indirect autoimmune signs, such as association with autoimmune disease (clinical aspect, hormone levels, and antibodies). The recovery of ovarian function may occur after regression of the autoimmune status and control of coexistent endocrine disease. Although ovarian biopsy is gold standard for detecting autoimmune cause of immune ovarian destruction, it is questionable whether it accurately represents the follicular density of the whole ovary, particularly in idiopathic POF, characterized with variable degree of ovarian function preservation [12, 31].

After confirming the diagnosis of POF and optimal assessment of ovarian reserve, including endocrine and ultrasonography markers for evaluation of ovarian volume and follicular pool, the urgent need to determine the optimum therapeutic hormonal regimens is required, both in terms of immediate menopausal symptoms relief and also for the protection against the long-term sequelae of estrogen deficiency, such as osteoporosis [30, 32–34]. In POF patients estrogen expresses dual useful action: the treatment of estrogen deficiency consequences; and the recovery of ovarian function, by restoration of receptor sensitivity to gonadotropins with salutary effect on folliculogenesis and conception, especially important in women seeking fertility [12, 35, 36]. Estrogen expresses crucial role in modulation of neuroendocrine environment to improve reproductive functioning. Dose, type and route of HRT are also very important. Dose should be higher than that used in an older age group, and the most suitable progesterone preparation should be combined with estrogen [35]. Estrogens are generally considered to enhance autoimmunity, through activating effector helper T lymphocytes and macrophages, potentially facilitating the maturation of pathogenic autoreactive B cells and diminishing the production of potentially protective B cells [37]. Oral estrogens appear to increase coagulation activation through procoagulant factors activation and reduction in anticoagulant factors such as antithrombin [38]. Thus transdermal HRT may be preferred in women with coagulant disturbances and more prone to thrombosis, such as patients with thrombophilias. As an essential prohormone in ovarian follicular steroidogenesis dehydroepiandrosterone (DHEA) could be an effective first step treatment of POF in the duration of 2–6 months before starting HRT [39]. Androgen replacement is useful in some instances with clinical signs and symptoms of androgen insufficiency, i.e. hypoactive sexual desire disorder (HSDD) [35, 40].

Immunosuppressive therapy, using different dose and term of glucocorticoids should be considered in a selected population of well-defined autoimmune POF patients, as well as in idioptahic POF patients, in whom the resumption of ovarian activity is possible, spontaneously, under HRT, and/or under immunomodulating treatment [14, 41, 42]. The combination of corticosteroids with pituitary suppression followed by ovarian stimulation with gonadotropins may be also benefitial in restoring ovarian function in patients with idiopathic POF [43, 44]. Other fertility issues should be considered in POF patients seeking fertility, including different regimes of ovulation induction and assisted conception techniques, such as *in vitro* fertilization (IVF) using donor gamets or embryos, or *in vitro* maturation (IVM) of oocytes derived from stem cells or primordial follicles [12, 30, 45].

Conclusion

The major aim in future research is to determine the "unknown etiology group", which represents the majority of POF patients. The pursuit of an autoimmune link offers an exciting research opportunity, with the possibility that some cases of POF might be temporarily reversible with immune suppression. Accepting the concept that POF is a heterogenous disorder in which some of the idiopathic forms are based on an abnormal self-recognition by the immune system will lead to novel approaches in the treatment of infertility in these patients. The ideal treatment strategy for young women with POF poses a clear challeng. Treatment should be multi-

disciplinary and individualized which includes the provision of proper counseling, nutrition supplement advice, HRT, immunosuppressive therapy in a selected population who may benefit from immunomodulatory therapy and possibly recover ovarian function, and reproductive health care including fertility issues. The choice, different needs of these women and individual risk factors must be taken into consideration.

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Received on March 12, 2012.
Revised on June 20, 2012.
Accepted on June 20, 2012.