Premature ovarian failure: immunological aspects and therapeutic strategies


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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, signifying a premature decline, rather than a failure in ovarian function, below the limit associated with fertility and steroidogenesis 4.

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-
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 cytokines, 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 an ovarian function 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 provoked 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. 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 etiology 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, tests, 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 5,22, 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

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 27. 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 be 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 thrombophilies. 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 idiopathic 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 beneficial 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 gametes 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 heterogeneous 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 challenge. Treatment should be multi-

disciplined 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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