

Impact of Autoimmunity on Oogenesis and Ovarian Morphology

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Compromised tolerance to ovarian components can lead to autoimmune oophoritis. Histological examination of affected ovaries reveals a mononuclear infiltrate, in many cases initially restricted to the follicular theca and sometimes associated with polycystic appearance. Autoimmune oophoritis interferes with follicle maturation and eventually diminishes the number of growing follicles, with a corresponding impact on fertility and hormonal secretion. In severe cases, all follicles advanced beyond the primordial stage are destroyed, leading to premature ovarian insufficiency (failure). Among known autoantigens, most important are the components of zona pellucida and of steroidogenic cells. Autoimmune ovarian disease is often associated with Addison's disease. In some cases, it is a manifestation of autoimmune polyendocrine syndrome. Little is known at present about the effects of systemic autoimmune diseases on the ovary, but data from patients and animal models show decreased ovarian reserve.

Key words: autoimmunity, oophoritis, premature ovarian failure, oocyte, fertility

Autoimmune diseases result from loss of normal immune tolerance to self-antigens. Due to the involvement of multiple complex regulatory mechanisms in their etiology and development, they are difficult to diagnose and especially to treat. This review addresses the effects of autoimmune diseases on oogenesis and overall ovarian morphology, which in recent years have been revealed as much more diverse and profound than previously estimated.

Impact of anti-ovarian and other organ-specific autoimmune responses

When discussing the influence of autoimmunity on oogenesis and overall ovarian function, autoimmune responses against ovarian components should be considered first. Autoantibodies against various ovarian antigens are frequently found in sera of women with unexplained infertility, though it is unclear in what proportion of cases they are a causative factor [2]. The phenotype of the positive women varies from asymptomatic (autoantibodies detected in sera of fertile controls) to varying degrees of autoimmune ovarian disease. This disease is manifested as autoimmune oophoritis and is characterized by mononuclear inflammatory cell infiltrate in the theca layer of growing follicles, with early follicles without lymphocytic infiltration [17]. At a later stage, the granulosa

layer can also be invaded, resulting in destruction of growing follicles. Even primordial follicles are eventually either damaged by the lymphocytes and inflammatory cells infiltrating the ovary, or recruited and exhausted. In its extreme form, autoimmune ovarian disease leads to complete abolition of ovarian function and premature ovarian insufficiency (failure), defined as amenorrhea before age 40 [19].

In a comprehensive study of 357 patients with premature ovarian failure, 14.3% showed signs of autoimmunity, though its pathogenetic significance could not be established [1]. Reliable diagnosis of autoimmune oophoritis requires ovarian biopsy, which is performed rarely because of the difficult access to the ovaries and the very limited importance of this diagnosis for the management of the condition [19]. While the role of autoimmunity as a causal factor in ovarian insufficiency is often difficult to estimate in patients, it has been unequivocally established in animal models. For certain mouse hybrids – (C57B1/6Cr x A/JCr)F1 (B6A) and (C3H/HeMs x 129/J)F1 (C31), creating and maintaining immune tolerance to antigens of growing ovarian follicles is problematic and requires the presence of a functional thymus. Neonatal thymectomy of the hybrid females leads to autoimmune oophoritis with rapid loss of oocytes and follicles at early adulthood, which in 60% of animals is complete by the age of 3 months. At a later age (12 months), the dysgenic ovaries show a tendency to develop trabecular tumors [14, 18].

Among the range of anti-ovarian autoantibodies, those directed against zona pellucida glycoproteins have been studied in most detail. Zona pellucida is a highly resistant formation of extracellular matrix that provides support for the oocyte and at the same time allows its communication with surrounding granulosa cells that form thin trans-zonal projections [15]. Given the significance of the zona for the maturing oocyte and the zygote, it is not surprising that immune responses targeting this structure jeopardize oogenesis and fertilization. In women treated for infertility by assisted reproduction techniques, negative correlation has been reported between serum positivity for anti-zona pellucida antibodies and success of the procedure [8]. Immunization of female BALB/c mice with murine zona pellucida glycoprotein ZP3 causes autoimmune oophoritis. The resulting autoantibodies penetrate into growing follicles, bind to the zona and eventually lead to inflammatory infiltration and destruction of the follicle [11]. Contraceptive vaccines based on zona pellucida components have been discussed for a long time, but have not yet found application in veterinary practice; the oophoritis they cause makes them unsuitable for humans [10]. In addition to zona zellucida glycoproteins, aldehyde dehydrogenase ALDH1A1 and selenium-binding protein SBP1 have been revealed as ovarian autoantigens associated with autoimmune ovarian disease in a subset of infertile patients [3].

Apart from the above mentioned ovary-specific reactions, the autoimmune response can target steroidogenic cells in general and affect the adrenal cortex besides the ovary, leading to autoimmune Addison's disease. More than half of the patients with autoimmune ovarian insufficiency have also adrenal autoimmunity [17], while over 6% of women with Addison's disease have also premature ovarian insufficiency [4]. In some women with adrenal autoimmunity, the ovarian morphology does not correspond to "classical" insufficiency with diminished number of follicles, but is characterized instead by numerous ovarian cysts. These patients have lean complexion and low testosterone levels, which distinguishes their condition from typical polycystic ovary syndrome [7]. Most women with such atypical polycystic ovaries are in their 30s. A parallel could be drawn between their condition and that of adolescents with autoimmune polyendocrine syndrome. These young women present with antibodies to steroidogenic cells, autoimmune oophoritis with cystic ovaries and a lymphocytic infiltrate in the steroidogenic theca [20]. It can be concluded that the course of the autoimmune process is highly variable, leading to a spectrum of severity and a wide range of age at diagnosis.

In this respect, it is noteworthy that polycystic ovary syndrome tends to be associated with another organ-specific autoimmune endocrine disorder, Hashimoto's thyroiditis [9]. The polycystic morphology can be explained with the initial restriction of the autoimmune response to the theca cells, while granulosa cells are preserved for a certain period [20]. The sequence of autoimmune ovarian disease is illustrated in **Fig. 1**.

Little is known about the effects of non-organ-specific (systemic) autoimmunity on the ovary. Women with systemic lupus erythematosus are often presumed to have normal fertility. However, measurements of anti-Müllerian hormone in these patients show lowered levels, indicating decreased ovarian reserve [13]. A proportion of women with lupus have amenorrhea associated with autoantibodies to corpus luteum [21]. It is possible that the impact of systemic autoimmunity on patients' ovaries is eclipsed by the more severe involvement of other organs (primarily the kidneys) and the gonadotoxic effect of cyclophosphamide treatment, which alone can cause premature ovarian insufficiency [12]. Therefore, animal models could provide useful information. The MRL/MpJ (MRL/+) mice that are genetically prone to systemic autoimmunity have a decreased number of ovarian follicles (including primordial follicles) and corpora lutea by the age of 3 months, compared to C57BL/6 mice [16]. Systemic autoimmunity can also be induced in animals without genetic predisposition by suitable treatments, e.g. zymosan [5, 6]. Research on such models will help to elucidate the effects of non-organ-specific autoimmune diseases on the ovary, with respect to oogenesis as well as endocrine function.

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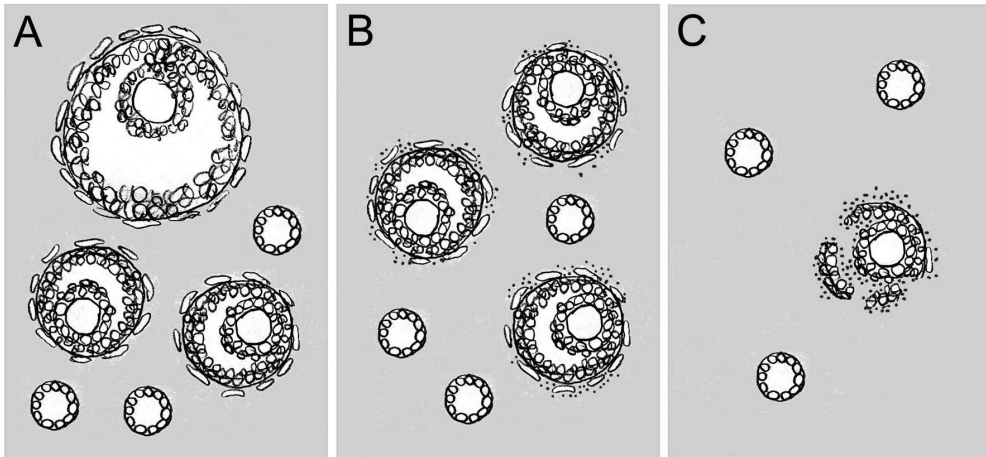


Fig. 1. Schematic drawings of progressive stages of autoimmune ovarian disease. A. Normal ovary, containing primordial, growing and preovulatory follicles. B. Oophoritis with theca infiltration (dots) hindering hormonal secretion, follicle growth and ovulation. In anti-zona pellucida response this stage may be skipped, while in anti-steroidogenic cell response it can be prolonged and lead to polycystic morphology. C. Penetration of the infiltrate into the granulosa and complete destruction of growing follicles. In a final stage (not shown), even primordial follicles are lost due to autoimmune targeting or excessive recruitment.

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