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Review

Autoimmune primary ovarian insufficiency ☆

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ABSTRACT

Primary ovarian insufficiency (POI) is defined as sustained amenorrhea, increased follicle-stimulating hormone and low estrogen levels, whereas diminished ovarian reserve (DOR) is characterized as regular menses and alterations of ovarian reserve tests. POI of autoimmune origin may be associated with adrenal autoimmunity, non-adrenal autoimmunity or isolated. This autoimmune disease is characterized by serum ovarian, adrenocortical or steroidogenic cell autoantibodies. POI of adrenal autoimmune origin is the most frequent type observed in 60–80% of patients. Clinically, amenorrhea is the hallmark of POI, however before menstruation stops completely, irregular cycles occur. Infertility, hot flushes, vaginal atrophy, and dyspareunia are also common. Autoimmune oophoritis is characterized by mononuclear inflammatory cell infiltrate in the theca cells of growing follicles, with early stage follicles without lymphocytic infiltration. This infiltrate includes plasma, B and T-cells. A novel classification criterion for autoimmune POI/DOR is proposed subdividing in three distinct categories (possible, probable and confirmed) according to autoantibodies, autoimmune disease and ovarian histology. Unfortunately, up to date guidelines for the treatment of autoimmune oophoritis are not available. Strategies to POI treatment include hormone replacement and infertility therapy. Assisted conception with donated oocytes has been proven to achieve pregnancy by intra cytoplasmic sperm injection in POI women.

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Contents

1. Introduction

The improvement of assisted reproductive technology has helped infertile men and women worldwide [1]. However, even recent treatments rely mainly on oocyte quality and quantity, otherwise known as ovarian reserve [2]. The most relevant factors that influence ovarian reserve and primordial follicle loss are: aging [3], gynecologic surgery, radiation, smoking [2], infections, genetic, immunosuppressive agents and autoimmune diseases [4–13].

Usually, autoimmunity occurs in women during reproductive age, and retrospective or cross-sectional studies have already reported an

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increased risk of premature menopause [4–13], also named primary ovarian insufficiency (POI) [14–16], premature ovarian insufficiency [17] or premature ovarian failure (POF) [18], and/or diminished ovarian reserve (DOR) [2] in autoimmune diseases, such as systemic lupus erythematosus (SLE) [4–13], thyroiditis [13,18] and dermatomyositis [7].

POI is defined as sustained amenorrhea before the age of 40 years, high follicle stimulating hormone (FSH) levels greater than 40 IU/L [6,8,9,11,12,17,19] and hypoestrogenism associated with infertility [14]. The term "insufficiency" is preferable to "failure" [15], because it encompasses ovarian dysfunction ranging from subfertility with residual follicular activity to complete follicle exhaustion [14], and is less stigmatizing [17].

As POI is the late manifestation of the follicular pool loss [8], alterations of more specific ovarian reserve tests, mainly anti-Müllerian hormone (AMH) and antral follicle count (AFC), precede this event [9,14]. In this review, we will adopt the term POI [14–16], to describe women with advanced ovarian dysfunction and DOR to describe women with initial alterations of ovarian reserve tests [2].

2. Etiology and epidemiology

The etiology of POI is multifactorial and includes different causes, such as idiopathic, X-chromosome alterations, autosomal genetic disorders, radiation therapy, infections, immunosuppressant drugs and autoimmune oophoritis [15,17,20,21].

Autoimmune disease is characterized by autoreactive T-cells and the presence of organ and non-organ-specific autoantibodies [11,14]. Autoimmune oophoritis can be diagnosed in women with histological inflammatory features in ovary biopsy and circulating ovarian and/or adrenal autoantibodies [14].

There are three different situations of autoimmune ovarian insufficiency: associated with adrenal autoimmunity, associated with non-adrenal autoimmunity and isolated idiopathic POI [18].

Typically, the strongest association of POI is with autoimmune Addison disease in the context of two types of autoimmune polyendocrine syndromes (APS) [14,18]: type I [autoimmune polyendocrinopathy candidiasis ectodermal dystrophy (APECED)] and type II (a polygenic syndrome with autoimmune Addison disease with adrenal insufficiency and other autoimmune illness without hypoparathyroidism) [15,22].

The POI may also be associated with localized or systemic non-adrenal disorders, such as thyroid diseases [13,19], hypoparathyreoidism, hypophysitis [23], type 1 diabetes mellitus, and non-endocrine autoimmune diseases, including SLE [5,8,11,24], Sjogren's syndrome [25], rheumatoid arthritis, immune thrombocytopenic purpura, autoimmune hemolytic anemia, pernicious anemia, vitiligo, alopecia areata, celiac disease, inflammatory bowel diseases, primary biliary cirrhosis, glomerulonephritis, multiple sclerosis, and myastenia gravis [18].

With regard to epidemiology, approximately 1–2% of women will have POI [19,20]. Of these women, 5% is believed to have autoimmune oophoritis [14], and adrenal autoimmune origin is the most frequent etiology, representing 60–80% of cases. Additionally, 10–30% of women with POI have a concomitant autoimmune disease [18], especially autoimmune thyroiditis and type 1 diabetes mellitus.

3. Clinical features and ovarian reserve markers

Autoimmune oophoritis *per se* is in most cases asymptomatic. However, acute abdominal pain, adnexal mass, and enlarged ovarian cysts have been reported [26].

Clinically, amenorrhea is the hallmark of POI [20,27], however before menstruation stops completely, irregular cycles occur. Infertility, hot flushes, vaginal atrophy, and dyspareunia are common symptoms [27]. Early menopause also increases the risk of sexual dysfunction, osteoporosis, cardiovascular mortality, psychological problems [20], and decreases health-related quality of life [3].

Laboratory diagnosis of POI is determined by increased serum levels of FSH, generally above 40 IU/L on at least two occasions, and low estrogen levels, generally lower than 50 pg/mL [20].

Since the first description of POI, ovarian reserve tests have improved, particularly in the last two decades. Basal serum FSH, although widely available, has demonstrated to have low accuracy in diagnosis of DOR, especially at early stages, the most important phase to be identified. Nowadays, AMH and AFC are the best non-dynamic tests to predict ovarian performance in human reproductive treatment [2]. AMH is produced by granulosa cells of early stage follicles and has the advantage to be FSH independent [9], which makes its level relatively stable during all menstrual cycle [8], and can be used in the early evaluation of DOR [16]. Different cut-off points ranging from 0.3 to 2.7 ng/mL have been studied and values lower than 1.0 ng/mL are strongly suggestive of DOR [2].

Ovarian reserve test includes ovary ultrasound to assess AFC [9]. AFC consists of the sum of antral follicles measuring 2–10 mm in mean diameter in both ovaries, counted by transvaginal ultrasonography at early follicular phase. Cutpoints ranging from 3 to 10 AFC have been studied [2], and values lower than 10 are suggestive of DOR. Therefore, AMH and/or AFC can be used to diagnose DOR, an initial sign of autoimmune oophoritis.

Finally, it is interesting to know that some studies have found a paradoxal pattern of increased total inhibin and inhibin B levels in the autoimmune POI [28], probably due to selective theca cell destruction.

4. Pathogenesis and autoantibodies

The follicle includes the oocyte encompassed by granulosa and thecal cells that are relevant for follicles development [5,8,20]. A plausible hypothesis for autoimmune oophoritis is a selective involvement of developing follicles, sparing primordial follicle in early phase, with increased ovaries size with luteinized cysts [26]. The subsequent progressive decrease of ovarian function and reserve was demonstrated to be due to activation of CD4 + T cells and ovary lymphocytic infiltration in mice experimental autoimmune oophoritis [29].

In humans, this autoimmune disease is characterized by serum ovarian autoantibodies detected mainly by indirect immunofluorescence [23,26,30] and enzyme-linked immunosorbent assay (ELISA) [26]. There are several reported target antigens involved in autoimmune oophoritis, such as zona pellucida/oocyte [21], granulosa cells, theca cells [25], corpus luteum [11,13] and steroidogenic enzymes: 17∝-hydroxilase (17∝-OH), cytochrome P450 side chain cleavage enzyme (P450scc) and 21-hidroxylase [21,30].

Importantly, among them, adrenocortical and steroidogenic autoantibodies are recognized as the best markers of autoimmune POI [21,23]. The latter autoantibodies are polyclonal IgGs that bind to cytoplasmic antigens common to adrenocortical cells, Leydig cells of testis and ovarian theca cells, and they bind specifically to 17∝-OH and P450scc [30]. These antibodies are usually found in POI associated with autoimmune Addison' disease, but they are uncommon in non-adrenal autoimmunity or in isolated idiopathic POI [31].

Other human and animals autoantibodies against different autoantigens have been studied, such as anti-luteinizing hormone (LH) receptor, anti-follicle-stimulating hormone receptor [14,21], anti-zona pellucida [32] and anticorpus-luteum antibodies [11,13,24]. However, the association between these antibodies and autoimmune POI has not been consistently confirmed [13,14].

5. Histology

Ovarian biopsy may be indicated in patients with circulating organ-specific autoantibodies to confirm autoimmune oophoritis [15,26]. The ovaries are not large organs, have considerable mobility inside the pelvis, and are surrounded by important vessels, including iliac vein and artery, all features that complicate the procedure. Therefore, the experience with ovarian histology in autoimmune oophoritis is limited [26],

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