Premature ovarian failure: Think 'autoimmune disorder'

A comprehensive look at the causes and co-morbidities of premature ovarian failure leads straight to an emphasis on underlying immunologic disorders—and the need for prompt diagnosis.

KEY POINTS

- The incidence of antiovarian antibodies in women with POF ranges widely (0-67%).
- Three diagnostic criteria comprise POF: amenorrhea lasting more than 4 months, age less than 40 years, and serum follicle-stimulating hormone >40 mIU/mL on two occasions at least one month apart.
- Several autoimmune disorders have been associated with POF; the most common is hypothyroidism with an incidence of 27%, followed by diabetes mellitus (2.5%) and Addison's disease (2.5%).
- Approximately 10% of women with Addison's have POF, and the same percentage applies conversely, with 10% of women with POF showing evidence of autoimmunity against the adrenal.
- Women with POF who experience a particularly increased level of sadness and stress will likely benefit from consulting a mental health care professional while their medical evaluation is taking place.

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By definition, premature ovarian failure (POF) occurs early—by age 40. As a result, the patient faces significant treatment issues for a decade or more than a woman who experiences natural menopause at age 51. In addition to subfertility, there are a number of hypoestrogenic ailments. None of these deficiencies may have been on a woman's mind at the time she was diagnosed with POF. Entering menopause prematurely also may create a significant physical and emotional impact.

The prevalence of POF varies by ethnicity: 0.1% to 1.4% among Caucasian, African-American, Hispanic, Chinese, and Japanese women. The estimated incidence of POF in the general population is between 0.3% and 1.1%.[1]

Although the pathophysiology of POF is diffuse, there is often a genetic component. However, an autoimmune process appears to play a major role as many women with POF often have associated autoimmune disorders. This review discusses the various causes, diagnoses, and co-morbidities and presents a diagnostic workup.

Diagnostic criteria for POF

A karyotype and autoimmune evaluation should be obtained on all patients presenting with POF. Although a distinct autoimmune workup has been developed for women diagnosed with POF, there is no definitive test that can precisely herald the development of associated autoimmune disorders or precisely anticipate a woman's chances of conceiving.

Three diagnostic criteria comprise POF:

- Amenorrhea lasting more than 4 months
- Age less than 40 years, and
- Serum follicle-stimulating hormone (FSH) >40 mIU/mL on two occasions at least one month apart.

Despite all these hits on the reproductive axis, Rebar and Conley's classic series found that women with POF and secondary amenorrhea continue to have intermittent ovarian function, as evidenced by ovulation in 24% and a pregnancy rate of 8% (Table 1).[2] One study reported a 60% rate of follicular activity in women with POF, although it is unclear how many of them had the autoimmune versus the non-autoimmune variety of ovarian failure.[3]

Focus on autoimmune causes

The etiology of POF can be divided into two broad categories: **ovarian follicle *depletion*** and **ovarian follicle *dysfunction*** (see Table 2 for an abbreviated list of findings). Our dis-

cussion will focus on the autoimmune causes within each category. The evidence for an autoimmune etiology is threefold: the presence of lymphocytic oophoritis, autoantibodies to ovarian antigens, and associated autoimmune disorders.

Using microsomal ovarian antibodies and oocyte antibodies, an autoimmune basis has been detected in as many as 69% of women with POF.[4] In fact, with a 1.1% prevalence of POF, the autoimmune version calculates to nearly 1.1 million women with premature ovarian autoimmunity in the United States, compared to about 1.4 million women with Hashimoto's thyroiditis.[5] Viewed in this way, POF is a fairly common autoimmune disease.

Possessing an autoantibody does not prove that one has clinical evidence of a disease. Conversely, an absence of ovarian autoantibodies does not prove that POF is absent. Ovarian autoantibodies have not been consistently identified due to the multiple ovarian antibody targets as well as variation in antibody test format and antigen presentation. Nevertheless, most studies have found a higher prevalence of antibodies in serum or follicular fluid samples from women with POF.

The extracellular matrix, or zona pellucida, surrounding a developing oocyte provides a barrier to protect the oocyte from immune cells (leukocytes, macrophages, T-lymphocytes, neutrophils, and eosinophils) as well as their products, such as antibodies.[6] The immune cells eventually populate the corpora lutea granulosa-lutein and theca-lutein cells in addition to the connective tissue stroma. In fact, macrophage secretory products, tumor necrosis factor-α, and interferon-γ have been shown to facilitate cellular apoptosis.[7]

Lymphocytic oophoritis

A review of the literature on oophoritis and POF turned up an 11% incidence of histologic evidence of oophoritis in 215 POF ovarian biopsies.[8] The oophoritis is characterized primarily by a cellular infiltrate of macrophages, natural killer cells, T-lymphocytes, plasma cells, and a few B-lymphocytes.[9] A possible trigger for the influx of lymphocytes may be the class II MHC molecules that have been identified on granulosa cells.[10] Early thymectomy in the mouse model can arrest immune development and lead to a deficiency in T-suppressor cells so that these mice demonstrate follicular degeneration and autoimmune oophoritis.[11]

Several reports describe an elaborate paracrine mechanism for lymphocytic oophoritis. A schematic representation is shown in Figure 1.[10,12-13]

TABLE 1

Clinical findings in 115 women with POF[2]

	Primary amenorrhea	Secondary amenorrhea
Karyotypic abnormalities	56%	13%
Y-chromosome present	10%	None
Symptoms of estrogen deficiency	22%	85%
Ovulation after diagnosis	None	24%
Pregnancy after diagnosis	None	8%

Autoantibodies to ovarian antigens

The published incidence of antiovarian antibodies in patients with POF ranges widely (0–67%), attesting to the difficulties in interpreting their role and understanding their clinical significance.[14-15] A number of factors account for the uncertainty—highly variable ELISA assays, transient appearance of antiovarian antibodies, and poor correlation between antibody levels and severity of disease. Antibodies interfering with FSH-cell-surface receptors have yet to be identified.[16-17]

Steroid cell antibodies of the IgG type have been found bound to ovarian hilar, granulosa, and theca cells. Overall, though, these antibodies are found in patients with Addison's disease rather than isolated POF. In a study of seven women with steroid cell autoantibodies and adrenal failure, 42.8% developed ovarian

TABLE 2

The etiology of premature ovarian failure

Ovarian follicle depletion
- Deficient initial follicle number
- Accelerated follicular atresia
  - Autoimmunity

Ovarian follicle dysfunction
- Enzyme deficiencies
- Autoimmunity
- Lymphocytic oophoritis
  - Gonadotropin-receptor blocking antibodies
  - Antibodies to gonadotropins
- Signal defects
- Gene mutations (inhibin α gene)
- Iatrogenic
- Idiopathic

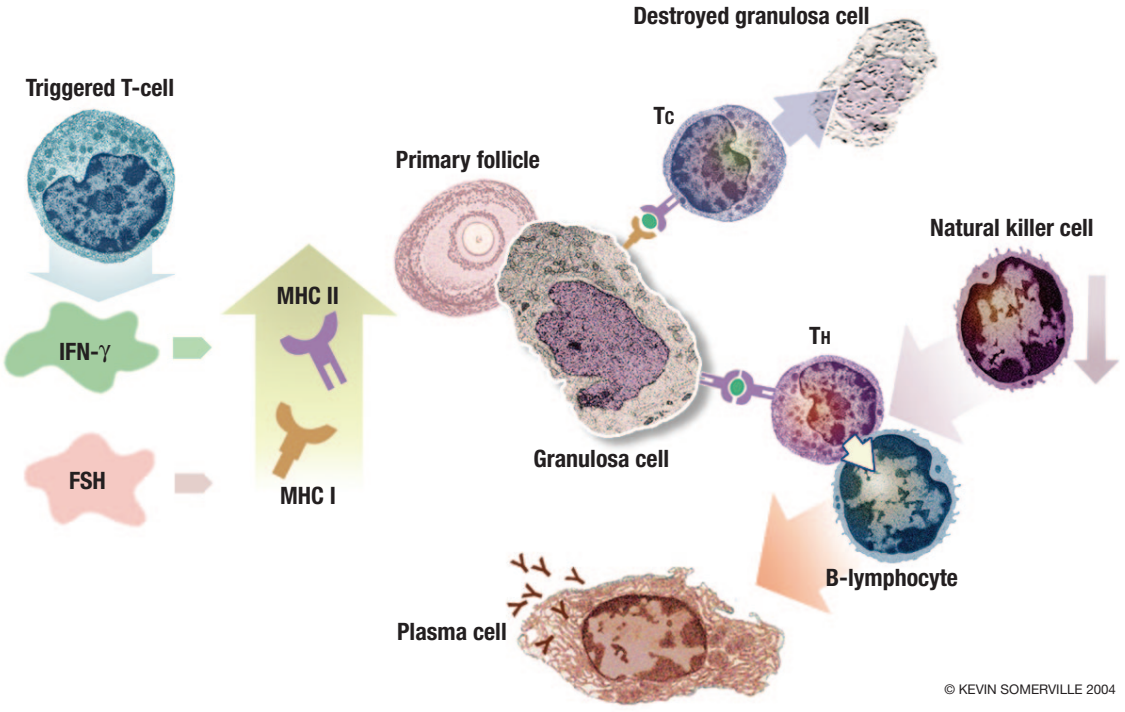

Figure 1. Mechanism of lymphocytic oophoritis. T-cells within the ovary invade granulosa cells and become activated, secreting interferon-γ (IFN-γ). The IFN-γ enhances expression of class I and II MHC on granulosa cells with the help of elevated follicle-stimulating hormone (FSH) values (secondary to diminished inhibin production by these cells). Type I MHC-expressing granulosa cells present their antigens to cytotoxic T-cells that result in the destruction of granulosa cells. In addition, the type II MHC allows the granulosa cells to act as antigen-presenting cells to T-helper cells, with resultant B-cell differentiation into autoantibody-secreting plasma cells. A decrease in natural killer cell activity in women with premature ovarian failure could potentiate the B and T cells.

failure within 10–15 years.[18] The role of zona pellucida antibodies and POF is yet to be determined.[19-20]

Associated autoimmune disorders

A genetic component to developing autoimmune POF is supported by the familial properties of both POF and autoimmune disorders. Approximately 3% of women with POF have an associated endocrine dysfunction known as autoimmune polyglandular syndrome (APS) type I or II.[18]

TABLE 3

Autoimmune diseases affecting other organs in women with POF

Addison's disease (2.5%)	Juvenile rheumatoid arthritis
Alopecia	Malabsorption syndrome
Asthma	Myasthenia gravis
Autoimmune polyglandular syndrome	Pernicious anemia
Chronic active hepatitis	Primary biliary cirrhosis
Crohn's disease	Quantitative immunoglobulin abnormalities
Diabetes mellitus (2.5%)	Rheumatoid arthritis
Glomerulonephritis	Sjögren's syndrome
Hypoparathyroidism	Systemic lupus erythematosus
Hypophysitis	Thyroid disease (27%)
Idiopathic thrombocytopenic purpura	Vitiligo

Autoimmune polyglandular syndrome (APS) type I and II:
- 60% of APS I have concomitant POF
- 4% of APS II have concomitant POF

Most common progression of subsequent autoimmune deficits:
thyroid → pancreas → adrenal

POF, premature ovarian failure.

APS type I is a rare autosomal recessive disorder characterized by multiple organ-specific autoimmunity secondary to a variety of autoantibodies directed against key intracellular enzymes. POF develops in 60% of patients with APS type I. Recently, 31% of 90 patients with APS I were found to have hypogonadism, and the side-chain cleavage enzyme was identified as the major gonadal autoantigen associated with APS I.[21] However, to date there is no clear definition of risk to develop clinical hypogonadism based on the presence of the side-chain cleavage enzyme autoantibody.

The more common **APS type II**, an autosomal dominant disorder, is associated with gonadal failure in only 4% of patients. Addison's disease is a component of both APS types, although POF is often seen with isolated Addison's disease.[22] Approximately 10% of women with Addison's have POF, and the same percentage applies conversely, with 10% of POF women showing evidence of autoimmunity against the adrenal.[23]

Several other autoimmune disorders have been associated with POF and are listed in Table 3. The most common of these is hypothyroidism with an incidence of 27%, followed by diabetes mellitus (2.5%) and Addison's disease (2.5%).[24] The clinical implications of these associated autoimmune diseases mandate a thorough initial screening and diagnostic workup, set forth in Table 4.

Is autoimmune POF reversible?

If the subset of autoimmune POF could be ameliorated by immunosuppression, this would suggest that not all follicles have been affected by the immune inactivation. Very few clinical studies, all uncontrolled and nonrandomized, have addressed this question using corticosteroids as immunosuppressive therapy. While there has been modest success with this approach,[25-27] placebo-controlled randomized clinical trials have yet to determine the optimal dose, safety profile, and efficacy of immune modulators for autoimmune oophoritis. In most instances, treatment fails to reverse the course of the disease.

The emotional side

This review would not be complete without discussing the intense emotional response to developing early menopause or POF. Feelings of despair may overwhelm any proposed treatment regimen. But if hopeful treatments can be developed, this would alleviate the huge distress currently felt by patients with POF, especially those who have not completed childbearing. Women in this situation not only face a sense of being "prematurely old" in a society that places a premium on youth, but also face a reality that they may not be able to become a biologic parent.

An understanding of the pathophysiology of POF is paramount to devising preventive strategies in affected families as well as developing therapeutic measures to aid in fertility outcome. Since a majority of POF has an autoimmune characteristic, this is a valuable target of future research. Activated CD4+ T-lymphocytes produce predominantly one of two characteristic cytokine profiles, T-helper1 (TH1) and T-helper2 (TH2). Further investigation should determine if the immune response seen with POF is due to a predominance of one profile or the other.

Beyond the POF findings, it will be interesting to examine whether similar etiologic factors play a role during the perimenopause period transitioning into menopause. For the moment, it is prudent to diagnose POF as soon as possible in addition to obtaining the appropriate diagnostic tests for related autoimmune disorders. Those women with POF who experience a particularly increased level of sadness and stress will likely benefit from consulting a mental health professional while their medical evaluation is taking place. □

TABLE 4

Diagnostic tests for women with POF

Karyotype	If onset < age 30 and primary amenorrhea
	Y-chromosome necessitates gonadectomy to prevent gonadoblastoma
	50% of gonadoblastomas will transform into dysgerminomas
All patients	
Type I diabetes	Glucose tolerance test
Thyroid disease	Thyroid-stimulating hormone, antithyroperoxidase antibodies
Hypoestrogenism-osteoporosis	Dual-energy X-ray absorptiometry (DEXA) scan bone densitometry
If signs and symptoms warrant	
Pernicious anemia	CBC with peripheral smear
Addison's disease*	Adrenal antibody test (titer <1:10 is normal) with adrenocorticotropic hormone (ACTH) stimulation test to confirm diagnosis[28]
	Low-dose ACTH stimulation test: Administer 1 mcg cosyntropin IM (cortisol should be >18 mcg/dL at 30 or 60 minutes)[29]
Hypoparathyroidism	Calcium and phosphorus
IgA deficiency (if frequent respiratory tract infections)	Total serum protein; albumin/globulin ratio
Pituitary tumor	MRI of sella turcica if signs and symptoms of central nervous system mass lesion

* Signs and symptoms include hyperpigmentation of gums and hand skinfolds, loss of pubic/axillary hair.
POF, premature ovarian failure.

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