



Autoimmune premature ovarian failure

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Premature ovarian failure (POF) is associated with amenorrhea, hypogonadism, and elevated gonadotropins before the age of 40 years. The age-specific incidence of POF is 1 in 100 by age 40 and 1 in 1000 by age 30. In women with primary amenorrhea, the prevalence of POF is 10% to 28%; in women with secondary amenorrhea, POF occurs in 4% to 18% [1].

Several lines of evidence suggest a possible role of immune system in the cause of POF. Once chromosomal and developmental causes have been excluded, autoimmunity is believed to account for up to 20% of the remaining POF cases, although the diagnosis usually is based on clinical grounds, such as an association with other autoimmune endocrinopathies [2]. The immune alterations may induce POF secondary to a depletion of follicles or a disruption of normal ovarian function.

Evidence that strongly suggests an autoimmune origin in some patients with POF includes cases associated with lymphocytic and plasma-cell infiltration of the ovary, with circulating autoantibodies to ovarian antigens, or with autoimmune disorders [3–6]. Evidence for organ-specific autoimmunity was found in 40% of patients with POF, with antithyroid autoimmunity being the most frequent cause (20%) [3].

Other evidence supporting the role of immune system in POF include its association with infectious diseases, findings of altered cell-mediated immunity, and recovery of ovarian function after immunosuppression.

Premature ovarian failure and autoimmune diseases

In developed countries, the most common cause of primary adrenal failure is autoimmunity, causing up to 75% to 80% of the cases of adrenal insufficiency [7].

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About 50% to 60% of autoimmune patients with Addison's disease have or develop other autoimmune disorders [8]. The adrenal failure and associated endocrine dysfunction are called the autoimmune polyglandular syndrome (APGS) type I and II, which are noted in 3% of patients with POF (Table 1) [9].

Autoimmune polyglandular syndrome type I consists of chronic hypoparathyroidism, chronic mucocutaneous candidiasis, and adrenal failure. It also is called autoimmune polyendocrinopathy, candidiasis, ectodermal dystrophy and occurs in young children [7]. It is an autosomal recessive disease caused by a single gene defect on chromosome 21q22.3 and is an autoimmune disorder that is localized outside the MHC [10]. POF in the form of primary amenorrhea develops in 60% of patients with APGS type I.

Autoimmune polyglandular syndrome type II, also known as Schmidt's syndrome, is characterized by autoimmune adrenal failure and either thyroid autoimmune disease or insulin-dependent diabetes mellitus [8]. It occurs in a much broader age range (third to fourth decade). The occurrence of POF in patients with APGS type II is variable. It has been estimated that 10% of patients with Addison's disease develop POF 5 to 14 years before adrenal dysfunction [11].

Most patients with POF do not have adrenal failure. In patients with POF, the reported frequency of coexisting autoimmune syndromes is highly variable and ranges from 0% to 57% [12]. This wide range may reflect different and biased referral patterns, study designs, performance of different screening tests, and dissimilar study populations. The most common immune disorder associated with idiopathic POF is hypothyroidism (27%). Addison's disease can be detected in 2.5% of patients. Another 2.5% may have diabetes mellitus [13]. Other associated autoimmune disorders include myasthenia gravis, Crohn's disease, vitiligo, and pernicious anemia. Systemic lupus erythematosus and rheumatoid arthritis also may be associated with POF.

Table 1

Components and associated disorders of autoimmune polyglandular syndrome types I and II

Characteristics	APGS type I	APGS type II
Components	Chronic mucocutaneous candidiasis Addison's disease Hypoparathyroidism	Addison's disease Autoimmune thyroid disease Type 1 diabetes mellitus Gonadal failure
Associated endocrinopathies	Insulin-dependent diabetes Ovarian failure Hypothyroidism	Lymphocytic hypophysitis Isolated adrenocorticotrophic hormone or LH and FSH deficiency
Associated disorders ^a	Vitiligo, alopecia, nail dystrophy, enamel vitiligo, alopecia, pernicious anemia, hypoplasia, pernicious anemia, tympanic myasthenia gravis, Celiac disease, membrane calcification, keratopathy, hepatitis, malabsorption	

^a Associated with both types of APGS.

Endocrine screening of 119 women with karyotypically normal spontaneous POF revealed 10 new cases of hypothyroidism and 3 new cases of diabetes mellitus. Twenty-two of women already were known to have hypothyroidism, and three women were known to have Addison's disease. No new cases of adrenal failure, hypoparathyroidism, or pernicious anemia were identified. These findings supported the use of initial routine screening for hypothyroidism and diabetes in such patients. It has been suggested that the screening for other associated autoimmune endocrine disorders should be considered only in patients with specific clinical conditions [13].

Immune markers

There are well-known associations between autoimmune endocrinopathies and MHC class II markers. Patients with POF have been reported to have an increased frequency of the MHC class II antigen HLA-DR3. Anasti and colleagues performed MHC class II immunophenotyping of HLA-DR antigens 1 to 10 on 102 North American whites with confirmed POF and on 102 control white women [14]. No significant increase in HLA-DR3 frequency was found in patients with POF when compared with that in the control group or when compared with that in a large reference population ($n = 1927$) that did not differ significantly from the control group. The patients with POF had an increased frequency of HLA-DR4 compared with the reference population (41% versus 23%; $P < 0.001$), but the investigators were unable to demonstrate increased HLA-DR4 frequency in the control group (31%; $P = 0.14$). The study was unable to confirm a significant increase in MHC class II HLA-DR3 frequency in patients with POF.

In a small study of patients with APGS type I and type II, HLA-A9 was more frequent in patients with the type II syndrome and ovarian failure [15]. Autoimmune Addison's disease is associated with HLA-B8, HLA-DR3, and, in particular, with the DR B1 0301 allele [16]. Ovarian failure in APGS type I has been associated with HLA-A28 [15]; however, this haplotype has not been associated with ovarian failure per se. In patients with APGS type I and ovarian failure, HLA-A3 was more frequent. There is currently no immune marker to predict isolated POF.

Antiovarian antibodies

The reported incidence of antiovarian antibodies in patients with POF is highly variable (between 0% and 67%). There are major problems in the interpretation of antiovarian antibodies. The assays used are also highly variable. In the first report of antiovarian antibodies in patients with POF, the cytoplasm of a rabbit was used as an antigen [17]. By using indirect immunofluorescence, the investigators noted antiovarian antibodies in 4 of 45 patients with POF and in 1 of 45 controls. The same technique was applied by using human ovarian tissue as an antigen. Indirect immunofluorescence assay has been proven to be cumbersome

and poorly reproducible, however. Some ELISAs were developed using various ovarian antigens, but their results were unclear.

The incidence of antiovarian antibodies differs according to the technique used to detect the antibodies. Using indirect immunofluorescence techniques on human ovarian tissue, the incidence of antiovarian antibodies was 33% to 40% in patients with Addison's disease and positive antiadrenal antibodies [18]. In patients with POF but without Addison's disease, antiovarian and antiadrenal antibodies were found to be positive in only 4% of patients; however, 44% of patients with POF might have one or more other organ-specific autoantibodies [19]. Patients with POF and organ-specific autoantibodies had a statistically significant decrease in dehydroepiandrosterone sulfate (DHEAS) production compared with those without autoimmunity; this finding awaits further study [19].

The circulating antiovarian antibodies were reported to be detected in 10% to 69% of women with POF and were found in a considerable number of controls [20]. In one study that used human ovarian antigen preparations from two different donors, 24% and 60% of patients with POF reacted in the ELISA, with frequent cross-reactivity with fallopian tube antigens. The variation in reactivity between ovary preparations was believed to be caused by a cyclical variation in antigenic proteins, which indicates the need to screen ovarian preparations for reactivity [2]. Ovarian preparations vary greatly in their capacity to bind these antibodies, and at least a proportion of ovarian antibodies detected by ELISA are not specific, because they cross-react with other antigens, such as those in the fallopian tube.

As mentioned earlier, the most commonly used techniques to identify ovarian antibodies are indirect immunofluorescence using various sources of ovarian tissue and ELISA. These two methods were compared, and neither was found to be reliable [21]. ELISA has shown that ovarian antibodies frequently are detected in Turner's syndrome and iatrogenic ovarian failure [2]. This method also only detected nonspecific ovarian antibodies.

Ovarian antibodies are not exclusive to patients with autoimmune Addison's disease; they occur in patients who have idiopathic ovarian failure, chromosomal abnormalities, and total-body irradiation and chemotherapy. The correlation between the presence of antiovarian antibodies and the severity of disease is poor. It is uncertain whether antiovarian antibodies are the cause or are formed secondary to antigen release after cellular injury. These antibodies also may be transient in nature. They may be present only in the initial stages of cellular damage. The clinical significance of antiovarian antibodies in POF remains to be determined.

Antibodies to gonadotropin receptors

There are reports of the presence of gonadotropin receptor antibodies in patients with POF. In two patients with myasthenia gravis and POF, the presence of an immunoglobulin G (IgG) antibody that blocked the binding of follicle-stimulating hormone (FSH) to its receptor was reported [22]. These findings were not confirmed by other studies.

In one study, 21 of 26 POF cases exhibited IgGs that inhibit FSH-induced synthesis of rat granulosa cell DNA without interfering FSH binding to its receptor [23]. These positive patients were characterized mainly by resistant ovaries.

These studies used nonhuman gonadotropin receptors to search for receptor-related antibodies. In a study using recombinant human gonadotropin receptor bioassay to detect IgG antibodies to gonadotropin receptors, none of the 38 patients with POF and 14 controls showed evidence of blocking IgGs [24]. Some investigators reported a nonimmunoglobulin, low-molecular-weight inhibitor of FSH binding (FSH receptor-binding inhibitors [FRBI]) in the sera of patients with POF; this finding awaits further investigation [25].

The significance of antibodies in POF that block the luteinizing hormone (LH) receptor is also questionable. Although one report [26] found specific LH-receptor blocking antibodies in patients with infertility and endometriosis, several studies have not demonstrated the presence of these antibodies in the serum of patients with POF [23,27–29].

Steroid-producing cell antibodies

The steroid-producing cell antibodies are of IgG type and bind to hilar cells, granulosa cells, theca cells, and the corpus luteum. They first were described by indirect immunofluorescence assay in tissue preparations from the placenta, adrenal gland, and ovary. The sera of patients with Addison's disease and POF reacted to these three tissues [25]. Patients with Addison's disease and primary or secondary amenorrhea have been shown to have detectable levels of steroid-producing cell antibodies in 95% and 60% of cases, respectively.

Among patients with adrenal failure and normal ovarian function, 40% of women with steroid-producing cell antibodies may develop ovarian failure within 10 to 15 years [9]. In 31 prospectively observed patients with APGS type I, the detection of steroid-producing cell antibodies preceded the development of POF in 11 patients. The sensitivity and specificity of steroid-producing cell antibodies to predict POF were calculated as 100% and 56%, respectively [30]. In a previous study, the sera of patients with Addison's disease, POF, and steroid-producing cell antibodies were toxic to human granulosa cells in culture [31].

Steroid-producing cell antibodies have been identified in patients with POF that is associated with Addison's disease. These antibodies usually are not present in patients with isolated POF [32,33].

Antibodies to steroidogenic enzymes

It has been proposed that steroid 21-hydroxylase (21-OH) may be a major autoantigen in autoimmune Addison's disease [34,35]. Autoantibodies to steroid 17 α -hydroxylase (17 α -OH) and the P450 side-chain cleavage enzyme (P450_{scc}) have been described [36,37]; however, there have been some discrepancies

between reports on the distribution of antibodies to these enzymes among patients with APGS types I and II [38,39]. In one study, 7 of 11 (64%) patients with APGS type I and 23 of 24 (96%) patients with APGS type II showed evidence of 21-OH antibodies. One third to one half of the patients with APGS types I and II had antibodies to 17 α -OH and P450scc. It seemed that the autoantibodies to 21-OH almost always were present when 17 α -OH or P450scc autoantibodies were detected. No antibodies to 21-OH, 17 α -OH, or P450scc were detected in 17 patients with POF and without evidence of autoimmunity [32]. This observation is consistent with other studies that reporting that steroid-producing cell autoantibodies usually are not found in patients with isolated POF [9,33,40].

Antibodies to zona pellucida

The zona pellucida is the acellular matrix shell that surrounds developing and ovulated oocytes and is also detectable in atretic follicles. Antibodies to zona pellucida were believed to interfere with sperm–oocyte interaction; they mostly are studied in women with unexplained infertility [41]. Animal models have suggested that the zona pellucida antibodies may interfere with follicular development and may lead to follicular depletion.

Anti-zona pellucida antibodies have been investigated in rabbits. In one study, rabbits that were immunized with zona pellucida antigen failed to ovulate, and their developing follicles disappeared [42]. The difference in the ultrastructural morphology suggests that this finding is an unlikely mechanism of POF in humans. Anti-zona pellucida antibodies that were detected by indirect immunofluorescence have been tested in 26 patients with POF and in 26 controls. One third of the normal control women had positive anti-zona pellucida antibodies [43]. Indirect immunofluorescence has no proven benefit in the evaluation and management of POF.

Autoantibodies in patients with idiopathic premature ovarian failure and without Addison's disease

In the context of endocrine disorders, thyroid autoimmunity is the most frequent (14%) abnormality reported in patients with POF and without autoimmune adrenal disease [16]. Other frequent abnormalities include the presence of parietal cell antibodies (4%), insulin-dependent diabetes (2%), and antibodies to acetylcholine receptors (2%). It has been reported that about a third of women with POF have positive serologic testing for antithyroid antibodies [44]. These antibodies are not seen in more than 10% of the female adult population [45]. This difference implies that women with POF are more susceptible to autoimmune disease.

In patients with POF, systemic lupus erythematosus, antinuclear antibodies, and rheumatoid factors also have been reported more frequently than in controls [16,46].

Oophoritis

The ovulation process has been comparable with inflammation [47]. The concept of the ovarian leukocyte system and its relevance to ovarian function has been reviewed [48]. The investigation of POF has concentrated on patients who develop lymphocytic oophoritis.

In a review of 215 reported ovarian biopsies in patients with POF, 11% had histologic evidence of oophoritis [16]. All patients with positive steroid-producing cell antibodies had lymphocytic oophoritis. Among the cases with oophoritis, 78% had antisteroid-producing cell antibodies. This finding supports the evidence that patients with Addison's disease are more likely to develop POF with lymphocytic oophoritis.

Autoimmune oophoritis may be mediated cellularly or humorally and seems to be the dominant cause of reversible POF [43]. Lymphocytic oophoritis is characterized by inflammatory infiltration of theca interna of developing follicles and sparing of primordial follicles. Lymphocytic infiltration is more prominent in mature follicles [49], which suggests that the expression of the self-antigen may be gonadotropin dependent. Lymphocytic infiltration may be seen in the hilum, with accumulation of lymphocytes around the neural tissue. The cellular infiltrate includes macrophages, natural killer (NK) cells, T lymphocytes, B cells, and plasma cells [50]. In most cases, follicle development progresses to the Graafian stage [51]. Lymphocytic oophoritis sometimes presents with markedly enlarged ovaries that contain luteinized cysts [52].

Immunohistochemical analysis of oophoritis reveals that the inflammatory cells are formed mainly by CD4⁺ and CD8⁺ T lymphocytes, B cells, macrophages, NK cells, and a large number of plasma cells [50]. By using an immunoperoxidase technique, an inappropriate expression of MHC class II molecules on the granulosa cells of four patients with POF has been demonstrated [53]. This increased expression of MHC II molecules was believed to trigger an influx of lymphocytes to the ovarian tissue. It also has been shown that the increased MHC II expression on the granulosa cells might be induced by gonadotropins and interferon γ [53,54].

It has been reported that 3.5% of patients with POF might have evidence of a recent infection with varicella and other infections, such as shigellosis or malaria [55]. In patients who contracted mumps during an epidemic, the incidence of oophoritis was reported as 3% to 7%; however, the onset of oophoritis did not correlate with the exact timing of the infection [11]. Cytomegalovirus-related oophoritis has been implicated in immunocompromised patients. The true incidence of oophoritis induced by a viral infection is unknown.

Large series of ovarian biopsies have not been reported in patients with POF, because the procedure has unknown clinical value, is expensive, and has surgical

risks. Information regarding oophoritis in the context of POF is based on observational studies and case reports. There is no criteria defining who should be biopsied and when. Ovarian biopsy, besides in a controlled trial, is not indicated clinically [56]. Because of these reasons, the true incidence of oophoritis and the histologic correlates of the condition in POF are unknown.

Cell-mediated immunity

It has been reported that, in the peripheral blood of patients with POF, increased numbers of CD4⁺ and CD8⁺ cells, B lymphocytes, and HLA-DR–positive activated T cells were found [6,57,58]. Some studies show decreased CD3⁺8⁺ lymphocytes (T-suppressor and cytotoxic cells) in patients with an initial period of POF, compared with women with natural menopause [59]. This finding may reflect the migration of these cells to a local compartment (ie, ovarian tissue).

In 63 patients with POF and in 50 patients with incipient ovarian failure characterized by infertility, regular cycles, and elevated early follicular-phase FSH, the evaluation of lymphocyte subsets showed similar abnormalities. In both groups of patients, there was a decrease in the percentage of T-suppressor cells, an increase in the ratio of T-helper cells to T-suppressor cells, a decrease in NK cells, and an increase in B lymphocytes and HLA-DR–positive activated T cells [60]. There were no statistically significant differences among these groups and 27 controls in autoantibodies, which included antibodies against adrenal cortex, islet cells, steroid-producing cells of the ovary, nuclear factors, smooth muscle, gastric parietal cells, thyroid microsomes, thyroglobulin, and acetylcholine receptors. The patients with incipient ovarian failure demonstrated intermediate findings between control group and POF group in terms of changes in immune cell subsets. It has been suggested that incipient ovarian failure might be a mitigated form of POF.

Low activity of NK cells (CD16⁺, CD56⁺, CD3[−]) was shown in 30% of patients with POF [61]. This finding have been described in other autoimmune endocrine disorders, such as Graves' disease, suggesting a similar pathophysiology in patients with POF. A decrease in NK cells might affect B and T cells and result in increased autoantibody production. It has been hypothesized that this decrease may reflect a greater susceptibility to viral infection, leading to direct or indirect destruction through development of autoimmune reactions as a result of antigen mimicry [6]. As noted previously, however, data are scarce about the viral infection-associated POF. Shimizu and co-workers reported a decrease in NK cells in patients with myasthenia gravis [62], and Erkeller-Yusel et al showed decreased NK cells in patients with systemic lupus erythematosus correlating with the activity of disease [63]. NK cells seemed to be the principal source of transforming growth factor (TGF)- β , which serves as an important costimulatory factor for CD8⁺ T cells in the development of suppressor activity [64]. These cells may have an important role in the down-regulation of anti-self and non-self immune responses in vivo by way of TGF- β production. Some investigators noted reduced sensitivity to *Candida* antigen in 11 of 20 patients with POF and in 2 of 10 controls [57].

Thymic hypoplasia or aplasia has been associated with POF. The pathogenic mechanism of thymectomy at an early age is the loss of regulatory or suppressor T cells that control the repertoire of autoreactive T-helper cells. The consequence of the loss of control of autoreactive cells is autoimmune damage of various tissues.

In mice, oophoritis was caused by thymectomy that was performed on day 3 of life [65]. The appearance of antiovarian antibodies occurs in an orderly progression that was potentiated by puberty, implying a gonadotropin-stimulated process. The lymphocytic oophoritis was most intense at 4 to 14 weeks after the thymectomy. The process seemed to be mediated by T cells, because adoptive transfer was noted in nude mice [66]. Although this histologic and immunologic picture is comparable with human oophoritis associated with POF, there are big differences between humans and mice. The thymus and gonads in humans develop completely in utero, whereas the thymus and gonads in mice continue to evolve postnatally (14 days after birth).

Primate experiments with in utero thymectomy revealed a role of the thymus in establishing the normal endowment of primordial follicles [67]. An aberrant ovarian function in the in utero thymectomized monkey was similar to that found in human thymic disorders, such as thymic aplasia and myasthenia gravis.

It has been reported that the hypoestrogenic state of patients with POF might be the cause of their altered immune status. A short-term deficiency of estrogen could impair T-cell activation in women receiving gonadotropin-releasing hormone (GnRH) analog treatment [68]. A lowered CD4⁺ to CD8⁺ ratio was reported in young subjects with estrogen deficiency caused by gonadal dysgenesis or hypothalamic-pituitary failure [69]. Although 2-year estrogen replacement therapy in patients with POF normalized many of the immune changes, which included the increase in the CD4⁺ to CD8⁺ ratio and a significant increase in the mean serum IgG concentration, the increase in activated T cells (MHC II+) remained unchanged [70].

Although the disturbances in lymphocyte subsets may support the concept of a cell-mediated autoimmune response, it remains to be determined whether this is the principal cause of the loss of ovarian function, either by destruction of oocytes or by rendering oocytes unresponsive. Damage to the ovarian tissues by other agents may uncover antigens that were unexposed previously, thereby secondarily inducing an autoimmune response.

Effects of immunologic therapies

There have been reports regarding the return of ovulatory function after the management of concomitant autoimmune disease with immunosuppressive treatment, especially with corticosteroids [71]. In an uncontrolled study, corticosteroid treatment for presumptive autoimmune POF was reported to restore ovulation [72]. Corenblum and colleagues reported ovulation in 2 of 11 patients with POF who were treated with corticosteroids in an open study [73]. The results of another study were more promising, although the study involved a variety of comedications [74].

Properly designed, prospective, randomized trials are needed to show the benefit of corticosteroids in the management of POF. Selection of patients is difficult in these trials. In many cases, autoimmune phenomena are present without overt disease. There are no appropriate tools to select patients in whom POF is of definite autoimmune origin. Any trial should be randomized and include all patients with idiopathic POF, not just those with other autoimmune diseases. The dose and duration of corticosteroid therapy need to be selected empirically.

The effect of corticosteroids on the ovarian response to exogenous gonadotropins was studied in a prospective, placebo-controlled, randomized, double-blind trial that included 100 patients with idiopathic POF [75]. The patients were randomized to daily receive 9 mg of dexamethasone or placebo at the time of gonadotropin treatment. Because no ovulation was recorded in first 36 patients, the study was discontinued. Corticosteroids failed to improve ovarian responsiveness in patients with POF [75].

Therapeutic interventions to restore ovarian function and achieve pregnancy have been reviewed [76]. Fifty-two case reports describing pregnancy or return of ovulation, 8 observational studies mentioning the number of patients that had become pregnant, 9 uncontrolled studies reporting patients who became pregnant with a specific intervention, and 7 controlled trials were evaluated. The study by van Kasteren et al was the only controlled study that used corticosteroids [75]. No tools were available to adequately categorize most POF patients according to the etiologic factors, presence of oocytes, or potential to achieve a pregnancy. Consequently, therapeutic interventions have been directed toward a heterogeneous group of patients with POF that is usually idiopathic in origin. Corticosteroids may be useful in autoimmune oophoritis that is characterized by the presence of autoantibodies against steroid-producing cells [16]. This form of POF is rare, however, and it would be practically impossible to collect enough patients to perform a randomized trial.

Plasmapheresis with thymectomy has been reported to be successful in a patient with myasthenia gravis, and intravenous immunoglobulin therapy has been effective in a patient with autoimmune polyglandular syndrome [71].

As discussed earlier, no therapy for infertile patients with POF has proved effective. Some anecdotal reports have suggested that high-dose, long-term prednisone therapy may be useful in treating autoimmune ovarian failure. Prednisone, when used in high-doses for long periods of time, has substantial side effects, including aseptic necrosis of bone, which often requires major surgical treatment [77]. Even with this known level of risk, patients with POF are being treated based on this anecdotal evidence. A prospective, randomized, controlled study of alternate-day prednisone therapy for autoimmune POF is being conducted by the National Institute of Child Health and Human Development [78]. This study is testing the hypothesis that a lower-risk therapy (alternate-day, lower-dose, shorter-term prednisone) causes a remission of autoimmune ovarian failure. There is no reliable blood test to identify patients who have POF. All patients will undergo a laparoscopic ovarian biopsy to confirm the presence of an autoimmune oopho-

ritis. The treatment will be deemed successful based on the return of ovulation as determined by weekly serum progesterone levels.

The use of immunosuppressive therapy is not supported by properly designed, prospective, randomized trials. Major complications can occur, such as iatrogenic Cushing's syndrome, osteonecrosis, and osteoporosis.

Course of premature ovarian failure

Initially, POF was considered irreversible. This notion of permanent cessation of ovarian function was challenged in later reports [79]. Young women with POF have intermittent ovarian follicle function [80], and nearly 20% of these women have ovulated spontaneously during 4 months of observation [81]. Spontaneous pregnancies have occurred after the diagnosis of POF [82–87].

Patients with POF constitute a heterogeneous population representing various discrete disease entities and various stages of disease. In contrast to the situation in postmenopausal women, an earlier study showed that ovarian biopsies of women with POF demonstrated the presence of primordial follicles in up to 50% of patients [88]. The direct casual mechanisms have not been demonstrated for any of the postulated causes in patients whose ovaries contain follicles. Spontaneous return of cyclic ovarian function and pregnancies in patients with POF have been reported [86,89]. These findings, although consistent with a fluctuating course for autoimmune disorders, makes it difficult to interpret data based on reversibility caused by specific treatments.

Follow-up of patients with premature ovarian failure

All patients with POF should be followed-up for the presence of signs and symptoms of associated autoimmune endocrine disorders, which include hypothyroidism, adrenal insufficiency, and diabetes mellitus. Annual screening is reasonable only for serum thyroid stimulating hormone (TSH) and fasting glucose [13]. Additional tests should be requested only if clinically indicated.

Summary

Autoimmune POF is a large category that requires better definition and characterization. Targeted methods to identify the antibodies responsible for POF are lacking. Once a woman develops ovarian failure, the antibody may have disappeared. It is not possible to determine whether POF is caused by a single antibody-mediated process or by more complex processes. There is no firm support for a major role for autoimmunity in the cause of POF. Although some patients' POF undoubtedly is caused by autoimmunity, such as in patients with Addison's disease, clear proof of autoimmunity is lacking in most cases of idiopathic POF. Autoimmunity remains a candidate for the

origin of POF, but better approaches and solid data are required to define its exact role.

To restore ovarian function in a young woman with autoimmune POF, the clinician needs a sensitive and specific noninvasive method to confirm that the woman has ovarian failure on an autoimmune basis and needs a treatment that has been proven safe and effective by prospective, randomized, controlled trial. No accurate serum marker is available to identify patients with POF that is caused by autoimmunity, and the specific antigens involved in the development of autoimmune POF have not been found. Ovarian biopsy is the only way to diagnose autoimmune POF with certainty, although the procedure is not indicated clinically unless it is included in an approved protocol for a clinical trial. A prospective, randomized, controlled study of alternate-day prednisone therapy for autoimmune POF documented by ovarian biopsy is being conducted by the National Institute of Child Health and Human Development. Until the results from this trial are available, there is still no treatment that has been proved effective by prospective, randomized, controlled study to restore fertility for these women.

References

- [1] Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. *Obstet Gynecol* 1986;67:604–6.
- [2] Wheatcroft NJ, Toogood AA, Li TC, et al. Detection of antibodies to ovarian antigens in women with premature ovarian failure. *Clin Exp Immunol* 1994;96:122–8.
- [3] Belvisi L, Bombelli F, Sironi L, et al. Organ-specific autoimmunity in patients with premature ovarian failure. *J Endocrinol Invest* 1993;16:889–92.
- [4] Coulam CB, Ryan RJ. Premature menopause. I: Etiology. *Am J Obstet Gynecol* 1979;133:639–43.
- [5] Kim JG, Moon SY, Chang YS, et al. Autoimmune premature ovarian failure. *J Obstet Gynaecol* 1995;21:59–66.
- [6] Pekonen F, Sieberg R, Makinen T, et al. Immunological disturbances in patients with premature ovarian failure. *Clin Endocrinol (Oxf)* 1986;25:1–6.
- [7] Betterle C, Volpato M. Adrenal and ovarian autoimmunity. *Eur J Endocrinol* 1998;138:16–25.
- [8] Betterle C, Volpato M, Greggio AN, et al. Type 2 polyglandular autoimmune disease (Schmidt's syndrome). *J Pediatr Endocrinol Metab* 1996;9(suppl):113–23.
- [9] Betterle C, Rossi A, Dalla Pria S, et al: Premature ovarian failure: autoimmunity and natural history. *Clin Endocrinol (Oxf)* 1993;39:35–43.
- [10] Nagamine K, Peterson P, Scott HS, et al. Positional cloning of the APECED gene. *Nat Genet* 1997;17:393–8.
- [11] Anasti JN. Premature ovarian failure: an update. *Fertil Steril* 1998;70:1–15.
- [12] LaBarbera AR, Miller MM, Ober C, et al. Autoimmune etiology in premature ovarian failure. *Am J Reprod Immunol Microbiol* 1988;16:115–22.
- [13] Kim TJ, Anasti JN, Flack MR, et al. Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. *Obstet Gynecol* 1997;89:777–9.
- [14] Anasti JN, Adams S, Kimzey LM, et al. Karyotypically normal spontaneous premature ovarian failure: evaluation of association with the class II major histocompatibility complex. *J Clin Endocrinol Metab* 1994;78:722–3.
- [15] Ahonen P, Koskimies S, Lokki ML, et al. The expression of autoimmune polyglandular disease

- type I appears associated with several HLA-A antigens but not with HLA-DR. *J Clin Endocrinol Metab* 1988;66:1152–7.
- [16] Hoek A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. *Endocr Rev* 1997;18:107–34.
- [17] Vallotton MB, Forbes AP. Antibodies to cytoplasm of ova. *Lancet* 1966;2:264–5.
- [18] Elder M, Maclaren N, Riley W. Gonadal autoantibodies in patients with hypogonadism and/or Addison's disease. *J Clin Endocrinol Metab* 1981;52:1137–42.
- [19] Doldi N, Belvisi L, Bassan M, et al. Premature ovarian failure: steroid synthesis and autoimmunity. *Gynecol Endocrinol* 1998;12:23–8.
- [20] Kim JG, Anderson BE, Rebar RW, et al. A biotin-streptavidin enzyme immunoassay for detection of antibodies to porcine granulosa cell antigens. *J Immunoassay* 1991;12:447–64.
- [21] Wheatcroft NJ, Salt C, Milford-Ward A, et al. Identification of ovarian antibodies by immunofluorescence, enzyme-linked immunosorbent assay or immunoblotting in premature ovarian failure. *Hum Reprod* 1997;12:2617–22.
- [22] Chiauzzi V, Cigorraga S, Escobar ME, et al. Inhibition of follicle-stimulating hormone receptor binding by circulating immunoglobulins. *J Clin Endocrinol Metab* 1982;54:1221–8.
- [23] van Weissenbruch MM, Hoek A, van Vliet-Bleeker I, et al. Evidence for existence of immunoglobulins that block ovarian granulosa cell growth in vitro: a putative role in resistant ovary syndrome? *J Clin Endocrinol Metab* 1991;73:360–7.
- [24] Anasti JN, Flack MR, Froehlich J, et al. The use of human recombinant gonadotropin receptors to search for immunoglobulin G-mediated premature ovarian failure. *J Clin Endocrinol Metab* 1995;80:824–8.
- [25] Sluss PM, Schneyer AL. Low molecular weight follicle-stimulating hormone receptor binding inhibitor in sera from premature ovarian failure patients. *J Clin Endocrinol Metab* 1992;74:1242–6.
- [26] Moncayo H, Moncayo R, Benz R, et al. Ovarian failure and autoimmunity. Detection of autoantibodies directed against both the unoccupied luteinizing hormone/human chorionic gonadotropin receptor and the hormone-receptor complex of bovine corpus luteum. *J Clin Invest* 1989;84:1857–65.
- [27] Austin GE, Coulam CB, Ryan RJ. A search for antibodies to luteinizing hormone receptors in premature ovarian failure. *Mayo Clin Proc* 1979;54:394–400.
- [28] Lambert A, Weetman AP, McLoughlin J, et al. A search for immunoglobulins inhibiting gonadal cell steroidogenesis in premature ovarian failure. *Hum Reprod* 1996;11:1871–6.
- [29] Tang VW, Faiman C. Premature ovarian failure: a search for circulating factors against gonadotropin receptors. *Am J Obstet Gynecol* 1983;146:816–21.
- [30] Ahonen P, Miettinen A, Perheentupa J. Adrenal and steroidal cell antibodies in patients with autoimmune polyglandular disease type I and risk of adrenocortical and ovarian failure. *J Clin Endocrinol Metab* 1987;64:494–500.
- [31] McNatty KP, Short RV, Barnes EW, et al. The cytotoxic effect of serum from patients with Addison's disease and autoimmune ovarian failure on human granulosa cells in culture. *Clin Exp Immunol* 1975;22:378–84.
- [32] Chen S, Sawicka J, Betterle C, et al. Autoantibodies to steroidogenic enzymes in autoimmune polyglandular syndrome, Addison's disease, and premature ovarian failure. *J Clin Endocrinol Metab* 1996;81:1871–6.
- [33] Weetman AP. Autoimmunity to steroid-producing cells and familial polyendocrine autoimmunity. *Baillieres Clin Endocrinol Metab* 1995;9:157–74.
- [34] Baumann-Antczak A, Wedlock N, Bednarek J, et al. Autoimmune Addison's disease and 21-hydroxylase. *Lancet* 1992;340:429–30.
- [35] Winqvist O, Karlsson FA, Kampe O. 21-Hydroxylase, a major autoantigen in idiopathic Addison's disease. *Lancet* 1992;339:1559–62.
- [36] Krohn K, Uibo R, Aavik E, et al. Identification by molecular cloning of an autoantigen associated with Addison's disease as steroid 17 α -hydroxylase. *Lancet* 1992;339:770–3.
- [37] Winqvist O, Gustafsson J, Rorsman F, et al. Two different cytochrome P450 enzymes are the

- adrenal antigens in autoimmune polyendocrine syndrome type I and Addison's disease. *J Clin Invest* 1993;92:2377–85.
- [38] Uibo R, Aavik E, Peterson P, et al. Autoantibodies to cytochrome P450 enzymes P450_{scc}, P450_{c17}, and P450_{c21} in autoimmune polyglandular disease types I and II and in isolated Addison's disease. *J Clin Endocrinol Metab* 1994;78:323–8.
- [39] Winqvist O, Gebre-Medhin G, Gustafsson J, et al. Identification of the main gonadal autoantigens in patients with adrenal insufficiency and associated ovarian failure. *J Clin Endocrinol Metab* 1995;80:1717–23.
- [40] Muir A, Maclaren NK. Autoimmune diseases of the adrenal glands, parathyroid glands, gonads, and hypothalamic-pituitary axis. *Endocrinol Metab Clin North Am* 1991;20:619–44.
- [41] Kamada M, Daitoh T, Mori K, et al. Etiological implication of autoantibodies to zona pellucida in human female infertility. *Am J Reprod Immunol* 1992;28:104–9.
- [42] Skinner SM, Mills T, Kirchick HJ, et al. Immunization with zona pellucida proteins results in abnormal ovarian follicular differentiation and inhibition of gonadotropin-induced steroid secretion. *Endocrinology* 1984;115:2418–32.
- [43] Kalantaridou SN, Davis SR, Nelson LM. Premature ovarian failure. *Endocrinol Metab Clin North Am* 1998;27:989–1006.
- [44] Santoro N. Research on the mechanisms of premature ovarian failure. *J Soc Gynecol Investig* 2001;8(Suppl):S10–2.
- [45] Hak AE, Pols HA, Visser TJ, et al. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. *Ann Intern Med* 2000;132:270–8.
- [46] Ishizuka B, Kudo Y, Amemiya A, et al. Anti-nuclear antibodies in patients with premature ovarian failure. *Hum Reprod* 1999;14:70–5.
- [47] Espey LL. Ovulation as an inflammatory reaction—a hypothesis. *Biol Reprod* 1980;22:73–106.
- [48] Bukulmez O, Arici A. Leukocytes in ovarian function. *Hum Reprod Update* 2000;6:1–15.
- [49] Irvine WJ, Chan MM, Scarth L, et al. Immunological aspects of premature ovarian failure associated with idiopathic Addison's disease. *Lancet* 1968;2:883–7.
- [50] Sedmak DD, Hart WR, Tubbs RR. Autoimmune oophoritis: a histologic study of involved ovaries with immunologic characterization of the mononuclear cell infiltrate. *Int J Gynecol Pathol* 1987;6:73–89.
- [51] Bannatyne P, Russell P, Shearman RP. Autoimmune oophoritis: a clinicopathologic assessment of 12 cases. *Int J Gynecol Pathol* 1990;9:191–207.
- [52] Rabinow SL, Berger MJ, Welch WR, et al. Lymphocyte dysfunction in autoimmune oophoritis: resumption of menses with corticosteroids. *Am J Med* 1986;81:347–50.
- [53] Hill JA, Welch WR, Faris HMP, et al. Induction of class II major histocompatibility complex antigen expression in human granulosa cells by interferon γ : a potential mechanism contributing to autoimmune ovarian failure. *Am J Obstet Gynecol* 1990;162:534–40.
- [54] Tidey GF, Nelson LM, Phillips TM, et al. Gonadotropins enhance HLA-DR antigen expression in human granulosa cells. *Am J Obstet Gynecol* 1992;167:1768–73.
- [55] Rebar RW, Connolly HV. Clinical features of young women with hypergonadotropic amenorrhea. *Fertil Steril* 1990;53:804–10.
- [56] Khastgir G, Abdalla H, Studd JW. The case against ovarian biopsy for the diagnosis of premature menopause. *Br J Obstet Gynaecol* 1994;101:96–8.
- [57] Mignot MH, Drexhage HA, Kleingeld M, et al. Premature ovarian failure. II: Considerations of cellular immunity defects. *Eur J Obstet Gynecol Reprod Biol* 1989;30:67–72.
- [58] Rabinow SL, Ravnkar VA, Dib SA, et al. Premature menopause: monoclonal antibody defined T lymphocyte abnormalities and antiovarian antibodies. *Fertil Steril* 1989;51:450–4.
- [59] Chernyshov VP, Radysh TV, Gura IV, et al. Immune disorders in women with premature ovarian failure in initial period. *Am J Reprod Immunol* 2001;46:220–5.
- [60] van Kasteren YM, von Blomberg M, Hoek A, et al. Incipient ovarian failure and premature ovarian failure show the same immunological profile. *Am J Reprod Immunol* 2000;43:359–66.

- [61] Hoek A, van Kasteren Y, de Haan-Meulman M, et al. Dysfunction of monocytes and dendritic cells in patients with premature ovarian failure. *Am J Reprod Immunol* 1993;30:207–17.
- [62] Shimizu H, Ichikawa Y, Yoshida M, et al. Lymphocyte subsets of the peripheral blood in myasthenia gravis determined by two-color flow cytometry. *Autoimmunity* 1990;6:173–82.
- [63] Ekeller-Yusel F, Hulstaart F, Hannet I, et al. Lymphocyte subsets in a large cohort of patients with systemic lupus erythematosus. *Lupus* 1993;2:227–31.
- [64] Horwitz DA, Gray JD, Ohtsuka K, et al. The immunoregulatory effects of NK cells: the role of TGF- β and implications for autoimmunity. *Immunol Today* 1997;18:538–42.
- [65] Sakaguchi S, Takahashi T, Nishizuka Y. Study on cellular events in post-thymectomy autoimmune oophoritis in mice. II: Requirement of Lyt-1 cells in normal female mice for the prevention of oophoritis. *J Exp Med* 1982;156:1577–86.
- [66] Taguchi O, Nishizuka Y. Autoimmune oophoritis in thymectomized mice: T cell requirement in adoptive cell transfer. *Clin Exp Immunol* 1980;42:324–31.
- [67] Healy DL, Bacher J, Hodgen GD. Thymic regulation of primate fetal ovarian-adrenal differentiation. *Biol Reprod* 1985;32:1127–33.
- [68] Ho HN, Wu MY, Chen HF, et al. In vivo CD3+CD25+ lymphocyte subpopulation is down-regulated without increased serum-soluble interleukin-2 receptor (sIL-2R) by gonadotropin releasing hormone agonist (GnRH-a). *Am J Reprod Immunol* 1995;33:134–9.
- [69] Ho PC, Tang GW, Lawton JW. Lymphocyte subsets in patients with oestrogen deficiency. *J Reprod Immunol* 1991;20:85–91.
- [70] Ho PC, Tang GW, Lawton JW. Lymphocyte subsets and serum immunoglobulins in patients with premature ovarian failure before and after oestrogen replacement. *Hum Reprod* 1993;8:714–16.
- [71] Morris RS, Sauer MV. New advances in the treatment of infertility in women with ovarian failure. *Curr Opin Obstet Gynecol* 1993;5:368–77.
- [72] Luborsky JL, Visintin I, Boyers S, et al. Ovarian antibodies detected by immobilized antigen immunoassay in patients with premature ovarian failure. *J Clin Endocrinol Metab* 1990;70:69–75.
- [73] Corenblum B, Rowe T, Taylor PJ. High-dose, short-term glucocorticoids for the treatment of infertility resulting from premature ovarian failure. *Fertil Steril* 1993;59:988–91.
- [74] Blumenfeld Z, Halachmi S, Peretz BA, et al. Premature ovarian failure—the prognostic application of autoimmunity on conception after ovulation induction. *Fertil Steril* 1993;59:750–5.
- [75] van Kasteren YM, Braat DD, Hemrika DJ, et al. Corticosteroids do not influence ovarian responsiveness to gonadotropins in patients with premature ovarian failure: a randomized, placebo-controlled trial. *Fertil Steril* 1999;71:90–5.
- [76] van Kasteren YM, Schoemaker J. Premature ovarian failure: a systematic review on therapeutic interventions to restore ovarian function and achieve pregnancy. *Hum Reprod Update* 1999;5:483–92.
- [77] Mankin HJ. Nontraumatic necrosis of bone (osteonecrosis). *N Engl J Med* 1992;326:1473–9.
- [78] National Institute of Child Health and Human Development. Available at: http://clinicalstudies.info.nih.gov/detail/A_1992-CH-0223.html.
- [79] Rebar RW, Erickson GF, Yen SS. Idiopathic premature ovarian failure: clinical and endocrine characteristics. *Fertil Steril* 1982;37:35–41.
- [80] Rebar RW, Cedars MI. Hypergonadotropic forms of amenorrhea in young women. *Endocrinol Metab Clin North Am* 1992;21:173–91.
- [81] Nelson LM, Anasti JN, Kimzey LM, et al. Development of luteinized graafian follicles in patients with karyotypically normal spontaneous premature ovarian failure. *J Clin Endocrinol Metab* 1994;79:1470–5.
- [82] Aiman J, Smentek C. Premature ovarian failure. *Obstet Gynecol* 1985;66:9–14.
- [83] Alper MM, Jolly EE, Garner PR. Pregnancies after premature ovarian failure. *Obstet Gynecol* 1986;67(Suppl):59S–62S.
- [84] Kreiner D, Drosch K, Navot D, et al. Spontaneous and pharmacologically induced remissions in patients with premature ovarian failure. *Obstet Gynecol* 1988;72:926–8.
- [85] Ohsawa M, Wu MC, Masahashi T, et al. Cyclic therapy resulted in pregnancy in premature ovarian failure. *Obstet Gynecol* 1985;66(Suppl):64S–7S.

- [86] Polansky S, De Papp EW. Pregnancy associated with hypergonadotropic hypogonadism. *Obstet Gynecol* 1976;47(Suppl):47S–51S.
- [87] Shangold MM, Turksoy RN, Bashford RA, et al. Pregnancy following the “insensitive ovary syndrome”. *Fertil Steril* 1977;28:1179–81.
- [88] Jones GS, De Moraes-Ruehsen M. A new syndrome of amenorrhoe in association with hypergonadotropism and apparently normal ovarian follicular apparatus. *Am J Obstet Gynecol* 1969;104:597–600.
- [89] Ledger WL, Thomas EJ, Browning D, et al. Suppression of gonadotrophin secretion does not reverse premature ovarian failure. *Br J Obstet Gynaecol* 1989;96:196–9.