Best Practice & Research Clinical Obstetrics and Gynaecology 60 (2019) 42–55

Contents lists available at ScienceDirect

Best Practice & Research Clinical Obstetrics and Gynaecology

journal homepage: www.elsevier.com/locate/bpobgyn

5

Premature ovarian insufficiency and autoimmune diseases

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Keywords:
Premature ovarian insufficiency
Autoimmune diseases
Antibodies
Antiovarian autoantibodies
Infertility

A B S T R A C T

Premature ovarian insufficiency (POI) is a clinical syndrome defined by loss of ovarian activity before the age of 40 years and has a potentially devastating effect upon women's health, both physically and psychologically. An underlying autoimmune disease has been identified in approximately 20% of patients with POI, the most common of which are disorders of the thyroid and adrenal glands. Nevertheless, in the majority of cases, the etiology is unknown. The damage mechanism to the ovary is usually caused by antibodies, and autoimmune POI is usually characterized by cellular infiltration of the theca cells of growing follicles by various inflammatory cells. Yet, other various factors and proteins of unknown clinical significance are present.

The major diagnostic tool for otherwise idiopathic POI is the presence of autoantibodies against various ovarian components that strongly support the option of autoimmune etiology of POI.

Treatment of the underlying cause of POI is the main strategy, although immunosuppressive therapy should be considered in a selected population of well-defined autoimmune POI and, as in idiopathic POI, in whom the resumption of ovarian activity is possible.

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https://doi.org/10.1016/j.bpobgyn.2019.07.008
1521-6934/

Introduction

Premature ovarian insufficiency (POI) is a clinical syndrome defined by loss of ovarian activity before the age of 40 years. The condition is characterized by menstrual disturbance (amenorrhea or oligomenorrhea) with elevated gonadotropin and low estradiol levels. POI is found in approximately 1% of women below the age of 40 years, 1:1000 women below 30 years, and 1:10,000 women below 20 years [1–3]. It may be affected by population characteristics such as ethnicity [4].

Premature ovarian insufficiency can occur by three major mechanisms: a reduced pool of oocytes; accelerated follicular atresia, or impaired folliculogenesis.

Two main histopathological types of POI have been described. In type 1 (afollicular), the ovarian follicles are completely depleted. Type 1 POI is usually associated with gonadal dysgenesis, chromosomal aberrations, and sex development disorders. The lack of ovarian follicles is due to absence of or failure of germinal cells to develop [5]. In type 2 (follicular), the ovarian follicular structures are preserved, and therefore, ovarian function may return. There are three forms of type 2 POI: (1) oophoritis, or inflammation of the ovarian follicles; (2) paucity of follicles present in the ovary; and (3) ovaries with numerous primordial follicles. Resistant ovary syndrome (ROS) has also been described [6]. ROS symptoms include clinical POI, hypergonadotropism, hypoestrogenism, and decreased sensitivity even to high-dose gonadotropins (Fig. 1).

The ovary is a common target of autoimmune attack in organ-specific and systemic autoimmune diseases [7–10]. The exact mechanism of autoimmunity in the pathophysiology of this disorder remains obscure; genetic or environmental factors may initiate the activation of the immune system [11]. Approximately 20% of patients with POI have been previously diagnosed with other concomitant autoimmune diseases, the most common of which are disorders of the thyroid, adrenal, and pancreas. In the majority of cases, the etiology is unknown. However, it has been reported that up to 40–50% of women with POI are positive for at least one organ-specific autoantibody [7,10,12], the most common being thyroid peroxidase Ab (24%) and antithyroglobulin antibodies (20%) [13]. Moreover, There is an increased incidence of gonadal insufficiency observed in patients with autoimmune disorders such as primary adrenal insufficiency (Addison's disease), autoimmune thyroid disease (Grave's or Hashimoto's disease) [14–16], and various gastrointestinal diseases (Table 1).

The main function of the immune system is to distinguish between self- and non-self-cells. Failure to downregulate controlling mechanisms may result in an excessive autoimmune response against self-antigens and the appearance of subsequent autoimmune disease [17]. An exaggerated autoimmune reaction such as autoimmune adrenal deficiency was first described with an association with

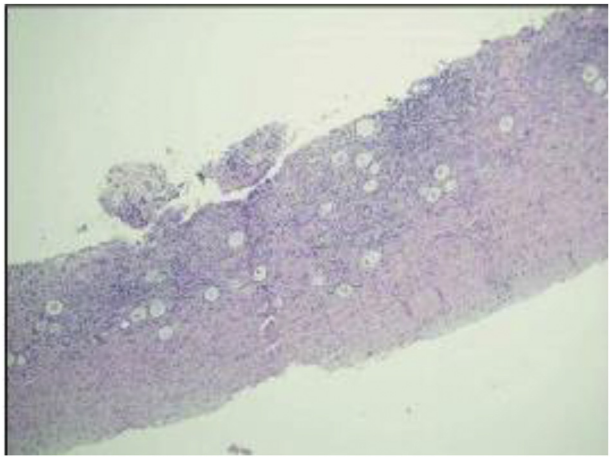

Fig. 1. An ovarian segment showing typical ROS histological appearance, taken from 16 years old female patient with menopausal levels of FSH and LH and undetectable Estrogen levels, treated in Sheba Medical Center, Israel.

Table 1
Auto immune diseases associated with POI.

Endocrine	Nonendocrine
Thyroid disease (hyper/hypo)	Chronic candidiasis (including APECED)
Addison's Disease	Idiopathic thrombocytopenic purpura (ITP)
Hypoparathyroidism	Vitiligo
Hypophysitis	Alopecia
Diabetes mellitus type 1	Autoimmune hemolytic anemia
	Pernicious anemia
	Systemic lupus erythematosus (SLE)
	Rheumatoid arthritis
	Sjögren's syndrome
	Primary Biliary Cirrhosis
	Chronic active hepatitis
	Celiac disease

atretic acceleration, excessive oocyte-wastage, and impaired folliculogenesis, resulting in POI [18]. The impact of the autoantibodies might be general, but in most cases, it is partial, organ-targeted, reversible, and associated with a fluctuating course of POI [14,19].

Autoimmune etiologies for POI are traditionally divided into two groups: endocrine and non-endocrine diseases (Table 1).

In POI, evidence for an autoimmune etiology is based on the presence of lymphocytic oophoritis, association with other autoimmune disorders, and autoantibodies to ovarian antigens, which has been clearly documented in several studies [15,20].

Mechanisms of damage to the ovary

Autoimmune ovarian damage is caused by several mechanisms: alteration of T-cell subsets and T-cell-mediated injury, increase in autoantibody-producing B-cells, and decrease in the number of effector suppressor/cytotoxic lymphocytes and the number and activity of natural killer cells [21]. Histopathological evidence of autoimmune ovarian involvement has been illustrated in 9–11% of the samples of ovarian biopsies and normal karyotypes in women with hypergonadotropic amenorrhea [14]. In POI, alterations in cellular immunity involving macrophage and dendritic cells are associated with a change in the CD4+/CD8+ ratio, as well as inappropriate expression of class II MHC antigens by granulosa cells [22].

Lymphocytic oophoritis and POI

Autoimmune oophoritis was first described in the presence of Addison's disease and is still usually detected jointly with Addison's disease [14]. Conversely, approximately 10% of women afflicted with Addison's disease develop POI [23]. Isolated POI is rare, occurring only in 3% of patients with typical oophoritis [14,24].

Autoimmune oophoritis is characterized by cellular infiltration of the theca cells of growing follicles by macrophages, natural killer cells, T-lymphocytes, plasma cells, and B-lymphocytes. The main target of the autoimmune attack is the steroid-producing cells [10], with sparing of the early-stage (primordial and primary) follicles. The developing follicles are surrounded by lymphocytic infiltration of the theca cells [25]. Perivascular and perineural inflammatory infiltrates are also seen [26]. Surprisingly, the size of the involved ovaries can be normal or enlarged [25]. Although the autoimmune attack causes follicular depletion in the final stage of the disease, systematic histological samples of ovarian tissues reveal detectable follicles of varying size and number in 40% of cases [14,27,28]. Hence, immunosuppressive agents may have a positive effect in restoring ovarian function, and the development of new immunosuppressive treatment could possibly restore fertility [16,21].

POI-associated autoimmune disorders

Several autoimmune disorders have been associated with POI; hypothyroidism is the most common and Addison's disease is the one with the highest prevalence of concurrent POI. Both endocrine (thyroid, hypoparathyroid, diabetes mellitus, and hypophysitis) and nonendocrine disorders (chronic candidiasis, idiopathic thrombocytopenic purpura, vitiligo, alopecia, autoimmune hemolytic anemia, pernicious anemia, systemic lupus erythematosus (SLE), rheumatoid arthritis, Crohn's disease, Sjögren's syndrome, primary biliary cirrhosis, and chronic active hepatitis) have been observed in association with autoimmune POI [29,30]. A review of literature regarding the relation between POI and autoimmunity indicates that autoimmune involvement is the main mechanism of POI in cases associated with other autoimmune diseases. However, in isolated POI, evidence supporting an autoimmune mechanism is weak [7,31]. High anti-Mullerian hormone and inhibin levels, low prevalence of histological evidence of oophoritis, and the occurrence of spontaneous pregnancy indicate transient ovarian damage and some degrees of functional ovarian preservation [32–34].

The ovaries appear to be frequently subject to a still poorly defined autoimmune attack associated with thyroid autoimmunity, anti-adrenal autoimmunity, and other, often non-organ-specific, autoimmune responses [14].

Other autoimmune-mediated causes of POI are described below:

Addison's disease

Autoimmune adrenal insufficiency may present as an isolated disease or may be associated with other autoimmune disorders [35]. Approximately 10–20% of patients with Addison's disease have POI, and 2.5–20% of women with POI show some evidence of adrenal autoimmunity [10]. The age of POI onset has been reported to be independent of the presence of Addison's disease [36]. POI usually occurs before the onset of adrenal involvement [7], but occasionally, Addison's disease may precede POI. The mean age of onset of each condition is 27 years for Addison's disease and 28.5 years for POI [37]. However, POI may precede Addison's disease by 8–14 years, and there is a 50% risk of development of adrenal insufficiency in women with adrenal autoimmunity. The association of POI with Addison's disease could be due to the presence of cross-reacting autoantibodies, particularly the side-chain cleavage enzyme, which react against auto-antigens common to steroid-producing cells from different origins [36,37]. Positive adrenal antibodies can be found in such cases of POI. An autoimmune response to the steroid-genetic enzymes and ovarian steroid cells appears to mediate ovarian function in these cases [38].

The underlying autoimmune disease that causes POI may be clinically apparent or a subclinical process with antiadrenal antibody production but without adrenal insufficiency. The antibodies directed against steroid-producing cells of various endocrine glands such as adrenal cortex cells, Leydig cells of the testis, placental syncytiotrophoblast, and theca cells of the ovary are known as steroid cell antibodies (StCAs). StCAs were detected in 60–87% of POI-associated adrenal involvement and 3–10% of patients with isolated POI [14,19,25,31,36,37]. StCAs are polyclonal immunoglobulins of the IgG class [39]. Certain enzymes involved in steroidogenesis are the targets for these autoantibodies. The main antigenic targets of StCAs are P450-17α-hydroxylase (17α-OH), P450-side-chain cleavage (P450scc), and 21-hydroxylase (21-OH) [35]. StCAs are present in some autoimmune diseases such as autoimmune polyglandular syndromes (APS); type I, type II, Addison's disease (AD), and POI [40]. Their prevalence is 60% in patients with APS-I, 25–40% in patients with APS-II, 60–87% in patients with POI-associated AD, and 3–10% in patients with isolated POI [31]. It is likely that 17α-OH and P450scc are the main molecular targets of StCAs in sera-positive patients with POI-associated AD [7,35].

The detection of antibodies against 17α-OH and P450scc in patients with Addison's disease was found to be a predictive factor for the development of POI [35]. However, it has been suggested that the presence of 21-OH antibodies in serum samples from women with autoimmune POI might be an important marker in identifying patients at risk of developing autoimmune adrenal insufficiency [35, 36). It has been demonstrated in past studies that patients with POI who show positive sera for StCAs are at risk for adrenal insufficiency, a potentially fatal condition, especially during pregnancy [35,41,42]. Moreover, untreated adrenal insufficiency might be associated with serious fetal and maternal complications such as postpartum adrenal crisis [42]. Therefore, identification of this subgroup of patients

with POI along with subclinical adrenal insufficiency is essential before making decisions about egg or embryo donation or when planning a pregnancy.

All patients with POI should be made aware of the symptoms of adrenal insufficiency and should undergo evaluation of adrenal function if such symptoms develop [43,44]. The best markers of occult autoimmune adrenal insufficiency are circulating 21-OH antibodies [44]. Patients who are suspected of POI and are positive for adrenal cortex antibodies should be referred to an endocrinologist for close follow-up and intrapregnancy monitoring of adrenal functions. Furthermore, patients with POI may benefit from routine screening of thyroid function and glucose tolerance because of the high incidence of POI and adrenal insufficiency comorbidity. However, as the frequency of other autoimmune diseases associated with POI is relatively low, wider endocrine screening is not required routinely.

Thyroid diseases

Thyroid autoimmunity is the most prevalently (25–60%) associated endocrine autoimmune abnormality reported in patients with POI without adrenal autoimmunity [45–47]. The presence of high levels of nonovarian, thyroid peroxidase antibodies leads to the development of clinical and subclinical hypothyroidism [45–47]. Thyroid autoimmune disease, most commonly Hashimoto's thyroiditis, is present in 14–27% of women at initial diagnosis of POI [11]. A case report has even described how hypothyroidism caused intermittent secondary amenorrhea and, eventually, POI at the age of 35 years in an otherwise healthy patient [48]. Therefore, it is reasonable to measure thyrotropin levels and test for the presence of thyroid peroxidase antibodies. All women with thyroid autoantibodies should be referred to an endocrinologist for additional evaluation and long-term follow-up [11].

The reported concurrence of thyroid disease with diabetes mellitus is 2.5% [10].

Autoimmune polyglandular syndromes (APS)

Autoimmune polyglandular syndromes (APS) are a series of disorders characterized by autoimmunity against two or more endocrine organs [18,49].

It has long been recognized that POI could be associated with nearly all organ-specific autoimmune diseases, and the combination of several autoimmune diseases in the same patient is referred to as APS [14, 41, 49). APS can be classified as APS 1, 2, and 3 (see Table 2).

Autoimmune polyglandular syndrome I (APS-I)

APS-I is probably the best-defined form of autoimmune-associated POI, also known as the autoimmune polyendocrinopathy–candidiasis ectodermal dystrophy (APECED) or Whitaker syndrome.

Table 2
Three types of autoimmune polyglandular syndrome (APS) [adapted from Yan G et al. [66].

APS type	Genetic Background	Clinical manifestation	Average age of appearance
I	AIRE gene, chromosome 21, autosomal recessive	Addison's disease; chronic mucocutaneous candidiasis; hypoparathyroidism; ectodermal dystrophy	3–5 years
II	HLA-DQ2 (DR3), HLA-DQ8 (DR4), autosomal dominant	Addison's disease; type 1 diabetes mellitus; autoimmune thyroid disease	30–40 years, female predominance
III	Same as APS-II	Autoimmune thyroiditis; diabetes mellitus,http://www.nlm.nih.gov/medlineplus/ency/article/000569.htm pernicious anemia; vitiligo; alopecia; myasthenia gravis; Sjogren's syndrome; no adrenal involvement	Middle age, mostly women

APECED is a rare autosomal recessive disorder without any association with a specific human leukocyte antigen (HLA) or haplotype [27,50]. It mainly affects children and is associated with mucocutaneous candidiasis, ectodermal defects, hypoparathyroidism, Addison's disease, and POI [8,27]. APS-I is caused by a mutation in the autoimmune regulator (AIRE) gene [21,51]. AIRE is of importance in the thymus, where it regulates self-tolerance from T-cell attack. Mutations in the gene have therefore been associated with attack against "self" antigens [52]. As a result, POI develops in 41–72% of patients with APS type I [8,10,27,37,41]. When compared with female subjects, male subjects experience testicular failure quite rarely (approximately 2% of carriers). Gonadal failure tends to appear at a younger age and is more prevalent than other forms of APS. Gonadal failure could be due to the mutations in the AIRE gene in patients with APS-I [35–37].

Autoimmune polyglandular syndrome II (APS-II)

APS-II, also called Schmidt–Carpenter syndrome, is an autosomal dominant disease linked to chromosome 6 and associated with HLA-B8DR3DR4 haplotypes. APS-II is a common condition and includes primary adrenal insufficiency (Addison's disease), autoimmune thyroid disease, insulin-dependent-diabetes, celiac disease, and myasthenia gravis. APS-II affects 14–20 million people with a female predominance. Five percent to 50% of patients have early ovarian or testicular failure [53], and the prevalence of POI is approximately 10–25% [9,37,38,49]. In APS-II, the alleles of human leukocyte antigens (HLAs) determine the targeting of specific tissues by autoreactive T cells, which leads to organ-specific autoimmunity as a result of loss of tolerance [52,53]. In general, Addison's disease precedes POI in patients with APS-I and occurs following POI in patients with APS-II [37]. It was suggested that steroid-producing cell antibodies (StCAs), 17α-OHAb, and P450sccAb are the immunological predictive markers of potential autoimmune POI in patients with autoimmune Addison's disease and various forms of APS [37].

Autoimmune polyglandular syndrome III (APS-III)

APS-III is quite similar to APS-II, except that there is no adrenal deficiency, but other autoimmune diseases such as pernicious anemia or vitiligo are often associated [9]. The prevalence of APS-3 among patients with POI is approximately 33% [29], making APS-III one of the most common co-syndromes of POI.

SLE

Corpus luteum antibodies are present in 22% of patients with SLE. The presence of corpus luteum antibodies in the patients who were all <40 years of age correlates with elevated serum FSH levels. Therefore, anti-corpus luteum antibodies could represent the first stage of altered ovarian function in patients with SLE [7].

Endometriosis

Endometriosis has been labeled an "autoimmune syndrome" because, as classical autoimmune diseases, endometriosis is characterized by polyclonal B-cell activation and production of multiple different autoantibodies. Approximately 40–60% of patients with endometriosis have elevated autoantibody titers when tested against a panel of autoantigens. These patients often possess specific anti-endometrial antibodies, anti-ovarian antibodies (AOA), antinuclear autoantibodies (ANA), smooth muscle autoantibodies (SMA), and antiphospholipid antibodies (APA) [7,33,54,55].

However, endometriosis per se will not cause POI, although antibodies can be found. Endometriosis sometimes extends to the ovaries, forming endometriomas (endometriosis cysts). Endometriomas are hypothesized of having a negative effect on the amount of functional ovarian tissue by two mechanisms: (1) space-occupying effect by applying physical pressure on the remaining normal follicle-containing ovarian tissue and (2) secretion of local inflammatory factors that damage the ovary. This process might be exacerbated by endometriosis surgery [56]. Generally, the number of ovarian follicles declines with age. However, this decline starts at an earlier age in with ovarian endometriosis [56].

Although the best surgical approach to endometriomas is uncertain, it is now recognized that any type of surgery could cause additional damage to already compromised ovarian function [57].

Ovarian endometriosis has been shown to have an adverse effect on ovarian physiology, by sonography and histology. Moreover, the local intrafollicular environment in the affected ovary is characterized by alterations of the granulosa cell compartment including reduced P450 aromatase expression and increased intracellular reactive oxygen generation. Recent studies have demonstrated that oocytes retrieved from patients with endometriosis are more likely to fail in vitro maturation and to show altered morphology and lower cytoplasmic mitochondrial content than those from women with other causes of infertility. Furthermore, meta-analyses have shown an association between endometriosis and a reduction in the number of mature oocytes retrieved. However, evidence is still not sufficient to be conclusive, especially with regard to the effects of different stages of the disease and the impact of patients' previous medical/surgical treatment [58]. Nevertheless, the main mechanism for follicular loss in endometriosis is still surgical intervention. Patients affected with severe endometriosis are at significant risk for ovarian tissue damage, which may lead to infertility, reduced response to ovarian stimulation and, occasionally, premature ovarian insufficiency. The risk of damage to the ovarian reserve in young patients is especially high following repeated surgical intervention and in the presence of bilateral endometriomas [59].

Immunization

There have been case reports linking POI with immunization leading to anti-ovarian antibody formation by molecular mimicry, especially with quadrivalent anti-HPV vaccine [60–62]. To date, there is no evidence associating HPV vaccinations and POI or establishing causation between the two. Further investigation in this area is still required [61]. Presently, our recommendation is that there is no reason to discourage patients from receiving HPV vaccination.

Laboratory findings

In a vast proportion of POI cases, an underlying cause is found after a diagnostic panel of antibodies is used. However, in a substantial number of POI cases, no antibodies are found. One of the reasons is that those antibodies might be unknown to our contemporary medical knowledge or undetectable by our laboratory equipment. The main reason idiopathic POI is so difficult to diagnose is that usually once it is discovered, the autoimmune attack has already passed and no evidence of any antibodies is left.

Following are the common antibodies known to be linked to POI:

Antiovarian autoantibodies

Antiovarian autoantibodies (AOAs) are usually considered an independent marker of autoimmune ovarian disease, although their specificity and pathogenic role are questionable. First identified in 1966, AOAs were also one of the first descriptions of antiovarian autoimmunity [63]. However, the role of AOA is still conflicting, particularly due to interlaboratory differences and the fact that many ovarian components may be potential antigens [64]. The investigation of antiovarian autoimmune reactions and autoantibodies may be severely hampered by the fact that POI represents the end stage of the disease. By the time of diagnosis, the follicular supply is exhausted and, presumably, also the target antigen for the autoimmune attack. Thus, the autoimmunity causing POI can be difficult to detect. Regardless, a high prevalence of AOAs (30–67%) and other organ- and nonorgan-specific autoantibodies has been observed in patients with POI [12,65,66]. AOA either may be a marker of primary or secondary immune dysfunction of the ovaries [8,20,65,67] or may be involved in the immunologic mechanisms causing POI [28,65,67]. AOAs have been detected in the serum prior to the onset of clinical presentation of POI [40]. AOAs have been speculated to be factors contributing not only to POI but also to infertility and in vitro fertilization and embryo transfer (IVF-ET) failures [68,69]. The uncertainty as to whether AOAs are causative or merely markers of another process is similar to the uncertainty over

the role of autoantibodies in other autoimmune diseases [70]. It is possible that several different antigens are involved in ovarian autoimmunity because both ovarian cellular and zona pellucida/oocyte antibodies have been reported [12,66]. A considerable number of known antigens have been identified as molecular targets of AOA; steroidogenic enzymes such as 17α-hydroxylase, desmolase (P450 side-chain cleavage), 3β-hydroxysteroid dehydrogenase, and 21-hydroxylase [12,65]. Human heat shock protein 90-β (strongly induced during chlamydial infections) and anti-α-enolase have also been identified as unique antigens in antiovarian autoimmunity associated with POI and infertility [12]. The correlation between antibody levels and severity of disease is poor [10]. A major weakness in the assessment of the role of AOAs is the high rate of false-positive results (poor specificity) [71], as these autoantibodies have been identified in a significant number of control patients [71] and may be naturally occurring (NAA) [72]. Presently, there is no valid serum marker specific for the diagnosis of autoimmune POI.

Other antibodies

Gonadotropin receptors have also been investigated as potential autoantibody targets. The majority of antiovarian autoantibodies are directed against the β-subunit of follicle-stimulating hormone (anti-FSH), which might modulate the recognition and binding of FSH to its receptor, hence pathologically influencing ovarian function [12]. The presence of anti FSH antibodies in association with an increased risk of ovarian failure is independent of reproductive hormonal levels [65].

More recently, a concept of functional autoantibodies both stimulating and/or suppressive has been suggested in autoimmune diseases. Functional antibodies have been described to act on “sister-organs” such as ovary, thyroid, and adrenal glands [33]. Abnormalities of cellular immunity, that is, T-lymphocytes (especially effector helper, CD4-positive T cells), macrophages, and dendritic cells, also have an important role in autoimmune reactions, particularly in the development of autoimmune lesions. These processes were described in POI and thus support autoimmune causation of POI [73,74].

Functional antibodies binding to various steroid hormone-producing cells [19], gonadotropins and their receptors [75], zona pellucida [76], oocyte [65], corpus luteum [7], and several other antibodies such as anticardiolipin and antinuclear antibodies [31] have been reported to be markers of ovarian autoimmunity. The multiplicity of the suspected auto antigens and related antibodies illustrates the variety of pathologic process that may lead to ovarian damage.

There are various factors and proteins with an unknown clinical significance, although found in the sera of patients with POI, including idiopathic POI and potentially mediated autoimmune damage in POI:

1. Anti-βFSH antibodies [77].
2. Gonadotropin receptor autoantibodies
3. Anti-zona pellucida (ZP) antibodies (the ZP is the extracellular matrix surrounding the human oocyte). Possible mechanism includes impaired communication between oocyte and granulose cells [78].
4. Antioocyte cytoplasm antibodies have been detected in patients with POI [65].
5. MATER (Maternal Antigen That Embryos Require), a 125 KDa protein with very little available information about the precise nature and function [14,32,50,79].
6. Aldehyde dehydrogenase1A1 (ALDH1AI) [80].
7. Selenium-binding protein 1 (SBP1) [80].
8. α-Enolase [80].
9. Heat Shock Protein 90 (HSP90), and more specifically, the HSP90β, is the most immunodominant antigen [81].
10. 3β-Hydroxysteroid dehydrogenase autoantibodies, particularly found in isolated idiopathic POI [81].

These antibodies require further investigation to determine the possible clinical importance.

Diagnosis and management

POI is a diagnosis that is difficult for women to accept. The loss of reproductive capabilities requires multidisciplinary management, which includes the provision of proper counseling, emotional support, nutrition supplement advice, HRT, possible immunosuppressive therapy, and reproductive health care including contraception and fertility issues [34].

Ovarian biopsy is the gold standard for detecting autoimmune involvement of ovarian tissue and the presence of developing follicles [14,22]. Nevertheless, ovarian biopsy is invasive and expensive. Additionally, it is questionable whether an ovarian biopsy accurately represents the follicular density of the entire ovary, particularly in idiopathic POI, characterized with variable degrees of ovarian function preservation [41,82]. Most POI ovaries contain only fibrous connective tissue covered by cuboidal epithelium, with atretic follicles or occasional corpora albicantia. However, the presence of follicles, either quiescent or growing, was also documented in approximately 15% of cases. This includes follicles of different sizes: primordial follicles (9%), primary follicles (12%), secondary follicles (10%), and early antral follicles in 4.5% of cases [83].

A noninvasive screening test is needed to avoid unnecessary ovarian biopsy and consequent ovarian damage. Antibodies to steroid-producing cells have been frequently found in patients with histological evidence of lymphocytic infiltration of ovarian tissue [14). A positive correlation between the presence of autoimmune oophoritis and serum adrenal cortex antibodies was previously described. Consequently, assessment of adrenal cortex autoantibodies in the sera of patients with POI has been recommended to select patients with autoimmune oophoritis [25]. A well-conducted study is needed to determine whether antibody levels can adequately replace ovarian biopsy.

Transitory estrogen deficiency, higher anti-Mullerian hormone and inhibin levels, higher spontaneous recovery of ovarian cycles, and/or pregnancy, whether hormone induced or spontaneous, suggest a partial, reversible autoimmune attack, particularly in idiopathic POI with a variable degree of ovarian function preservation [32–34]. POI associated with anti-adrenal autoimmunity represents a homogeneous and well-characterized subgroup of ovarian failure, whereas in other forms of POI, there are diverse clinical, immunological, and histological features.

The presence of autoantibodies against various ovarian targets strongly supports the hypothesis of an autoimmune etiology of POI. Different autoantibodies were found in different clinical features of autoimmune POI. Patients with POI associated with autoimmune disease of the adrenal frequently present with autoantibodies that recognize several types of steroid-producing cells of the adrenal cortex, testis, placenta, and ovary, therefore called steroid cell antibodies (SCA). The prevalence of SCA is ~60% in patients with APS-I, 25–40% in patients with APS-II, and almost 78–100% in patients with both.

Addison's disease and POI [14,19,43]. These statistics allow us to use this available and minimally invasive tool for diagnosis, especially when compared with the previously described ovarian biopsy. In patients with POI not associated with adrenal autoimmunity, and in isolated, or idiopathic POI, the prevalence of SCA remains as low as 10%. In those patients, other autoantibodies are found, either ovarian or nonovarian, as previously described.

The clinician should suspect an autoimmune mechanism among patients with an overt autoimmune disorder and patients with POI or low ovarian reserve at a young age. An autoimmune workup should be considered for couples with unexplained infertility.

The European Society of Human Reproduction and Embryology (ESHRE) published the following recommendations for investigation of suspected POI [4] (only the autoimmune-related recommendations are specified here):

1. Screening for 21OH-Ab (or alternatively adrenocortical antibodies (ACA)) should be considered in women with POI of unknown cause or if an immune disorder is suspected
2. Refer POI patients with a positive 21OH-Ab/ACA test to an endocrinologist for testing of adrenal function and to rule out Addison's disease
3. Screening for thyroid (TPO-Ab) antibodies should be performed in women with POI of unknown cause or if an immune disorder is suspected

4. In patients with a positive TPO-Ab test, thyroid-stimulating hormone (TSH) should be measured every year
5. There is insufficient evidence to recommend routine screening of women with POI for diabetes
6. The possibility of POI being a consequence of a medical or surgical intervention should be discussed with women as part of the consenting process for that treatment.
7. In a significant number of women with POI, the cause is not identified and these women are described as having unexplained or idiopathic POI.

Treatment of autoimmune-derived POI

Lymphocytic infiltration of the theca layer of developing follicles and sparing of primary and primordial follicles presents the possibility of resumption of ovarian function by immunosuppressive treatments [84]. However, in most instances, treatment with immunosuppressive agents fails to reverse the course of ovarian autoimmunity or to enhance the ovarian response to gonadotropins [10]. Numerous studies have recommended cell-mediated and humoral immunity suppression by glucocorticoids or anti-B-cell therapies for reversal of infertility or resumption of ovarian function in selected groups of patients with autoimmune POI [27,85,86]. It should be borne in mind that no study was randomized, controlled, or well selected [85]. Indeed, published reports were mostly case series [86].

Treatment modalities such as high doses of corticosteroids may cause serious complications such as Cushing syndrome and knee osteonecrosis. Reports on the use of IVIg as a treatment method for an underlying autoimmune diseases related to POI are scarce, mainly case reports in patients with a complicated medical background such as vasculitis and Crohn's disease [87]. Another possible treatment option is to bypass ovarian maturation with in vitro maturation (IVM) of oocytes derived from primordial follicles or stem cells [47,88]. When POI is permanent and prolonged, the only option may be oocyte donation [47,88].

Currently, there is no specific treatment modality for autoimmune oophoritis with proven efficacy and safety confirmed by prospective randomized placebo-controlled studies. Considering the few patients seen with POI in any IVF center, it is doubtful if such trials will ever be conducted.

Although in most cases POI is idiopathic, and there is need for further testing to seek a specific etiology, such as autoimmune and genetic studies, the latter being especially important in familial POI. The strong association of POI with APS makes screening for APS essential [67,88]. In idiopathic POI, attention should be paid to indirect autoimmune signs, such as association with possible autoimmune diseases (clinical aspects, hormone levels, and antibodies). Ovarian function may return after regression of the autoimmune status and control of coexistent endocrine disease. After confirming the diagnosis of POI and assessment of ovarian reserve, including endocrine and ultrasonography markers for evaluation of ovarian volume and follicular pool, there is an urgent need to determine the optimal therapeutic hormonal regimens, in terms of both immediate menopausal symptom relief and protection against the long-term sequelae of estrogen deficiency, such as osteoporosis [42,88,89].

In patients with POI, estrogen is used to overcome the effects of estrogen deficiency and to encourage recovery of ovarian function by restoration of receptor sensitivity to gonadotropins with a salutary effect on folliculogenesis and conception [47,90,91]. The dose should be higher than that used in the older age groups. However, oral estrogens may increase coagulation activation [90,92]. Therefore, transdermal HRT may be preferable in women with coagulation disturbances and those more prone to thrombosis, such as in the presence of hereditary thrombophilias. Androgen replacement is useful in some patients with clinical signs and symptoms of androgen insufficiency, that is, HSDD (hypoactive sexual desire disorder) [90,93].

Immunosuppressive therapy, with steroids should be considered in a selected population of well-defined autoimmune POI and as in idiopathic POI, in whom the resumption of ovarian activity is possible [28,85,86]. Other fertility issues should be considered in patients with POI seeking fertility, including different regimes of ovulation induction and assisted conception techniques, such as gamete or embryo donation or IVM with oocytes derived from post antral follicles [47,88].

Conflict of interest statement

None declared.

Practice points

- POI is a common result of an autoimmune attack, although, in most cases, the etiology is unknown.
- Screening for POI should be conducted among female patients with an overt autoimmune disease for early detection.
- Currently, there is no effective treatment for POI; treatment should focus on the underlying autoimmune cause to hopefully reverse the ovarian damage.

Research agenda

- POI and other autoimmune diseases are closely linked. Further genomic analyses are required in the region of the FMR locus to specify the genetic predisposition.
- Some cases of POI, particularly the isolated ones may have a basis in molecular mimicry, in which microorganisms may induce the autoimmune response. Research is required into the specific microorganisms, which may be involved.
- After ovarian follicular destruction has occurred, POI cannot be reversed. It is necessary to define earlier stages of the disease to avoid progression to the end stage.
- If a specific gene is found to be associated with POI, gene therapy might prevent the occurrence of this irreversible situation.

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