REVIEW

Premature ovarian insufficiency (POI) and autoimmunity-an update appraisal

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Abstract

Purpose Primary ovarian insufficiency (POI) represents ovarian dysfunction related to very early aging of the ovaries. While the cause of POI in a majority of clinical cases remains undefined, autoimmunity is responsible for approximately 4–30% of POI cases. In the present paper, we aim to provide a critical appraisal and update review on the role of autoimmunity in POI patients.
Methods A literature review was conducted for all relevant articles reporting on POI and autoimmunity. PubMed/MEDLINE and the Cochrane library were searched for the best available evidence on this topic.
Results Patients with POI and coexisting autoimmunity are indistinguishable from those with negative autoimmune screen with regard to age of onset, prevalence of primary amenorrhea, or their endocrine profiles. A specific noninvasive reliable diagnostic test for the diagnosis of an autoimmune etiology is lacking; therefore, patients should be screened for the most common autoantibodies, i.e., steroid cell antibodies, anti-ovarian antibodies, and anti-thyroid antibodies. Moreover, treatment strategies to POI infertility are lacking and controversial.
Conclusions Nowadays, guidelines for the treatment of autoimmune POI are not available. Moreover, since diagnostic and treatment strategies to POI infertility are still lacking and controversial, further large clinical studies are needed to investigate the true impact of autoimmunity on POI and to identify the selected groups of patients who are most likely to benefit from immunossuprresive treatment.

Keywords Primary ovarian insufficiency (POI) · Autoimmunity · Diagnosis · Steroid cell antibodies · Anti-ovarian antibodies · Anti-thyroid antibodies · Immunossuprresive

Introduction

The number of oocytes in the human ovaries is determined during fetal life and progressively decreases throughout the female reproductive life span. The maximum number of oocytes is 6 to 7 million at approximately 20 weeks gestational age, decreases to approximately 1 to 2 million at birth and to 300,000–500,000 at puberty. From puberty to the age of 51 years—coinciding with the average menopausal age [1–3]—there is a progressive age-related decline in both egg quality and number, which is responsible to decrease fecundity. While the reductions in oocyte quantity and quality with advanced age (typically in the mid-40s) are a normal physiologic occurrence termed diminished ovarian reserve (DOR) [4], some women experience DOR much earlier and become prematurely infertile. Of notice, the majority of follicles are lost to atresia during the maturation process [5, 6]. Within each woman, there are large variations in the number of oocytes and the rate of ovarian oocytes pool depletion [7], with limited knowledge of what controls this number.

Premature ovarian failure (POF) is defined by the presence of postmenopausal levels of FSH (> 40 IU/L) in woman under 40 years of age, with four or more months of secondary amenorrhea [8–11]. POF affects ~ 1% of women before the age of 40 and 0.1% before the age of 30 [12, 13], and is characterized by infrequent or absent periods, infertility, menopausal symptoms, and long-term adverse effects of estrogen deprivation. Treatment should be therefore primarily directed at symptom resolution, including a psychosocial support for women facing this devastating diagnosis. Of notice, POF represents the most

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extreme cases of a much larger group of 10% women with so-called premature ovarian aging (POA) [14].

Histological examination of ovaries from POF patients shows either a complete loss of ovarian follicles or the persistence of more or less abundant follicles. The latter represents ~40% of POF patients [15] and is in agreement with ultrasound studies that have demonstrated residual follicular structures in 41–60% of patients with POF [16, 17]. Of notice, while follicular depletion might be the consequence of non-autoimmune causes, it may also be the final stage of an autoimmune disease, where inflammation has ceased following the elimination of all autoantigens.

A decade ago, the term primary ovarian insufficiency (POI) was introduced to represent ovarian dysfunction related to very early aging of the ovaries. The terminology of POI is considered to better represent this POA condition [18], because there is intermittent and unpredictable ovarian function and spontaneous ovulations in 50% and 20%, respectively and about 5–10% of these women conceive after the diagnosis is made [11, 19].

In recent years, the known aetiologies of POI have expanded, although the cause of POI in a majority of clinical cases remains undefined. POI can be iatrogenic (as a consequence of ovarian surgery, chemo-radiotherapy, etc.), caused by genetic/chromosomal aberrations, infections, environmental factors, metabolic (diabetes type 1, galactosemia, etc.), and endometriosis or it can be associated with autoimmune disorders [19, 20].

According to the ESHRE Guideline Group on POI [21], patients with POI should undergo a thorough investigation, which includes:

- Chromosomal analysis
- Autosomal genetic testing only in cases suggestive of a specific mutation (e.g., blepharophimosis–ptosis–epicanthus inversus syndrome)
- Fragile-X premutation testing
- Screening for 21OH-Ab (or alternatively adrenocortical antibodies (ACA)
- Screening for thyroid antibodies
- Routine screening POI women for diabetes or infection is not recommended

Autoimmune causes of POI should be suspected in the presence of anti-ovarian antibodies (AOAs), the histological evidences of lymphocytic oophoritis, or any associated autoimmune disorder [15, 22]. While the coexistence of autoimmune disorders is common in POI patients, histological signs of oophoritis were detected only in those with circulating adrenal or AOAs [23, 24].

Autoimmunity is responsible for approximately 4–30% of POI cases [25, 26]. Patients with POI and coexisting autoimmunity are indistinguishable from those with negative autoimmune screen with regard to age of onset, prevalence of primary amenorrhea, or their endocrine profiles, with 30% of those experiencing a return of menstruation had a positive antibody screen. Yet, according to the aforementioned ESHRE Guideline Group, the diagnostic autoimmune workup for POI should be restricted only to the measurements of antibodies to ACA/21OH and thyroid antibodies and TPO-Ab [21].

Prompted by the aforementioned information, in the present review, we aim to provide a critical appraisal and update review on the role of autoimmunity in POI infertile patients.

The immune system and ovarian physiology

The immune system plays a crucial role in ovarian physiology [27]. Depletion of macrophages/dendritic cells in CD11c-diptheria toxin receptor transgenic mice resulted in loss of ovarian vascular integrity, reduction in mature follicles, and impaired ovulation [28–30]. Moreover, systemic pro-inflammatory conditions were shown to alter ovarian homeostasis and detrimentally affect follicular dynamics [31]. The human ovary is a common target to autoimmune attack, with the consequent occurrence of ovarian dysfunction manifested by POI, polycystic ovary syndrome, unexplained infertility, or endometriosis [32]. In POI patients, evidences for autoimmune cause relate on the presence of either lymphocytic oophoritis, association with other autoimmune disorders, or the presence of AOAs [10, 14].

Cellular immunity

Abnormalities of the cellular immunity play an important role in pathogenesis of autoimmune POI [33–35]. The absolute count and percentage of peripheral blood T-lymphocytes, especially CD4+ T cells, were found to be increased in patients with POI [33], while the number and activity of natural killer (NK) cells seemed to be reduced [36, 37]. POI patients were shown to have low levels of CD8+/CD57+ T cells (cytotoxic T lymphocytes) and an overall increase of the CD4+/CD8+ ratio [38, 39], which could be the result of chronic hypoestrogenism [40]. Moreover, blood monocytes of POI patients demonstrated an abnormal response to chemotactic agents in vitro [36, 40], whereas dendritic cells from the same patients presented a reduced capacity to aggregate with T-lymphocytes.

Kobayashi have recently examined the relationship between peripheral blood regulatory T (Treg) cells and autoantibodies in POI. They observed decreased numbers of effector Treg cells and increased CD4+ CD69+ activated T cells in peripheral blood in POI, supporting the aforementioned observations suggesting that POI is an autoimmune disease [41].

The role of cytokines has also been described in causing follicular atresia in POF [42, 43]. This coexistence of an impaired cellular immune response with autoimmune ovarian

inflammation may further illustrate the complex defects of immune regulation in autoimmune ovarian disease.

Humoral immunity

The detection of autoantibodies directed against various ovarian targets was first reported mainly in patients with POI and an associated adrenal autoimmune disease [44–46]. The antibodies, polyclonal immunoglobulins of the IgG class, were directed against various types of steroid-producing cells, such as adrenal cortex, ovarian theca interna and corpus luteum, testicular Leydig cells, and placental trophoblasts [44, 47–49], and were therefore called steroid cell antibodies (SCA). Moreover, the observed IgG1-dominated SCA might suggest a predominant Th1 response [50].

The highest prevalence (87–100%) of SCA was noticed in patients with both Addison's disease and POI [22, 45, 46, 48, 51]. In a long-term study, it was demonstrated that approximately one- third of normally cycling women with polyendocrinopathy and SCA will develop ovarian failure [46, 52]. On the other hand, the prevalence of SCA is < 10% in patients with isolated POI and those with autoimmune pathologies other than Addison's disease [46, 51, 53, 54]. Moreover, while testing idiopathic POI patients' sera for various organ-specific and non-organ-specific antibodies, the percentage of patients with at least one autoantibody ranged between 34 and 92% [17, 38, 55–57]. The molecular nature of SCA in idiopathic POF patients is still unclear.

Anti-oocyte antibodies were identified in 1966, and this was also one of the first descriptions of anti- ovarian autoimmunity [58]. Anti-ovarian antibodies have several recognized targets—the ooplasm, the zona pellucida, the granulosa cells, the 3beta-OH hydroxysteroid dehydrogenase (3b-HSD), and the gonadotrophin receptors [15, 46, 57, 59–64]. Corpus luteum antibodies, for example, are present in 22% of patients with SLE, correlating with elevated serum FSH in young patients < 40 years of age. Their detection might therefore represent the first stage of impaired ovarian function in SLE patients [22]. Another example is the detection of anti-ovarian autoantibodies directed against the β-subunit of follicle-stimulating hormone (anti-FSH) in association with POI. These autoantibodies might influence ovarian function by modulating the recognition and binding of FSH to its receptor [65, 66].

While 40% of patients presenting with occult ovarian failure had antiovarian antibodies, there is poor correlation between AOA levels and severity of disease, and no correlation was observed between these antibodies and serum FSH or inhibin B levels [67]. Moreover, AOAs may appear months or years before the onset of clinical symptoms [68–70]; thus, AOAs could be considered as independent markers of autoimmune ovarian disease and could predict future POI in women with unexplained infertility.

The most commonly used methods to detect AOAs are immunoprecipitation of radiolabelled human ovarian protein [71], enzyme-linked immunosorbent assay (ELISA), and indirect immunofluorescence. Another limitation in assessing the role of AOAs is the high rate of false positive results [72]. Of notice, the detection of these AOAs is not still validate, and in the hitherto published data, neither the specificity nor the diagnostic significance of these antibodies has been universally established.

Autoimmune Oophoritis

As part of the diagnosis of autoimmune POI, detecting autoimmune ovarian destruction by ovarian biopsy should have been the gold standard. However, since biopsy per se detrimentally affect ovarian reserve, together with the observation that there is no proven safe and effective treatment to restore fertility in these patients, ovarian biopsy cannot be recommended in the routine clinical workup [73].

Autoimmune oophoritis was first described in patient with Addison's disease and adrenal immunity [15] Much more frequently, ovaries are also being subject to autoimmune attack associated with thyroid autoimmunity, or other, often non-organ-specific, autoimmune responses [15]. Of notice, histological evidence of oophoritis is rare in POI patients with nonadrenal autoimmunity [15].

Histological examination of the ovaries of POI patients with associate adrenal autoimmunity usually reveals the persistence of ovarian follicles with autoimmune oophoritis, as reflected by follicles surrounded by mononuclear inflammatory cell (plasma B and T cells), in particular, around steroid-producing cells of the pre-ovulatory follicles and corpora lutea while sparing the primordial and primary follicles [74–82]. Of notice, immunohistochemical staining demonstrates the presence of T-lymphocytes (CD4+ CD8+), which is in agreement with the suggested role of T lymphocytes in ovarian autoimmunity [77]. Moreover, perivascular and perineural inflammatory infiltrates were also reported [77, 82]. This unique pathophysiologic process led to the possibility of developing immunosuppressive treatments, aiming to restore fertility in these patients [24].

POI and autoimmune disorders

It has long been recognized that POI could be associated with various organ-specific autoimmune diseases, such as adrenal autoimmunity, first described by Duff and Bernstein in 1933 [83]. The prevalence of associated clinical autoimmune disease in POI patients varies between 10 and 55% [17, 46, 53, 84, 85], with thyroid disorders representing the most common and can be detected in 12–40% of the patients [46, 53, 86–91].

While screening patients presenting with idiopathic POI for the presence of autoimmune disorders, Ayesha et al. found thyroid autoimmunity to be the most common autoimmune disease associated with POI [92]. Moreover, low DHEAS was observed in 65% of patients, suggesting the possibility of adrenal dysfunction. Adrenal autoimmunity is the second most common autoimmune disease associated with POI [67, 93], while diabetes mellitus is seen in 2.5% of the cases [67].

The association between POI and clinical autoimmune disease has been further described alone; with other endocrine disorders, such as hypothyroidism, Hashimoto thyroiditis, Graves' disease, and diabetes mellitus [94–96], with several organ-specific autoimmune diseases, such as Hashimoto thyroiditis, Graves' disease, rheumatoid arthritis, Crohn's disease, Coeliac disease, myasthenia, pernicious anemia, vitiligo, and multiple sclerosis; as well as with non-organ-specific disorders, such as idiopathic thrombocytopenia and systemic lupus erythematosus [46, 53, 54, 84, 87, 97].

POI associated with adrenal autoimmunity

While approximately 10–20% of Addison patients have POI, 2.5–20% of women with POI demonstrate some evidences of adrenal autoimmunity [93, 98]. This association might be a consequence of cross-reacting autoantibodies that react against common antigens on steroid-producing cells in different systems [54, 93]. No difference in the age at onset of POI was observed in patients with or without Addison's disease [54]. Moreover, autoimmune POI may occur before or closely after the onset of adrenal involvement [22, 93].

Since untreated Addison disease could be associated with serious fetal and maternal complications [99], the identification of POI patients with associated adrenal autoimmunity and subclinical adrenal insufficiency is mandatory before embarking on infertility treatment. Measurements of adrenal cortex autoantibodies by indirect immunofluorescence technique or antibodies against 21-OH by immunoprecipitation assay, rather than morning serum cortisol, are the preferred screening tests to detect asymptomatic adrenal insufficiency in these patients [98]. Final diagnosis should be made by the standard ACTH stimulation test [98].

Because of the particular association with Addison's disease, three different conditions have been described: POI associated with adrenal autoimmunity, POI associated with nonadrenal autoimmunity, and isolated, idiopathic POI. POI may be detected either before, after, or simultaneously with the onset of the other autoimmune disorders. Moreover, concerning Addison's disease, POI usually precedes the adrenal disease [96, 100], emphasizing the need for adrenal function testing, attempting to early detection of this potentially life-threatening condition.

POI and autoimmune polyglandular syndrome (APS)

POI may also be associated with more than one autoimmune disease in the same patient, known as APS [100]. APS are disorders characterized by autoimmunity against two or more endocrine organs with clinical diversity. POI may precede the clinical manifestation of APS and be an alarming sign of multiple endocrine and immunologic dysfunction [101]. Three different types of APS have been described: (i) APS-I, also called APECED (autoimmune polyendocrinopathy- candidiasis-ectodermal dystrophy), and includes adrenal and parathyroid autoimmunity. The prevalence of POI in APS-I is 39–72% at the age of 15–40 years, respectively [102]. (ii) APS-II, also called Schmidt Carpenter syndrome, includes adrenal and thyroid autoimmune disease autoimmunity as well as type I diabetes. The prevalence of POI in APS-II is ~ 10% at the age of 40 years [89]. (iii) APS-III includes autoimmune diseases, such as pernicious anemia or vitiligo, without Addison disease [89]. The prevalence of APS-III in patients with POI is 33.7% [103].

Autoimmune oophoritis associated with APS type 1 or 2 is responsible for 2–10% of POI cases [104] and is associated with the presence of SCA directed against various steroidogenic enzymes involved in steroidogenesis pathways, e.g., 21-hydroxylase, 17-hydroxylase, and cytochrome P450 side-chain cleavage, or adrenal enzymes [104]. Nevertheless, in approximately 10% of these patients, neither P450scc nor 17α-OH antibodies were detected in their sere [51]). Falroni et al. have also found that patients with POI associated to Addison disease are often (> 91%) positive for one of the following ASC [17α-OH antibodies, P450scc antibodies, and 3β–hydroxysteroid dehydrogenase (3β-HSD) antibodies], while only 3% of the patients with isolated POI are positive for these SCA [51].

POI in these patients is a consequence of ovarian degeneration, following the destruction of the growing theca cells, with the subsequent decrease in estradiol production and the compensatory rise in circulating gonadotropins. Unlike idiopathic POI, these patients present with high inhibin B levels, which reflect the presence of functional intact granulosa cells within the quiescent follicles [105].

POI associated with nonadrenal autoimmunity

Various other autoimmune disorders have been associated with POI. Both endocrine (thyroid, hypoparathyroid, diabetes mellitus, hypophysitis) and non-endocrine disorders (chronic candidiasis, idiopathic thrombocytopaenic 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 [106, 107]. As previously

mentioned, thyroid disorders representing the most common associated non-adrenal autoimmune disorders, with the coexisting high titers of serum anti-thyroid peroxidase and antithyroglobulin antibodies, which may lead to clinical or subclinical hypothyroidism. Osuka et al. [108] have recently evaluated the serum levels of anti-Müllerian hormone (AMH) and thyroid autoantibodies in 153 euthyroid infertile women with normal menstrual cycles. No significant differences were found in serum AMH levels between the antithyroperoxidase or antithyroglobulin antibodies positive women and the antibody-double negative women. On the other hand, serum AMH levels negatively correlated with TSH levels in patients who were either positive for antithyroperoxidase or antithyroglobulin antibodies. They therefore concluded that thyroid autoantibodies are not likely to influence ovarian reserve in euthyroid women whose TSH levels fall within the normal range although elevated TSH levels may be involved in the decline of serum AMH levels [108].

Of notice, that while the prevalence of nonadrenal autoimmune diseases is higher among women with POI than in the general population, there is no direct or compelling evidence to indicate a cause and effect relationship.

Treatment of autoimmune POI

Women with POI should be tested for anti-adrenal antibodies (most easily demonstrated against the 21-hydroxylase enzyme, CYP21) and for anti-thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulain antibodies). The presence of the aforementioned antibodies might suggest an autoimmune cause of POI. In addition to further evaluation and treatment of adrenal and thyroid abnormalities, in cases where needed, attempt should be made to improve patients' fertility. This is specifically true in those with high inhibin B levels, which reflect the presence of functional intact granulosa cells within the quiescent follicles [105].

Autoimmune oophoritis with sparing of primary and primordial follicles might suggest immunosuppressive therapy as a possible treatment for restoring ovarian function. Indeed. immunomodulation therapy has been reported to normalize ovarian function in POI patients, specifically the use of high-dose corticosteroid and intravenous immunoglobulin treatment [57, 109, 110]. Corenblum et al. have demonstrated normalization of ovarian function with the consequent conception, in 2 out of 11 patients treated with high-dose glucocorticoids (prednisone 25 mg four times per day) for 2 weeks. Moreover, they noticed that the results were best with women with concomitant autoimmune thyroid disease and POI of < 2 years' duration [110]. In addition, Blumenfeld et al. have demonstrated the presence of autoreactivity of at least one class of the tested antibodies in 31 of their 40 POI patients (77%). In 15 patients with autoimmune activity who have undergone fertility treatment, 12 pregnancies were achieved following induction of ovulation by gonadotropin and fluocortolone [57].

Of notice, none of the hitherto published studies are randomized controlled trials, with the majority being case series studies. Moreover, serious complications following high-dose glucocorticosteroids administration should not be ignored.

Gleicher et al. have recently argued that an autoimmune attack on the zona reticularis of the adrenal glands could affect ovarian function by shutting down adrenal androgen production and, thereby causing hypo-androgenism, which now has been well established to adversely affect ovarian performance [111]. So affected women, especially with adrenal and thyroid autoimmunity and the combination of low testosterone and low-DHEAS (which is almost exclusively an adrenal product), may benefit from the DHEA supplementation [112].

Furthermore, normalization of ovarian function has also been observed in patients treated for Myasthenia gravis using thymectomy [113, 114]. Other possible, not commonly used, experimental treatments might be the use monoclonal antibodies (e.g., TNF-α inhibitors) when treating POF caused by autoimmune ovarian damage, aiming to restore the immune response with T helper-2 preponderance [115, 116], or offering ovarian tissue cryopreservation using vitrification followed by in vitro activation of the dormant/suppressed follicles [117].

Conclusion

Diagnosis of autoimmune etiology for POI remains difficult and relies on several clinical, immunological, and histological features that should be investigated in these patients. The involvement of autoimmunity has been most extensively studied in POI; however, the benefit of performing a wider endocrine function setting and autoantibody screening in the absence of clinical symptoms, still remains questionable, except for adrenal and thyroid diseases, due to the very low frequency of the other autoimmune associations [118].

POI patients should undergo a comprehensive evaluation including a search for autoimmunity. While a specific noninvasive reliable diagnostic test for the diagnosis of an autoimmune etiology is lacking, nowadays, patients should be screened for the most common autoantibodies, i.e., steroid cell antibodies, anti-ovarian antibodies, and anti-thyroid antibodies (anti-thyroid peroxidase and anti-thyroglobulain antibodies).

Those with positive autoantibodies may be also screened for serum inhibin B levels, which might be suggestive for the presence of functional intact quiescent follicles. In addition to further evaluation and treatment of concomitant abnormalities (adrenal and thyroid), immune-modulating therapy may be offered to those wishing to restore ovarian function.

Of notice, nowadays, guidelines for the treatment of autoimmune POI are not available. Moreover, while strategies to POI infertility therapy using corticosteroid to restore ovarian function has been suggested, the use of this immunosuppressive is still controversial [119–121], and further prospective, randomized, controlled studies are needed. Emotional support is also important for these patients to help them to deal with conceive difficulties.

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Compliance with ethical standards

Ethics approval and consent to participate Not applicable.

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References

1. Baker TG. A quantitative and cytological study of germ cells in human ovaries. Proc R Soc Lond B Biol Sci. 1963;158:417–33.
2. Block E. Quantitative morphological investigations of the follicular system in women; variations at different ages. Acta Anat (Basel). 1952;14(1–2):108–23.
3. Faddy MJ, Gosden RG, Gougeon A, Richardson SJ, Nelson JF. Accelerated disappearance of ovarian follicles in mid-life: implications for forecasting menopause. Hum Reprod. 1992;7(10): 1342–6.
4. Sharara FI, Scott RT, Seifer DB. The detection of diminished ovarian reserve in infertile women. Am J Obstet Gynecol. 1998;179(3 Pt 1):804–12.
5. Baerwald AR, Adams GP, Pierson RA. Ovarian antral folliculogenesis during the human menstrual cycle: a review. Hum Reprod Update. 2012;18(1):73–91.
6. Baker SJ, Spears N. The role of intra-ovarian interactions in the regulation of follicle dominance. Hum Reprod Update. 1999;5(2): 153–65.
7. Hansen KR, Knowlton NS, Thyer AC, Charleston JS, Soules MR, Klein NA. A new model of reproductive aging: the decline in ovarian non-growing follicle number from birth to menopause. Hum Reprod. 2008;23(3):699–708.
8. de Moraes-Ruehsen MJG. Premature ovarian failure. Fertil Steril. 1967;18:440–61.
9. WR R. Premature ovarian failure. Obstet Gynecol 2009;113: 1355–1363.
10. LM N. Primary ovarian insufficiency. N Engl J Med 2009;360: 606–614.
11. Welt CK. Primary ovarian insufficiency: a more accurate term for premature ovarian failure. Clin Endocrinol. 2008;68(4):499–509.
12. Coulam CB, Adamson SC, Annegers JF. Incidence of premature ovarian failure. Obstet Gynecol. 1986;67(4):604–6.
13. Haller-Kikkatalo K, Uibo R, Kurg A, Salumets A. The prevalence and phenotypic characteristics of spontaneous premature ovarian failure: a general population registry-based study. Hum Reprod. 2015;30(5):1229–38.
14. Gleicher N, Kushnir VA, Barad DH. Prospectively assessing risk for premature ovarian senescence in young females: a new paradigm. Reprod Biol Endocrinol. 2015;13:34.
15. Hoek A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. Endocr Rev. 1997;18(1):107–34.
16. Mehta AE, Matwijiw I, Lyons EA, Faiman C. Noninvasive diagnosis of resistant ovary syndrome by ultrasonography. Fertil Steril. 1992;57(1):56–61.
17. Conway GS, Kaltsas G, Patel A, Davies MC, Jacobs HS. Characterization of idiopathic premature ovarian failure. Fertil Steril. 1996;65(2):337–41.
18. Pastore LM, Christianson MS, Stelling J, Kearns WG, Segars JH. Reproductive ovarian testing and the alphabet soup of diagnoses: DOR, POI, POF, POR, and FOR. J Assist Reprod Genet. 2018;35(1):17–23.
19. Komorowska B. Autoimmune premature ovarian failure. Prz Menopauzalny. 2016;15(4):210–4.
20. Maclaran KPN. Premature ovarian failure. J Fam Plann Reprod Heal Care. 2011;37:35–42.
21. Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, et al. ESHRE guideline: management of women with premature ovarian insufficiency. Hum Reprod. 2016;31(5):926–37.
22. Forges T, Monnier-Barbarino P, Faure GC, Béné MC. Autoimmunity and antigenic targets in ovarian pathology. Hum Reprod Update. 2004;10(2):163–75.
23. La Marca A, Brozzetti A, Sighinolfi G, Marzotti S, Volpe A, Falorni A. Primary ovarian insufficiency: autoimmune causes. Curr Opin Obstet Gynecol. 2010;22(4):277–82.
24. Silva CA, Yamakami LY, Aikawa NE, et al. Autoimmune primary ovarian insufficiency. Autoimmun Rev. 2014;13:427–30.
25. Ebrahimi M, Asbagh FA. The role of autoimmunity in premature ovarian failure. Iran J Reprod Med. 2015;13(8):461–72.
26. Jiao X, Zhang H, Ke H, Zhang J, Cheng L, Liu Y, et al. Premature ovarian insufficiency: phenotypic characterization within different etiologies. J Clin Endocrinol Metab. 2017;102(7):2281–90.
27. Wu R, Van der Hoek KH, Ryan NK, Norman RJ, Robker RL. Macrophage contributions to ovarian function. Hum Reprod Update. 2004;10(2):119–33.
28. Turner EC, Hughes J, Wilson H, Clay M, Mylonas KJ, Kipari T, et al. Conditional ablation of macrophages disrupts ovarian vasculature. Reproduction. 2011;141(6):821–31.
29. Cohen-Fredarow A, Tadmor A, Raz T, Meterani N, Addadi Y, Nevo N, et al. Ovarian dendritic cells act as a double-edged pro-ovulatory and anti-inflammatory sword. Mol Endocrinol. 2014;28(7):1039–54.
30. Ono Y, Nagai M, Yoshino O, Koga K, Nawaz A, Hatta H, et al. CD11c+ M1-like macrophages (MΦs) but not CD206+ M2-like MΦ are involved in folliculogenesis in mice ovary. Sci Rep. 2018;8(1):8171.
31. Boots CE, Jungheim ES. Inflammation and human ovarian follicular dynamics. Semin Reprod Med. 2015;33(4):270–5.
32. Petríková J, Lazúrová I. Ovarian failure and polycystic ovary syndrome. Autoimmun Rev. 2012;11(6–7):A471–8.
33. Mignot MH, Drexhage HA, Kleingeld M, Van de Plassche-Boers EM, Rao BR, Schoemaker J. Premature ovarian failure. II: considerations of cellular immunity defects. Eur J Obstet Gynecol Reprod Biol. 1989;30(1):67–72.
34. Melner MH, Feltus FA. Editorial: autoimmune premature ovarian failure - endocrine aspects of a T cell disease. Endocrinology. 1999;140(8):3401–3.
35. Nelson LM. Autoimmune ovarian fdailure: comparing the mouse model and the human disease. J Soc Gynecol Investig. 2017;8(1 Suppl Proceedings):S55–7.
36. Pekonen F, Siegberg R, Mäkinen T, Miettinen A, Yli-Korkala O. Immunological disturbances in patients with premature ovarian failure. Clin Endocrinol. 1986;25(1):1–6.

37. Hoek A, van Kasteren Y, de Haan-Meulman M, Hooijkaas H, Schoemaker J, Drexhage HA. Analysis of peripheral blood lymphocyte subsets, NK cells, and delayed type hypersensitivity skin test in patients with premature ovarian failure. Am J Reprod Immunol. 1995;33(6):495–502.

38. Miyake T, Sato Y, Takeuchi S. Implications of circulating autoantibodies and peripheral blood lymphocyte subsets for the genesis of premature ovarian failure. J Reprod Immunol. 1987;12(3):163–71.

39. Chernyshov VP, Radysh TV, Gura IV, Tatarchuk TP, Khominskaya ZB. Immune disorders in women with premature ovarian failure in initial period. Am J Reprod Immunol. 2001;46(3):220–5.

40. Hoek A, van Kasteren Y, de Haan-Meulman M, Schoemaker J, Drexhage HA. Dysfunction of monocytes and dendritic cells in patients with premature ovarian failure. Am J Reprod Immunol. 1993;30(4):207–17.

41. Kobayashi M, Nakashima A, Yoshino O, Yoshie M, Ushijima A, Ito M, et al. Decreased effector regulatory T cells and increased activated CD4+ T cells in premature ovarian insufficiency. Am J Reprod Immunol. 2019;81(6):e13125.

42. Coulam CB, Stern JJ. Immunology of ovarian failure. Am J Reprod Immunol. 1991;25(4):169–74.

43. Naz RK, Thurston D, Santoro N. Circulating tumor necrosis factor (TNF)-α in normally cycling women and patients with premature ovarian failure and polycystic ovaries. Am J Reprod Immunol. 1995;34(3):170–5.

44. Elder M, Maclaren N, Riley W. Gonadal autoantibodies in patients with hypogonadism and/or addison's disease. J Clin Endocrinol Metab. 1981;52(6):1137–42.

45. Sotsiou F, Bottazzo GF, Doniach D. Immunofluorescence studies on autoantibodies to steroid-producing cells, and to germline cells in endocrine disease and infertility. Clin Exp Immunol. 1980;39(1):97–111.

46. Betterle C, Rossi A, Dalla Pria S, Artifoni A, Pedini B, Gavasso S, et al. Premature ovarian failure: autoimmunity and natural history. Clin Endocrinol. 1993;39(1):35–43.

47. Anderson JR, Goudie RB, Gray K, Stuart-Smith DA. Immunological features of idiopathic Addison's disease: an antibody to cells producing steroid hormones. Clin Exp Immunol. 1968;3(2):107–17.

48. Irvine WJ, Chan MMW, Scarth L, Kolb FO, Hartog M, Bayliss RIS, et al. Immunological aspects of premature ovarian failure associated with idiopathic addison's disease. Lancet. 1968;2(7574):883–7.

49. Irvine WJ, Chan MM, Scarth L. The further characterization of autoantibodies reactive with extra-adrenal steroid-producing cells in patients with adrenal disorders. Clin Exp Immunol. 1969;4(5):489–503.

50. Brozzetti A, Marzotti S, La Torre D, Bacosi ML, Morelli S, Bini V, et al. Autoantibody responses in autoimmune ovarian insufficiency and in Addison's disease are IgG1 dominated and suggest a predominant, but not exclusive, Th1 type of response. Eur J Endocrinol. 2010;163(2):309–17.

51. Falorni A, Laureti S, Candeloro P, Perrino S, Coronella C, Bizzarro A, et al. Steroid-cell autoantibodies are preferentially expressed in women with premature ovarian failure who have adrenal autoimmunity. Fertil Steril. 2002;78(2):270–9.

52. 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(3):494–500.

53. Ruehsen M. de M, blizzard RM, Garcia-Bunuel R, Jones GS. Autoimmunity and ovarian failure. Am J Obstet Gynecol. 1972;112(5):693–703.

54. Dal Pra C, Chen S, Furmaniak J, Smith BR, Pedini B, Moscon A, et al. Autoantibodies to steroidogenic enzymes in patients with premature ovarian failure with and without Addison's disease. Eur J Endocrinol. 2003;148(5):565–70.

55. Mignot MH, Schoemaker J, Kleingeld M, Rao BR, Drexhage HA. Premature ovarian failure. I: the association with autoimmunity. Eur J Obstet Gynecol Reprod Biol. 1989;30(1):59–66.

56. Belvisi L, Bombelli F, Sironi L, Doldi N. Organ-specific autoimmunity in patients with premature ovarian failure. J Endocrinol Investig. 1993;16(11):889–92.

57. Blumenfeld Z, Halachmi S, Alik Peretz B, Shmuel Z, Golan D MA and, Brandes JM. Premature ovarian failure - the prognostic application of autoimmunity on conception after ovulation induction. Fertil Steril 1993; 59(4):750–755.

58. Vallotton M, Forbes A. Antibodies to cytoplasm of ova. Lancet. 2003;2(7457):264–5.

59. Tonacchera M, Ferrarini E, Dimida A, Agretti P, De Marco G, De Servi M, et al. Gonadotrophin receptor blocking antibodies measured by the use of cell lines stably expressing human gonadotrophin receptors are not detectable in women with 46,XX premature ovarian failure. Clin Endocrinol. 2004;61(3):376–81.

60. Kamada M, Daitoh T, Mori K, Maeda N, Hirano K, Irahara M, et al. Etiological implication of autoantibodies to zona pellucida in human female infertility. Am J Reprod Immunol. 1992;28:104–9.

61. Koyama K, Hasegawa A, Mochida N, Calongos G. Follicular dysfunction induced by autoimmunity to zona pellucida. Reprod Biol. 2005;5(3):269–78.

62. Kinoshita A, Tanaka H, Komori S, Hasegawa A, Koyama K. Autoimmunity to zona pellucida possibly causes premature ovarian failure (POF). J Reprod Immunol. 2006;71:155.

63. Damewood MD, Zacur HA, Hoffman GJ, Rock JA. Circulating antiovarian antibodies in premature ovarian failure. Obstet Gynecol. 1986;68(6):850–4.

64. Luborsky JL, Visintin I, Boyers S, Asari T, Caldwell B, Decherney A. Ovarian antibodies detected by immobilized antigen immunoassay in patients with premature ovarian failure. J Clin Endocrinol Metab. 1990;70(1):69–75.

65. Gobert B, Jolivet-Reynaud C, Dalbon P, Barbarino-Monnier P, Faure GC, Jolivet M, et al. An immunoreactive peptide of the FSH involved in autoimmune infertility. Biochem Biophys Res Commun. 2001;289(4):819–24.

66. Haller-Kikkatalo K, Salumets A, Uibo R. Review on autoimmune reactions in female infertility: antibodies to follicle stimulating hormone. Clin Dev Immunol. 2012;2012:762541.

67. Lebovic DI, Naz R. Premature ovarian failure: Think "autoimmune disorder.". Sex Reprod Menopause. 2004;2:230–3.

68. Wheatcroft NJ, Rogers CA, Metcalfe RA, Lenton EA, Cooke ID, Weetman AP. Is subclinical ovarian failure an autoimmune disease? Hum Reprod. 1997;12(2):244–9.

69. Luborsky J, Pong R. Pregnancy outcome and ovarian antibodies in infertility patients undergoing controlled ovarian hyperstimulation. Am J Reprod Immunol. 2000;44(5):261–5.

70. Cameron IT, O'Shea FC, Rolland JM, Hughes EG, De Kretser DM, Healy DL. Occult ovarian failure: a syndrome of infertility, regular menses, and elevated follicle-stimulating hormone concentrations. J Clin Endocrinol Metab. 1988;67(6):1190–4.

71. Coulam CB, Ryan RJ. Premature menopause. I Etiology Am J Obstet Gynecol. 1979;133(6):639–43.

72. Novosad JA, Kalantaridou SN, Tong Z, Bin NLM. Ovarian antibodies as detected by indirect immunofluorescence are unreliable in the diagnosis of autoimmune premature ovarian failure: a controlled evaluation. BMC Womens Health. 2003;3(1):2.

73. Khastgir G, Abdalla H, Studd JWW. The case against ovarian biopsy for the diagnosis of premature menopause. BJOG An Int J Obstet Gynaecol. 1994;101(2):96–8.

74. Coulam CB, Kempers R, Randall RV. Premature ovarian failure: evidence for the autoimmune mechanism. Fertil Steril. 1981;36(2):238–40.

75. Gloor E, Hurlimann J. Autoimmune oophoritis. Am J Clin Pathol. 1984;81(1):105–9.

76. Rabinowe SL, Berger MJ, Welch WR, Dluhy RG. Lymphocyte dysfunction in autoimmune oophoritis. Resumption of menses with corticosteroids. Am J Med. 1986;81(2):347–50.

77. Sedmak DD, Hart WR, Tubbs RR. Autoimmune oophoritis: a histopathologic study of involved ovaries with immunologic characterization of the mononuclear cell infiltrate. Int J Gynecol Pathol. 1987;6(1):73–81.

78. Wolfe CD, Stirling RW. Premature menopause associated with autoimmune oophoritis: case report. Br J Obstet Gynaecol. 1988;95(6):630–2.

79. Biscotti C, Hart W, Lucas J. Cystic ovarian enlargement resulting from autoimmune oophoritis. Obstet Gynecol. 1989;74(3 Pt 2): 492–5.

80. Lonsdale RN, Roberts PF, Trowell JE. Autoimmune oophoritis associated with polycystic ovaries. Histopathology. 1991;19(1): 77–81.

81. Suh YL. Autoimmune oophoritis-a case report. J Korean Med Sci. 1992;7(3):284–90.

82. Bannatyne P, Russell P, Shearman RP. Autoimmune oophoritis: a clinicopathologic assessment of 12 cases. Int J Gynecol Pathol. 1990;9(3):191–207.

83. C DG and B. Five cases of Addison's disease with socalled atrophy of adrenal cortex. Johns Hopkins Med J. 1933;52:67–83.

84. Coulam CB. The prevalence of autoimmune disorders among patients with primary ovarian failure. Am J Reprod Immunol. 1983;4(2):63–6.

85. Aiman J, Smentek C. Premature ovarian failure. Obstet Gynecol. 1985;66:9–14.

86. Shah A, Mithal A, Bhatia EGM. Extraovarian endocrine abnormalities innorth Indian women with premature ovarian failure. Natl Med J India. 1995;8:9–12.

87. Rebar RW, Erickson GF, Yen SS. Idiopathic premature ovarian failure: clinical and endocrine characteristics. Fertil Steril. 1982;37(1):35–41.

88. Goswami R, Marwaha RK, Goswami D, Gupta N, Ray D, Tomar N, et al. Prevalence of thyroid autoimmunity in sporadic idiopathic hypoparathyroidism in comparison to type 1 diabetes and premature ovarian failure. J Clin Endocrinol Metab. 2006;91(11):4256–9.

89. Schatz DA, Winter WE. Autoimmune polyglandular syndrome II: clinical syndrome and treatment. Endocrinol Metab Clin N Am. 2002;31(2):339–52.

90. Poppe K, Glinoer D, Van Steirteghem A, Tournaye H, Devroey P, Schiettecatte J, et al. Thyroid dysfunction and autoimmunity in infertile women. Thyroid. 2003;12(11):997–1001.

91. Rees MC. Premature menopause: hormone replacement therapy is indeed indicated. BMJ. 2008;336(7654):1148.

92. Ayesha, Jha V, Goswami D. Premature ovarian failure: an association with autoimmune diseases. J Clin Diagnostic Res 2016;10(10):QC10-QC12.

93. Reato G, Morlin L, Chen S, Furmaniak J, Rees Smith B, Masiero S, et al. Premature ovarian failure in patients with autoimmune addison's disease: clinical, genetic, and immunological evaluation. J Clin Endocrinol Metab. 2011;96(8):E1255–61.

94. Crispell KR, Parson W. The administration of purified growth hormone to a female with hypoadrenalism, hypothyroidism, diabetes mellitus, and secondary amenorrhea, simulating panhypopituitarism. J Clin Endocrinol Metab. 1952;12(7):881–9.

95. Rupp JJ, Paschkis KE. Pluriglandular insufficiency simulating panhypopituitarism; report of two cases. Am J Med. 1955;18(3): 507–12.

96. Turkington RW, Lebovitz HE. Extra-adrenal endocrine deficiencies in Addison's disease. Am J Med. 1967;43(4):499–507.

97. LaBarbera AR, Miller MM, Ober C, Rebar RW. Autoimmune etiology in premature ovarian failure. Am J Reprod Immunol Microbiol. 1988;16(3):115–22.

98. Bakalov VK, Vanderhoof VH, Bondy CA, Nelson LM. Adrenal antibodies detect asymptomatic autoimmune adrenal insufficiency in young women with spontaneous premature ovarian failure. Hum Reprod. 2002;17(8):2096–100.

99. Ambrosi B, Barbetta L, Morricone L. Diagnosis and management of Addison's disease during pregnancy. J Endocrinol Investig. 2003;26(7):698–702.

100. Kim JG, Moon SY CY and LJ. Autoimmune premature ovarian failure. J Obstet Gynecol. 1995;59–66.

101. Saif A, Assem M. Premature ovarian failure could be an alarming sign of polyglandular autoimmune dysfunction. Endocr Regul. 2017;51(2):114–6.

102. Perheentupa J. APS-I/APECED: the clinical disease and therapy. Endocrinol Metab Clin N Am. 2002;31(2):295–320.

103. Szlendak-Sauer K, Jakubik D, Kunicki M, Skórska J, Smolarczyk R. Autoimmune polyglandular syndrome type 3 (APS-3) among patients with premature ovarian insufficiency (POI). Eur J Obstet Gynecol Reprod Biol. 2016;203:61–5.

104. Welt CK. Autoimmune oophoritis in the adolescent. Ann N Y Acad Sci. 2008;1135:118–22.

105. Tsigkou A, Marzotti S, Borges L, Brozzetti A, Reis F, Candeloro P, et al. High serum inhibin concentration discriminates autoimmune oophoritis from other forms of primary ovarian insufficiency. J Clin Endocrinol Metab. 2008;93(4):1263–9.

106. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune adrenal insufficiency and autoimmune polyendocrine syndromes: autoantibodies, autoantigens, and their applicability in diagnosis and disease prediction. Endocr Rev. 2002;23(3):327–64.

107. Ebrahimi M, Asbagh FA. Pathogenesis and causes of premature ovarian failure: an update. Int J Fertil Steril. 2011;5(2):54–65.

108. Osuka S, Iwase A, Goto M, Takikawa S, Nakamura T, Murase T, et al. Thyroid autoantibodies do not impair the ovarian reserve in euthyroid infertile women: a cross-sectional study. Horm Metab Res. 2018;50(7):537–42.

109. Cowchock FS, McCabe JL, Montgomery BB. Pregnancy after corticosteroid administration in premature ovarian failure (polyglandular endocrinopathy syndrome). Am J Obstet Gynecol. 1988;158:118–9.

110. 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.

111. Gleicher N, Kushnir VA, Darmon SK, Wang Q, Zhang L, Albertini DF, et al. Suspected ontogeny of a recently described hypoandrogenic PCOS-like phenotype with advancing age. Endocrine. 2018;59:661–76.

112. Gleicher N, Kushnir VA, Darmon SK, Wang Q, Zhang L, Albertini DF, et al. New PCOS-like phenotype in older infertile women of likely autoimmune adrenal etiology with high AMH but low androgens. J Steroid Biochem Mol Biol. 2017;167:144–52.

113. Lundberg POPB. Disappearance of amenorrhea after thymectomy. Cas report Acta Soci Med Ups. 1969;74:206–8.

114. Bateman BG, Nunley WC, Kitchin JD. Reversal of apparent premature ovarian failure in a patient with myasthenia gravis. Fertil Steril. 1983;39(1):108–10.

115. Gleicher N. Some thoughts on the reproductive autoimmune failure syndrome (RAFS) and Th-1 versus Th-2 immune responses. Am J Reprod Immunol. 2002;48(4):252–4.

116. Simon A, Laufer N. Repeated implantation failure: clinical approach. Fertil Steril. 2012;97(5):1039–43.

117. Suzuki N, Yoshioka N, Takae S, Sugishita Y, Tamura M, Hashimoto S, et al. Successful fertility preservation following ovarian tissue vitrification in patients with primary ovarian insufficiency. Hum Reprod. 2015;30(3):608–15.

118. Kim TJ, Anasti JN, Flack MR, Kimzey LM, Defensor RA, Nelson LM. Routine endocrine screening for patients with karyotypically normal spontaneous premature ovarian failure. Obstet Gynecol. 1997;89(5 Pt 1):777–9.

119. Jin M, Yu Y, Huang H. An update on primary ovarian insufficiency. Sci China Life Sci. 2012;55(8):677–86.

120. V. K. Does ovarian autoimmunity play a role in the pathophysiology of premature ovarian insufficiency. J Midlife Heal. 2010;1:9–13.

121. Kalantaridou SN, Braddock NJ, Patronas LM. Treatment of autoimmune premature ovarian failure. Hum Reprod. 1999;14(7): 1777–82.