

Does ovarian autoimmunity play a role in the pathophysiology of premature ovarian insufficiency?

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ABSTRACT

Premature Ovarian Failure (POF) is an important cause of amenorrhoea and infertility. However some women may spontaneously ovulate and conceive. Primary ovarian insufficiency (POI) is thus the preferred term. POF / POI is multifactorial in etiology. Autoimmunity is an important mechanism for accelerated destruction of ovarian follicles. The present review focuses on the role of autoimmunity in the pathophysiology of POI. Antibodies to multiple ovarian antigens have been proposed as markers of ovarian autoimmunity. However, there has been lack of clinically proven sensitive and specific serum tests to confirm autoimmune involvement in POI. The review details recently developed specific test for antiovarian antibodies (AOA) that has enabled identification of different molecular antigenic targets in the ovary. The application of this specific test for AOA has brought to light the need for screening for autoimmunity prior to patients undergoing IVF technique.

Key Words: Premature ovarian insufficiency, ovarian autoimmunity, amenorrhoea

INTRODUCTION

Premature ovarian failure (POF) is a term usually used to describe women younger than 40 years of age who present with amenorrhea. Diagnosis of POF is on the basis of follicle stimulating hormone level in the menopausal range associated with amenorrhea before the age of 40. Women diagnosed with the POF suffered from anovulation and hypogonadism and presented with primary or secondary amenorrhea, infertility, sex steroid deficiency, and elevated gonadotrophins.^[1] POF is the causative factor in 10–28% of women presenting with amenorrhea and in 4–18% with secondary amenorrhea.^[2,3]

The course of POF is poorly defined.^[4] Perhaps 50% of spontaneously affected woman have the evidence of follicular activity and probably 25% ovulate even before the diagnosis is established. Some of these women even conceive. It is increasingly felt that it may be appropriate to refer to them as patients with “primary ovarian insufficiency.” The term primary ovarian

insufficiency (POI) originally suggested by Albright appropriately describes a continuation of impaired ovarian function and is also less stigmatizing than the terms used previously.^[5]

Two mechanisms are probably involved in POI, namely follicle dysfunction and follicle depletion.^[6] The existing follicles in the ovary, in follicle dysfunction, do not function normally due to some pathological process such as for e.g. FSH-receptor mutation.^[7] On the other hand, in women with follicle depletion there are no primordial follicles probably due to inadequate initial pool of primordial follicles or destruction of follicles due to toxins or autoimmune mechanisms.^[5]

Variety of possible causes of POI reflects the heterogeneity of POI. None of the causes seems to predominate. In the majority of the cases, the cause of POI is unknown. The number of women with POI is increasing. The primary goal of the scientists working in this area should be to focus on the etiology of POI.^[8] Some of the causes can lead to complete absence of oocytes, and others can lead to inability of follicles to mature or to disordered folliculogenesis. The causes could be chromosomal, genetic, autoimmune, metabolic (galactosemia), infection (mumps), and iatrogenic.^[9]

Among the several mechanisms that account for

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the pathogenesis of spontaneous POI, genetic and autoimmune mechanisms play a major role. X-chromosome abnormalities have been systematically reviewed by Persani *et al.*^[10] Normal ovarian function requires two functioning X chromosomes. In the Turner Syndrome, there is a complete loss of the second chromosome resulting in the most severe and irreversible POI often clinically evident prior to menarche.^[11] Prevalence of other genetic defects causing POI has been difficult to determine. Gene for blepharophimosis/ptosis/POI syndrome has been recently reported but has not been seen commonly in patients with POI. Of the various knock out mice models created with deficient ovarian function, the most interesting one is a heterozygous FSH receptor knock out mouse, which has exhibited a reduced follicle reserve and early ovarian depletion.^[11] Application of these transgenic results for the elucidation of clinical disease will be ultimately extremely useful for understanding the pathogenesis of POI. This area holds tremendous potential. Another approach has been to analyze the genome of affected and unaffected individuals, which also represents a very promising area.

In this review, we will focus on the role of autoimmunity in the pathophysiology of POI.

The human ovary can be a target for an autoimmune attack under various circumstances. Clinically, the ensuing ovarian dysfunction often results in premature ovarian insufficiency characterized by amenorrhea lasting 4–6 months and is classically defined as secondary amenorrhea accompanied by a hypergonadotropic-hypoestrogenic condition before the age of 40 years.^[12] It has long been recognized that POI could be associated with nearly all organ-specific and non-organ-specific autoimmune diseases, and its association with the endocrine glands such as the thyroid, pancreas, and adrenal glands has been reported.^[13]

Vallotton and Forbes^[14] were the first to describe the presence of antibodies to rabbit ova cytoplasm using sera from POI patients. Autoimmune POI (AI-POI) is characterized by organ-specific targeting of the immune response accompanied by tissue destruction, which can have widespread systemic complications in severe cases. The disease affects 1% of the general population.^[15] However, figures indicating prevalence of antibodies in POI patients varied among investigators. Damewood *et al.*^[16] reported an incidence of 51.85% (14/27 positive for antibodies), Luborsky *et al.*^[17] reported 73.3% (33/45 positive for antibodies), and Yan *et al.*^[18] reported 64.7% (11/17 positive for antibodies). There could be

several reasons for the differences among the study results. First, study design elements, such as antibody test format and antigen preparation and criteria for study and comparison groups differ. Second, there may be several antigenic targets, and often only one may have been assessed. Moncayo *et al.*^[19] developed an ELISA using microsomes from bovine corpora lutea as the antigen. Luborsky *et al.*^[17] developed an ELISA kit using total human ovary/oocytes as antigen and showed that sera from 71% of women with POF in their study had antibodies either to whole ovary or to oocytes. Wheatcroft *et al.*^[20] reported an incidence ranging from 24% to 60%, depending on the source of ovarian antigen. This difference was attributed to a cyclical variation in antigenic proteins. Using human ovarian tissue homogenate, Fenichel *et al.*^[21] carried out ELISA and showed a 59% incidence of antiovarian antibodies in patients with POF, of which the IgG isotype prevailed and was followed by IgM and finally IgA isotypes. In 1997, Wheatcroft *et al.*^[22] reported that at the present time there is no validated serum marker that can establish with certainty a diagnosis of AI-POI. A review published in 2006 reported that autoantigens and specific autoantibodies for the diagnosis of autoimmune POF remain to be determined.^[23]

Antibodies to several potential ovarian antigens were proposed as markers of ovarian autoimmunity. They were LH receptor,^[24] FSH receptor^[25,26] zona pellucida (ZP),^[27] and several other antigens.^[22]

One of the major drawbacks in the detection of ovarian antibodies in serum is the rate of false positives. A commercially available kit for detection of antiovarian antibodies was reported to have poor specificity as nearly one-third of normally menstruating women also tested positive.^[28] One of the probable causes of nonspecificity could be due to the presence of naturally occurring antibodies (NAA). The presence of NAA has long been known, and they react to various cellular self-constituents. Their major role in the first line of defense mechanisms has also been well elucidated in immunology textbooks. They are also known to play a role in the clearance of aging cells.^[29] One of these NAA is the antibody that is directed against the ubiquitous protein albumin. Sansonno *et al.*^[30] suggested that antialbumin antibodies (AAA) may have a possible role in the removal of effete albumin moieties. Louzir *et al.*^[31] demonstrated the presence of AAA in sera from 56 patients with hepatitis B-virus-related chronic liver disease and 30 normal individuals. Their results indicated that, regardless of their origin, autoantibodies are present in high amounts in the sera of individuals. Beck *et al.*^[32] have also shown the presence of AAA

directed against bovine serum albumin (BSA) in their study involving children with neuroblastoma. These studies indicate the existence of NAA. In the context of POI, a false-positive report indicating autoimmunity as the mechanism of spontaneous POI could put young women at risk of inappropriate therapy, with serious consequences such as development of osteonecrosis due to glucocorticoid therapy.^[33] As the clinicians' diagnosis will be based exclusively and extensively on the detection of the presence or absence of ovarian antibodies, it is crucial that the diagnosis is a foolproof.

A review of the literature revealed that there was no clinically proven sensitive and specific serum test to confirm autoimmune involvement in POI. Reports from various investigators support the fact that there is antibody-mediated attack to the ovary in women with POI, but due to the lack of specific tests, the marker antigen(s) responsible for the autoimmune attack remained elusive. Therefore, the need of the hour was a simple and specific test for ovarian antibodies, which would provide a useful serological marker in POI, enabling patients with ovarian autoimmunity to be identified early in the course of the disease. Consequently, they may have a chance of successful ovulations and thereby successful pregnancies.

An early and specific diagnosis of POI (especially AI-POI) is now possible with the test developed by us.^[34] This will be extremely useful for diagnosis as well as therapy for these women. The test enabled specific detection of antiovarian antibodies (AOAs) along with the identification of different molecular and cellular antigenic targets in the ovary.^[35] This is important because^[1] it will help identify antigenic targets that will lead to the development of reagents to screen for AOAs that could serve as an analytical tool to detect the disease and consequently design a drug regimen for treatment^[2]; it will help in elucidating the mechanism of disease development, progression, and consequent ovarian damage; and^[3] it will provide information about the novel proteins in the ovary and also aid in deciphering their role in ovarian biology.

Results from our laboratory clearly showed that there are specific AOAs in the sera of patients with POF. In patients who had failed at IVF-ET, AOA positivity as detected by western blotting and immunohistochemistry (IHC), could be involved in POI.^[35] Reactivity of AOAs to ovarian cell types has been shown by indirect immunofluorescence (IIF).^[36-39] However, there was no specificity, and it varied according to source of ovarian tissue and maturation state. It has been reported that the IHC results by several researchers have been

tabulated as positive or negative, but specific reaction sites are rarely depicted pictorially.^[40] However, our IHC data very clearly showed reactivity with specific cellular targets.^[35] Reactivity of POF patient sera with ZP has been reported.^[27,41] It was suggested that ZP could be an important ovarian antigen. However, our data clearly indicated that, besides ZP, several proteins from other cellular targets such as oocytes, corpus luteum, theca, and granulosa cells are also involved in ovarian autoimmunity, and therefore, there cannot be a diagnostic test on the basis of one single biomarker.^[35] It is possible that in patients showing reactivity to oocytes and granulosa cells the antibodies may damage the bidirectional communication which is necessary for proper folliculogenesis as reported recently.^[42]

A specific noninvasive test is particularly important for a reliable diagnosis of an autoimmune etiology and is essential to detect concomitant or future associated disorders, as well as to select the patients in whom immune-modulating therapy may restore, at least temporarily, ovarian function and fertility. Glucocorticoid therapy has been suggested to restore ovarian function.^[43] A prospective, randomized controlled study of alternate prednisone therapy for AI-POF was taken up at clinical center of the National Institutes of Health. However, lack of a noninvasive diagnostic serum marker necessitated histological confirmation of the disease using biopsy before prednisone administration.

Repeated IVF attempts are likely to induce production of AOAs because of repeated hormonal stimulation^[19] and repeated microtrauma during oocyte retrieval.^[44] It has been shown by these researchers that these antibodies could affect egg development and embryo development and could be responsible for implantation failures. There are the reports showing higher prevalence of these antibodies in patients with IVF failures than those with IVF success.^[45] It has also been stressed that follicular aspiration may not be the cause for antiovarian autoimmunization.^[46] Moreover, in some cases, AOAs appear after follicular aspiration, whereas in other cases, preexisting AOA levels increase with the number of IVF attempts.^[47] Therefore, testing for the presence of AOAs in women before initiation into the IVF-ET program should be recommended because this would help to counsel the patients regarding the reproductive outcome with IVF. We also propose that the AOA test should be a part of the battery of tests included for infertility treatment and management.

Very little is known about the precise nature of the ovarian antigens that are recognized by the antibodies

in sera. Antigens of oocyte,^[14] corpus luteum,^[37] granulosa cells,^[16] and ZP^[41] have been reported to act as autoantigens; however, their molecular identity and pathophysiologic significance remain obscure. The oocyte seems to be the most often targeted cell of AOA detected in cases of ovarian diseases as well as in women with poor assisted reproductive technologies (ART) outcomes.^[32,48]

A thorough literature review on infertility with autoimmune involvement has indicated that very few proteins have been formally identified and characterized using sera of women with infertility.^[28,49] One report demonstrated autoantibodies to α -enolase,^[50] and several reports have shown the presence of circulating antibodies directed toward different ovarian structures.^[16,17,22,51] Identification and systematic characterization of target antigens are the prerequisites for elucidation of the underlying immunologic mechanisms and also for devising better approaches for the diagnosis and treatment of POI leading to infertility.^[52] Once their identity has been established, they could be used for simple, noninvasive diagnostic tests to screen large populations of women with infertility or repeated implantation failures as well as to screen patients before and after enrollment in an IVF-ET program.

Although a number of tests have been developed to detect these antibodies, neither their specificity nor their diagnostic relevance has been established. Novosad and coworkers^[28] reported that indirect immunofluorescence was not a good method to detect AOA because even the controls in their study group were found to have AOA. Our group developed a novel blocking protocol^[34] that appreciably reduced the nonspecific reactivity. Using this simple and specific test, we identified a number of specific multiple molecular and cellular targets.^[35] From the large number of samples screened, we found that the oocyte is the major target of these AOA.^[35] Presently, once the diagnosis of POI is established, usually *in vitro* fertilization using donor oocytes is recommended. However, in view of oocyte being a major target of AOA as seen from our data it may be advisable to screen the patient for AOA before recommending *in vitro* fertilization with donor oocytes.

Using the test developed by us, we demonstrated multiple molecular and histological auto immune targets in the ovary using sera of infertile women having AOA^[51] and HSP90 was identified as the immunodominant target. The involvement of multiple antigenic targets, the high prevalence of anti-HSP90 antibodies, and a broad gamut of immunological

disorders, in which anti-HSP90 antibodies are found, supports the hypothesis that anti-HSP90 antibodies could be present in patients with a putative defect in immunoregulation. On the basis of our findings, we propose that presence of anti-HSP90 antibodies could be used as one of the diagnostic markers for ovarian failure and thereby infertility. The other molecular targets reported by us^[35] are being actively pursued with a view toward using them in a protein-based or peptide-based microarray. These assays could definitely improve specific, noninvasive diagnosis of the disease and help in early treatment.

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