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A ROLE OF OVARIAN AUTOIMMUNITY IN THE PATHPHYSIOLOGY OF PREMATURE OVARIAN INSUFFICIENCY

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 hypoestrogenism and presented with primary or secondary amenorrhea, infertility, sex steroid deficiency, and elevated gonadotrophins [1, p. 245] POF is the causative factor in 10 28 % of women presenting with amenorrhea and in 4 18 % with secondary amenorrhea [2, p. 236; 3, p. 45]. The course of POF is poorly defined [4, p. 112]. 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, p. 38]. Two mechanisms are probably involved in POI, namely follicle dysfunction and follicle depletion [6, p. 253]. 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, p. 86]. 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, p. 39]. The primary goal of the scientists working in this area should be to focus on the etiology of POI [8, p. 99]. 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, p. 123]. Among the several mechanisms that account for 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, p. 96]. 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, p. 176]. 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, p. 29]. 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, p. 49]. 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, p. 68]. Vallotton and Forbes [14, p.66] 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, p. 78]). 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, p. 58]. developed an ELISA using microsomes from bovine corpora lutea as the antigen. Luborsky et al [17, p. 39]. 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.

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, p. 238] corpus luteum [17, p. 69], granulosa cells [16, p. 128], and ZP [21, p. 62] 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 [22, p. 89]. 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, p. 146]. One report demonstrated autoantibodies to α-enolase, [30, p. 66] and several reports have shown the presence of circulating antibodies directed toward different ovarian structures [16, p. 49; 17, p. 57; 22, p. 86] 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 [36, p. 89]. 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.

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