LARC – методи також високорентабельні, на відміну від КОК і презервативів. Найбільш рентабельним являється використання імплантатів. Імплантат являється більш економічно ефективним, ніж КОК або ін'єкції прогестерону, а також являється більш економічно ефективним методом, ніж Cu – BMC, але додаткові відношення економічної ефективності з часом значно зменшуються. Імплантат являється економічно більш ефективним, ніж LNG – BMC, до 3 років використання.

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

The literature review is dedicated to the current state of usage antiovarian antibodies at premature ovarian failure. It has been analyzed literature sources in which there are indicated role of autoimmunity in the pathophysiology of premature ovarian insufficiency.

Key words: ovarian insufficiency, ovarian autoimmunity.

Огляд літератури присвячено сучасному стану питання використання антиовaріальних антитіл при передчасній оваріальній недостатності. Проаналізовано літературні джерела, в яких наведено роль аутоімунних процесів в передчасній оваріальній недостатності.

Ключові слова: оваріальна недостатність, оваріальний аутоімунний процес.

Обзор литературы посвящен современному состоянию вопроса использования антиовариальных антител при преждевременной овариальной недостаточности. Проанализированы литературные источники, в которых показана роль аутоиммунных процессов в преждевременной овариальной недостаточности.

Ключевые слова: овариальная недостаточность, овариальный аутоиммунный процесс.

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. Wheatcroft et al [20, p. 66]/ 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. A review published in 2006 reported that autoantigens and specific autoantibodies for the diagnosis of autoimmune POF remain to be determined [23, p. 245].

Antibodies to several potential ovarian antigens were proposed as markers of ovarian autoimmunity. They were LH receptor, [24, p. 58] FSH receptor [25, p. 36; 26, p. 56] zona pellucida (ZP), [27, p. 56] and several other antigens [22, p. 56].

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, p. 48]. 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. An early and specific diagnosis of POI (especially AI-POI) is now possible with the test developed by us [30, p. 49]. 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 [16, p.56]. This is important because [1, p. 133] 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, p. 49]. Results from 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 [29, p. 29]. Reactivity of AOAs to ovarian cell types has been shown by indirect immunoflourescence (IIF) [19, p. 44]. Reactivity of POF patient sera with ZP has been reported [27, p. 63; 11, p. 187]. 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 [28, p. 68]. It is possible that inpatients showing reactivity to oocytes and granulosa cells the antibodies may damage the bidirectional communication which is necessary for proper folliculogenesis as reported recently. [21, p. 94]. 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 [13, p. 66]. 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, p. 45] and repeated microtrauma during oocyte retrieval [24, p. 88]. 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 [25, p. 87]. It has also been stressed that follicular aspiration may not be the cause for antiovarian autoimmunization [26, p. 69]. Moreover, in some cases, AOAs appear after follicular aspiration, whereas in other cases, preexisting AOA levels increase with the number of IVF attempts [27, p. 69] 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, 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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