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Chapter 3

Autoantibodies: Key Mediators of Autoimmune Infertility

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Abstract

Autoimmune diseases have gender bias with predominance in females, autoimmune infertility (AI) being no exception. This chapter will focus on AI in females with brief reference to the same in males. Autoimmune diseases have established protocols for detection and management of ensuing infertility, however similar protocols for unexplained infertility [tubal blockage, endometriosis, premature ovarian insufficiency (POI), undiagnosed underlying autoimmune disease (Sjögren's syndrome, IBS, celiac disease) and tubal blockage] are not established. Endometriosis and POI, in particular, have autoimmune etiology yet lack specific and sensitive biomarkers for accurate diagnosis. If autoantibodies are indeed diagnosed, then treatment regimen focuses on AI which has known adverse effects. The detection of natural antibodies as autoantibodies presents a viable alternative to organ specific biomarker panel for better management of AI.

Keywords: autoantibodies, premature ovarian insufficiency, endometriosis, autoimmune infertility

1. Introduction

As per *immunculus* concept, natural antibodies (NAbs) are formed in response to gut microflora and environment in addition to self-antigens through feedback network to maintain homeostasis [1–3] bridging innate and adaptive immune response. Thus, any chronic inflammation combined with compromised central tolerance can culminate into autoimmune disease [4]. However, autoimmune diseases have gender bias with prevalence in females owing to 'autoimmune X chromosome' and autoimmune infertility (AI) is no exception [5]. Concomitantly, reproductive

autoimmune failure could result from an activated immune system or by anti-ovarian antibodies (AOA) alone as described in endometriosis patients [6]. Other reproductive disorders such as POI, polycystic ovary syndrome (PCOS), unexplained infertility, and repeatedly unsuccessful IVF attempts may be responsible for the pathophysiology of preeclampsia or spontaneous abortions and may also have presence of multiple autoantibodies (AAbs) [7–11].

Immune dysregulation is the cause of unexplained or idiopathic infertility in 20–30% of infertile couples [12]. AI is diagnosed when spontaneously synthesized antibodies bind or react with sperm/oocyte to prevent any one or several events: fertilization, acrosome reaction, capacitation or embryo implantation. Despite much research into organ specific biomarkers, no specific and sensitive biomarkers have been identified making detection of AI elusive. Organ-specific autoimmune disease gets treated using established protocols without sufficient consideration for fertility of women. Detection of AAbs mandates management of endometriosis, POI and other idiopathic infertility as an autoimmune disease with the treatment having adverse effects. This chapter will focus on AI, briefly in males but mainly in females, to include:

1. autoantigenic targets identified in female infertility with special emphasis on endometriosis and POI,
2. current understanding of effect of autoantibodies using animal models of disease,
3. including (AAbs) as diagnostic tools: current practices and
4. future research.

2. Male autoimmune infertility: anti-sperm antibodies (ASA)

Sperm are specialized haploid cells with autoantigenic and isoantigenic potential. Thus, ASA can be present in blood, semen, follicular fluid and cervicovaginal secretions affecting sperm movement, capacitation, fertilization and embryo implantation [13, 14]. ASA are far more frequent than oocyte antibodies.

In testis, the Sertoli cells through tight junctions form the impervious blood-testis barrier of two compartments: basal and adluminal. Basal compartment, which houses spermatogonia and young spermatocytes, is connected to vasculature through phagocytic Sertoli cells, which in turn act as antigen presenting cells to induce tolerance. The adluminal surface housing sperm undergoing meiosis and spermiogenesis is segregated from vasculature. Thus leakage of autoantigens from basal compartment can potentially generate ASAs. However, the exact mechanism of ASA generation is still unclear [13]. In some cases, Human Leucocyte Antigen system is associated with ASA and AI [15]. In 0.9–4% of normal fertile adult males as well as pre-pubertal boys, ASA are found in blood serum, seminal plasma, or directly attached to sperm surface indicating these to be NAbs generating confusion on their role in human infertility [16, 17].

Very few ASA are sperm specific [18] and never directed to multiple organs (except in animals). These can appear more frequently due to testicular failures: cryptorchidism, undescended testes, mobile testes and orchitis (especially due to infectious diseases such as mumps). Additionally, varicocele increases the risk of ASA production by two-fold [19]. The reduced testosterone levels due to altered Leydig cell function in undescended testes could theoretically result in reduced T regulatory cells and compromised central tolerance, however, exact mechanism is unclear. Elevated ASA could lead to low sperm count or low progressive motility. Hence, surgery at an early age, followed by steroid therapy to suppress immune reaction is recommended to prevent future infertility in cases with testicular failure.

ASA could be against carbohydrate moieties and sperm antigens example integral membrane proteins (exposed due to undescended testes) mainly through molecular mimicry. Natural ASA are reported in rodents due to sperm antigenic 'leak' to ensure immune tolerance. ASA are generally associated with genital tract infections. Vasectomy induces AAbs to antigens of mature human sperm [20, 21] with HLABw22 and A28 having increased predisposition post vasectomy [22]. Incidence reported is 61% pre- and 73–80% post-vasectomy. Antigens could be of either testicular or epididymal origin (epididymal maturation) with Abs directed to acrosome, equatorial and postacrosomal regions, tail midpiece and sperm nucleus. This could be due to sperm leakage in either the vas or cauda epididymis [21]. AutoAbs to FA-1 antigen (44%) and protamine (28%) seen post vasectomy in sera (none in seminal plasma) with prevalence of reduced fertilization rate *in vitro*. These were either of IgG, M or A subclass [23]. Post vasectomy ASA are seen only in serum while in seminal plasma and ejaculate post vasovasostomy. Fertile men with no ASA before vasovasostomy will show ASA that can affect sperm count [24, 25]. Further, there is no overlap of ASA between infertile men, post vasectomy [26] and post vasovasostomy. However, there are conflicting reports on their influence on pregnancy rate [27, 28]. **Table 1** enlists ASA in men with autoimmune infertility.

High titers of IgA-ASA found in seminal plasma of infertile men bind sperm head and impair fertilizing ability, the IgG elicit opsonization, and IgM from vaginal washings of vaginitis cases reduce fertilization by 44% [13]. ASAs directed to surface antigens are clinically relevant since they affect semen quality (not morphology or count) by any one of: premature acrosome reaction making the sperm moribund, sperm agglutination leading to impairment in cervical mucus penetration, opsonization through female genital tract via complement pathway.

ASA may aid sperm capacitation with no adverse effects on sperm-oocyte fusion. However, ASA binding outer acrosomal membrane proteins are washed away during procedure and do not affect IVF-intracytoplasmic sperm injection (IVF-ICSI) outcomes unlike those in females which are reported to reduce cleavage rate [47–49], with multiple autoantigenic targets necessary for AI [50].

Typically in women, the mucosal immunity protects entire reproductive tract up to Fallopian tubes against incoming sperm or any microbes. Thus vaginal and cervical secretions may contain ASA due to multiple semen exposures causing autoantigenicity to seminal fluid proteins. In rare cases of Human Seminal Plasma Allergy, first exposure can elicit antibodies [51] though it is not always associated with infertility [52, 53].

Autoantigen	Body fluid compartment	Function	Reference
Nuclear autoantigenic sperm protein (NASP) histone binding	Serum	Lowers fertilization rate	[29]
Protamines	Serum	–	[30]
DNA polymerase	Seminal plasma	–	[31]
YLP 12 peptide	Serum	acrosome reaction, union of sperm-oocyte	[32]
HSP70, 70-2 and 90	Serum	Acrosome reaction	[26]
Disulfide isomerase ER60	–	–	[26]
Sperm agglutination antigen-1 (SAGA-1)	–	–	[33]
Alpha enolase	Serum	–	[34]
Rab GDP-dissociation inhibitor beta		–	
Elongation factor 2		–	
Human G-phosphogluconate dehydrogenase, decarboxylating		–	
GAPDH-2		–	
L-Lactate dehydrogenase C chain		–	
ATP synthase beta chain mitochondrial precursor		–	
Proacrosin binding protein sp32	Seminal plasma	–	
CRISP-2		–	
ESP	Serum	Intra-acrosomal	[35]
SAMP 32			[36, 37]
SAMP14/ PH-20/hyaluronidase			[38]
AKAP 3		Fibrous sheath of the principal piece of the sperm tail	[39]
CABYR			[40–42]
RSP44		A radial spoke protein present in the axonemes of both sperm tail and cilia	[43]
FSP95		Fibrous sheath antigen	[44]
SLLP1		Intra-acrosomal protein	[44]
Zona pellucida			[8]
FSH			[45]
hESP	Serum	Sperm-egg binding and fusion	[46]

Table 1. List of autoantigens in men with autoimmune infertility.

ASA in females are of IgG, IgA and IgE subtypes in blood, lymph and cervical-vaginal mucus [50]. IgA antibodies in the cervical secretions can bind and agglutinate sperm with eventual clearance by circulating macrophages while the predominant IgG [54] can lead to opsonization and local clearance of antibody-antigen complexes. The uterus and Fallopian tubes are also

protected by circulating macrophages and NK cells that clear the incoming sperm. Thus sperm coated with IgA-ASA are unaffected unlike those by IgG which are opsonized and cleared via macrophages. Both subtypes in the mucus individually affect fertilization alone while a combination significantly affects fertilization rate [55–58].

IgA alloantibodies to FSH are seen in some normal fertile women and can be produced during tolerance to partner antigens (sperm proteins and shared maternal antigens) through semen [59, 60]. Patients with increased intestinal permeability in bowel inflammatory disease show higher production of ASA through molecular mimicry or epitope sharing between intestinal microbes and spermatozoa [61]. An upregulated normal mucosal immune response could lead to the elevated levels of anti-FSH IgA antibodies in IVF patients. Another possible explanation could be a deficit in producing antibodies that neutralize anti-FSH immunoglobulins, which has been noted in patients who produce ASA [62]. These results together suggest that the elevated values of anti-FSH IgA in IVF patients could represent a failure in mucosal tolerance in the genital tract, which could be genetically determined [12] (**Table 2**). Enlists ASA detected in sera of women.

2.1. Diagnostic approaches and treatment modalities for couples with ASA

Presence of ASA in serum of seminal fluid binding to sperm outer membrane antigens and thereby altering fertilization rate are relevant, is inversely correlated with pregnancy and not a good indicator of pregnancy outcome. Testing for ASA is indicated for men with genitourinary infections (e.g., Chlamydia) or acquired genital tract obstructions. Nevertheless, these ASA may not always hinder pregnancy.

Sexually active homosexual individuals who have also undergone pelvic surgery should be advised to test for ASA [69]. Routine semen samples can be tested for sperm bound antibodies by IgG-mixed antiglobulin reaction (IgG-MAR [70]), immunobead test (IBT) [71] or sperm-MAR test [72]. However, none of the available diagnostic tests quantitate, are neither effective nor specific [73, 74]. Hence, instead of ineffective generalized immunosuppressive therapy IVF-ICSI should be considered [75–79].

Post vasovasostomy couples are advised IVF for pregnancy depending on body mass index and age which affect serum testosterone levels as well as ASA in men. In these cases, IVF may be beneficial only after testing for hypogonadism and serum testosterone levels [80]. ASA post

ASA	Body fluid compartment	Function	Reference
80 kDa protein	Serum	–	[63, 64]
BS 17		–	[65]
rSMP-B	–	–	[66]
Acrosin	Serum	Sperm-oocyte interaction	[67]
H-Y antigen		Secondary recurrent miscarriage	[68]

Table 2. List of autoantigenic targets against sera of women with ASA.

vasovasostomy can cause necrospermia and deteriorate sperm count hence IVF-ICSI using testicular sperm is an option [81].

3. Female autoimmune infertility

Women are prone to autoimmune diseases due to hormonally dictated cytokine and chemokine milieu [82] often leading to other autoimmune dysfunctions [83] including reproductive autoimmune failure. Gleicher and co-workers [6] postulated that endometriosis could be an autoimmune disease and studies from our lab show 30% prevalence [84]. Commonly seen serum AAbs are anti-phospholipid, anti-nuclear, anti-thyroid, anti-annexin V, anti-prothrombin, anti-laminin, anti-ZP (**Table 3** for entire list), with the high level of NK cells as the risk factors but not as those pathognomonic [85]. However, none of the AAb biomarkers tested were effective [86]. A recent study reported better sensitivity of 6 new biomarkers [87]. With detection of AAbs to steroid producing cells and thyroglobulin in cases with concomitant adrenal or thyroid disease in PCOS, it is now considered an autoimmune disease. However, anti-ovarian antibodies were reported in only one study [7, 88] with no clarity on their role in PCOS pathogenesis [89]. Organ-specific AAbs such as ovary, adrenal and thyroid (endocrine autoimmune) disease are reported to cause infertility due to premature ovarian insufficiency (POI) [90].

Both PCOS and endometriosis are also causative factors of POI. 40–60% women with endometriosis possess anti-ovarian Abs in addition to anti-endometrial Abs [103]. Several AAbs to non-organ specific targets are seen in women with unexplained infertility [104]. Further, 22% of patients with SLE show anti-corpus luteum antibodies and elevated FSH levels typical of POI [57] and 60% POI cases are of autoimmune origin [105, 106]. POI is typically detected late with both non-organ and organ-specific antibodies in conjunction with an autoimmune disease thus evading a specific and accurate biomarker for diagnosis and prognosis [107, 108]. Whether AAbs are causative of or a by-product of underlying disease is unclear.

Nevertheless, elaborate animal models of the disease as well as case studies have provided relevant data. Day three neonatal thymectomy mouse model showed that multi-organ autoimmune disease prevails. Immunization with a single antigen causes oophoritis alone while those to multiple antigens completely compromises ovarian function. Additionally, concomitant presence of the autoantigens was mandatory [109].

Efforts to identify target autoantigens based on discovery of an ovary specific autoantigen by ELISA, immunofluorescence or immunohistochemistry approach were unfruitful. This interference was due to non-specific reactivity of natural albumin antibodies [110]. Attempts to identify target autoantigens using sera and proteomics approach were fruitful enough to identify several somatic proteins: alpha actin, alpha actinin-4, heat shock proteins 70 and 90β in 30% of POI and 26% of IVF-ET failure cases [100, 111, 112]. Of these, 47% cases showed presence of AAbs to HSP90β. Reactivity of these antibodies was seen against several follicular components (**Table 4**). Note, besides oocyte the corpus luteum seems to be a major cellular target while HSP90β the molecular target contributing to early POI (bold and italics in **Table 4**) [111]. AAbs to MATER led to assuming it to be an ovary specific target [113] however, these

Autoantibodies	Compartment	Reference
Zona pellucida (ZP3, ZP2)	Peritoneal, follicular fluids, cervical-vaginal mucus	[50]
Anti-phospholipid	Cervical, serum	
Anti-cardiolipin	Serum	
Anti-HAL	Peritoneum	
Anti annexin 5		
FSH, β-subunit	Serum	[9, 12, 91–93]
17α-hydroxylase, desmolase (P450-side chain cleavage)		
3β-hydroxysteroid dehydrogenase		
21-hydroxylase		
Antinuclear autoantibodies (ANA)		
SMOOTH muscle autoantibodies (SMA)		
Anti-endometrial Abs		
Thyroid peroxidase		[94]
Alpha enolase		[95]
Aldehyde dehydrogenase		
Syntaxin 5		[86]
Cancer antigen 125 (CA125)		
Cancer antigen 19.9 (CA19.9)		
Serine/threonine-protein kinase (PDIK1L)		
Selenium binding protein 1		[96]
Heat-shock protein 90-β	Serum	[97]
LH receptor		[98, 99]
α-Actin	Serum	[100, 101]
α-Actinin-4		
HSPA5 (HSP70)		
Stomatin-like protein 2		[84, 87]
Tropomodulin 3 (TMOD3)		
Tropomyosin 3 (TPM3)		
Double stranded DNA	–	[89]
Angiotensin II type 1 receptor agonistic autoantibodies	Serum	[102]

Table 3. List of autoantigenic targets against sera of women with reproductive infertility.

AAbs were also seen in idiopathic hypoparathyroidism cases only in context of autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome [114].

Though a 75–90% accuracy was observed in ELISA assays using immunodominant epitopes from the identified targets, the AAbs were also present in normal population, highlighting the

Condition	Age at detection	Cellular target	Molecular target
POI	22	Oocyte, theca, *corpus luteum*	***90***
	33	Oocyte, *corpus luteum*	30
	38		45, ***90***
	24		***90***, 97
	33	Oocyte, theca, *corpus luteum*	97
	39	Oocyte, theca	***90***
	33	Theca	120
	38	Oocyte	***90***
	33	Ooplasm and nucleus of oocyte, theca	
	35	Oocyte	55
	36		97
	35	Oocyte of primordial follicle	*70*, 75
	32	Oocyte	70
	35	Granulosa, *corpus luteum*	30, 45
IVF-ET	29	Oocyte, *corpus luteum*	97
	28		120
	39		30, ***90***
	32	Oocyte	120
	34		50, 75, ***90***
	30	Oocyte, granulosa	80, 97
	28	Oocyte	120
	31	Theca	45, 97
	29	Oocyte	***90***, 120
	32		30, 50, ***90***
			90
	33	Oocyte	***90***, 97
	30	Zona pellucida	45

Table 4. List of antigens and cellular targets detected using sera of women with premature ovarian insufficiency (POI) and in vitro fertilization-embryo transfer (IVF-ET); compiled from [97].

fact that these were NAbs. These were also validated to induce aPOI in a mouse model. The immunodominant epitopes tested were able to induce POI and alter ovarian cytoarchitecture. Folliculogenesis was severely affected at each developmental stage with gross lack of mature Graafian follicles and a persistent corpus luteum [101].

AAbs to a single immunodominant epitope (EP6) HSP90β led to 9% dissociated oocyte-cumulus complexes, granulosa cells undergoing apoptosis, 48% empty follicles, and 12% degenerated follicles. These animals demonstrated significant pre- and post-implantation loss

with concomitant decrease in fertility index along with an increased polymorphonuclear cell infiltration of the ovarian follicles. The infiltration may have contributed to generation of antibodies against the EP6 peptide [115, 116].

In normal physiological inflammatory processes like ovulation, follicular atresia, corpus luteum regression and tissue remodeling, the ovarian leukocytes like T cells and macrophages play an important role [117, 118]. Interestingly, NAbs especially, IgM play a role in clearing apoptotic cells, maintaining B cell homeostasis, inflammation, atherosclerosis and autoimmunity. Any drop in IgM levels is associated with ineffective clearance of apoptotic cells culminating into autoimmune disease. Alternatively, strong and persistent recognition of apoptotic cells by such NAbs may overactivate the immune system and cause chronic inflammation [3]. Corticosteroid treatment resolves the ensuing infertility [119]. However, there are no randomized controlled trials (RCT) to date. Our animal studies showed high dose corticosteroid was better able to rescue fertility in mice immunized with immunodominant epitopes of HSPA5 (**Table 5**). An interesting finding was the epitope spreading observed: AAbs to HSPA5 cross-react with immunodominant epitope (EP6) of HSP90β at high titer [120]. Thus, autoreactivity to HSP90β could have diagnostic and prognostic value.

Thyroid autoimmunity is commonly found with other systemic autoimmune diseases [121, 122] and is associated with anti-phospholipid syndrome (APS) due to anti-phospholipid antibodies [123] which in turn mediate recurrent miscarriages common to APS [124]. Thus women with thyroid autoimmunity and APS have greater risk of recurrent miscarriages mandating screening for anti-phospholipid antibodies. AAbs to ANA (12%), ANCA (20%), AECA (24%), ACLA (8%), anti-dsDNA (0%), β2 microglobulin (14%), and anti-HLA antibodies (10%) have been reported among Indian RSA patients [125]. This indicates that women with thyroiditis, endometriosis, SLE, APS also run the risk of repeated miscarriages.

At least 20–30% of POI cases have an additional autoimmune disorder [126] including several endocrinopathies, thyroid diseases, Addison's disease, rheumatoid arthritis and polyglandular

AutoAb target	Cellular target	Effect on estrus cycle	Delay in vaginal plug	Preimplantation loss	Fertility reduction	Effect of corticosteroid treatment
Alpha actinin-4	Ooplasm, theca and corpus luteum	Not determined	30%	24%	32%	44%
HSPA5	Ooplasm, granulosa, theca and corpus luteum		–	44%		
Alpha actin	Ooplasm, granulosa and theca,		30%	36.4%		
HSP90-beta (EP6)	Granulosa cells, developing embryo	Not significant	Not determined			
MATER/NALP5 (parathyroid autoantigen)	oocytes of later-stage small follicles	Not determined				

Table 5. Effect of autoantibodies on fertility and extent of rescue with corticosteroid therapy.

syndrome with greater prevalence of thyroid autoimmunity (14–27% at initial diagnosis) and thyroid peroxidase AAbs [127, 128]. At least 10% women with Addison's disease manifest AAbs to 21- or 17-hydroxylase and autoimmune oophoritis [129]. Thyroid peroxidase antibodies (TPO Abs) are also prevalent in PCOS cases. Thus, these along with HSP90β could be included in an antibody detection panel.

In women with endometriosis, use of biomarkers including CA-125 for diagnosis of endometriosis was prohibited [130, 131]. However as per recent guidelines, use of biomarkers has been recommended for both diagnosis and disease monitoring [132] and is still a researchable area. Anti-endometrial antibodies exist but their sensitivity and accuracy varies from 0 to 100% [131, 133, 134].

3.1. Treatment modalities and management of autoimmune infertility

Endometriosis management guidelines are valid for women with mild to moderate disease and do not recommend hormonal therapy for managing ovulation to improve fertility rate [135]. Despite reduction in ovarian function, one time laparoscopic operation to remove endometriosis and improve pregnancy rates is often recommended [136, 137]. Adjunctive hormonal therapy is prohibited pre- or post-surgery to improve pregnancy rates [138]. Intra uterine insemination along with controlled ovarian stimulation is recommended 6 months post-surgery since it shows similar pregnancy rates as that of women with unexplained infertility [139]. ART can also be recommended especially in cases of tubal factor or male factor infertility as controlled ovarian stimulation does not increase chances of recurrence of endometriosis after IVF/ICSI [140–143] however, it may not always be effective [144, 145].

POI seems to be an end-stage disease in women with an autoimmune disorder since it is detected at a late stage when the ovary has been substantially ravaged with little scope for fertility management. Thus treatment options for fertility management of women with POI are limited. Counseling for early marriage and pregnancy to complete the family is applicable only in case of early diagnosis or known familial origin. Other options include egg donation and IVF-ICSI or surrogacy. The women are administered corticosteroids in case of known autoimmune disease diagnosis and advised IVF-ICSI when AAb titers fall. However, this is not an option since it entails risk of osteoporosis and iatrogenic Cushing's syndrome [119]. In most cases, adoption is the only option along with psychological counseling and cardiovascular and bone health management of hypoestrogenism effects [146].

Additionally, there should be efforts to increase awareness among reproductive endocrinologists to recommend testing for undiagnosed autoimmune disease to couples on a case basis before embarking on ART-IVF [147].

4. Future research

Presence of AAbs is hallmark of autoimmune disease with no clarity on their role in disease pathogenesis and ensuing AI. With few exceptions these are not organ-specific indicating them

to be NAbs [148–151]. Obtaining clarity on role of AAbs will guide further treatment modalities for patients with AI [93, 101, 152]. Global high dose immunosuppressive therapy seems to be the only effective option for autoimmune reproductive failure despite its shortcomings [153, 154].

Targeted interventional therapy by inducing antigen-specific tolerance is another option [155, 156]. Till such a time as a definitive therapy is available, pan autoimmune disease diagnostic panels can be designed using autoantigenic targets (recombinant proteins or peptides) such as β2-glycoprotein I and HSP90β (EP6) [151, 157–159] followed by management with corticosteroid therapy. A loss of reactivity to key autoantigens (predetermined to affect ovarian function) would serve as biomarkers to better manage immunosuppressant therapy.

5. Conclusion

The very lack of any organ-specific biomarker till date along with the preponderance of NAbs indicates that warped self-tolerance would lead to AI. AAbs in females alone appear to be significant in AI. Fertility studies need to be undertaken to gauge effect of such AAbs identified thus far and immunodominant epitopes gleaned could prove useful to design a pan autoimmune disease diagnostic peptide array to manage AI. Global immunosuppressant therapy and IVF-ICSI are the only current hope for such couples.

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Conflict of interest

None.

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References

[1] Poletaev A, Boura P. The immune system, natural autoantibodies and general homeostasis in health and disease. Hippokratia. 2011;**15**(4):295-298. PMCID: PMC3876841

[2] Siloşi I, Siloşi CA, Boldeanu MV, Cojocaru M, Biciuşcă V, Avrămescu CS, Cojocaru IM, Bogdan M, Folcuţi RM. The role of autoantibodies in health and disease. Romanian Journal of Morphology and Embryology. 2016;**57**(2):633-638. PMID: 27833954

[3] Panda S, Ding JL. Natural antibodies bridge innate and adaptive immunity. Journal of Immunology. 2015;**194**:13-20. DOI: https://doi.org/10.4049/jimmunol.1400844. PMID: 25527792

[4] Weiss G, Goldsmith LT, Taylor RN, Bellet D, Taylor HS. Inflammation in reproductive disorders. Reproductive Sciences. 2009;**16**(2):216-229. DOI: 10.1177/1933719108330087. PMID: 19208790

[5] Gleicher N, Kushnir VA, Barad DH. Prospectively assessing risk for premature ovarian senescence in young females: A new paradigm. Reproductive Biology and Endocrinology. 2015;**13**:34. DOI: 10.1186/s12958-015-0026-z. PMID: 25906823

[6] Gleicher N, El-Roeiy A, Confino E, Friberg J. Is endometriosis an autoimmune disease? Obstetrics & Gynecology. 1987;**70**(1):115-122. PMID: 3110710

[7] Fénichel P, Gobert B, Carré Y, Barbarino-Monnier P, Hiéronimus S. Polycystic ovary syndrome in autoimmune disease. Lancet. 1999;**353**(9171):2210. PMID: 10392989. DOI: 10.1016/S0140-6736(99)00256-1

[8] Forges T, Monnier-Barbarino P, Faure GC, Béné MC. Autoimmunity and antigenic targets in ovarian pathology. Human Reproduction Update. 2004;**10**(2):163-175. PMID: 15073145. DOI: 10.1093/humupd/dmh014

[9] Geva E, Amit A, Lerner-Geva L, Lessing JB. Autoimmunity and reproduction. Fertility and Sterility. 1997;**67**(4):599-611. PMID: 9093180

[10] Matarese G, de Placido G, Nikas Y, Alviggi C. Pathogenesis of endometriosis: Natural immunity dysfunction or autoimmune disease? Trends in Molecular Medicine. 2003; **9**(5):223-228. PMID: 12763528

[11] Reimand K, Talja I, Metsküla K, Kadastik Ü, Matt K, Uibo R. Autoantibody studies of female patients with reproductive failure. Journal of Reproductive Immunology. 2001; **51**(2):167-176. PMID: 11543855

[12] Haller-Kikkatalo K, Salumets A, Uibo R. Review on autoimmune reactions in female infertility: Antibodies to follicle stimulating hormone. Clinical & Developmental Immunology. 2012;**2012**:762541. PMID: 22007255. DOI: 10.1155/2012/762541

[13] Restrepo B, Cardona-Maya W. Antisperm antibodies and fertility association. Actas Urologicas Españolas. 2013;**37**(9):571-578. PMID: 23428233. DOI: 10.1016/j.acuro.2012.11.003

[14] Vazquez-Levin MH, Marín-Briggiler CI, Veaute C. Antisperm antibodies: Invaluable tools toward the identification of sperm proteins involved in fertilization. American Journal of Reproductive Immunology. 2014;**72**:206-218. PMID: 24863647. DOI: 10.1111/aji.12272

[15] Omu AE, Al-Qattan F, Ismail AA, Al-Taher S, Al-Busiri N. Relationship between unexplained infertility and human leukocyte antigens and expression of circulating autogeneic and allogeneic antisperm antibodies. Clinical and Experimental Obstetrics & Gynecology. 1999;**26**(3–4):199-202. PMID: 10668156

[16] Lu JC, Huang YF, Lu NQ. Antisperm immunity and infertility. Expert Review of Clinical Immunology. 2008;**4**(1):113-126. PMID: 20477591. DOI: 10.1586/1744666X.4.1.113

[17] Filippini A, Riccioli A, Padula F, Lauretti P, D'Alessio A, De Cesaris P, Gandini L, Lenzi A, Ziparo E. Control and impairment of immune privilege in the testis and in semen. Human Reproduction Update. 2001;**7**(5):444-449. PMID: 11556490

[18] Dörr H, Bohring C, Krause W. Are antisperm antibodies indeed sperm-specific? Andrologia. 2005;**37**:185-187. PMID: 16266397. DOI: 10.1111/j.1439-0272.2005.00675.x

[19] Bozhedomov VA, Lipatova NA, Rokhlikov IM, Alexeev RA, Ushakova IV, Sukhikh GT. Male fertility and varicocoele: Role of immune factors. Andrology. 2014;**2**:51-58. PMID: 24285668. DOI: 10.1111/j.2047-2927.2013.00160.x

[20] Phadke AM, Padukone K. Presence and significance of autoantibodies against spermatozoa in the blood of men with obstructed vas deferens. Journal of Reproduction and Fertility. 1964;**7**:163. PMID: 14139599

[21] Tung KSK. Human sperm antigens and antisperm antibodies. I. Studies on vasectomy patients. Clinical and Experimental Immunology. 1975;**20**:93-104. PMID: 1106922

[22] Law HY, Bodmer WF, Mathews JD, Skegg DC. The immune response to vasectomy and its relation to the HLA system. Tissue Antigens. 1979;**14**(2):115-139. PMID: 386565

[23] Naz RK, Deutsch J, Phillips TM, Menge AC, Fisch H. Sperm antibodies in vasectomized men and their effects on fertilization. Biology of Reproduction. 1989;**40**:163-173. PMID: 2804205

[24] Kay DJ, Clifton V, Taylor JS, Boettcher B. Anti-sperm antibodies and sperm profiles in re-anastomosed men. Reproduction, Fertility, and Development. 1993;**5**:135-139. PMID: 8234889

[25] Royle MG, Parslow JM, Kingscott MM, Wallace DM, Hendry WF. Reversal vasectomy: The effects of sperm antibodies on subsequent fertility. British Journal of Urology. 1981; **53**:654-659. PMID: 7032642

[26] Bohring C, Krause W. Differences in the antigen pattern recognized by antisperm antibodies in patients with infertility and vasectomy. The Journal of Urology. 2001;**166**(3): 1178-1180. PMID: 11490318

[27] Meinertz H, Linnet L, Fogh-Andersen P, Hjort T. Antisperm antibodies and fertility after vasovasostomy: A follow-up study of 216 men. Fertility and Sterility. 1990;**54**(2):315-321. PMID: 2379630

[28] Lu WH, Liang XW, Gu YQ, Li H, Wu ZG, Chen ZW. The relationship between changes of serum antisperm antibodies before and post vasovasostomy and pregnancy rate. Zhonghua Nan Ke Xue. 2006;**12**(1):32-35, 38. PMID: 16483155

[29] Batova IN, Richardson RT, Widgren EE, O'Rand MG. Analysis of the autoimmune epitopes on human testicular NASP using recombinant and synthetic peptides. Clinical & Experimental Immunology. 2000;**121**(2):201-209. PMID: 10931132

[30] Samuel T, Linnet L, Rümke P. Post-vasectomy autoimmunity to protamines in relation to the formation of granulomas and sperm agglutinating antibodies. Clinical and Experimental Immunology. 1978;**33**(2):261-269. PMID: 102476

[31] Higgins PJ, Witkin SS, Bendich A. Inhibition of human seminal fluid DNA polymerase by an IgG fraction of seminal plasma from vasectomized men. Journal of Reproduction and Fertility. 1978;**54**(1):97-102. PMID: 101659

[32] Naz RK, Packianathan JLR. Antibodies to human sperm YLP12 peptide that is involved in egg binding inhibit human sperm capacitation/acrosome reaction. Archives of Andrology. 2000;**45**(3):227-232. PMID: 11111871

[33] Diekman AB, Norton EJ, Westbrook VA, Klotz KL, Naaby-Hansen S, Herr JC. Antisperm antibodies from infertile patients and their cognate sperm antigens: A review. Identity between SAGA-1, the H6-3C4 antigen, and CD52. American Journal of Reproductive Immunology. 2000;**43**(3):134-143. PMID: 10735589

[34] Domagała A, Pulido S, Kurpisz M, Herr JC. Application of proteomic methods for identification of sperm immunogenic antigens. Molecular Human Reproduction. 2007; **13**(7):437-444. PMID: 17507387. DOI: 10.1093/molehr/gam026

[35] Wolkowicz MJ, Shetty J, Westbrook A, Klotz K, Jayes F, Mandal A, Flickinger CJ, Herr JC. Equatorial segment protein defines a discrete acrosomal subcompartment persisting throughout acrosomal biogenesis. Biology of Reproduction. 2003;**69**:735-745. PMID: 12773409. DOI: 10.1095/biolreprod.103.016675

[36] Hao Z, Wolkowicz MJ, Shetty J, Klotz K, Bolling L, Sen B, Westbrook VA, Coonrod S, Flickinger CJ, Herr JC. SAMP32, a testis-specific, isoantigenic sperm acrosomal membrane-associated protein. Biology of Reproduction. 2002;**66**(3):735-744 11870081

[37] Rao J, Herr JC, Reddi PP, Wolkowicz MJ, Bush LA, Sherman NE, Black M, Flickinger CJ. Cloning and characterization of a novel sperm-associated isoantigen (E-3) with defensing and lectin-like motifs expressed in rat epididymis. Biology of Reproduction. 2003; **68**(1):290-301. PMID: 12493725

[38] Shetty J, Wolkowicz MJ, Digilio LC, Klotz KL, Jayes FL, Diekman AB, Westbrook VA, Farris EM, Hao Z, Coonrod SA, Flickinger CJ, Herr JC. SAMP14, a novel, acrosomal

membrane-associated, glycosylphosphatidylinositol-anchored member of the Ly-6/urokinase-type plasminogen activator receptor superfamily with a role in sperm-egg interaction. The Journal of Biological Chemistry. 2003;**278**(33):30506-30515. PMID: 12788941

[39] Mandal A, Naaby-Hansen S, Wolkowicz MJ, Klotz K, Shetty J, Retief JD, Coonrod SA, Kinter M, Sherman N, Cesar F, Flickinger CJ, Herr JC. FSP95, a testis-specific 95-kilodalton fibrous sheath antigen that undergoes tyrosine phosphorylation in capacitated human spermatozoa. Biology of Reproduction. 1999 Nov;**61**(5):1184-1197. PMID: 10529264

[40] Naaby-Hansen S, Mandal A, Wolkowicz MJ, Sen B, Westbrook VA, Shetty J, Coonrod SA, Klotz KL, Kim YH, Bush LA, Flickinger CJ, Herr JC. CABYR, a novel calcium-binding tyrosine phosphorylation-regulated fibrous sheath protein involved in capacitation. Developmental Biology. 2002;**242**(2):236-254. PMID: 11820818

[41] Sen B, Mandal A, Wolkowicz MJ, Kim YH, Reddi PP, Shetty J, Bush LA, Flickinger CJ, Herr JC. Splicing in murine CABYR and its genomic structure. Gene. 2003;**310**:67-78. PMID: 12801634

[42] Kim YH, Jha KN, Mandal A, Vanage G, Farris E, Snow PL, Klotz K, Naaby-Hansen S, Flickinger CJ, Herr JC. Translation and assembly of CABYR coding region B in fibrous sheath and restriction of calcium binding to coding region A. Developmental Biology. 2005;**286**(1):46-56. PMID: 16139264

[43] Shetty J, Klotz KL, Wolkowicz MJ, Flickinger CJ, Herr JC. Radial spoke protein 44 (human meichroacidin) is an axonemal alloantigen of sperm and cilia. Gene. 2007; **396**(1):93-107. PMID: 17451891. DOI: 10.1016/j.gene.2007.02.031

[44] Mandal A, Klotz KL, Shetty J, Jayes FL, Wolkowicz MJ, Bolling LC, Coonrod SA, Black MB, Diekman AB, Haystead TA, Flickinger CJ, Herr JC. SLLP1, a unique, intra-acrosomal, non-bacteriolytic, c lysozyme-like protein of human spermatozoa. Biology of Reproduction. 2003;**68**(5):1525-1537. PMID: 12606493

[45] Westhoff WE, Slootstra JW, Puijk WC, Kuperus D, Flinterman JF, Schaaper WM, Oonk HB, Meloen RH. Detection of epitopes on follicle-stimulating hormone and FSH antiserum-induced suppression of bioactivity of follicle stimulating hormone and luteinizing hormone. Journal of Reproductive Immunology. 1996;**30**(2–3):133-149. PMID: 8816329

[46] Wolkowicz MJ, Digilio L, Klotz K, Shetty J, Flickinger CJ, Herr JC. Equatorial segment protein (ESP) is a human alloantigen involved in sperm-egg binding and fusion. Journal of Andrology. 2008;**29**(3):272-282. PMID: 17978344

[47] Francavilla F, Santucci R, Barbonetti A, Francavilla S. Naturally-occurring antisperm antibodies in men: interference with fertility and clinical implications. An update. Frontiers in Bioscience. 2007;**12**:2890-2911. PMID: 17485267

[48] Mandelbaum SL, Diamond MP, AH DC. Relationship of antisperm antibodies to oocyte fertilization in in vitro fertilization-embryo transfer. Fertility and Sterility. 1987;**47**:644-651. PMID: 3552746

[49] Tian X, Zhang L, Wu Y, Yang C, Liu P. Relationship between serum antisperm antibodies and anticardiolipin antibodies and clinical pregnancy outcome in an in vitro fertilization and embryo transfer program. Chinese Medical Journal. 1999;**112**(1):34-36. PMID: 11593637

[50] Brázdová A, Senechal H, Peltre G, Poncet P. Immune aspects of female infertility. International Journal of Fertility & Sterility. 2016;**10**(1):1-10. PMID: 27123194

[51] James DW. Pernicious vomiting of pregnancy due to sensitivity to semen. Western Journal of Surgery, Obstetrics, and Gynecology. 1945;**53**:380-382

[52] Ebo DG, Stevens W, Bridts C, De Clerck L, Bernstein I. Human seminal plasma anaphylaxis (HSPA): Case report and literature review. Allergy. 1995;**50**:747-750. PMID: 8546271

[53] Weidinger S, Ring J, Köhn F. IgE-mediated allergy against human seminal plasma. Chemical Immunology and Allergy. 2005;**88**:128-138. PMID: 16129942. DOI: 10.1159/000087830

[54] Johansson M, Lycke N. Immunology of the human genital tract. Current Opinion in Infectious Diseases. 2003;**16**:43-49. PMID: 12821829

[55] Clarke GN, Lopata A, McBain JC, Baker HW, Johnston WI. Effect of sperm antibodies in males on human in vitro fertilization (IVF). American Journal of Reproductive Immunology and Microbiology. 1985;**8**:62-66. PMID: 4025668

[56] Matson PL, Junk SM, Spittle JW, Yovich JL. Effect of antispermatozoal antibodies in seminal plasma upon spermatozoal function. International Journal of Andrology. 1988; **11**:101-106. PMID: 3286524

[57] Junk SM, Matson PL, Yovich JM, Bootsma B, Yovich JL. The fertilization of human oocytes by spermatozoa from men with antispermatozoal antibodies in semen. Journal of In Vitro Fertilization and Embryo Transfer. 1986;**3**:350-352. PMID: 3805851

[58] de Almeida M, Gazagne I, Jeulin C, Herry M, Belaisch-Allart J, Frydman R, Jouannet P, Testart J. In vitro processing of sperm with auto-antibodies and in-vitro fertilization results. Human Reproduction. 1989;**4**:49-53. PMID: 2708503

[59] Hegde UC, Ranpura S, D'Souza S, Raghavan VP. Immunoregulatory pathways in pregnancy. Indian Journal of Biochemistry & Biophysics. 2001;**38**(4):207-219. PMID: 11811615

[60] Luboshitzky R, Kaplan-Zverling M, Shen-Orr Z, Nave R, Herer P. Seminal plasma androgen/oestrogen balance in infertile men. International Journal of Andrology. 2002; **25**(6):345-351. PMID: 12406366

[61] Dimitrova D, Kalaydjiev S, Mendizova A, Piryova E, Nakov L. Circulating antibodies to human spermatozoa in patients with ulcerative colitis. Fertility and Sterility. 2005;**84**(5): 1533-1535. PMID: 16275264. DOI: 10.1016/j.fertnstert.2005.05.041

[62] Naz RK, Ahmad K, Menge AC. Anti-idiotypic antibodies to sperm in sera of fertile women that neutralize antisperm antibodies. The Journal of Clinical Investigation. 1993;**92**(5):2331-2338. PMID: 8227348. DOI: 10.1172/JCI116837

[63] Bandivdekar AH, Gopalkrishnan K, Garde SV, Fernandez PX, Moodbidri SB, Sheth AR, Koide SS. Antifertility effect in rats actively immunized with 80kDa human semen glycoprotein. Indian Journal of Experimental Biology. 1992;**30**:1017-1023. PMID: 1293024

[64] Bandivdekar AH, Vernekar VJ, Moodbidri SB, Koide SS. Characterization of 80 kDa human sperm antigen responsible for immunoinfertility. American Journal of Reproductive Immunology. 2001;**45**(1):28-34. PMID: 11211944

[65] Wei SG, Wang LF, Miao SY, Zong SD, Koide SS. Fertility studies with antisperm antibodies. Archives of Andrology. 1994;**32**(3):251-262. PMID: 8074581

[66] Koide SS, Wang L, Kamada M. Antisperm antibodies associated with infertility: Properties and encoding genes of target antigens. Proceedings of the Society for Experimental Biology and Medicine. 2000;**224**:123-132. PMID: 10865226

[67] Veaute C, Furlong LI, Bronson R, Harris JD, Vazquez-Levin MH. Acrosin antibodies and infertility. I. Detection of antibodies towards proacrosin/acrosin in women consulting for infertility and evaluation of their effects upon the sperm protease activities. Fertility and Sterility. 2009;**91**(4):1245-1255. PMID: 18439585. DOI: 10.1016/j.fertnstert.2007.12.072

[68] Nielsen HS, Wu F, Aghai Z, Steffensen R, van Halteren AG, Spierings E, Christiansen OB, Miklos D, Goulmy E. H-Y antibody titers are increased in unexplained secondary recurrent miscarriage patients and associated with low male : Female ratio in subsequent live births. Human Reproduction. 2010;**25**(11):2745-2752. PMID: 20823116. DOI: 10.1093/humrep/deq242

[69] Marshburn PB, Kutteh WH. The role of antisperm antibodies in infertility. Fertility and Sterility. 1994;**61**:799-811. PMID: 8174713

[70] Jager S, Kremer J, van Slochteren-Draaisma T. A simple method of screening for antisperm antibodies in the human male: Detection of spermatozoan surface IgG with the direct mixed agglutination reaction carried out on untreated fresh human semen. International Journal of Fertility. 1978;**23**:12-21 30704

[71] Bronson R, Cooper G, Rosenfeld D. Membrane bound sperm-specific antibodies: Their role in infertility. In: Vogel H, Jagiello G, editors. Bioregulators in Reproduction. New York: Academic Press; 1981. pp. 521-527

[72] Comhaire FH, Hinting A, Vermeulen L, Schoonjans F, Goethals I. Evaluation of the direct and indirect mixed antiglobulin reaction with latex particles for the diagnosis of immunological infertility. International Journal of Andrology. 1987;**11**:37-44. PMID: 3258588

[73] Nikolaeva MA, Kulakov VI, Korotkova IV, Golubeva EL, Kuyavskaya DV, Sukhikh GT. Antisperm antibodies detection by flow cytometry is affected by aggregation of antigen-antibody complexes on the surface of spermatozoa. Human Reproduction. 2000;**15**(12): 2545-2553. PMID: 11098024

[74] Hjort T. Antisperm antibodies. Antisperm antibodies and infertility: An unsolvable question? Human Reproduction. 1999;**14**:2423-2426. PMID: 10527960

[75] Kamischke A, Nieschlag E. Analysis of medical treatment of male infertility. Human Reproduction. 1999;**14**(Suppl 1):1-23. PMID: 10573021

[76] Nagy ZP, Aragona C, Greco E. Results of ICSI in the treatment of male immunological infertility. Andrologia. 1999;**31**:316-317. PMID: 10526648

[77] Check ML, Check JH, Katsoff D, Summers-Chase D. ICSI as an effective therapy for male factor with antisperm antibodies. Archives of Andrology. 2000;**45**:125-130. PMID: 11111859

[78] Mardesic T, Ulcova-Gallova Z, Huttelova R, Muller P, Voboril J, Mikova M, Hulvert J. The influence of different types of antibodies on in vitro fertilization results. American Journal of Reproductive Immunology. 2000;**43**:1-5. PMID: 10698033

[79] Lombardo F, Gandini L, Dondero F, Lenzi A. Antisperm immunity in natural and assisted reproduction. Human Reproduction Update. 2001;**7**:450-456. PMID: 11556491

[80] Hinz S, Rais-Bahrami S, Kempkensteffen C, Weiske WH, Miller K, Magheli A. Effect of obesity on sex hormone levels, antisperm antibodies, and fertility after vasectomy reversal. Urology. 2010;**76**(4):851-856. DOI: 10.1016/j.urology.2010.01.055. PMID: 20430424

[81] Chavez-Badiola A, Drakeley AJ, Finney V, Sajjad Y, Lewis-Jones DI. Necrospermia, antisperm antibodies, and vasectomy. Fertility and Sterility. 2008;**89**(3):723.e5-723.e7. PMID: 17612533. DOI: 10.1016/j.fertnstert.2007.04.007

[82] Smith-Bouvier DL, Divekar AA, Sasidhar M, Du S, Tiwari-Woodruff SK, King JK, Arnold AP, Singh RR, Voskuhl RR. A role for sex chromosome complement in the female bias in autoimmune disease. The Journal of Experimental Medicine. 2008;**205**(5): 1099-1108. PMID: 18443225. DOI: 10.1084/jem.20070850

[83] Tuohy VK, Kinkel RP. Epitope spreading: A mechanism for progression of autoimmune disease. Archivum Immunologiae et Therapiae Experimentalis (Warsz). 2000;**48**(5):347-351. PMID: 11140461

[84] Gajbhiye R, Suryawanshi A, Khan S, Meherji P, Warty N, Raut V, Chehna N, Khole V. Multiple endometrial antigens are targeted in autoimmune endometriosis. Reproductive Biomedicine Online. 2008;**16**(6):817-824. PMID: 18549691

[85] Gleicher N, Barad D. Unexplained infertility: Does it really exist? Human Reproduction. 2006;**21**(8):1951-1955. PMID: 16684842. DOI: 10.1093/humrep/del135

[86] Nisenblat V, Bossuyt PM, Shaikh R, Farquhar C, Jordan V, Scheffers CS, Mol BW, Johnson N, Hull ML. Blood biomarkers for the non-invasive diagnosis of endometriosis. Cochrane Database of Systematic Reviews. 2016;**1**(5):CD012179. PMID: 27132058. DOI: 10.1002/14651858.CD012179

[87] Gajbhiye R, Bendigeri T, Ghuge A, Bhusane K, Begum S, Warty N, Sawant R, Padte K, Humane A, Dasmahapatra P, Chauhan A, Khan S. Panel of autoimmune markers for noninvasive diagnosis of minimal-mild endometriosis. Reproductive Sciences. 2017; **24**(3):413-420. PMID: 27485360. DOI: 10.1177/1933719116657190

[88] Mobeen H, Afzal N, Kashif M. Polycystic ovary syndrome may be an autoimmune disorder. Scientifica (Cairo). 2016;**2016**:4071735. PMID: 27274883. DOI: 10.1155/2016/4071735

[89] Petrikova J, Lazurova I, Dravecka I, Vrbikova J, Kozakova D, Figurova J, Vaczy Z, Rosocha J. The prevalence of non-organ specific and thyroid autoimmunity in patients with polycystic ovary syndrome. Biomedical Papers of the Medical Faculty of the University Palacky, Olomouc, Czech Republic. 2015;**159**(2):302-306. PMID: 25485530. DOI: 10.5507/bp.2014.062

[90] Hoek A, Schoemaker J, Drexhage HA. Premature ovarian failure and ovarian autoimmunity. Endocrine Reviews. 1997 Feb;**18**(1):107-134 Review. PMID: 9034788

[91] Mathur S, Peress MR, Williamson HO. Autoimmunity to endometrium and ovary in endometriosis. Clinical and Experimental Immunology. 1982;**50**(2):259-266. PMID: 6759000

[92] Ulcová-Gallová Z, Bouse V, Svábek L, Turek J, Rokyta Z. Endometriosis in reproductive immunology. American Journal of Reproductive Immunology. 2002;**47**(5):269-274. PMID: 12148541

[93] Zou SH, Yang ZZ, Zhang P, Song DP, Li B, Wu RY, Cong X. Autoimmune disorders affect the in vitro fertilization outcome in infertile women. Zhonghua Nan Ke Xue. 2008; **14**(4):343-346. PMID: 18481429

[94] Poppe K, Glinoer D, Van Steirteghem A, Tournaye H, Devroey P, Schiettecatte J, Velkeniers B. Thyroid dysfunction and autoimmunity in infertile women. Thyroid. 2002;**12**(11):997-1001. PMID: 12490077. DOI: 10.1089/105072502320908330

[95] Sarapik A, Haller-Kikkatalo K, Utt M, Teesalu K, Salumets A, Uibo R. Serum antiendometrial antibodies in infertile women—Potential risk factor for implantation failure. American Journal of Reproductive Immunology. 2010;**63**(5):349-357. PMID: 20132165. DOI: 10.1111/j.1600-0897.2010.00808.x

[96] Yu-Rice Y, Edassery SL, Urban N, Hellstrom I, Hellstrom KE, Deng Y, Li Y, Luborsky JL. Selenium-binding protein 1 (SBP1) autoantibodies in ovarian disorders and ovarian cancer. Reproduction. 2017;**153**:277-284. PMID: 27965399. DOI: 10.1530/REP-16-0265

[97] Pires ES, Meherji PK, Vaidya RR, Parikh FR, Ghosalkar MN, Khole VV. Specific and sensitive immunoassays detect multiple anti-ovarian antibodies in women with infertility. The Journal of Histochemistry and Cytochemistry. 2007;**55**(12):1181-1190. PMID: 17652265. DOI: 10.1369/jhc.7A7259.2007

[98] Wheatcroft NJ, Toogood AA, Li TC, Cooke ID, Weetman AP. Detection of antibodies to ovarian antigens in women with premature ovarian failure. Clinical and Experimental Immunology. 1994;**96**(1):122-128. PMID: 8149656

[99] Moncayo H, Moncayo R, Benz R, Wolf A, Lauritzen C. Ovarian failure and autoimmunity. Detection of autoantibodies directed against both the unoccupied luteinizing hormone/human chorionic gonadotropin receptor and the hormone-receptor complex of

ovine corpus luteum. The Journal of Clinical Investigation. 1989;**84**(6):1857-1865. PMID: 2592563. DOI: 10.1172/JCI114372

[100] Mande PV, Parikh FR, Hinduja I, Zaveri K, Vaidya R, Gajbhiye R, Khole VV. Identification and validation of candidate biomarkers involved in human ovarian autoimmunity. Reproductive Biomedicine Online. 2011;**23**(4):471-483. PMID: 21890413. DOI: 10.1016/j.rbmo.2011.06.013

[101] Mande PV, Thomas S, Khan S, Jadhav S, Khole VV. Immunization with ovarian autoantigens leads to reduced fertility in mice following follicular dysfunction. Reproduction. 2012;**143**(3):309-323. PMID: 22143970. DOI: 10.1530/REP-11-0221

[102] Kobayashi Y, Yamamoto T, Chishima F, Takahashi H, Suzuki M. Autoantibodies isolated from patients with preeclampsia induce soluble endoglin production from trophoblast cells via interactions with angiotensin II type 1 receptor. American Journal of Reproductive Immunology. 2015;**73**:285-291. PMID: 25376533. DOI: 10.1111/aji.12340

[103] Komorowska B. Autoimmune premature ovarian failure. Prz Menopauzalny. 2016;**15, 4**: 210-214. PMID: 28250725. DOI: 10.5114/pm.2016.65666

[104] Cervera R, Balasch J. Bidirectional effects on autoimmunity and reproduction. Human Reproduction Update. 2008;**14**(4):359-366. PMID: 18499707. DOI: 10.1093/humupd/dmn013

[105] Luborsky JL, Visintin I, Boyers S, et al. Ovarian antibodies detected by immobilized antigen immunoassay in patients with premature ovarian failure. The Journal of Clinical Endocrinology and Metabolism. 1990;**70**:69-75. PMID: 2104631. DOI: 10.1210/jcem-70-1-69

[106] Lebovic DI, Naz R. Premature ovarian failure: Think 'autoimmune disorder'. Sexuality, Reproduction & Menopause. 2004;**2**(4):230-233

[107] 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. Endocrine Reviews. 2002;**23**:327-364. PMID: 12050123. DOI: 10.1210/edrv.23.3.0466

[108] Ebrahimi M, Akbari Asbagh F. Pathogenesis and causes of premature ovarian failure: An update. International Journal of Fertility & Sterility. 2011;**5**:54-65. PMID: 24963360

[109] Bagavant H, Thompson C, Ohno K, Setiady Y, Tung KS. Differential effect of neonatal thymectomy on systemic and organ-specific autoimmune disease. International Immunology. 2002;**14**(12):1397-1406. PMID: 12456587

[110] Pires ES, Parte PP, Meherji PK, Khan SA, Khole VV. Naturally occurring anti-albumin antibodies are responsible for false positivity in diagnosis of autoimmune premature ovarian failure. The Journal of Histochemistry and Cytochemistry. 2006 Apr;**54**(4):397-405 Epub 2005 Nov 14. PMID: 16286665

[111] Pires ES, Khole VV. A block in the road to fertility: Autoantibodies to heat-shock protein 90-beta in human ovarian autoimmunity. Fertility and Sterility. 2009 Oct;**92**(4):1395-1409. DOI: 10.1016/j.fertnstert.2008.08.068 Epub 2008 Nov 19. PMID: 19022436

[112] Pires ES, Choudhury AK, Idicula-Thomas S, Khole VV. Anti-HSP90 autoantibodies in sera of infertile women identify a dominant, conserved epitope EP6 (380-389) of HSP90 beta protein. Reproductive Biology and Endocrinology. 2011;**9**:16. DOI: 10.1186/1477-7827-9-16. PMID: 21272367

[113] Tong ZB, Nelson LM. A mouse gene encoding an oocyte antigen associated with autoimmune premature ovarian failure. Endocrinology. 1999;**140**:3720-3726. PMID: 10433232. DOI: 10.1210/endo.140.8.6911

[114] Tomar N, Kaushal E, Das M, Gupta N, Betterle C, Goswami R. Prevalence and significance of NALP5 autoantibodies in patients with idiopathic hypoparathyroidism. The Journal of Clinical Endocrinology and Metabolism. 2012;**97**(4):1219-1226. PMID: 22278434. DOI: 10.1210/jc.2011-3093

[115] Choudhury A, Khole VV. HSP90 antibodies: A detrimental factor responsible for ovarian dysfunction. American Journal of Reproductive Immunology. 2013;**70**(5):372-385. PMID: 23662883. DOI: 10.1111/aji.12136

[116] Choudhury A, Khole VV. Immune-mediated destruction of ovarian follicles associated with the presence of HSP90 antibodies. Molecular Reproduction and Development. 2015;**82**(2):81-89. PMID: 25653208. DOI: 10.1002/mrd.22428

[117] Bukulmez O, Arici A. Leukocytes in ovarian function. Human Reproduction Update. 2000;**6**:1-15. PMID: 10711825

[118] Wu R, Van der Hoek KH, Ryan NK, Norman RJ, Robker RL. Macrophage contributions to ovarian function. Human Reproduction Update. 2004;**10**:119-133. PMID: 15073142. DOI: 10.1093/humupd/dmh011

[119] Kalantaridou SN, Braddock DT, Patronas NJ, Nelson LM. Treatment of autoimmune premature ovarian failure. Human Reproduction. 1999;**14**(7):1777-1782. PMID: 10402388

[120] Kadam KM, Mande PV, Gawas N, Ahire S, Khole VV. Autoantibodies to heat-shock protein, HSPA5, and epitope spreading: High-dose dexamethasone therapy rescues ovarian function in experimental autoimmune ovarian insufficiency mouse model. American Journal of Reproductive Immunology. 2016;**75**:580-593. PMID: 26840828. DOI: 10.1111/aji.12494

[121] Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. Autoimmunity Reviews. 2015;**14**(2):174-180. PMID: 25461470. DOI: 10.1016/j.autrev.2014.10.016

[122] Robazzi TC, Adan LF. Autoimmune thyroid disease in patients with rheumatic diseases. Revista Brasileira de Reumatologia. 2012;**52**(3):417-430. PMID: 22641595

[123] Versini M. Thyroid autoimmunity and antiphospholipid syndrome: Not such a trivial association. Frontiers in Endocrinology. 2017;**8**:175. PMID: 28785243. DOI: 10.3389/fendo.2017.00175

[124] Souza SS, Ferriani RA, Santos CM, Voltarelli JC. Immunological evaluation of patients with recurrent abortion. Journal of Reproductive Immunology. 2002;**56**:111-121. PMID: 12106887

[125] Shankarkumar U, Pradhan VD, Patwardhan MM, Shankarkumar A, Ghosh K. Autoantibody profile and other immunological parameters in recurrent spontaneous abortion patients. Nigerian Medical Journal. 2011;**52**(3):163-166. PMCID: PMC3213746. DOI: 10.4103/0300-1652.86126

[126] Petríková J, Lazúrová I. Ovarian failure and polycystic ovary syndrome. Autoimmunity Reviews. 2012;**11**(6–7):A471-A478. PMID: 22154711. DOI: 10.1016/j.autrev.2011.11.010

[127] Goswami R, Marwaha RK, Goswami D, Gupta N, Ray D, Tomar N, Singh S. Prevalence of thyroid autoimmunity in sporadic idiopathic hypoparathyroidism in comparison to type 1 diabetes and premature ovarian failure. Journal of Clinical Endocrinology and Metabolism. 2006;**91**(11):4256-4259. PMID: 16895958. DOI: 10.1210/jc.2006-1005

[128] Nelson LM. Clinical practice. Primary ovarian insufficiency. The New England Journal of Medicine. 2009;**360**:606-614. PMCID: PMC2762081. DOI: 10.1056/NEJMcp0808697

[129] Kifor O, Moore FD Jr, Delaney M, Garber J, Hendy GN, Butters R, Gao P, Cantor TL, Kifor I, Brown EM, Wysolmerski J. A syndrome of hypocalciuric hypercalcemia caused by autoantibodies directed at the calcium-sensing receptor. The Journal of Clinical Endocrinology and Metabolism. 2003;**88**(1):60-72. PMID: 12519831. DOI: 10.1210/jc.2002-020249

[130] Mol BW, Bayram N, Lijmer JG, Wiegerinck MA, Bongers MY, van der Veen F, Bossuyt PM. The performance of CA-125 measurement in the detection of endometriosis: A meta-analysis. Fertility and Sterility. 1998;**70**:1101-1108. PMID: 9848302

[131] May KE, Conduit-Hulbert SA, Villar J, Kirtley S, Kennedy SH, Becker CM. Peripheral biomarkers of endometriosis: A systematic review. Human Reproduction Update. 2010; **16**:651-674. PMID: 20462942. DOI: 10.1093/humupd/dmq009

[132] Dunselman GAJ, Vermeulen N, Becker C, Calhaz-Jorge C, D'Hooghe T, De Bie B, Heikinheimo O, Horne AW, Kiesel L, Nap A, Prentice A, Saridogan E, Soriano D, Nelen W. ESHRE guideline: Management of women with endometriosis. Human Reproduction. 2014;**29**(3):400-412. PMID: 24435778. DOI: 10.1093/humrep/det457

[133] May KE, Villar J, Kirtley S, Kennedy SH, Becker CM. Endometrial alterations in endometriosis: A systematic review of putative biomarkers. Human Reproduction Update. 2011;**17**(5):637-653. PMID: 21672902. DOI: 10.1093/humupd/dmr013

[134] Fassbender A, Burney RO, DF O, D'Hooghe T, Giudice L. Update on biomarkers for the detection of endometriosis. BioMed Research International. 2015;**2015**:130854. PMID: 26240814. DOI: 10.1155/2015/130854

[135] Hughes E, Brown J, Collins JJ, Farquhar C, Fedorkow DM, Vandekerckhove P. Ovulation suppression for endometriosis. Cochrane Database of Systematic Reviews. 2007: CD000155. PMID: 17636607. DOI: 10.1002/14651858.CD000155.pub2

[136] Nowroozi K, Chase JS, Check JH, Wu CH. The importance of laparoscopic coagulation of mild endometriosis in infertile women. International Journal of Fertility. 1987;**32**:442-444. PMID: 2891631

[137] Jacobson TZ, Duffy JM, Barlow D, Farquhar C, Koninckx PR, Olive D. Laparoscopic surgery for subfertility associated with endometriosis. Cochrane Database of Systematic Reviews. 2010:CD001398. PMID: 20091519. DOI: 10.1002/14651858.CD001398.pub2

[138] Yap C, Furness S, Farquhar C. Pre and post-operative medical therapy for endometriosis surgery. Cochrane Database of Systematic Reviews. 2004:CD003678. PMID: 15266496. DOI: 10.1002/14651858.CD003678.pub2

[139] Werbrouck E, Spiessens C, Meuleman C, D'Hooghe T. No difference in cycle pregnancy rate and in cumulative live-birth rate between women with surgically treated minimal to mild endometriosis and women with unexplained infertility after controlled ovarian hyperstimulation and intrauterine insemination. Fertility and Sterility. 2006;**86**:566-571. PMID: 16952506. DOI: 10.1016/j.fertnstert.2006.01.044

[140] D'Hooghe TM, Denys B, Spiessens C, Meuleman C, Debrock S. Is the endometriosis recurrence rate increased after ovarian hyperstimulation? Fertility and Sterility. 2006;**86**: 283-290. PMID: 16753162. DOI: 10.1016/j.fertnstert.2006.01.016

[141] Benaglia L, Somigliana E, Vercellini P, Benedetti F, Iemmello R, Vighi V, Santi G, Ragni G. The impact of IVF procedures on endometriosis recurrence. European Journal of Obstetrics, Gynecology, and Reproductive Biology. 2010;**148**:49-52. PMID: 19800161. DOI: 10.1016/j.ejogrb.2009.09.007

[142] Benaglia L, Somigliana E, Santi G, Scarduelli C, Ragni G, Fedele L. IVF and endometriosis-related symptom progression: Insights from a prospective study. Human Reproduction. 2011;**26**:2368-2372. PMID: 21715451. DOI: 10.1093/humrep/der208

[143] Coccia ME, Rizzello F, Gianfranco S. Does controlled ovarian hyperstimulation in women with a history of endometriosis influence recurrence rate? Journal of Women's Health (2002). 2010;**19**:2063-2069. PMID: 20831441. DOI: 10.1089/jwh.2009.1914

[144] Bianchi PH, Pereira RM, Zanatta A, Alegretti JR, Motta EL, Serafini PC. Extensive excision of deep infiltrative endometriosis before in vitro fertilization significantly improves pregnancy rates. Journal of Minimally Invasive Gynecology. 2009;**16**(2):174-180. PMID: 19249705. DOI: 10.1016/j.jmig.2008.12.009

[145] Papaleo E, Ottolina J, Vigano P, Brigante C, Marsiglio E, De Michele F, Candiani M. Deep pelvic endometriosis negatively affects ovarian reserve and the number of oocytes retrieved for in vitro fertilization. Acta Obstetricia et Gynecologica Scandinavica. 2011; **90**:878-884. PMID: 21542809. DOI: 10.1111/j.1600-0412.2011.01161.x

[146] Webber L, Davies M, Anderson R, Bartlett J, Braat D, Cartwright B, Cifkova R, De Muinck Keizer-Schrama S, Hogervorst E, Janse F, Liao L, Vlaisavljevic V, Zillikens C, Vermeulen N. ESHRE guideline: Management of women with premature ovarian insufficiency. Human Reproduction. 2016;**31**(5):926-937. PMID: 27008889. DOI: 10.1093/humrep/dew027

[147] Klonoff-Cohen H. 2017. https://www.fertstertdialog.com/users/16110-fertility-and-sterility/posts/19876-klonoff-cohen-consider-this

[148] Dighiero G, Lymberi P, Holmberg D, Lundquist I, Coutinho A, Avrameas S. High frequency of natural autoantibodies mice in normal Newborn. Journal of Immunology. 1985;**134**(2):765-771. PMID: 4038410

[149] Dighiero G, Guilbert B, Fermand JP, Lymberi P, Danon F, Avrameas S. Thirty-six human monoclonal immunoglobulins with antibody activity against cytoskeleton proteins, thyroglobulin, and native DNA: Immunologic studies and clinical correlations. Blood. 1983; **62**(2):264-270. PMID: 6409187

[150] Savitskaya YA, Duarte C, Marín N, Téllez R, Alfaro A, Ibarra C. Identification of circulating natural antibodies against endogenous mediators in the peripheral blood sera of patients with osteoarthritis of the knee: A new diagnostic frontier. Journal of Molecular Biomarkers & Diagnosis. 2012;**3**:135. DOI: 10.4172/2155-9929.1000135

[151] Zhen X, Qiao J, Li R, Wang L, Ping L. Serologic autoimmunologic parameters in women with primary ovarian insufficiency. BMC Immunology. 2014;**15**:11. PMID: 24606591. DOI: 10.1186/1471-2172-15-11

[152] Cline AM, Kutteh WH. Is there a role of autoimmunity in implantation failure after in-vitro fertilization? Current Opinion in Obstetrics & Gynecology. 2009;**21**(3):291-295. PMID: 19469047

[153] Boumpas DT, Chrousos GP, Wilder RL, Cupps TR, Balow JE. Glucocorticoid therapy for immune mediated diseases: Basic and clinical correlates. Annals of Internal Medicine. 1993;**119**:1198-1208. PMID: 8239251

[154] Boumpas DT, Austin HA 3rd, Vaughan EM, Yarboro CH, Klippel JH, Balow JE. Risk for sustained amenorrhea in patients with systemic lupus erythematosus receiving intermittent pulse cyclophosphamide therapy. Annals of Internal Medicine. 1993;**119**(5):366-369. PMID: 8338289

[155] Otsuka N, Tong Z-B, Vanevski K, Tu W, Cheng MH, Nelson LM. Autoimmune oophoritis with multiple molecular targets mitigated by transgenic expression of mater. Endocrinology. 2011;**152**(6):2465-2473. PMID: 21447630. DOI: 10.1210/en.2011-0022

[156] Zhang D, Tu E, Kasagi S, Zanvit P, Chen Q, Chen W. Manipulating regulatory T cells: A promising strategy to treat autoimmunity. Immunotherapy. 2015;**7**:1201, 11. PMID: 26568117-1211. DOI: 10.2217/imt.15.79

[157] Vojdani A. Antibodies as predictors of complex autoimmune diseases. International Journal of Immunopathology and Pharmacology. 2008;**21**:267-278. PMID: 18547471. DOI: 10.1177/039463200802100203

[158] Busnelli A, Paffoni A, Fedele L, Somigliana E. The impact of thyroid autoimmunity on IVF/ICSI outcome: A systematic review and meta-analysis. Human Reproduction Update. 2016;**22**(6):775-790. PMID: 27323769. DOI: 10.1093/humupd/dmw019

[159] Unuane D, Velkeniers B, Anckaert E, Schiettecatte J, Tournaye H, Haentjens P, Poppe K. Thyroglobulin autoantibodies: Is there any added value in the detection of thyroid autoimmunity in women consulting for fertility treatment? Thyroid. 2013;**23**(8):1022-1028. PMID: 23405888. DOI: 10.1089/thy.2012.0562

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