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

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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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