A Review: Have we Identified the Risk Factors for the Formation of Antisperm Antibodies?

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Abstract

Spermatozoa were first demonstrated as immunogenic more than a century ago. Subsequent research has lead to the discovery of antisperm antibodies (ASA) and their effects on infertility. However, the precise etiology of the formation of ASA is yet to be worked out in spite of the large number of research conducted on it. During these investigations, many scientists have exposed the risk factors for the formation of ASA while others expressed the controversies.

This article reviews the research that investigated the possible risk factors for the formation of ASA in human. A comprehensive, English language, recent literature was searched using Medline and print journals. Predisposing factors for the development of ASA in healthy males and females as well as in infertility were assessed.

It was found that none of the research done so far strongly proves the association between ASA and any of the risk factors. However, this article compares and contrasts the available research data. The controversy over the causes for the development of ASA to some extent reflects the inadequacies of well-designed and case controlled studies and lack of exact cut-off points of the presence of ASA in samples in clinical trials.

Keywords

Antisperm antibodies; Risk factors; Etiology; Genital surgery; Pelvic infections; Alcohol and smoking; Intrauterine insemination; Autoimmune diseases

Abstract

Antisperm antibodies (ASA) are antibodies against sperm antigens which present within the reproductive tract/secretions and in blood in both males and females. It is established that ASA can negatively impact fertility by affecting sperm motility, cervical mucus penetration, gamete fusion and potentially even the first steps of embryo development [1]. The precise mechanism of generation of these antibodies is not clear. When spermatozoa are produced at puberty they express antigens not previously encountered by the immune system. These immunogenic spermatozoa, with a breach of immune-regulatory mechanisms in human reproductive system may expose to it resulting in an inflammatory reaction and formation ASA [2]. However, the formation of ASA does not occur in every individual who has a breach of immune-regulation and all individuals with ASA do not posses those interferences.

Numerous studies have attempted to discover the etiology of ASA formation. Up to date, the precise mechanism is yet to be revealed. However, most of the authors have shown risk factors for the formation of ASA. A research study done in Sri Lanka by the author also has demonstrated some of the risk factors. The study was done on a population of 230 infertile couples and ASA IgA and IgG types were detected on serum, cervical mucus and semen using sperm MAR latex bead test. This review article discusses and explores the associated risk factors that have been suggested by other research done so far and compares with the authors’ study.

Age

Different studies have shown the existence of age dependence in the incidence of sperm antibodies in animals and in human as well. Flickinger et al. have demonstrated a significant rise in ASA levels with age in normal male Lewis rats [3]. A study done in South Karnataka, India with infertile males (age range 20-50 years) has shown an increase of the prevalence of ASA with the individuals age [4]. The highest prevalence was seen between 31–40 years age group. Some studies have employed predominantly healthy individuals and demonstrated conflicting results. A large scale study by Kalaydjiev et al. again on healthy individuals has investigated different age groups, starting with newborn and their mothers up to subjects older than 88 years, using four sperm antibody assays [5]. They have showed low incidence of ASA in pre pubertal ages, a rise during reproductive age with a gradual decline with aging [5]. The study done in Sri Lanka by the author including 230 infertile couples did not show a significant difference in incidence among the age groups in both males (36.9 ± 5.0 years) and females (33.4 ± 4.1 years) [6,7]. This whole study population was within the reproductive age and was a selective population of infertile couples. On par with this finding, as a majority, the published literature demonstrates that there is no age dependent tendency in the incidence of ASA.

Duration of marriage and duration of infertility

Several mechanisms have been postulated for the development of immunity to sperm in males and females. It is believed that breach of blood testis barrier in males and mechanical or chemical disruption of the mucosal layer of female genital tract may permit exposure to foreign sperm antigens and, ultimately ASA formation [8]. It is also expected to have high incidence of ASA in females following repeated contacts with sperm antigen in a period of duration. However, the reason most women do not develop an immune response after repeated sperm exposure is not yet established [9]. Referring to the study done by the author has shown that there was no statistically significant difference between the incidence of ASA and duration of marriage as well as duration of infertility [6]. In contrast one study has shown a significant inverse association of ASA with duration of

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infertility [4]. However, lack of research data in relation to duration of marriage or infertility, makes it impossible to come to a definite conclusion.

Occupation

Though the type of occupation of the male partner has been widely studied in relation to the state of infertility, the impact of the same on immune-infertility is not clear. Occupations which expose the individuals to heat, vibration, radiation and stress have been suggested as risk factors for infertility although there impact on immune-infertility is questionable. Occupational exposure to lead or mercury has been found to make proteins better antigens. The production of auto-antibodies to nervous system protein is one example of such effect. Shamy et al. have assessed serum ASA levels in healthy male workers exposed to lead (n=50) or to mercury (n=39) using ELISA technique and compared to a matched control group (n=39) [10]. Antisperm antibodies were detected in 90% of workers exposed to lead with the predominance of the IgG type and 84.6% of workers exposed to mercury with the predominance of the IgM type [10]. Referring to the study done by the author, the 460 infertile individuals were grouped into seven different occupational categories such as professionals, managers and clerical, skilled workers etc and analyzed the significance of presence of ASA. It was found that no individuals were repeatedly exposed to heavy metals, heat, vibration or radiation in the study group and the incidence of ASA in different occupational categories was not significant [6]. Another explanation for a positive association with heavy metal exposure and presence of ASA is that damage caused by these metals to the blood testis barrier would allow them to appear in semen and expose spermatogenetic cells to blood increasing the likelihood of the development of antisperm antibodies. However, the results should be interpreted with caution as in some studies lack of control population, different laboratory tests and type of reporting centers may weaken the strength of the study results.

Type of infertility

Presence of ASA can be found in primary as well as in secondary infertility in both males and females. Secondary infertility in men has been demonstrated in men who develop varicoceles [11,12] or who undergo genito-urinary surgeries [13,14]; both conditions that are well known for ASA formation. In females, it has been shown a tenuous association between the prevalence of ASA in women’s sera and recurrent miscarriages [15]. Referring to the authors’ research, there was 19.54% incidence of ASA among primary infertile couples (n=174) and 25% incidence among secondary infertile couples (n=56). No significant difference found in the incidence of ASA between primary infertility and secondary infertility [6]. ASA may prevail in both types of infertility in both males and females as it could develop with time, influenced by other conditions. Clinical data are scarce in this aspect up to now.

Environmental pollution

Apart from the occupational environmental effects on formation of ASA, exposure to environmental pollution (out of occupation) such as heat, radiation, sound and vibration etc on formation of ASA has not been studied and published in recent English literature. The reasons for lack of such research would be the requirement of sufficient number of volunteering subjects in a particular area with environmental pollution and a truly unexposed comparable population as the control. A significant step forward in this field would be to identify the environmental risk factors for the formation of ASA.

Associated genito-urinary conditions in males

Sperm have foreign antigens because they are most likely to develop in an immune privileged site and not present until after puberty. There are several hypotheses for ASA formation in men. Theoretically, the blood testis barrier may be breached by a variety of mechanisms resulting in exposure of immunogenic sperm antigens to the immune system, initiating an immune response resulting in an inflammatory reaction and ASA formation [8]. It is suggested that chronic obstructions of male reproductive tract, congenital states like bilateral absence of vas deference, acquired conditions like varicoceles, cryptorchidism, testicular trauma, torsion and biopsy may play a role in formation of ASA [15]. Some studies have shown that after vasectomy, approximately 50% of men produce ASA [16,17]. Fu et al. have demonstrated that testicular injury can induce and elevation of ASA, which could last a very long time [18]. Likewise, significant higher incidence of ASA has been shown in men with varicoceles/varicocelecomies [11,12]. It was observed as a statistically significant association (P-value=0.036) between the presence of ASA and a history of genital surgery in the author’s study [6,7]. Majority of them had undergone varicocelectomy. Theoretically, presence of varicoceles can also induce formation of ASA as impaired venous drainage of the testis may result in damage to the seminiferous tubules and lead to ASA production. The surgery may alleviate that, though causing disruption of the tissues of blood testis barrier facilitating ASA formation. Contradictory to these evidence, Heidenreich et al. and Verajankorva et al. have elicited that varicoceles is not a risk factor for ASA production [19,20]. In their study, Verajankorva et al. have analyzed predisposing factors for male immunological infertility and demonstrated lower levels of ASA in patients with varicoceles in a population of 508 infertile patients [20].

With available data, it is evident that in some instances though the blood testis barrier is clearly disturbed, ASA formation is not regularly triggered. This fact demonstrates that the pathophysiology of ASA formation is still unclear [9]. However, it is recommended to screen infertile males with a history of varicocelectomy / any genital surgery for antisperm antibodies in initial infertility workup.

Associated infections of the genital tract in males

Infections of the male genital tract as a cause of formation of antisperm antibodies, has not sufficiently supported by clinical studies so far [9].

Witkin et al. have suggested that organisms of genital tract may act as initiators through inflammatory process and lead to the formation of antibodies against the bacterial membrane carbohydrates that could cross react with sperm surface carbohydrates [21]. Witkin again in 1996 showed that chlamydia infections of the male genital tract (MRT), which are associated with antisperm antibody formation on ejaculated spermatooza, are likely to be transmitted to the female partner [22]. However, newer studies show no association between chronic inflammatory / infectious diseases of the MRT and the presence of ASA. Studies by Eggert-Kruse et al. have also shown that Cytomegalo virus infection in the genital tract of infertile patients is not a significant cause of infertility [23]. Another study done on prostate abnormalities has found that chronic prostatitis does not
induce antibodies to spermatozoa, thus not causing ASA-induced immune infertility [24].

A large scale study by Marconi et al. evaluated chronic inflammatory and infectious diseases of the MRT analyzing common bacteria including Chlamydia trachomatis and Neisseria gonorrhoea, yeasts, and mycoplasma [25]. They have demonstrated that there is no association between chronic inflammatory or infectious diseases of the MRT and the presence of ASA in semen [25]. The discrepancy in earlier studies may have occurred due to use of deferent detecting methods to screen ASA and also different studies have taken various cut off levels for ASA as the significant level.

**Associated auto-immune conditions in males**

Infertility may have the potential to disrupt genital tract tissue and ASA formation. History of mumps infection has been shown to cause abnormal semen parameters. One study has shown a significant lower percentage of normal sperm morphology in men with a history of mumps of a group of 243 fertile men [26]. Some authors believe that pre-pubertal mumps normally does not cause any impairment in fertility [27]. However, it is suggested that formation of ASA is basically caused by mumps orchitis. In the authors’ study it was observed that 27.83% of the infertile males had mumps in childhood, and none had mumps orchitis. Incidence of ASA in men with childhood mumps was not significant compared to the men without childhood mumps [6]. The causal link between mumps orchitis and ASA is not well established. Masarani et al. also have demonstrated that both the incidence and the level of serum ASA among mumps orchitis patients were low, and that it has not supported the hypothesis of an enhanced humoral immunity against spermatozoa [28]. In recent studies some authors have suggested a possible cross reactivity of antibodies to spermatozoa in individuals who have a systemic autoimmune disease. Shi et al. have investigated antisperm antibodies in the sera of 70 males with systemic autoimmune diseases and 80 healthy controls, by using the indirect-immuno bead test [29]. Among males with systemic autoimmune diseases, the incidence of ASA was 7.1%, and there was no ASA positives existed in healthy males. With the significantly higher incidence of ASA in males with systemic autoimmune diseases, they have concluded that systemic autoimmune diseases may be one of the risk factors for developing ASA in men [29]. Referring to the author’s study, neither the males gave a history of rheumatoid arthritis, autoimmune thyroid disease or any other systemic autoimmune disease, nor were the females who gave a history of any systemic autoimmune illness had ASA. Hence, a statistical analysis could not be made with the presence of ASA with autoimmune illnesses [6,7]. More studies are needed in this regard to name systemic autoimmune diseases as a risk factor.

**Use of addictables in males**

In the authors’ study, of the total sample, 13% men were smokers. There was no significant correlation found with smokers and non-smokers in the incidence of ASA [6]. By reviewing the literature on impact of smoking, alcohol and other addictables on immune infertility, it is evident that the effects remain inconclusive. The studies on smoking and sperm abnormalities show a limited effect of smoking on conventional sperm parameters. It has been observed that smoking had an adverse effect on the progressive sperm motility, irrespective of total amount of cigarettes smoked per day [30]. Supportive evidence is found in the studies of other investigators as well [31,32]. Studies on cigarette smoking and incidence of antisperm antibodies are limited. A study by Ludwikowski et al. has shown an increased occurrence of ASA in smoking patients, though statistically not significant [33]. The data on alcohol show an apparent protective effect of moderate alcohol drinking on sperm parameters, probably due to the antioxidant effect of some alcoholic beverages [34]. Close et al. have studied the relationship of current use of cigarettes, marijuana and alcohol to the parameters of seminal fluid analysis, sperm penetration assay and sperm autoimmunity in 164 men from infertile couples [35]. In that study users of cigarettes, marijuana or alcohol showed no decrease in sperm count, motility or percentage of oval sperm, and no difference in prevalence of antisperm antibodies compared to non-users [35]. In the authors’ study too, there was no significant correlation found with alcohol consumption and incidence of ASA where 31.1% males of the sample consumed alcohol though none of them admitted addiction. Lack of literature indicates that the understanding of these conditions in the development of ASA is incomplete.

**Role of intra-uterine inseminations in females**

In females a possible contributory factor for the formation of antisperm antibodies is repeated intrauterine inseminations with washed spermatozoa. There is a theoretical concern that IUI may induce antisperm antibodies in women as in IUI, processed sperm bypass the physiological immune barriers of female genital tract. Also in IUI, washing of sperms removes immuno-suppressive properties of seminal plasma which can lead to an immune response against sperms in female tissues. Livi et al. have demonstrated the risk of subsequent risk of immunity to sperms in women following intrauterine inseminations [36]. Intrauterine insemination is widely used for the treatment of infertility as a result of cervical or male factor infertility or empirically before in vitro fertilization. Different studies have shown that in male immunological infertility, a well-timed IUI is an effective treatment method [37], and that IUI does not induce significant ASA production in women [38]. Referring to the authors’ study, though there was no statistically significant relationship found, the incidence of ASA was proportionately higher among women those who had previous IUIs (11.7%) compared to the women who did not have IUIs (5.88%). There are mixed reports on how useful is the intrauterine insemination for treatment of female and male immune infertility [39]. The lack of standardized methods and an established cut-off point for ASA detection in the samples makes the comparison difficult among different clinical trials.

**Presence of pelvic inflammatory disease in females**

It is assumed that bacterial infections of the upper genital tract, in particular with Chlamydia trachomatis, may stimulate the immune system [40,41], perhaps via exposure of the spermatozoa to immunologically competent cells in inflammatory conditions. Some authors indeed have demonstrated a direct association of pelvic inflammatory disease (PID) with the incidence of ASA in women [42]. Cunningham et al. have studies ASA to sperm surface antigens in null gravid women with primary upper genital tract infections [42]. They have shown that as many as 56% of women with a primary episode of PID had antisperm antibodies [42]. In addition, there was a significant level of circulating ASA in 69% of women with past pelvic infection. In the authors’ study, out of five females who have had episodes of PID, one was positive for ASA. Therefore the incidence of ASA among females having PID was 20% compared to incidence in PID free females (8%) [6]. Though the association of ASA with PID
is markedly high, sufficient number of subjects is needed to make a statistical analysis.

In contrast, other research does not show a direct relationship. A retrospective case control study including 90 infertile women and 80 healthy women, has found that ASA were significantly higher in infertile women, but without a significant difference between the incidence of ASA in infertile women with past or current Chlamydia trachomatis infection [43]. Accordingly, Krause et al. have stated that infections of the genital tract as a cause of formation of ASA, has not sufficiently supported by clinical studies so far [9].

**Associated systemic auto-immune conditions in females**

There is no recent English language literature found on this association. Some research show association between different systemic auto-immune diseases with infertility, but none has conducted to investigate these diseases as a risk factor for the formation of ASA in females. Referring to the authors study, it was observed that 9.1% of the females had autoimmune diseases as autoimmune thyroiditis, rheumatoid arthritis, psoriasis etc [6]. However, none of these females were positive for ASA. More research is needed to express the association of this factor.

**Conclusion**

Reviewing all the associated factors that have been investigated for the formation of ASA, it is evident that all these entities and presence of ASA is still controversial. The discrepancy of these conflicting results are mostly due to the use of different screening tests with various cut off levels of ASA and lack of randomized and controlled study populations. However, it is recommended to screen individuals for the presence of ASA in initial infertility workup when they present with history of genital / pelvic surgeries and females with pelvic inflammatory disease where a strong correlation have been shown in many studies. Nonetheless, multi-centered large scale studies are need to establish the predisposing factors for the formation of ASA, which enables the clinicians to make early detections; hence select appropriate treatment modalities.

**References**


