ASA in the Female

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Abstract

This article briefly reviews our knowledge about antisperm antibodies (ASA) in females and outlines several hypotheses regarding the etiology of sperm immunity in women.

There is evidence that strong ASA in females can reduce the chances of conception and ASA from female sera have also been found to inhibit in vitro fertilization (IVF) in humans and some animal models. Several possible factors leading to the development of ASA in human females have been proposed, including cross-reactivity with microbial antigens, and the possible role of antibody idiotypes and interferon gamma-mediated potentiation of the antisperm immune response in women whose male partners have ASA in their semen. It is vital that more research is conducted in this area if we are to understand female immuno-modulation in response to sperm antigenicity.

10.1 Introduction

The main aim of this chapter is to review selected literature which is pertinent to understanding why some females develop sperm immunity, with primary focus on antisperm antibodies (ASA) detectable in serum, follicular fluid, or cervical mucus. Another important aim is to discuss several aspects/observations from animal models which have so far received little consideration from the clinical perspective with the objective of stimulating more research focus in these areas. Other chapters in

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this volume cover in detail the tests available for detecting ASA (Chap. 13), antigens (Chap. 2), impact on assisted reproduction (Chap. 15), and treatment of immune infertility (Chap. 16) and other important aspects.

10.2 Historical Background

During the first few decades of the twentieth century, many studies in animals had indicated that homologous or heterologous immunization of females with sperm or testis preparations could induce sperm antibody activity and infertility (see Katsh [1] for review). The considerable evidence derived from animal models, combined with preliminary evaluation of patients, provided stimulus for "clinical trials" involving immunization of women with their partner's semen with the aim of inducing immuno-contraception. Baskin [2] reported on a study of 20 fertile women immunized three times intramuscularly at weekly intervals, with their partner's whole ejaculate. All but one of the women showed sperm immobilizing activity in their serum by 1 week after the last injection which persisted for up to 1 year. One woman became pregnant after 12 months when the sperm immobilizing activity was no longer detectable in her serum. These trials demonstrated that women could be immunized to develop sperm immobilizing activity and that this was associated with reduced fecundity.

Further significant evidence for female ASA association with human infertility awaited the report by Franklin and Dukes in 1964 [3]. They found that 20.1 % of 214 women undergoing infertility investigations had detectable sperm agglutinating activity in their serum. Women with unexplained infertility had a much higher incidence (72.1 %) than women with organic causes for their infertility (8.4 %) or fertile women (5.7 %). It should be noted that this study found a very high incidence of ASA, and the results are not supported by recent studies using immunologically specific procedures such as the immunobead test (IBT). However, this report was notable from an historical perspective in that it stimulated significant interest in the idea that female immunological responses to sperm could be involved in the development of otherwise unexplained infertility and in the concept of an antisperm contraceptive vaccine.

10.3 More Recent Studies on ASA in Females

Since the early reports described above, a multitude of studies have examined the effects of ASA on sperm-cervical mucus penetration, in vitro fertilization (IVF) and infertility. Many review articles have described the clinical and experimental research in this area [4–7]. It is pertinent however to review some of the background information and studies which are relevant to explaining the pathogenesis of female immuno-infertility associated with ASA.

The uterine cervix is a highly competent mucosal immune site (for review, see [8]) which contains many IgA-positive plasma cells located in the subepithelial

layers of the endocervix. Most of the IgA in cervical mucus is secretory IgA consisting of two IgA monomers linked by J-chain and secretory piece. The secretory IgA antibodies directed against potential pathogens and occasionally sperm [9] can immobilize the invaders by cross-linking them to the cervical mucus strands, effectively blocking their progress to the upper reaches of the reproductive tract [10]. There are obviously mechanisms which normally prevent such immunological reactions to sperm in women. However, in a small percentage of couples, these are somehow circumvented or disrupted, resulting in local and often circulating ASA production and reduced chances of natural conception. In women with otherwise unexplained infertility, sperm antibody activity has been detected in cervical mucus in more than 10 % of cases [11–13].

Investigations using zona-free hamster eggs or salt-stored human zona pellucidae indicated that high level ASA might be expected to interfere with human fertilization [4], but this could not be adequately confirmed using fresh human oocytes until the availability of routine clinical IVF around 1985. Retrospective analysis of IVF results by Clarke et al. [14] provided some of the first evidence that ASA from female serum could inhibit the fertilization of viable human oocytes by human spermatozoa. They observed a fertilization rate of only 15 % for patients who had significant titers of IgG and IgA class ASA in their serum, which at that time was used as a supplement in the IVF culture medium, versus 69 % for those patients where replacement serum was used during the fertilization culture. Their later experimental results confirmed that very high titer ASA of IgG immunoglobulin class in female serum could effectively inhibit fertilization of fresh human oocytes [15]. Subsequent reports from other laboratories have also indicated that high level ASA can inhibit human fertilization [16–18]. In addition, more recent animal studies have also provided considerable evidence that experimentally induced sperm isoimmunity could have detrimental effects on fertility and in vitro fertilization [4]. Consequently, it is now generally accepted, at least with strong sperm immunity, that ASA can block sperm functions such as cervical mucus penetration and fertilization and thereby impair fertility.

10.4 Clinical Evaluation of ASA

It is strongly recommended that both the female and male partners should be tested for ASA during infertility assessment. The initial investigation of the male partner of an infertile couple should include a direct mixed antiglobulin reaction (MAR) screen for sperm-bound antibodies [7]. A positive result (>50 % of motile sperm being antibody coated) should be followed up with a repeat test and preferably mucus penetration testing to make an assessment of the potential functional significance of the antibodies. High levels of circulating antibodies in the female may severely reduce the chances of successful treatment by IVF [4] or donor insemination. Assessment of in vitro sperm-mucus interaction by means of the capillary (Kremer) test and/or the semen/cervical mucus contact test (SCMCT) may suggest the likely presence of sperm antibodies in CM, even though circulating ASA may

have been weak or undetectable. The presence of antibodies in CM can be confirmed by testing liquefied CM using the indirect MAR. The presence of high CM antibody levels and associated negative or low titer circulating ASA suggests a good prognosis for treatment of the couple by intrauterine artificial insemination. In contrast, the presence of high antibody concentrations or titers both locally and systemically suggests a poor prognosis. Couples with apparently intractable immuno-infertility can be effectively treated using intracytoplasmic sperm injection (ICSI) [19].

10.5 Postfertilization Effects of ASA on Fertility

Definitive studies in various animal models have shown an association between ASA and pre- or postimplantation embryonic degeneration [20]. In one study on rabbits, reproductive tract secretions containing ASA were found to cross-react with rabbit morulae and blastocysts, resulting in embryotoxic effects during in vitro culture [21]. In a number of tightly controlled experiments, this group demonstrated that only secretory IgA (sIgA) from the uterine fluid of semen-immunized does was embryotoxic during in vitro culture. In contrast, blood sera with high levels of ASA were not embryotoxic, nor were IgG fractions isolated from the immune uterine fluid (IUF). Absorption of IUF with either sperm or anti-sIgA removed the embryotoxicity, thereby providing evidence of specificity. Other experiments indicated that the sperm antigen stimulating the sIgA embryotoxic antibody in IUF was distinct from the antigen stimulating IgG and IgA class ASA with the ability to inhibit fertilization. In unpublished observations, absorption of the IUF with paternal lymphocytes did not remove the embryotoxicity, indicating that transplantation antigens were unlikely to be involved. Additional investigations suggested that the antigen responsible for the sIgA-associated embryotoxicity was a subsurface component. Thus, immunization of does with isolated sperm membrane fractions resulted in reduced fertilization, whereas immunization with submembrane fractions caused only the postfertilization effects on embryos.

Why should ASA react with embryos? Firstly, the sperm membrane is integrated as a mosaic into the zygote membrane during the process of fertilization, so that sperm antigens are incorporated, although at relatively low densities, into the developing embryo [22]. Secondly, embryonic gene expression commencing from the four to eight cell stage results in the synthesis of various developmental antigens which can cross-react with sperm antigens (for review, see Menge and Naz [23]). Consequently, during embryo development and perhaps particularly around the time of blastocyst hatching, there is a chance for the ASA to bind to cross-reacting embryonic antigens and potentially cause embryo degeneration or possibly prevent implantation.

There is also some evidence for postfertilization effects associated with ASA in humans. Concerning negative effects, Warren Jones [24] reported that around 50 % of pregnancies conceived in women with ASA subsequently ended in first trimester spontaneous miscarriages. Similar observations have been reported by other groups

[11, 25]. In the latter study, it was found that 7/16 (44 %) of women who miscarried were positive for ASA in their serum, compared with only 2/17 (12 %) of women who had successful ongoing pregnancies. Examination of the immunoglobulin classes of the antibodies revealed that IgA was significantly ($p < 0.01$) more common in those women who miscarried. The IgA class antibodies in serum may be a marker for local secretory IgA in the female reproductive tract. However, despite the strong evidence in rabbits, it is still not known whether sIgA class ASA in humans are embryotoxic. In another clinical study [26], it was found that of 173 women referred for a history of three or more consecutive spontaneous miscarriages, there was a significantly higher incidence of sperm immobilizing antibodies when compared with the infertile group. Interestingly, they also observed a higher incidence of ASA in the group of women shown to have an immunological basis for their recurrent miscarriages (for example, couples sharing at least three HLA determinants, or couples with the female showing a relatively low response to her partner's lymphocytes in mixed lymphocyte culture). Other groups have reported a significant association between ASA and some autoantibodies such as antiphospholipids, which may be involved in deleterious effects on the fetus. In contrast to the studies cited above which have reported an association between ASA and recurrent miscarriage, others have not seen a statistically significant association [27, 28]. Further investigations in this area would be useful, particularly focusing on the possible involvement of subsurface sperm antigens which react with IgA class ASA. It is important to note that sperm antibodies specific for subsurface antigens are unlikely to be detected by assays such as the immunobead test (IBT) or the MAR which are designed to measure reactivity with membrane antigens on motile sperm. It could be very informative to conduct a clinical investigation of IVF patients with repeated implantation failure or early spontaneous miscarriages, using a new generation of highly specific ELISA and immunofluorescence assays in conjunction with the MAR (unfortunately immunobeads are no longer available so the IBT has become obsolete).

With respect to positive effects of sperm immunity, there is some evidence from analysis of IVF data, suggesting that some ASA may be associated with increased implantation rates [29, 30]. If confirmed, this could add an interesting new dimension to our analysis and understanding of sperm immunity. It also underlines the potential importance of efforts to develop routine assays, which can identify sperm antibodies reacting with defined antigens.

10.6 Origins of ASA in Females

It is obvious that normal fertile women do not usually mount strong immune reactions to sperm, resulting in high titers of ASA capable of blocking sperm function and reducing fertility. Although it is still uncertain what exact mechanism is acting to suppress the female immune response to sperm antigen after sexual intercourse, there are several possible ways in which this could occur. Firstly, experimental evidence indicates that seminal plasma contains potent immunosuppressive factors.

Some sperm antigens may carry suppressor epitopes, which could inhibit an effective B-cell response and ensuing sperm antibody production. The potential relevance of asymmetric immunoglobulin in modulating sperm immunity also requires thorough evaluation [31]. If the initial immunosuppressive mechanisms fail to prevent the initiation of sperm antibody production, then it is also possible that anti-idiotype antibodies, if produced in sufficient quantities, could inhibit production of the related idiotype (anti-idiotypes are discussed in more detail below). Despite these hypothesized safeguards, a small proportion of women do develop significant levels of ASA in their blood and reproductive tract.

What information is currently available regarding the development of or predisposing factors for sperm immunity in females? Observations of potential relevance to understanding the underlying causes of ASA in women include evidence that they are more likely to have detectable sperm antibodies if their male partner also has ASA in his semen [32]. Another important observation was that in about one-third of cases women apparently react only to their partner's sperm antigens, rather than to sperm-specific antigens [33]. Several hypotheses have been proposed in order to explain the origins of female sperm immunity and the observed association between male and female sperm immunity in a proportion of couples.

The first hypothesis is based on observations that human spermatozoa have antigens which cross-react immunologically with certain microbial antigens. Thus, Sarkar [34] reported that antibodies with specificity for certain yeast mannan molecular configurations cross-reacted with sperm membrane antigens. For example, 75 % of sera from men with ASA were found to react with the one, six yeast mannan specificity. In addition, some patients reacted with the one, three mannan specificity or with chemotype C1 from Salmonella paratyphi C. In another investigation, Blum et al. [35] observed a strong association between Chlamydia antibodies and ASA in young women using oral contraceptives. Similarly, Cunningham et al. [36] reported that 56 % of women with primary pelvic inflammatory disease (PID) had ASA detectable by the indirect mixed agglutination reaction. Sera from these patients uniformly reacted with a 69 Kd band by western blotting. Because both partners would be likely to be exposed to the same microbes during unprotected sexual intercourse, they would also be expected to have an increased chance of concurrently developing ASA. In summary, although several clinics have reported significant associations between genital tract infections and ASA [35, 36], a more recent and very thorough study did not confirm such an association [37]. More research in this fascinating area should be encouraged.

A second interesting hypothesis was based on the observation by Steven Witkin [38] that antibody-coated sperm stimulated in vitro interferon gamma (IFN-γ) synthesis by lymphocytes from female donors. In contrast, antibody-free sperm did not cause IFN-γ production. Given the evidence that IFN-γ induces macrophages to express Ia antigen (MHC class II marker) on the cell surface, the resulting juxtaposition of sperm antigen and Ia on the macrophage cell surface would be expected to facilitate the recruitment of T-helper cells and subsequent initiation of ASA production by B lymphocytes. These observations are consistent with the finding that women are more likely to develop sperm antibodies if their partner has sperm

autoimmunity. Of significant relevance here is a recent investigation [39] which demonstrated the complexity of the in vitro cytokine response when peripheral blood mononuclear cells (PBMCs) from infertile women were incubated with sperm antigens for up to 5 days. Crucially, this study found that sperm antigens induce differential cytokine response patterns in PBMCs from infertile women with ASA, versus those without ASA, or fertile controls. Specifically, the study observed a marked increase in IL-2 and IL-4 in the former group. The authors concluded that if these changes also occur in vivo, then the modulated cytokine environment could facilitate potentiation of the Th2-type response with heightened ASA production. Logically, the ASA could be of either the female partner or from her male partner if he had sperm autoimmunity.

A third tentative hypothesis has recently been postulated [40] based on the likelihood that if a male had ASA in his semen, then during repeated acts of sexual intercourse his female partner would be expected to develop a range of anti-idiotype antibodies which could potentially facilitate an immune response to his sperm. A summary of the background to this hypothesis is presented below.

Jerne [41] proposed that antibodies should be antigenic to the individual's own immune system, resulting in the production of autoantibodies directed against the unique (idiotypic) parts of the antibody which comprise the antigen-binding site. The result is a network of idiotype/anti-idiotype interactions which are involved in regulation and modulation of the immune system. The antigen-binding site of the anti-idiotype mimics the original antigenic structure which was recognized by the individuals' immune system (Fig. 10.1). Consequently, immunization against a particular antibody idiotype can potentially provide a means of stimulating an immune response directed towards the original "native" antigen. There have been numerous investigations into the application of anti-idiotypes for generating enhanced immune responses to cancer cells and infectious agents [42].

Several groups have shown that polyclonal heterologous anti-idiotype antibodies can be generated against the idiotypes on monoclonal ASA [43–45] and that the anti-idiotype could significantly inhibit the binding of the monoclonal antibody to sperm. Testing of the anti-idiotype supported the hypothesis that its' ability to inhibit the original monoclonal antibody was due to its antigen-binding site forming a similar shape to the original antigenic epitope, the so-called internal antigen image [44].

If the male partner had ASA in his semen, how would the female immune system respond to repeated exposure to these antibodies? In light of the above information about idiotype/anti-idiotype responses, it is possible that the female would produce anti-idiotype antibodies, which could ultimately potentiate an antisperm immune response. It is also important to note that the female could potentially form anti-idiotype antibodies directed against the male partner's antibodies specific for intracellular sperm components, in addition to those specific for sperm membrane antigens. The associated "parallel set" of anti-anti-idiotypes could also potentially react with some sperm surface epitopes. In other words, it is feasible that the idiotype hypothesis could potentially explain most of the observed range of female ASA activity.

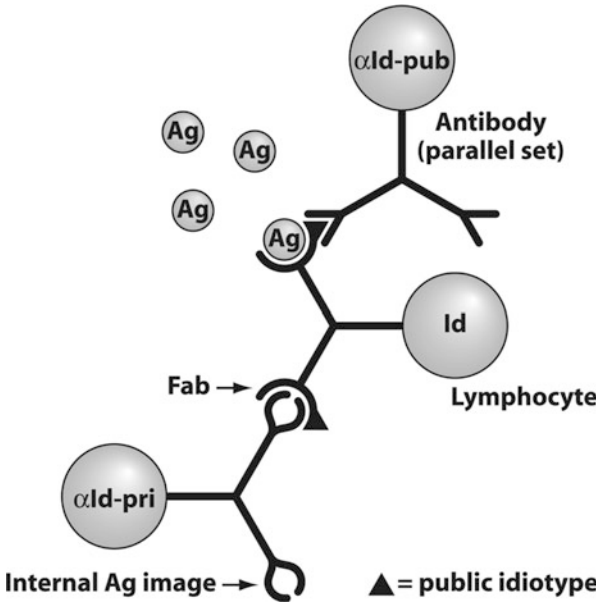

Fig. 10.1 The immune response to antigen (*Ag*) generates antibodies bearing unique idiotypic (*Id*) signatures comprising the antigen-binding site or paratope of the antibody [47]. The individual's immune system subsequently sees the unique Id as foreign and responds by forming anti-Id (*α-Id*) antibodies, some of which recognize public Ids (*Id-pub*) present on other antibodies of different Ag specificity, while some recognize internal or private (*Id-pri*) parts of the Fab (internal Ag image). The former may recruit B lymphocytes producing antibodies of various specificities (the parallel set), while the latter can potentially augment the production of antibodies reacting with the original Ag

An extremely interesting study by Naz et al. [46] demonstrated the presence of anti-idiotype antibodies in women (albeit against their own antibodies, rather than their partner's, however it provides solid evidence that women can produce anti-idiotype antibodies against sperm antibodies). These authors concluded that both fertile and infertile women form immune responses to sperm, but that sperm antibodies are usually not detected in fertile women because their reactivity in assays is blocked by high levels of anti-idiotype antibodies. They concluded that higher levels and incidence of sperm antibodies are detected in infertile women because their sera contain relatively low concentrations of the blocking anti-idiotype antibodies. However, an alternative explanation of these findings is more consistent with current knowledge about the immune response [47]. Thus, higher levels of anti-idiotype antibodies to a particular antigen lead to active suppression of the host immune response, whereas low levels can lead to a significant stimulation of production of the idiotype (i.e., sperm antibody in this case). Thus, with respect to the study by Naz et al. [46], it is probable that sperm antibodies were not detected in the fertile women because their production had been inhibited by the anti-idiotype antibodies, rather than the anti-idiotype antibodies blocking the binding of sperm antibodies during the assay. Low concentrations (nanogram range) of anti-idiotype antibodies

on the other hand can lead to enhancement of the immune response to the original antigen (ie sperm in this case). Naz et al. [46] detected anti-idiotype antibodies in only 3/23 infertile women, but the sensitivity of their assay at this concentration range may have been a factor. Further investigation of this phenomenon is vital in order to improve our understanding of female immune reactions to sperm.

With regard to the idiotype hypothesis, further research is still required in order to try to understand the relationship between anti-male idiotype antibody, which could be generated in women exposed to semen containing ASA, and anti-female anti-idiotype antibody formed when women react to their own sperm antibodies. Another consideration is whether seminal plasma contains anti-idiotype antibody in suitable amounts to have direct effects on the female immune system?

It is quite possible that the development of ASA in some women may involve one or more of the several postulated mechanisms operating in concert. For example, the stimulation by antibody-coated sperm of IFN-γ gamma synthesis in the female partner's lymphocytes could potentially augment her immunological response to antibody idiotypes in semen (cytokines such as IL-2 and IL-4 may also be involved, as discussed above). It is also feasible that some women initially respond to microbial antigens (microbes attached to the sperm surface can also stimulate IFN-γ gamma production by the female's lymphoid cells), resulting in the formation of antibodies which cross-react with sperm – this immune response could then be maintained over a longer period by her ongoing exposure and response to antisperm idiotypes in semen and/or generation of anti-idiotype antibodies against her own sperm antibodies. The relationship between the three hypothesized mechanisms requires investigation.

Conclusions

Unfortunately there has been relatively little research interest in female sperm immunity in recent years. Further understanding of the reactivity of the female immune system to semen antigenicity, including experimental investigation of the idiotype hypothesis, may help to explain immuno-infertility, but could also have significant implications for the development of immuno-contraceptive vaccines and for the wider understanding of normal pregnancy and its' associated pathology. Thus, the recognition of the male partner's antibody idiotype spectrum in semen by the female's immune system provides a potentially important means of cross talk, which could prove vital for the establishment of normal pregnancy. It would also be very interesting to explore the possible implications of idiotype responses within the seminal priming hypothesis proposed by Robertson [48].

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