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Review Article:

The Immunopathogenesis of Antisperm Antibodies in Men: Role of Trauma, Infection, Surgery and Breakdown of Immune Privilege

[1]Nnodim Johnkennedy, [1]Nnawuihe Chika,[2]Maduike Chukwunonso Victor, [3]Nwaokoro Joakin Chidozie, [3]Uche Olive Iwuagwu, and [1]Nnodim Amarachi Promise

[1]Department of Medical Laboratory Science, Imo State University, Owerri Imo State.
[2]Department of Medical Laboratory Science, Madonna University Elele, Rivers State
[3]Department of Public of Health, School of Health, Federal University of Technology Owerri Nigeria

ABSTRACT:
Antisperm antibodies (ASA) are immunoglobulins against sperm surface or intracellular antigens and are a significant but poorly understood component of immunological male infertility. Under normal physiological conditions developing germ cells are protected from improper immune identification by a combination of structural, cellular and molecular mechanisms collectively called testicular immune privilege. The blood-testis barrier, Sertoli-cell immunoregulatory activity, local anti-inflammatory mediators and systemic immunological tolerance suppress immune responses to sperm-specific antigens. However, trauma, infection, surgery, obstruction of the reproductive system, and other pathologic events may interfere with these protective mechanisms. Exposure of antigen-presenting cells to normal sequestered sperm antigens can stimulate activation of T lymphocytes, B-cell differentiation and generation of sperm-reactive IgG and IgA antibodies. In addition, inflammation can affect the blood–testis and blood–epididymis barriers through cytokine signalling, oxidative stress and tissue damage, which may enhance antigen exposure and immune activation. The vasectomy is one of the better described surgical triggers, as stoppage of sperm transport may cause extravasation of sperm, granuloma formation and increased antigen exposure. Local immunological homeostasis can be disrupted in a similar fashion by genital infections (e.g., epididymo-orchitis) and other inflammatory disorders. Testicular trauma and torsion can cause direct testicular injury and release of germ-cell antigens. Clinical implications of ASA depend on antibody class, antigen specificity, titre, sperm binding site and extent of sperm coating. Functionally relevant antibodies can cause sperm agglutination, poor motility, altered cervical mucus penetration, aberrant capacitation, interference with the acrosome reaction and impaired sperm-oocyte contact. However, the clinical relevance of ASA is still inconsistent and major guidelines do not suggest frequent testing for ASA in the first work-up of male infertility. The overview of the immunopathogenesis of ASA emphasises trauma, infection, surgery and disruption of male reproductive immune privilege and points out diagnostic limits and topics for additional investigation.
Keyword: antisperm antibodies; male infertility; immune privilege; blood-testis barrier; trauma; infection; vasectomy; autoimmune; sperm antigens; immunopathogenesis.

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INTRODUCTION

Male infertility is a complex reproductive condition including genetic, endocrine, anatomical, infectious, environmental and immunological variables . One of the immunological pathways in male infertility is the formation of antisperm antibodies (ASA). These antibodies recognise the antigenic determinants on the spermatozoa and can be found on the surface of sperm or in bodily fluids, including serum and seminal plasma. ASA have been recognised for decades but their exact role in infertility remains complicated as antibodies may be found in males without obvious infertility and some infertile men have no demonstrable ASA. Contemporary evaluations consequently highlight that the existence of ASA should not be automatically taken as evidence of causation[1].

The key biological puzzle is why the immune system normally tolerates spermatozoa despite the reality that many sperm-specific antigens originate after the establishment of central immunological tolerance. During spermatogenesis, germ-cell proteins may not have been presented during thymic development. Thus, the male reproductive system needs specialised systems to avoid deleterious immune responses directed against growing germ cells. The blood–testis barrier (BTB) established mostly by specialised junctional complexes

***Corresponding Author:** Nnodim Johnkennedy
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between Sertoli cells separates basal and adluminal compartments of the seminiferous epithelium and significantly contributes to the protection of developing germ cells. But immune privilege is not created by the physical barrier alone. Sertoli cells, testicular macrophages, cytokines, regulatory immune cells and immunosuppressive chemicals generate a highly regulated local environment[2].

Disruption of these systems allows sperm antigens to be available for immune surveillance. Trauma, infection, inflammation, vasectomy, vasectomy reversal and other reproductive tract surgeries have been considered as possible triggers of ASA. In a recent systematic literature review, infectious diseases, vasectomy and vasectomy reversal, varicocele, cryptorchidism, inguinal or genital surgery, HPV infection, bacterial seminal communities, torsion and testicular trauma were among the studied conditions in relation to ASA production, although strength and consistency of evidence varies between individual conditions[3].

This review discusses the immunopathogenesis of ASA development with particular reference to trauma, infection, surgery and disturbance of immunological privilege.

Immune Privilege of the Male Reproductive System

The testis is an immunologically specialised organ in which immune protection and immune surveillance must co-exist. Germ cells in development need to be protected from immune mediated destruction yet the testis has to maintain sufficient innate immune potential to respond to pathogens. Testicular immune privilege is thus better viewed as an actively managed state than just physical exclusion from immune cells.

This system's key component is the BTB. Sertoli-cell connections partition the seminiferous epithelium into basal and adluminal compartments. The latter contains germ cells which are in meiosis and postmeiosis, and which express antigens that could potentially be recognised as foreign by the immune system. Thus the barrier restricts interaction between these antigens and circulating immune constituents. Crucially, the BTB is comprised of morphological, physiological and immunological components and not just tight junctions[4].

Sertoli cells are also actively involved in immunological control. They secrete immunomodulatory substances, phagocytose apoptotic germ cells and modulate the local immune-cell activity. Testicular macrophages and regulatory lymphocyte populations also help to create an environment favouring tolerance rather than inflammation. The regulatory environment comprises anti-inflammatory mediators including transforming growth factor-β and interleukin-10.

In the epididymis and other regions of the male reproductive tract there are also specialised barriers and immunoregulatory mechanisms. Immune protection of sperm is thus not limited to the seminiferous epithelium. Disruption of the route for sperm generation, maturation or transport can change antigen exposure and immune regulation[5].

Development of Antisperm Antibodies

The creation of ASA might be regarded as a multistep process. Tissue injury, infection, obstruction, or surgical intervention, first, disturb the usual anatomical and immunological separation between sperm antigens and immune surveillance. Second, specific antigens of sperm are available to antigen presenting cells. Third, innate inflammatory pathways provide danger signals and cytokines that improve antigen processing and presentation. Finally, T-helper cells can give signals to B-cell activation and class switching and differentiation into antibody-producing plasma cells.

The generated antibodies may be of IgG and IgA class mostly. The World Health Organization's laboratory manual describes direct sperm antibody testing: the mixed antiglobulin reaction (MAR) test and the immunobead test, which determine the presence of antibodies on spermatozoa.

The sperm antigens that are targeted are diverse. Antibodies can recognise proteins involved in sperm motility, membrane integrity, capacitation, the acrosome or the interface with the female reproductive tract and oocyte. Hence, two men with ostensibly comparable amounts of sperm-bound antibodies may have differing reproductive outcome[6]

Trauma as a Trigger for the Formation of Antisperm Antibodies.

One of the classical pathways hypothesised for ASA formation is testicular and epididymal damage Physical harm can damage seminiferous tubules, Sertoli-cell junctions, epididymal epithelium or other reproductive tissues. Such injury may allow the release of spermatozoa and sperm antigens into tissue compartments where they can be met by antigen presentation cells.

Trauma can therefore have two concurrent impacts; direct breakdown of the physical barrier and stimulation of inflammatory signalling. Injured cells secrete danger-associated chemical patterns to initiate innate immune pathways. Inflammatory cytokines and reactive oxygen

species may further compromise barrier integrity, establishing a positive feedback loop in which inflammation increases antigen exposure and antigen exposure maintains immune activation.
The clinical connection between trauma and ASA is not definitive. Not all men who have testicular injury acquire clinically significant ASA. Therefore, individual vulnerability, severity and location of damage, genetic background, immunological modulation and level of tissue destruction are likely to influence antibody formation.
Another pertinent example is torsion of testicles. Testicular microenvironment may be damaged by oxidative and inflammatory stress after ischaemia and reperfusion. ASA has been studied in relation to torsion but the data are less convincing than those for vasectomy. The broader implications of trauma are to show how loss of tissue integrity can expose a usually sequestered reproductive antigen to immune attack.[7]

Infection and Inflamation

Infection is one of the most studied categories of possible ASA causes. Bacterial and viral infections of the male genital tract can be responsible of epididymitis, orchitis or epididymo-orchitis with tissue inflammation and breakdown of reproductive barriers. Infectious diseases, including Chlamydia trachomatis, were among the most commonly studied sources of ASA production in a recent systematic review.
Several linked mechanisms may promote ASA through infection. Microbial compounds trigger pattern recognition receptors on the testicular and reproductive-tract cells. This results in activation of innate immune responses including inflammatory cytokines, chemokines and recruitment of leukocytes. Under physiological conditions, the testicular immune system can react against infections and maintain immunological privilege . But chronic or intense inflammation may upset this equilibrium and damage the BTB and associated epithelial barriers.[7]
Epididymo-orchitis is of particular concern because the epididymis is a vital region for sperm maturation. Inflammation can compromise the integrity of the epithelium and reveal sperm antigens when sperm are concentrated in the reproductive canal. The local infiltration of macrophages, neutrophils and lymphocytes might enhance antigen processing and presentation.
Sexually transmitted infections could also be an indirect factor. Recurrent or chronic vaginal infections may cause persistent inflammation, oxidative stress and epithelium damage. However, a previous infection should not be seen as evidence that ASA caused later infertility. A large number of illnesses independently affect sperm quantity, motility, morphology and DNA integrity and it is difficult to identify the impact of antibodies per se.
Specifically, mumps-related orchitis, a form of viral orchitis, has long been associated with testicular inflammation and decreased spermatogenesis. The role of ASA in mediating reproductive impairment following such infections is not so well established compared with the direct impact of inflammation and tissue injury[8]

Surgical and Iatrogenic Injury

Surgery of the male reproductive tract is another major setting for the formation of ASAs. Procedures that interrupt the integrity of the reproductive tract may allow sperm to escape into the surrounding tissues and lymphatic drainage.
Vasectomy is the most common surgical context in which antisperm immunity has been shown to develop. Disruption of the vas deferens hinders proper sperm transport and can raise intraluminal pressure. Later, sperm may extravasate from the obstructed reproductive tract and is notably associated with sperm granuloma development or abnormalities in the integrity of the epididymal and vasal epithelium[9].
The immune system may then come across sperm antigens in an inflammatory environment. These antigens can be carried by antigen-presenting cells to regional lymphoid tissue, where adaptive immune responses may be generated. It has been shown historically that there are high rates of sperm agglutinating antibodies after vasectomy, but the prevalence and titres of antibodies vary between communities and individuals.
Importantly, the presence of ASA following vasectomy does not necessarily indicate clinically significant infertility when reproduction is desired. Contemporary evidence suggests that ASA are unlikely to be a key factor of infertility following an otherwise successful vasectomy reversal in many men[10].
Vasovasostomy and vasoepididymostomy may re-establish the transport of sperm but do not necessarily abolish pre-existing immune reactions. Antibody titres may still be high following reversal. Differences between serum and seminal-plasma antibody responses have been reported and the association between antibody level and pregnancy is complex[11].
The persistence of ASA following the restoration of reproductive tract continuity highlights an important immunologic principle: once adaptive immune memory

is established, simple repair of the anatomic barrier may not immediately reverse the immune response.

Other operations involving the testes, epididymis, vas deferens or inguinal region may theoretically contribute to ASA development when they produce tissue injury, blockage or exposure of sperm antigens. The evidence is not as conclusive as for vasectomy. ASA has been explored in relation to inguinal hernia repair and other genital or inguinal surgeries, although findings are heterogeneous[12].

Breaking Immune Privilege: A Common Path

Trauma, infection and surgery are clinically different, but may share a same immunopathological pathway: This model highlights that ASAs are not necessarily the fundamental pathogenic event. Many of them may be a downstream indication of a wider disturbance of reproductive immune homeostasis.

Recent immunological studies have demonstrated the importance of pattern-recognition receptors, inflammatory signalling, complement pathways, oxidative stress and inflammasome activation in disruption of testicular immune homeostasis. However, much of the molecular data is still obtained from laboratory models and translation to human ASA-associated infertility will require further prospective research[13].

Functional Impact of Antisperm Antibodies

The reproductive effects of ASAs are dependent on their specificity, immunoglobulin type, concentration, binding location and functional activity. Antibodies attached to spermatozoa may cause agglutination, immobilisation or alteration of contact with the female reproductive system.

One known mechanism is reduced sperm motility through cervical mucous. Sperm coated with antibodies may also have alterations in motility and a decreased capacity to travel forward via the female reproductive canal. Other effects suggested are interference with capacitation, acrosome response, zona pellucida interaction and sperm–oocyte membrane fusion[14]. Complement activation may contribute an additional mechanism of sperm damage, especially when antibody-coated sperm come into contact with complement components in reproductive fluids. However, the relative contribution of distinct pathways to normal human infertility varies widely.

Therefore, antibody positivity does not alone define the therapeutic importance of ASA. Antibodies attached to sperm in a male with normal sperm function may not be clinically significant for immune-mediated infertility, but antibodies directed against functionally key sperm proteins may have more impact [15].

Laboratory Diagnosis

Laboratory research of ASA might be direct and indirect. Direct techniques search for antibodies linked to the spermatozoa. Among the main tests listed in the WHO semen laboratory manual are the MAR test and the immunobead test.[16]

The direct MAR test detects antibody-coated motile sperm in fresh semen . The immunobead test involves washed spermatozoa and can provide information on antibody class and sperm-surface binding. According to WHO guidelines, the main immunoglobulin classes found on sperm are IgG and IgA and the two direct tests may not always give the same results[17]. Serum testing for ASA may reveal systemic antibody responses, however the status of serum antibodies does not necessarily correlate well with sperm-bound antibodies. Thus, the clinical context and the semen findings must be taken into account in the interpretation[18].

Importantly, routine ASA testing is not advised in the initial evaluation of male infertility by major professional guidelines. According to the American Society for Reproductive Medicine/American Urological Association policy, testing for ASA should not be included in the first examination of male infertility. NICE also advises against routine testing for ASA[19].

This is not a statement regarding the biological irrelevance of ASA but rather an expression of scepticism about the capacity of ASA testing to influence clinical care in the absence of clinical context.

Clinical and Therapeutic Considerations

Management of suspected immunological male infertility should start with diagnosis and treatment of underlying causes. A history of trauma, infection, surgery on the genitalia, vasectomy, blockage, or inflammatory illness of the testicle may provide valuable etiologic information.

Treatment of the active infection is appropriate when infection is proven. Correction of the anatomical blockage or other underlying pathology may be essential. However, the targeted treatment to decrease ASA has not been so well established. Previous treatments have included corticosteroids and other immunomodulatory

medications, but concerns about efficacy and side effects have limited their routine use[20].

Assisted reproductive technologies can overcome some of the functional limitations induced by sperm-bound antibodies. Depending on the general reproductive situation of the couple, procedures such as intrauterine insemination, in vitro fertilisation, or intracytoplasmic sperm injection may be explored. The decision should be individualised and not based on ASA positive alone [21]

CONCLUSION:

Formation of antisperm antibodies is a complex result of impaired immunological tolerance in the male reproductive system. The normal testis and male genital tract have very specific mechanisms in place to shield the developing germ cells against improper immune attack. The reproductive immune privilege is maintained by the synergistic action of the blood–testis barrier, Sertoli-cell activity, local immunosuppressive mediators and regulatory immune populations.

Trauma, infection and surgery may alter this balance by direct tissue injury, barrier collapse, sperm leaking, inflammatory signalling and increased antigen presentation. The most well known example of surgery-associated antisperm immunity is vasectomy. Genital infections and inflammatory illnesses may undermine immunological privilege via cytokine-driven tissue destruction. These apparently disparate stimuli converge on a single pathway that includes introduction of sperm-specific antigens to the immune system and subsequent adaptive immunological activation.

However, ASA positive does not necessarily mean infertility. Their therapeutic effects rely on the specificity of the antibody, the immunoglobulin class, the sperm-binding features, and the functional consequences. Current guidelines for the initial examination of male infertility do not support routine testing for antisperm antibodies. Future research should focus on the identification of clinically relevant sperm antigens, the standardisation of laboratory methods and the determination of the immunological phenotypes that truly indicate decreased fertility. A better understanding of reproductive immune privilege may eventually enhance diagnosis and care of males with immunological-mediated reproductive failure.

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