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Etiology of Antisperm Antibodies in Infertile Men: A Review Article

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ABSTRACT: The presence of antisperm antibodies (ASAs) in infertile males is the underlying cause of 'immune infertility'. The mechanism by which ASAs induce male infertility is not completely comprehended. Immune infertility is caused by the presence of antisperm antibodies (ASAs). While this form of infertility is very uncommon in men, it is crucial from a clinical and theoretical standpoint to comprehend the implications, targets, risk factors, and causes of male reproductive issues induced by ASAs. The main factors contributing to the cause of this condition are well recognized as anomalies in the blood-testis barrier and/or blood-epididymal barrier. Among the various parameters impacted, sperm motility is the most commonly detected. The present study elucidates the fundamental principles of ASAs, as well as their causes and risk factors.

1. INTRODUCTION

Antisperm antibodies (ASAs) were first documented in infertile males in 1954. Antisperm antibodies (ASA) are immunoglobulins that specifically bind to antigens present on the membrane of sperm cells. Normally, fully developed sperm cells are located behind a protective barrier called the blood-testis barrier, which prevents them from being attacked by the immune system of the male. Nevertheless, when the blood-testis barrier is weakened as a result of injury or sickness, fully developed germ cells (which act as antigen carriers) become vulnerable to the immune system, resulting in the production of anti-sperm antibodies (ASA) (Gupta et al., 2022).

It is the sertoli cells that are accountable for the creation of the barrier between the blood and the testis. By establishing strong connections between neighboring cells, they are able to accomplish this. These connections, in turn, cause the seminiferous epithelium to be partitioned into distinct sections. The apical compartment provides natural protection for germ cells, preventing immune system recognition and ensuring that mature spermatozoa remain undetected by the immune system. Consequently, an immunological response against spermatozoa can happen when damage to the testicles, epididymis, or vas deferens exposes sperm to the immune system (Kaur et al., 2014).

previous studies illustrated that ASA exert a significant deteriorating impact of on sperm count, sperm movement and sperm consistency (Cui et al., 2015). On the other hand, ASAs have been reported in 5.0%–15% of infertile men, so they they might play a role to male infertility in humans (Lu et al., 2019). Silva et al. (2021) When it comes to the development of this condition, the key elements that contribute to its development are abnormalities in the blood-testis barrier and/or the blood-epididymal barrier. Sperm motility is the parameter that is reported to be impaired most frequently. Nevertheless, only a limited number of risk factors and ASA targets that are clearly characterized have been identified up until recently. Proteins that are involved in the interaction between sperm and oocytes have become the most significant among them. In a recent study that involved 145 patients, it was found that 41.39% of the patients (60 individuals) had low ASA levels, which are defined as values below 50%. The remaining 58.6% of the patients (85 individuals) had high ASA levels, defined as being equal to or greater than 50%. A separate investigation conducted on men with infertility revealed that out of 19 individuals with low ASA levels, 13 of them (equivalent to 68.39%) successfully achieved pregnancy, with 6 of them (equivalent to 31.59%) having spontaneous conception. Out of the 29 men with elevated ASA levels, 21 (72.39%) successfully achieved pregnancy, with 11 (38%) of them conceiving naturally (Abouelgreed et al., 2021).

An important topic of discussion is the contentious nature of particular risk variables that play a role in the development of ASA. Contradictory findings have been obtained as a result of the complex etiology and consequences of infertility-related conditions, which can be considered risk factors for antisperm antibodies (ASA). Additionally, the ambiguous mechanisms of ASA formation and the diverse research environments, which include a variety of methods for detecting ASA and the thresholds that are

utilized, have contributed to the creation of these findings. These issues are hindering advancements in the field of immunological infertility, according to our perspective (Silva et al., 2021).

Many facters were considered as causes or risk factors for formation of ASAs, including Varicocele, obstruction, urogenital inflammatory conditions, undescended testis, testicular cancer, testicular torsion, surgical trauma to testes or scrotum (Gupta et al., 2022).

CRYPTORCHIDISM

Cryptorchidism is a congenital disorder that is frequently observed in male neonates and is widely recognized. It is defined by the absence of one or both testes from the scrotum. This disease is widely recognized as a substantial cause of infertility within the medical community, despite the inconsistent results of previous research. (Marconi & Weidner 2017). Cryptorchidism can elicit an immunological reaction against sperm antigens during childhood, irrespective of the position of the testes or the performance of orchiopexy. Furthermore, it appears that individuals going through puberty are more susceptible to producing antibodies that target and attack sperm cells(Sinisi et al., 1998). In terms of ASA positivity, specifically in the natural killer cell surface receptors, individuals with cryptorchidism were not observed to have any genetic anomalies. With the help of these receptors, these cells are able to identify and eliminate abnormal cells while avoiding destructive attacks on good cells (Niepiekło-Miniewska et al. 2015).

VASECTOMY

Vasectomy, a surgical procedure for male sterilization that entails the severing or sealing of both vas deferens, may induce an immunogenic response, which could lead to the development of anti-sperm antibodies (ASA). The extensive documentation of the association between vasectomy and ASA production confirms its status as one of the most universally recognized risk factors for ASA production. (Azizi et al., 2015). ASA is closely linked to obstructive azoospermia, particularly following vasectomy, with 70% to 100% of men showing ASA presence post-procedure (Lee et al., 2009). It is necessary to conduct additional research in order to investigate the connection between HLA antigens and the production of ASA proteins. The reason for this is that there is convincing evidence that there is a significant relationship between HLA-A28 antigens and the synthesis of ASA after vasectomy (Silva et al., 2021).

VARICOCELE

Varicocele is a medical disorder characterized by the abnormal growth and twisting of the veins in the spermatic cord. It is often detected in males during standard physical examinations. Despite its prevalence, the etiology and associated pathophysiological mechanisms of varicocele are not fully understood. The existing data on varicocele's potential impact on ASA formation is controversial (Marconi & Weidner 2017),

Varicoceles are present in around 5%–15% of the overall population and in 30%–40% of males who experience infertility. In theory, if the venous drainage from the testis is impaired, it could result in damage to the seminiferous tubules and subsequently lead to the production of ASA. Varicocele prevalence peaks during puberty, affecting 15–19% of adolescents, potentially influencing their future reproductive potential (Chereshnev et al., 2021). A recent systematic review indicates a notably higher ASA presence in men with varicocele, detected through direct mixed antiglobulin reaction test (MAR) or indirect (ELISA) methods. This implies an immunological aspect in infertile men with varicocele, possibly impacting their treatment (Falcone et al., 2024). A separate investigation, employing the ELISA technique, detected immunoglobulins attached to sperm in 32% (27 out of 84) of infertile men who had detectable varicoceles. Among these men, IgA was present in 85% of cases, IgG in 67%, and IgM in 74% of cases with ASA (Mazumdar & Levine, 1998).

The occurrence of ASAs in varicocele is followed by a decrease in sperm properties. particularly, asthenozoospermia may result from presence of ASAs, due to a deterioration in progressive sperm motility, in addition to decreased sperm count, with dysfucntion of the acrosome reaction (Chereshnev et al., 2021).

Anyhow, contrasting findings were presented by Kanevskaya et al., who found that ASAs did not significantly increase in infertile men with varicocele compared to those without it. Their investigation found no statistically significant link between anti-sperm antibodies (ASAs) and male infertility in cases with varicocele. Multiple additional study teams have also demonstrated that varicocele does not have an impact on ASA concentrations, and ASAs do not have an effect on sperm parameters in varicocele. Furthermore, the ASA levels in both varicocele individuals with fertility issues and those without fertility issues were comparable. A separate investigation conducted on males with infertility found that the levels of ASA in individuals who had a current or previous varicocele were even lower compared to infertile men who did not have varicocele (Kanevskaya et al., 2010).

CHRONIC BACTERIAL INFECTIONS

Furthermore, it has been noted that the existence of ASAs can be linked to numerous long-lasting bacterial illnesses. Patients suffering from chronic prostatitis have a threefold higher likelihood of developing ASAs compared to individuals who do not have

this ailment. While the precise mechanism is not completely comprehended, it is possible that it is connected to inflammatory harm to the male genital glands and a disruption in the local immune system, which can lead to the body's immune system attacking sperm cells (Condorelli et al., 2017).

Inflammation may potentially result in genital canal damge and ASA production. A previous study by Kortebani et al. (1992) has investigated WBC concentration in seminal fluid taken from from 279 infertile males. About 87 of the samples had increased WBC. Sperm motility was slowed, sperm morphology was anomalous, and semen fructose levels were lower in samples with leukocytospermia than in samples without, as a result (Mazumdar & Levine, 1998).

Chlamydia in the bacteria that are correlated to abnormal seminal properties, while *Sphingobium* the bacterial agent commonly found in seminal fluid with elevated ASA levels (Weng *et al.* 2014). In any caseThe relationship between the existence of chlamydial antibodies and ASA has been the subject of recent research, but the findings are not unanimous. Some researchers, such as Martínez-Prado and Camejo Bermúdez (2010), among those who have reported an association, others have no (Eggert-Kruse et al., 2015).

There is a suggestion that ASAs could be generated as a result of cross-reactivity with foreign antigens, such as bacteria, viruses, fungi, and allergens (Niedzielski et al., 2013). Within this particular framework, there has been evidence of molecular mimicry occurring between sperm and bacteria. This mimicry can result in the development of cross-reactivity problems between anti-sperm antibodies (ASAs) in humans and antibodies produced against bacteria. A sperm immobilization factor (SIF) that is derived from bacteria has the potential to immobilize both human spermatozoa and bacteria that are known to migrate. This is a promising possibility. This is because both spermatozoa and bacteria have a common receptor for SIF, which has been recently discovered. The researchers proposed the possibility of utilizing these receptors for intravaginal treatment to improve fertility. In the context of ASA, it was postulated that the cross-reactivity between sperm antigens and external antigens could potentially stimulate the production of ASA. This hypothesis warrants more investigation (Prabha et al. 2011).

VIRAL INFECTIONS

Despite variations between studies, the primary conclusion in the context of viral infection is the higher prevalence of ASAs on the sperm surface, which is accompanied by a significant decrease in sperm motility. These findings were observed in Hepatitis C virus (HCV) infected men as well as in papilloma virus (HPV) infected infertile men. Additionally, a decrease in ASA prevalence and an improvement in motility were reported in men vaccinated against HPV (Garolla et al., 2018, Hussein et al. 2017).

Despite the fact that certain recent studies suggest that viral infections may negatively impact sperm motility by inducing the production of anti-sperm antibodies (ASAs), the results are inconsistent. There is no correlation between the content of semen and the presence of HPV, as well as the presence of ASA, as supported by numerous studies. Although an adequate number of samples were available, these investigations employed varying thresholds to determine ASA positive. For instance, Garolla et al. (2013) defined the threshold for ASA positivity according to WHO criteria (≥50%), while other studies used thresholds of >10% (Hussein et al., 2017), ≥30% (Schlehofer et al., 2012), or did not mention a threshold at all (Luttmer et al. 2016, Garolla et al. 2018).

CONCLUSIONS

The presence of antisperm antibodies (ASA), which are antibodies that target sperm, is a factor that contributes to the more severe symptoms of immune infertility. This type of infertility on male fertility is not totally understood, and this includes the causes, risk factors, targets, and effects of the condition. This particular form of infertility is not very common, and its occurrence is relatively modest. Both abnormalities in the blood–testis barrier and/or abnormalities in the blood–epididymal barrier are the primary factors that are responsible for the development of this condition. The criterion that is modified the most frequently has to do with the number of times that sperm motility is seen. This is a fact, with the majority of individuals agreeing with this statement.

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