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REVIEW

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Male immune infertility: a million dollar question in medically assisted reproduction

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Abstract

Male factor infertility accounts for approximately 30–50% of all infertility cases. The primary causes include genetic abnormalities, sexually transmitted infections, physical or anatomical issues, hormonal imbalances, lifestyle factors, and environmental influences. Despite significant advances in diagnostic techniques, an identifiable cause remains elusive in nearly 40% of cases. One less commonly recognized factor is male immune infertility, which results from the presence of antisperm antibodies (ASA) in semen. These antibodies are typically identified through an extended semen analysis. Under normal physiological conditions, spermatogenesis and sperm transport occur within an immune-privileged environment. However, when the blood-testis barrier is compromised due to trauma, infection, or surgery, ASA may form. The effects of ASA on fertility can vary, but evidence indicates that ASA presence may impair sperm motility and capacitation, promote sperm agglutination, and be associated with DNA fragmentation. To address these challenges, assisted reproductive technologies (ART), including intrauterine insemination (IUI), *in vitro* fertilization (IVF), and intracytoplasmic sperm injection (ICSI), are commonly used. These methods have proven to be effective in overcoming ASA-related infertility and improving reproductive outcomes. Given the ongoing debate and uncertainty surrounding the clinical relevance of ASA, this paper aims to review existing literature, explore the concept of male immune infertility, identify its risk factors, outline current methods for ASA detection, evaluate the role of ASA in ART, highlight both the strengths and limitations of current research, and contribute to a clearer understanding of this complex condition. After our literature review, we could confirm that multicentric studies with large groups of patients related to this topic are rarely found, and that there are many uncertainties regarding the clinical significance of ASA. The complete system of diagnosing male immune infertility lacks precise guidelines that infertility clinics could use in their routine male infertility check-ups.

Keywords

Male infertility; Male immune infertility; Antisperm antibodies; The mixed antiglobulin reaction (MAR) test; Assisted reproductive technology

1. Introduction

Male infertility has become one of the most challenging health concerns worldwide. Male reproductive disorders account for approximately 50% of infertility cases and are influenced by multiple factors, including epigenetic regulation alongside genetic and environmental factors [1, 2]. Infertility in men is often associated with dysfunction of spermatogenesis, which manifests as poorer sperm quality [3, 4]. The diagnosis is typically based on semen analysis, used to identify semen-related abnormalities by assessing sperm concentration, motility, and morphology [5, 6]. The main causes of male infertility include genetic factors, sexually transmitted infections, physical causes, hormonal deficits, lifestyle factors, and environmental influences. The quality of the environment has a great impact on a healthy lifestyle. Exposure to environmental pollution can have serious consequences for human health. Heavy metals, accumulated in the food chain, bind to estrogen and androgen receptors and block different actions, induce reactive oxygen species (ROS), apoptosis, necrosis, and immunosuppression [7–11]. Despite continuous advances in diagnostic methods and approaches, the etiology of infertility still remains unexplained in 40% of affected men [12–15].

One of the less widely recognized factors for male infertility is the so-called male immune infertility, characterized by antisperm antibodies (ASA) in semen, which can be detected by extended sperm analysis [16, 17]. ASA can also be detected in serum, cervical mucus, follicular fluid, and

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oviductal washing. The term immune infertility is used if spontaneously occurring antibodies binding to antigens of the gametes impair sperm-oocyte interaction [18]. According to the latest World Health Organization (WHO) Manual for the Laboratory Examination and Processing of Human Semen [17], the mere presence of ASA is insufficient for a diagnosis of immunological infertility; it must also be demonstrated that these antibodies significantly interfere with sperm function. Although the impact of ASA on fertility varies among individuals, it is well established that certain ASA are associated with impaired fertility. The presence of ASA in semen interferes with sperm motility, leading to sperm agglutination and lower capacitation [19]. Some ASA have also been associated with DNA fragmentation, which is shown by elevated reactive oxygen species [20]. The correlation between ASA and infertility was first reported by Wilson [21] in 1954. Shortly thereafter, Rumke and Hellinga confirmed the presence of ASA in human sperm [22], prompting numerous subsequent studies that further established the link between ASA and abnormal fertilization [23–26]. ASA is defined as an immunoglobulin with antibody activity against a sperm antigen that plays a role in fertility, but not every antibody that binds to the sperm surface influences sperm function. This is because most autoantibodies present in biological fluids do not cause autoimmune diseases, as they do not alter the function of their corresponding antigens. Therefore, not all ASA will have a role in infertility, either because the antibodies do not bind to the functional domain of the antigen or because the cognate antigen is not involved in the process of fertilization [18]. Methods used nowadays measure only immunoglobulins that bind to sperm components. The predominant immunoglobulin classes for ASA in semen are immunoglobulin G (IgG) and immunoglobulin A (IgA); while immunoglobulin M (IgM) is rarely detected, likely due to its relatively large molecular size [27]. All immunoglobulin classes can be detected in both men and women, in female reproductive tract secretions, seminal fluid (sperm-bound and free), and serum. Kremer and Jager [28] suggested that IgA antibodies may have a greater clinical importance for fertility outcomes than IgG antibodies. While IgG predominates in serum and IgA in mucosal surfaces, a strong correlation exists between the two, because both can be found bound to sperm surface antigens. If we wanted to detect a specific ASA that causes infertility, the ideal scenario would be finding the standard sperm antigens, which would be sperm-specific, play a key role in fertilization, and raise a long-lasting antibody response locally in the genital tract and also in circulation [29]. Some sperm antigens are involved in the activation of zona pellucida (ZP) binding (trypsin, proacrosin, acrosin); in acrosome reaction (M42), in ZP penetration (MS 207), and some in sperm-egg membrane fusion (PH-30 and M29) [30]. ASA are far more frequent than oocyte antibodies, but we can still find some ASA-related infertility in female partners, particularly following immunization through exposure to semen. Although women typically do not produce ASA in response to sperm, some infertile women have been found to possess these antibodies. In such cases, the presence of ASA may contribute to infertility; however, the underlying reason why most women do not mount an immune response to sperm remains unclear [31]. As previously mentioned, in women, sperm antigens are foreign antigens; in men, however, self-tolerance to sperm surface antigens fails to develop during immunologic maturation at puberty when spermatogenesis begins. Usually, spermatogenesis, semen production, and transport are immune-privileged [32]. Different immunologic and anatomic mechanisms support maintenance of self-tolerance in the testis, and when these barriers are disrupted, ASA can be formed. Anatomic mechanisms responsible for immunological homeostasis are tight junctions between Sertoli cells and epididymal cells, which form the basis of the barrier to isolate the site of spermatogenesis, and low-permeability capillaries, which reduce the migration of antibodies and lymphocytes into the seminiferous tubules. Immunologically, the presence of a lymphocyte population within the testis is dominated by regulatory T cells and the production of anti-inflammatory cytokines; a process referred to as local immunoregulation [33]. Despite significant advances in understanding all these regulatory mechanisms, they are still not completely understood. Nevertheless, there is strong evidence indicating that the disruption of these mechanisms triggers the formation of ASA. While male immune infertility is often overlooked or superficially considered in daily clinical practice, we prepared this narrative review to summarize what is known on this field, to highlight new perspectives why to consider this topic more often in daily practice, and to highlight issues needed to be solved to better understand male immune infertility.

2. Risk factors

The aforementioned barriers may be disrupted by infections and inflammation, autoimmune diseases, inguinal hernia or hernia repair, varicocele, vasectomy, cryptorchidism, and testicular trauma [34, 35] (Fig. 1).

2.1 Infections and inflammation

Infections of the reproductive tract can be the cause of disruptions in the blood-testis barrier (BTB) and for local inflammation, both of which may contribute to ASA formation. However, the exact role of inflammatory processes in the male genital tract and the formation of ASA remains a matter of debate. Inflammation of the prostate could be related to the formation of ASA [36]. However, Hoover and Naz [37] reported no correlation between prostatic hyperplasia and prostate cancer with the formation of ASA. Nevertheless, considering that these types of prostate disorders usually lead to an increase of circulating prostate-specific antigen (PSA), which is responsible for dissolving the seminal coagulum and allowing sperm to swim freely, we could expect that men with increased PSA levels would also exhibit ASA in seminal plasma, potentially affecting fertilization. Naz and Butler [38] supported this in their study, although they could not determine whether it is a direct cause of infertility or merely an associated finding. Another factor worth considering are the cases of epididymal abnormalities, such as epididymitis, since ASA-positive patients exhibit some chronic epididymal inflammation [39].

We can divide infections into two main groups: viral and bacterial infections. On one hand, viral infections include

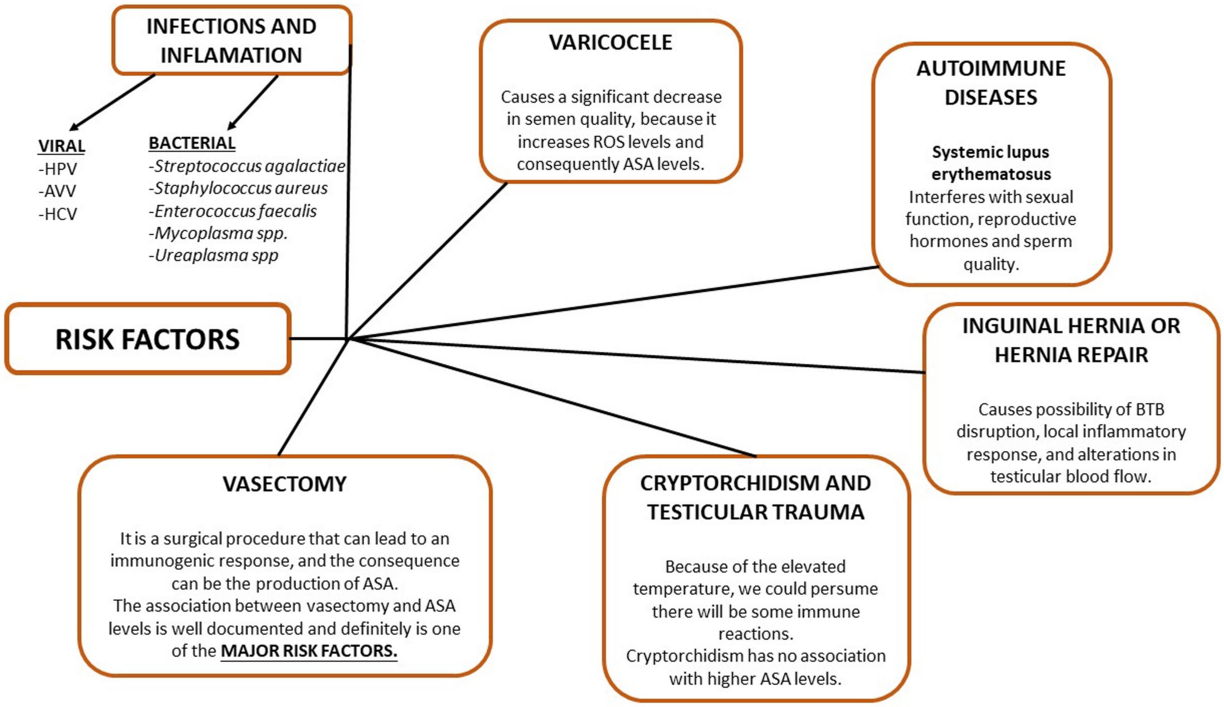

FIGURE 1. Risk factors for ASA production. BTB: blood-testis barrier; HPV: human papillomavirus; AVV: adeno-associated virus; HCV: hepatitis C virus; ASA: antisperm antibodies; ROS: reactive oxygen species.

cases of human papillomavirus (HPV), adeno-associated virus (AVV), and hepatitis C virus (HCV). These infections can affect the semen and the reproductive tract tissue, they may trigger different autoimmune reactions and an increase in ASA production, which then results in higher levels of ASA on the sperm surface and causes a significant decrease in sperm motility [40]. Several studies [41–43] have confirmed this in HCV and HPV infertile men, suggesting that viral infections are a significant contributing factor to male infertility. Hussein *et al*. [41] conducted a study on 30 HCV-infected individuals and 30 healthy control subjects. They measured liver enzymes and reproductive hormones, performed computer-assisted semen analysis (CASA), determined IgG and IgA in semen, and measured HCV-RNA in serum. IgG and IgA levels were higher in HCV patients, and sperm concentration, total motility, and progressive motility were lower in HCV patients. Correlations between examined semen parameters and viral load were nonsignificant, but still, they claim HCV may be responsible for increased IgG and IgA levels. Garolla and co-workers [42] included 151 infertile couples with the detection of HPV in semen, counselled to receive adjuvant HPV vaccination (79 accepted vaccination, 72 did not and became the control group). They evaluated the effect on reproductive outcome of HPV vaccination by recording progressive sperm motility, ASA levels, spontaneous pregnancies, miscarriages, and live births. Their results show that progressive sperm motility and ASA levels were improved in the vaccine group, and that adjuvant vaccination was associated with enhanced HPV healing in semen cells and an increased rate of natural pregnancies and live births. The question of whether the presence of HPV in semen is associated with impairment of semen quality, was analyzed in a large cohort study by Luttmer *et al*. [43]. They tested male partners for HPV-DNA, counted sperm concentration and motility, and determined ASA levels with MAR test. Their study concluded that the presence of HPV in semen was not associated with the age of the participants, seminal pH, semen volume, total sperm count, sperm concentration, progressive motility, or the presence of antisperm antibodies. Among the viral infections mentioned above, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) also needs to be mentioned. We found no specific literature claiming that SARS coronavirus is correlated with higher ASA levels, but recent evidence report that SARS coronavirus could also lead to fertility damage by utilizing the angiotensin-converting enzyme 2 (ACE-2) receptor expressed on testicular tissue [44]. Taken together, these studies underscore the need for further investigation to elucidate the underlying pathophysiological mechanisms and clarify the clinical significance of respiratory virus infections in male fertility.

Bacterial infections, on the other hand, have been correlated with *Streptococcus agalactiae*, *Staphylococcus aureus*, and *Enterococcus faecalis*. In most cases, ASA production increases due to molecular mimicry between sperm and bacteria, leading to cross-reactivity issues between bacterial antibodies and ASA [45]. Based on epidemiological and experimental evidence, there has been a growing awareness of the role of infectious diseases in autoimmunity via molecular mimicry and cross-reactivity. Molecular mimicry is one of the leading mechanisms by which infectious agents may induce autoimmunity, and this occurs when similarities between self and foreign-peptides favour an activation of autoreactive B or T cells by foreign-derived peptides. Currently, four major criteria are used to define molecular mimicry: "(1) similarity between a host epitope and an epitope of a microorganism or environmental agent, (2) detection of antibodies or T cells that cross-react with both epitopes in patients, (3) epidemio-

logical link between exposure to the environmental agent or microbe, and (4) reproducibility of autoimmunity in an animal model following sensitization with the appropriate epitopes either following infection with the microbe or exposure to the environmental agent." [46]. Although these criteria have been in place for many years, they remain difficult to demonstrate conclusively in humans. Challenges include insufficient epidemiological power, study limitations, and issues such as long latency between exposure and disease onset. Additionally, humans encounter numerous infections throughout life, yet only a small subset lead to autoimmune responses [47]. In increased ASA production related to bacterial infections, heat shock proteins (HSP), also known as chaperones, are potential causative agents, because these proteins are released in response to stressful conditions. The bacterial heat shock protein 60 (HSP60) protein, the major antigenic determinant during an infection, has approximately 50% homology with human HSP60, which can lead to cross-reactivity and may result in reproductive issues through ASA production [48]. The existence of molecular mimicry leading to cross-reactivity between sperm and bacteria was mentioned in the study by Prabha *et al*. [49], where they claimed that sperm immobilization factor isolated from *Staphylococcus aureus* immobilizes human spermatozoa, as well as motile bacteria, showing that sperm immobilization factor receptor might be shared by bacteria and human spermatozoa. Their results show that ASA in humans cross-reacted with bacterial antibodies, sperm immobilization factor, isolated from *Staphylococcus aureus*, immobilized spermatozoa, and motile bacteria, higher concentrations of sperm immobilization factor even caused sperm death. With all gathered facts, they concluded that molecular similarity between bacteria and spermatozoa exists. Interestingly, the most well-known sexually transmitted bacteria, *Chlamydia trachomatis*, is not reported in correlation with ASA production [50].

Although *Mycoplasma spp*. and *Ureaplasma spp*. are natural inhabitants of the male urethra, they can become pathogenic and contribute to genital infections related to male infertility. In andrology, the most relevant species are *Mycoplasma genitalium* and *Mycoplasma hominis*. These two pathogens may trigger inflammatory processes that could theoretically lead to ASA formation, but no correlation with ASA levels has been demonstrated. The only identified consequence of the pathogen binding to spermatozoa was the occurrence of sperm agglutination [51].

Mycoplasma hominis is usually associated with changing semen parameters, particularly density and motility, as shown by Rose and Scott [52], who incubated spermatozoa with mycoplasma overnight and observed pathogen binding to sperm head, tail, and midpiece. On the contrary, Diaz-Garcia and coworkers [53], reported that a short-term semen exposure to *Mycoplasma hominis* does not reduce sperm viability.

Mycoplasma genitalium is linked to male urethritis, prostatitis, infertility, and may induce sperm DNA damage. Some *in vitro* studies show that its attachment to spermatozoa can cause sperm agglutination and reduced motility [54]. Svenstrup *et al*. [55], noted that *Mycoplasma genitalium* can bind to the midpiece region of spermatozoa, and then be transported by motile sperm.

2.2 Varicocele

Varicocele is a well-known factor contributing to infertility and abnormal semen parameters. It is often detected during routine examinations, where an abnormal enlargement of the spermatic cord veins can be observed. Several possible mechanisms have been proposed to explain the impact of varicocele on fertility, including blood stasis leading to toxin accumulation, hormonal imbalances, temperature dysregulation, oxidative stress, and testicular hypoperfusion [56]. Even though varicocele has been linked with levels of ASA, findings still remain inconsistent. Veräjänkorva *et al*. [57] claim there is no correlation between levels of ASA and varicocele, a conclusion supported by Bozhedomov *et al*. [58]. However, they noted that while varicocele itself is not an immediate cause of autoimmune reactions against spermatozoa, it represents a very important cofactor of immune infertility due to testicular trauma in varicocele patients. They also demonstrated a significant decrease in semen quality correlated with levels of ROS in ASA-positive varicocele patients, which were notably higher than in ASA-negative varicocele patients. A recent study [59] investigated ASA positivity in the semen of men with and without varicocele (control group) and compared different detection tests—MAR test, immunobead (IB) direct and indirect test, and enzyme-linked immunosorbent assay (ELISA) testing. After reviewing 151 abstracts, 6 articles met the inclusion criteria and were included in the meta-analysis. With MAR test 39.8% of patients with varicocele tested positive for ASA, compared to 17% in control group ($p = 0.04$); with IB test 50% of patients with varicocele tested positive for ASA, compared to 15.4% in control group ($p = 0.09$); with ELISA test 37.1% patients with varicocele tested positive for ASA, compared to 15.8% in control group ($p < 0.01$). They confirmed that ASA positivity is significantly higher among men with varicocele than those without varicocele when tested by MAR test or ELISA test. This suggests the presence of an immunological pathology in infertile men with varicocele. Despite the limited number of studies available, current evidence supports the view that varicocele plays an important role in ASA levels.

2.3 Autoimmune diseases

Autoimmune diseases are health conditions that occur when the immune system mistakenly produces antibodies that attack the body's own cells [60]. Considering that "immune infertility" is also an autoimmune disorder, we could predict that ASA levels are elevated in men with other autoimmune diseases [18]. One such condition is lupus erythematosus, in which increased levels of ASA have been reported. Shiraishi *et al*. [61] compared men with and without systemic autoimmune diseases and found higher levels of ASA in the group of men with autoimmune diseases than in men without, suggesting that systemic autoimmune diseases may represent a risk factor for ASA development in men. Conversely, ankylosing spondylitis, juvenile dermatomyositis, and antiphospholipid syndrome have not been associated with higher ASA [62, 63]. One of the world's most well-known autoimmune diseases, multiple sclerosis (MS), has likewise not been linked with higher ASA levels to date. However, MS is a chronic disease

that can cause a wide range of symptoms and disabilities, raising important questions regarding its impact on fertility and reproduction. Massarotti *et al*. [64] addressed three important questions in their study; (a) Is multiple sclerosis correlated with conditions that increase the risk of infertility? (b) Does multiple sclerosis cause infertility *per se*? (c) Do disease-modifying therapies (DMTs) or other therapies for multiple sclerosis impact gonadal function in men? They concluded that the issue of fertility in men with MS has not been thoroughly investigated, and that only indirect data from population registries are available. Nonetheless, some data indicate that up to 70% of men with MS experience erectile dysfunction, and up to 50% of men exhibit alterations in ejaculation [65]. Despite these findings, no links were observed between MS and ASA levels. Similarly, Li and coworkers [66] conducted a Mendelian randomization study to assess the causal relationship between MS and abnormal spermatozoa. Their results indicated that patients with MS have a higher risk of sperm abnormalities, and that reproductive and fertility issues in men with MS warrant special attention from clinicians. The most relevant factor identified was the higher levels of ROS, which is linked to chronic inflammation; however, this study also found no correlation with ASA levels. In summary, men with MS could be subfertile due to disease-related ejaculation and/or erection dysfunction and/or inflammatory effects, but a clear correlation with higher ASA levels has not yet been determined.

2.4 Vasectomy

Vasectomy is a surgical procedure performed to prevent fertility in males. It can lead to an immunogenic response, which may result in the production of ASA. While researchers hold differing opinions regarding the above mentioned risk factors for elevated ASA levels; they unanimously agree that vasectomy is one of the most firmly established factors associated with increased ASA levels [67]. In a study by Lee *et al*. [68] that included 484 men with male infertility who had undergone ASA testing, serum ASA levels were found to be higher in men after vasectomy. Similarly, Azizi *et al*. [69] examined 110 vasectomized men and reported the presence of ASA in 95% of participants. These findings demonstrate that the association between vasectomy and ASA levels is well-documented and firmly supported as one of the major risk factors. However, regardless of the reason for performing this procedure in the first place, we can still say it has a negative effect on fertility, but it's not the reason for primary infertility associated with ASA.

2.5 Cryptorchidism and testicular trauma

Cryptorchidism, the most prevalent congenital abnormality involving male genitalia, is a well-known factor of infertility. Also referred to as an undescended testis, it results from the failure of one or both testes to descend into the scrotum. Cryptorchidism is also found in patients diagnosed with Prader-Willi Syndrome (PWS). Genital abnormalities are the rule in PWS patients and cryptorchidism in particular is present in 85–100% of cases [70, 71]. Due to the elevated intra-abdominal temperature, we could presume that some immune reactions might occur; however, cryptorchidism is primarily associated with impaired germ cell maturation [72]. No clear association between cryptorchidism and ASA levels has been shown, and infertility associated with cryptorchidism is not immunological [73]. As mentioned above, elevated temperature could induce some immune reactions, which can be influenced by an individual's genetic constitution. Niepiekło-Miniewska *et al*. [74] studied gene system encoding immunoglobulin receptors (KIRs) and found that there were no differences among cryptorchidic patients and healthy controls in terms of ASA levels.

Another potential cause of ASA production described in the literature is testicular trauma, which may disrupt the blood-testis barrier and expose sperm antigens to the immune system. However, the association between these conditions and ASA remains controversial [35].

2.6 Inguinal hernia or hernia repair

Inguinal hernia is a relatively common medical condition that can be quickly resolved with a minor surgical procedure. An inguinal hernia is a hernia (protrusion) of abdominal cavity contents through the inguinal canal. Some risk factors for developing a hernia are smoking, obstructive pulmonary disease, collagen vascular disease, obesity, strenuous physical activity, chronic constipation, connective tissue disorder, *etc*. Some predispositions to hernias can also be genetic [75]. Because surgical intervention is required, there is a potential risk of BTB disruption, local inflammatory response, and alterations in testicular blood flow, which could, in turn, have an impact on ASA development and infertility. Currently, two standardized surgical techniques are widely used: open hernia repair with mesh placement to close the hernia and laparoscopic repair. Generally, no significant differences in postoperative quality of life between these two methods are reported [76]. However, there are some links between immunological reactions triggered by these surgical procedures and some inflammatory processes. Štula and coworkers [77], on one hand, investigated testicular disorders related to infertility following inguinal hernia mesh repair. They included 43 male patients and analyzed ASA levels, but they found no significant differences and concluded that inguinal hernia mesh repair does not have a clinically significant influence on ASA levels. On the other hand, Negri *et al.* [78] conducted a study with 2258 infertile male patients who underwent ASA testing and urologic examination; among them, 191 had a history of inguinal hernia repair, and found increased ASA levels in patients who underwent andrological surgery or hernia repair. In summary, we can conclude that because of the limitations of the existing evidence and some conflicting results in studies, we cannot determine for sure if inguinal hernia repair does or does not lead to clinically significant immunological reactions. Nevertheless, assessing ASA levels could be useful in patients with a history of hernia repair in order to provide better insight into unexplained infertility.

3. ASA testing

The antigen analysis should be restricted to antigens of the outer sperm membrane, because it seems to be accepted that only ASA binding to sperm membrane are of relevance [18]. Detection of ASA has evolved over the years; indications for ASA testing are typically based on routine semen analysis findings, with sperm agglutination as one of the main indicators for positive ASA levels. Although agglutinations can also appear due to other factors, there is still a strong correlation between ASA and agglutinations [79]. In a study by Verón *et al*. [80], they included men undergoing routine semen analysis, ASA evaluation with direct SpermMar test, and computer-assisted sperm analysis (CASA). Their results showed that about one-third of patients with sperm agglutinations were also ASA positive, while only 3% were ASA positive without agglutinations. The presence of ASA is also linked with reduced sperm count, motility, and vitality. Because it is so difficult to define a narrow subset of patients who should undergo ASA testing, the 5th edition of WHO laboratory manual recommends seminal testing for ASA as a routine semen check-up [81]. As mentioned earlier, two immunoglobulin classes (IgG and IgA) are most common in semen, and can be detected with direct tests: the mixed antiglobulin reaction (MAR) test and the immunobead (IB) test. The IB test is performed on a washed semen sample, whereas the MAR test is performed on a fresh sample. Direct test provides information about the type of antibodies, when present, and their specific location (sperm head, tail, or midpiece). A limitation of the direct tests is their requirement for fresh semen samples with good sperm motility. If the percentage of motile spermatozoa is very low (<10% progressive spermatozoa), direct testing cannot be performed, and indirect tests must be used instead. An indirect test is then used to detect sperm-specific immunoglobulins in sperm-free fluids, such as heat-inactivated serum and seminal plasma. When performing an indirect test, the suspected fluid should be incubated with ASA-free donor sperm, allowing for a potential sperm-antibody interaction to occur [17]. The essential step of an ASA assay is the preparation of sperm antigens, which can be prepared by different methods. Antigens are divided into groups as follows; sonicated sperm antigens, cavitated sperm antigens, sperm antigen epitopes prepared by phage-display techniques, various recombinant sperm antigens, and antigen extract made by treatment of freeze-thawed sperm pools. It is difficult to address which test is optimal; MAR and IB are frequently used, but they are not able to identify specific antigens because of the relatively large “labels” (erythrocytes, latex beads, polystyrol beads), so there exist some other options. Other tests capable of ASA detection include sperm agglutination test, sperm immobilization test, immunofluorescence assays, enzyme-linked immunosorbent assay (ELISA), flow cytometry and radiolabeled antiglobulin assays (RIA) [30].

3.1 The mixed antiglobulin reaction (MAR) test

The mixed antiglobulin reaction (MAR) test provides less information than other tests, but it is quick, inexpensive, and sufficiently sensitive to yield valid results [82]. For the MAR test, an unwashed sample of semen is mixed with latex beads coated with anti-human antibodies, and in the presence of ASA, the anti-human antibodies on the beads will bind to the antibodies on the sperm surface. As a result, motile spermatozoa become coated with beads, which can be observed under the microscope. Usually, spermatozoa continue to move around with the beads attached, but if agglutinates become massive, the movement of spermatozoa can be blocked. The aim is to determine the percentage of motile spermatozoa with attached beads. Spermatozoa that lack surface antibodies can be seen swimming freely among the particles. The recommendation is that at least 200 motile spermatozoa should be evaluated. The criteria for a positive ASA result vary among sources. According to the 5th edition of the WHO Laboratory Manual, the reference value is 50% for both IgG and IgA [81]. The 6th edition of the manual, however, does not specify an exact reference value for a positive ASA result; instead, they recommend that each laboratory establish its own reference value based on testing a large population of fertile and infertile men to distinguish between normal and pathological semen samples [17]. However, as per the manufacturer of SpermMar test from FertiPro, a positive ASA result is when at least 40% or more of spermatozoa are bound to latex beads.

3.2 The direct and the indirect immunobead test

The direct immunobead (IB) test is less commonly used and is more time-consuming than the MAR test, but it provides information about antibodies on spermatozoa that have been masked before. In this test, a washed sperm sample is used and mixed with covalently-bound anti-human immunoglobulins against IgG and IgA. If the beads bind to motile spermatozoa, this indicates the presence of surface-bound antibodies on the spermatozoa. The indirect immunobead test is used to detect ASA in sperm-free fluids (serum, seminal plasma, testicular fluid), and is useful in semen samples where motility is not adequate for the MAR test. In this test, antibody-free donor spermatozoa bind to ASA that is present in the tested fluid; the sample is then evaluated in the same manner as the direct IB test. Both procedures are different from the MAR test. According to the 5th edition of the WHO manual, the consensus value of 50% motile spermatozoa with bead particles is considered a threshold value [81].

3.3 Detection of ASA in seminal plasma by ELISA technique

An enzyme-linked immunosorbent assay (ELISA) has been developed and evaluated for the detection of equine ASA. It could detect ASA by the antigen absorbed in the solid phase, and antihuman globulin conjugated to alkaline phosphatase as a developing reagent. The ELISA assay detects IgM, IgG, and IgA in serum, cervical mucus, and seminal plasma [30]. Typically, the ELISA plate is coated with a mixture of spermatozoa proteins, which are recognized by ASA. Samples and standards are pipetted into the wells and then incubated, allowing any ASA present to bind to the immobilized sperm proteins. After all initial steps of the procedure, the color of

the solution changes, and the intensity of this color change is measured. The ELISA method is a more standardized test demonstrating the correlation between seminal and sperm-bound ASA values. It also has the advantage of long-term sample storage ability, unlike MAR and IBT, which require fresh samples. However, it is used less frequently in routine diagnostics because MAR and IBT tests are faster and more cost-effective [83, 84]. But this is not the only reason for not being used so frequently, ELISA test also requires fixation of whole sperm or use of membrane extracts. Fixation may lead to membrane damage or denaturation of sperm antigens, which can result in a false-positive or false-negative result [30].

3.4 Sperm agglutination tests and sperm immobilization test (SIT)

The sperm agglutination test requires fresh motile spermatozoa and includes the tray agglutination test, gelatin agglutination test, and glass agglutination test. Agglutinates can be formed by any amorphous material present in the semen sample, non-specific immunoglobulins, as well as nonimmunoglobulin proteins, which can all lead to false-positive results. The class of immunoglobulin cannot be identified; that's why this method is not recommended for routine use.

Sperm immobilization test (SIT) means counting the motile spermatozoa under the microscope, which makes this method highly subjective. Because sperm-immobilization assays are limited in their detection of IgA and can give false-negative results, this method is also not recommended for routine use [30].

3.5 Immunofluorescence assays (IFAs)

As a conclusion from the study by Bohring *et al*. [85] immunofluorescence assays in the diagnosis of immune infertility should be encouraged, particularly if MAR test is positive and the acrosome function is questioned. However, there are some shortcomings for these assays. The method is unable to detect the number of antibody molecules or antigens involved in the binding. It can only detect the immunoglobulin class of the antibody concerned [18]. Despite some positive facts about this method, IFAs are not recommended for routine use, because the results based on IFAs are unreliable [30].

3.6 Flow cytometry and radiolabeled antiglobulin assay (RIA)

One of the not recommended methods for routine use in ASA detection is flow cytometry. Flow cytometry was used as a promising method for the determination of the number of sperm binding ASA, because it may be able to determine the exact amount of IgG and IgA in individual sperm samples [86]. However, Nikolaeva *et al*. [87] concluded that it does not always give an objective result, and for that, the practical use of flow cytometry has been limited.

Radiolabeled antiglobulin assay (RIA) provides no information about the proportion of antibodies bound to sperm or the region where antibodies bind, similar as ELISA. Also, antigens are not biochemically identified and those relevant for the process of fertilization might not be contained in the antigen mixture.

4. Anti-sperm antibodies in assisted reproductive technology (ART)

Assisted reproductive technology (ART) encompasses all fertility-related treatments and is most frequently performed secondary to infertility. The most commonly used ART is *in vitro* fertilization (IVF). Infertility etiologies in which IVF is usually used include diminished ovarian reserve, ovarian failure, ovulatory dysfunction, male factor infertility, unexplained infertility, *etc*. [88]. ASA can have an impact on male fertility at different levels, often manifesting as abnormalities detected at routine semen analysis. Reported effects of ASA include decreased motility and concentration, sperm agglutinations, poorer capacitation, and alterations in the acrosome reaction [19]. Furthermore, there are some reports of a negative impact of ASA on embryo development and implantation after conventional IVF [89, 90]. Even though there are several reports highlighting the potential influence of ASA on male fertility, the overall impact remains insufficiently evaluated, despite significant advancements in assisted reproduction. Techniques used in ART to overcome the impact of ASA are intrauterine insemination (IUI), IVF, and intracytoplasmic sperm injection (ICSI). A shared feature among these procedures is sperm preparation for ART, which includes sperm washing, a step that can dilute certain unbound antibodies. In IVF and ICSI cases, the swim-up technique is also used. If ASA-positive samples are identified in advance, additional washing can be performed. It appears that ASA primarily binds to spermatozoa post-ejaculation, meaning that by adding a few milliliters of culture medium to the collection cup would create a dilution that could prevent at least some ASA binding to motile spermatozoa, as the detachment of already bound antibodies appears to be much less likely [91].

4.1 IUI

A primary mechanism whereby ASA can interfere with fertility is the ability of the sperm to penetrate through the cervical mucus. With IUI, we can bypass the cervical mucus, which is the main reason IUI has been widely used as the first-line treatment [83]. However, uncertainties remain regarding the effectiveness of IUI. Although data vary among studies, evidence suggests that IUI can overcome some of the mechanisms of ASA interference and should be an approach for selected patients who have been diagnosed with so-called male subfertility [92]. In a retrospective cohort study, Barbonetti *et al*. [93] investigated the relationship between the percentage of ASA levels in natural and IUI-assisted live births. Men in this study had to be at least 50% positive at the IgG MAR test and were divided into two groups (100% and 50–99% MAR test). In the first group (100% MAR), the live birth rate per couple after IUI was significantly higher than the natural live birth rate (LBR) ($p = 0.0004$). In 38 out of 44 couples with 100% MAR, there were 14 live births after IUI (LBR = 36.8%), and the natural live birth per couple in the same group was only 4.5%. In contrast, among the men in the 50–99% MAR group, LBR after IUI was not higher. The findings emerging from this

study indicate that in a group with couples where a male partner has a 100% positive IgG MAR test, the percentage of natural LBR is very low, compared with the percentage of natural LBR in a group with couples where male partner has a 50–99% positive IgG-MAR. This finding indicates that different ASA levels have different impacts on reproduction outcomes. They also showed that IUI can represent an effective treatment even in 100% positive IgG-MAR. Similar results were presented by Francavilla *et al*. [92]. Earlier, Ombelet *et al.* [94] compared the results between IUI and IVF treatment in couples where the male partner had to have at least a 50% positive MAR test (IgG or IgA). Both IUI and IVF achieved high pregnancy rates (64% and 47%), but the authors concluded that IUI should be the first-line therapy in male immunological infertility. Although all these studies had relatively small sample sizes and differences in the ASA positivity thresholds used, their results consistently support IUI as an effective first-line treatment for carefully selected couples.

4.2 IVF

Another technique used for semen samples with positive ASA is *in vitro* fertilization (IVF). After semen collection, the sample is washed and then subjected to swim-up procedure, which may help decrease the number of antibodies. Several studies have investigated whether positive ASA levels have an impact on fertilization rate and live birth rate after IVF. Lu *et al.* [95] conducted a study with 399 couples comparing the fertilization rate, pregnancy rate, and live birth rate between couples with ASA-positive male partners (n = 39) and ASA-negative male partners (n = 360) after IVF. ASA was detected in serum using the ELISA test. Their results show that in the ASA-positive group, the fertilization rate was lower than in the ASA-negative group (41.7% *vs*. 54.8%, $p = 0.03$), alongside the quality of the embryos, which was lower in the ASA-positive group (18.9% *vs*. 35.2%, $p < 0.001$). Pregnancy rate (38.5% *vs*. 61.1%, $p = 0.01$) and live birth rate (20.5% *vs*. 42.5%, $p = 0.01$) were also lower in the ASA-positive group. Similarly, Clark [96] confirmed that high levels of ASA reduce fertilization rate after IVF. He was focusing on IgA antibodies and compared a group of male partners with high levels of IgA with a group of male partners with negative ASA levels. A similar study was made by Vujisić *et al*. [97], where they compared fertilization rate and pregnancy rate between ASA-positive and negative groups. Their samples were analysed by direct MAR test, but their results did not give such a clear difference between those two groups; fertilization rate and pregnancy rate were not significantly different. Comparable findings were reported by Zini *et al*. [98], who examined reproductive outcomes after 106 cycles of IVF and found no significant relationship between ASA-positive levels and reproductive outcomes after IVF. Direct ASA levels were measured in fresh semen by MAR test and the test was considered positive if >50% of the motile sperm were covered with antibody (IgG or IgA). The fertilization rates and clinical pregnancy rates were also not significantly different in ASA-positive and ASA-negative groups (68% *vs*. 66%), and (42% *vs*. 52%). Overall, the data about the impact of ASA levels on reproductive outcomes is still controversial; some studies indicate that the presence of ASA negatively affects fertilization and live birth rates, whereas others found no difference. The different results in the studies mentioned in this paragraph may be a consequence of using different methods for ASA detection, usually MAR test or ELISA, different thresholds for positive sperm samples, and small groups of ASA-positive male partners, because the majority of the study population were ASA-negative male partners.

4.3 ICSI

ICSI has become an alternative for managing couples affected by ASA, because microinjection of sperm into the oocyte cytoplasm can minimize the effects of ASA on spermatozoa-zona pellucida binding. Similar to those on IVF, there are studies that assessed ICSI and reproductive outcomes, typically by comparing groups of ASA-positive male partners to groups of ASA-negative male partners and examining if there are any differences in reproductive outcomes. Lu *et al*. [95] conducted the same study for ICSI as for IVF mentioned above, evaluating fertilization rate, pregnancy rate, and live birth rate between the ASA-positive group and the ASA-negative group. They included 155 couples for ICSI cycles, where 19 male partners were ASA-positive and 136 were considered ASA-negative. Their results show that all the three outcome factors were comparable, with no significant differences between the groups. Pregnancy rate was 52.6% in ASA-positive group and 61.8% in ASA-negative group, and live birth rate was 47.4% *vs*. 44.1%. Esteves *et al.* [99] performed a retrospective study to analyze the influence of ASA on the outcome after ICSI. They used the direct IB test for evaluation of ASA levels in 351 semen samples. Male participants were divided into four groups according to their percentage of ASA levels (I. (n = 194): 0–10% ASA; II. (n = 107): 11–20% ASA; III. (n = 33): 21–50% ASA and IV. (n = 17): 51–100% ASA) and compared fertilization rates (I. = 80%, II. = 75.0%, III. = 75.0%, IV. = 82.4%), clinical pregnancy rates (I. = 53.5%, II. = 52.8%, III. = 52.0%, IV. = 50%), and miscarriage rates (I. = 21.7%, II. = 10.8%, III. = 23.0%, IV. = 25.0%), between the four groups. The results showed no significant differences among groups, suggesting that varying levels of autoimmunity against spermatozoa do not affect ICSI outcomes. Results in favour of better outcomes after ICSI for ASA-positive male partners were presented in the study by Mercan *et al.* [100], where they found that fertilization rate was seemingly higher in ASA-positive group (70%) than in the ASA-negative group, 63% ($p = 0.06$). However, there was no difference regarding pregnancy rate (36% *vs*. 39%) and live birth rate (36% *vs*. 30%). Similar findings were observed by Nagy *et al*. [101], who also noted a higher fertilization rate in the ASA-positive group than in the ASA-negative group ($p = 0.046$) but found a greater proportion of poor-quality embryos. They concluded that fertilization, embryo development, and pregnancy rates after ICSI are not significantly affected by the proportion of antibody-bound spermatozoa; however, ICSI should be considered the treatment of choice for patients with high levels of ASA in their semen. They claim that ICSI is the better choice because antisperm antibodies do not interfere with the fertilization process when we deposit spermatozoon into the

cytoplasm of the egg, so we get better fertilization rates as in standard IVF. It is difficult to find an explanation for this outcome, but one of the possible explanations might be that immunoglobulins against spermatozoa facilitate the acrosome reaction and thus increase the fertilization of the microinjected spermatozoon [102]. Additionally, like we know, ASA can cause sperm agglutination and interfere with sperm motility, which could make the affected spermatozoa incapable of successful fertilization through standard IVF procedures. In such cases, ICSI may provide better outcomes.

4.4 IVF or ICSI?

To achieve optimal reproductive outcomes, there is always the question of how to best overcome male immunological infertility. To find an answer to that question, several researchers decided to compare IVF and ICSI outcomes in couples with a known male immune infertility factor. Zini *et al*. [98] examined the relationship between ASA levels and reproductive outcomes, specifically fertilization and pregnancy rates, following IVF or ICSI. They analyzed IVF and ICSI cycles separately and found no relationship between ASA levels and either fertilization (67% *vs*. 59%) or pregnancy rate (55% *vs*. 47%). They concluded that ASA levels are not related with improved reproductive outcomes. This finding was further supported by their subsequent systematic review and meta-analysis, in which they suggested that both IVF and ICSI remain viable options for infertile couples with semen ASA [103]. A trend in the increase of the rates of live births in ICSI versus IVF within the ASA-positive group was observed by Lu *et al*. [95], however, it lacked a statistical significance. Live birth rate in IVF cycles was 20.5% and in ICSI cycles 47.4%, (p = 0.07). This may be due to the relatively small number of patients with ASA-positive results included in both the ICSI and IVF groups, so future studies with larger cohorts are therefore warranted to determine whether this trend achieves statistical significance.

5. Treatment and medical therapy

In ART, established procedures (IUI, IVF, and ICSI) have enhanced our ability to manage male infertility cases with poor semen quality and also cases with known male immunological infertility. Nevertheless, it is essential to note that these methods cannot be considered as a universal solution for the management of ASA. Various strategies have been mentioned to improve the potentially harmful effects of ASA, reducing gamete exposure to ASA, and then resulting in improved gamete function. These strategies are categorised in three groups: methods to remove ASA already bound to sperm, methods to decrease ASA production, and ART [27].

In the group of reducing ASA production are so-called condom therapy and systemic corticosteroid treatment. As a conventional medication for infertile males with higher levels of ASA, immunosuppressive therapies using corticosteroids or cyclosporine may be promising, as such immunosuppressive medications usually manage autoimmune disorders [104]. Corticosteroid therapy has emerged as the predominant strategy for immunosuppression. Zaki *et al.* [105] conducted a study on rat testicular sperm aspiration with four therapeutic approaches for ASA. This included treatment with dexamethasone (DEX), azathioprine (AZA), frankincense, and anti-ASA secondary antibodies. They reported that a low-dose corticosteroid treatment may be beneficial in such cases. They reported promising results referring to lower ASA levels after treatments; however, a debate among researchers about the side effects of this therapy on otherwise healthy men is ongoing, underscoring the need for caution when extrapolating results from experimental models to clinical practice. Encouraging findings were also reported by Taiyeb *et al*. [106], where ASA positive male patients were divided in two groups—one was treated with prednisolone and one was untreated. They compared sperm motility, fertilization rate, embryo cleavage, and chemical and clinical pregnancy rate. The treated group demonstrated improvements in sperm motility, fertilization, cleavage, and clinical pregnancy rates compared with untreated patients; however, these differences were observed only in IVF cycles, not in ICSI. The data from these two studies show there are some potential benefits of the use of corticosteroid therapy, but some other older studies have failed to replicate these results, showing no significant benefits [107, 108]. In conclusion, several critical issues remain unresolved before corticosteroid therapy can be considered a standard treatment, especially regarding the corticosteroid type, dosage, treatment duration, and patient selection. Condom therapy was mentioned in a review of Li [109] as theoretically, repeated sperm exposure to the female reproductive tract results in ASA formation, so condom use would decrease sperm exposure and consequently decrease ASA production. But the results of this method were not valid, so this method is not used anymore.

In the group of methods trying to remove ASA already bound to sperm, we can find sperm washing and fertilization antigen (FA-1) treatment. Sperm washing is a laboratory technique routinely used in ART and can reduce the level of ASA and improve the chance of conception. However, it is difficult to completely elute antibodies from the sperm surface, so the results can be a little bit disappointing. For FA-1 treatment, more research is still needed to confirm this approach, but mostly this method consists of removing antibodies from sperm surface by immune adsorption and permitting an increased acrosome reaction (AR). Menge *et al*. [110] concluded that the FA-1 sperm antigen appears to significantly free sperm cells coated with autoantibodies in the semen. Reducing sperm-bound antibodies that inhibited the AR, allowed the sperm cells to undergo successful AR induction by calcium ionophore (in 78% of the sperm samples with present IgG and IgA antibodies, improvement was shown).

An interesting study on potential ASA treatment was made by Al-Daghistani [111], who observed the effectiveness of *Staphylococcus* protein A (SPA) in improving sperm penetration ability and reducing ASA levels in immunologically infertile males. SPA binds to the fragment crystallizable region (Fc region) of human IgG and immobilized protein A adsorbents have previously been used to remove human IgG from the serum in the treatment of autoimmune diseases [112]. After treating the sperm of ASA-positive male patients, the number of fast progressive movement did not significantly increase, but the number that deeply penetrated the mucus

increased significantly. These findings may be useful for the process of sperm preparation before IUI. Also, a significant reduction of ASA levels after SPA treatment was observed, but the author concluded that despite these promising results, caution is warranted until well-designed clinical trials confirm the efficacy of SPA.

One of the potential treatments for autoimmune male infertility mentioned in the literature are plasmapheresis and hemosorption. Effects of these two were studied and presented by Tiktinskiĭ *et al*. [113]. They included 289 male partners with autoimmune male infertility and oligoasthenozoospermia (19–37 years old) and divided them into three groups by the level of ASA in blood and sperm. Patients of group I. had high ASA levels in blood, but low in sperm and received a course of plasmapheresis. Patients of group II. had high levels of ASA in blood and sperm and got a course of hemosorption and plasmapheresis. Patients in group III. had low ASA levels in blood but high ASA levels in sperm and received efferent therapy only after medication. They concluded that the treatment reduced elevated levels of ASA in the blood and sperm, which resulted in improvement of spermiogram parameters and efficacy of ART, and it could be considered as an option in autoimmune male infertility treatment.

6. Conclusions

Male immune infertility represents a complex and still insufficiently understood condition. Although several potential mechanisms by which antisperm antibodies (ASA) impair fertility have been proposed, current evidence does not clearly identify which pathways are most clinically relevant. Notably, some antisperm antigens can inhibit fertilization under *in vitro* conditions while not impairing fertility *in vivo* [25], underscoring the challenges in translating experimental observations into clinical practice. Because our manuscript primarily focuses on *in vitro* fertilization, our literature review indicates that research specifically addressing male immune infertility remains limited, with findings often contradictory and based on small, heterogeneous study populations. Despite these inconsistencies, assisted reproductive technologies (ART), particularly intrauterine insemination (IUI), *in vitro* fertilization (IVF), and intracytoplasmic sperm injection (ICSI), remain the most reliable and widely accepted approaches for managing ASA-associated infertility. These techniques bypass or reduce the impact of immune-mediated interference and currently offer the highest likelihood of reproductive success. Although several effective alternative treatment options do exist, they are not widely recognized, and their implementation depends critically on the identification of relevant antigens. At present, no antibody-specific therapy for male immune infertility is available. Alternative strategies aimed at reducing the effects of antisperm antibodies, such as, oral corticosteroids for their immunosuppressive properties or treatments with *Staphylococcus* protein A, have been explored. Additionally, two studies comparing traditional Chinese medicine (with or without acupuncture) to corticosteroids reported a greater reduction in ASA levels with traditional Chinese medicine [114, 115]. However, despite these preliminary findings, corticosteroid therapy raises concerns in otherwise healthy men due to the potential side effects, and the evidence supporting *Staphylococcus* protein A and traditional Chinese medicine remains limited to small, single-center studies. These approaches, therefore, cannot yet be recommended for routine clinical use. As a result, assisted reproductive techniques continue to be regarded as the first-line interventions for couples affected by male immune infertility. The heterogeneity of ASA effects further complicates clinical decision-making. ASA may impair cervical mucus penetration, sperm motility, or sperm–oocyte interactions, and the predominant site of interference may differ among patients. Identifying the specific mechanism involved could allow more targeted and effective selection of ART methods, thereby improving reproductive outcomes for affected couples. Despite increasing awareness of male immune infertility, substantial uncertainty persists regarding both the clinical utility of ASA testing and the optimal strategies for managing ASA-positive patients. Numerous detection methods exist, such as the MAR and IB tests, sperm agglutination and immobilization tests, ELISA, radiolabeled antiglobulin assays, flow cytometry, and immunofluorescence assays, each with its own advantages and limitations. Although several techniques have shown promising results, they are not recommended for routine use due to concerns about reliability. Currently, the MAR test, IB test, and ELISA remain the standard methods, yet MAR and IB testing suffer from subjectivity, low positive rates, and poorly defined positivity thresholds. These limitations and uncertainties, combined with inconsistent evidence, have led some clinicians to question the value of ASA testing and even abandon it in clinical practice. A particularly critical challenge is the absence of validated, fertility-relevant antigens. ASA are found in both infertile and fertile men, suggesting that only a subset of antigen targets are clinically meaningful. Future research should, therefore, prioritize the identification of specific sperm antigens and epitopes, including recombinant proteins, that correlate reliably with impaired fertility. Such biomarkers could improve diagnostic accuracy and guide individualized treatment strategies.

Overall, key issues in this field include: (1) the lack of consensus on threshold values defining ASA positivity, (2) small sample sizes and methodological heterogeneity across studies, (3) the absence of validated, effective treatments beyond assisted reproductive techniques, (4) variability and limitations in ASA detection methods, and (5) the absence of a well-defined, fertility-relevant sperm antigen. Addressing these issues through larger, well-designed, standardized, and methodologically robust studies will be essential for clarifying the role of ASA in male reproductive physiology and for developing more effective diagnostic criteria and targeted therapeutic strategies.

AVAILABILITY OF DATA AND MATERIALS

Data sharing is not applicable to this article, as no datasets were generated or analysed during the current study.

AUTHOR CONTRIBUTIONS

SO and MS—conception and design of the study; literature review. SO—manuscript drafting. AA, MS and HBF—critical revision of the manuscript. All the authors revised and edited the important contents of the manuscript and read and approved the final version.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Martin Stimpfel is serving as one of the Editorial Board members of this journal. We declare that Martin Stimpfel had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to BB.

REFERENCES

[1] Sharma P, Kaushal N, Saleth LR, Ghavami S, Dhingra S, Kaur P. Oxidative stress-induced apoptosis and autophagy: balancing the contrary forces in spermatogenesis. Biochimica et Biophysica Acta: Molecular Basis of Disease. 2023; 1869: 166742.

[2] Yan G, Tian F, Liu P, Sun J, Mao J, Han W, *et al*. Sheng Jing decoction can promote spermatogenesis and increase sperm motility of the oligozoospermia mouse model. Evidence-Based Complementary and Alternative Medicine. 2021; 2021: 3686494.

[3] Aslani F, Sebastian T, Keidel M, Fröhlich S, Elsässer HP, Schuppe HC, *et al*. Resistance to apoptosis and autophagy leads to enhanced survival in Sertoli cells. Molecular Human Reproduction. 2017; 23: 370–380.

[4] Wang Q, Xie JF, Yao TT, Wang XX, Guo QW, Wang LS, *et al*. MicroRNA-30a-5p regulates cypermethrin-induced apoptosis of Sertoli cells by targeting KLF9 *in vitro*. Reproductive Toxicology. 2023; 119: 108414.

[5] De Kretser DM, Baker HW. Infertility in men: recent advances and continuing controversies. The Journal of Clinical Endocrinology & Metabolism. 1999; 84: 3443–3450.

[6] Thonneau P, Marchand S, Tallec A, Ferial ML, Ducot B, Lansac J, *et al*. Incidence and main causes of infertility in a resident population (1,850,000) of three French regions (1988–1989). Human Reproduction. 1991; 6: 811–816.

[7] Colborn T, vom Saal FS, Soto AM. Developmental effects of endocrine-disrupting chemicals in wildlife and humans. Environmental Health Perspectives. 1993; 101: 378–384.

[8] Choi SM, Yoo SD, Lee BM. Toxicological characteristics of endocrine-disrupting chemicals: developmental toxicity, carcinogenicity, and mutagenicity. Journal of Toxicology and Environmental Health, Part B. 2004; 7: 1–24.

[9] Bhardwaj JK, Paliwal A, Saraf P. Effects of heavy metals on reproduction owing to infertility. Journal of Biochemical and Molecular Toxicology. 2021; 35: e22823.

[10] Auricchio F, Migliaccio A, Castoria G, Rotondi A, Di Domenico M, Pagano M. Activation-inactivation of hormone binding sites of the oestradiol-17 beta receptor is a multiregulated process. Journal of Steroid Biochemistry and Molecular Biology. 1986; 24: 39–43.

[11] Ballini A, Arrigoni R, Crocetto F, Risolo R, Colapietro R, Bellavita R, *et al*. Heavy metal pollution and male fertility: an overview on adverse biological effects and socio-economic implications. Endocrine, Metabolic & Immune Disorders—Drug Targets. 2023; 23: 129–146.

[12] Krausz C, Riera-Escamilla A. Genetics of male infertility. Nature Reviews Urology. 2018; 15: 369–384.

[13] Lee JA, Ramasamy R. Indications for the use of human chorionic gonadotropic hormone for the management of infertility in hypogonadal men. Translational Andrology and Urology. 2018; 7: S348–S352.

[14] Lotti F, Maggi M. Sexual dysfunction and male infertility. Nature Reviews Urology. 2018; 15: 287–307.

[15] Winters BR, Walsh TJ. The epidemiology of male infertility. Urologic Clinics of North America. 2014; 41: 195–204.

[16] Dondero F, Lenzi A, Gandini L, Lombardo F. Immunological infertility in humans. Experimental and Clinical Immunogenetics. 1993; 10: 65–72.

[17] World Health Organization. WHO laboratory manual for the examination and processing of human semen, 6th ed. WHO Press: Geneva, Switzerland. 2021.

[18] Bohring C, Krause W. Immune infertility: towards a better understanding of sperm (auto)-immunity: the value of proteomic analysis. Human Reproduction. 2003; 18: 915–924.

[19] Curi SM, Ariagno JI, Chenlo PH, Mendeluk GR, Pugliese MN, Sardi Segovia LM, *et al*. Asthenozoospermia: analysis of a large population. Archives of Andrology. 2003; 49: 343–349.

[20] Zhang H, Zhao E, Zhang C, Li X. The change of semen superoxide dismutase and acrosin activity in the sterility of male patients with positive antisperm antibody. Cell Biochemistry and Biophysics. 2015; 73: 451–453.

[21] Wilson L. Sperm agglutinins in human semen and blood. Experimental Biology and Medicine. 1954; 85: 652–655.

[22] Rumke P, Hellinga G. Autoantibodies against spermatozoa in sterile men. American Journal of Clinical Pathology. 1959; 32: 357–363.

[23] Alexander NJ. Antibodies to human spermatozoa impede sperm penetration of cervical mucus or hamster eggs. Fertility and Sterility. 1984; 41: 433–439.

[24] Bronson RA, Fusi F, Cooper GW, Phillips DM. Antisperm antibodies induce polyspermy by promoting adherence of human sperm to zona-free hamster eggs. Human Reproduction. 1990; 5: 690–696.

[25] Yeh WR, Acosta AA, Seltman HJ, Doncel G. Impact of immunoglobulin isotype and sperm surface location of antisperm antibodies on fertilization *in vitro* in the human. Fertility and Sterility. 1995; 63: 1287–1292.

[26] Clarke GN, Hyne RV, du Plessis Y, Johnston WI. Sperm antibodies and human *in vitro* fertilization. Fertility and Sterility. 1988; 49: 1018–1025.

[27] Mazumdar S, Levine AS. Antisperm antibodies: etiology, pathogenesis, diagnosis, and treatment. Fertility and Sterility. 1998; 70: 799–810.

[28] Kremer J, Jager S. Characteristics of anti-spermatozoal antibodies responsible for the shaking phenomenon with special regard to immunoglobulin class and antigen-reactive sites. International Journal of Andrology. 1980; 3: 143–152.

[29] Naz RK. Antisperm immunity for contraception. Journal of Andrology. 2006; 27: 153–159.

[30] Lu JC, Huang YF, Lu NQ. Antisperm immunity and infertility. Expert Review of Clinical Immunology. 2008; 4: 113–126.

[31] Tsuji Y, Mitsuo M, Yasunami R, Sakata K, Shibahara H, Koyama K. HLA-DR and HLA-DQ gene typing of infertile women possessing sperm-immobilizing antibody. Journal of Reproductive Immunology. 2000; 46: 31–38.

[32] Jager S, Kremer J, De Wilde-Janssen IW. Are sperm immobilizing antibodies in cervical mucus an explanation for a poor postcoital test? American Journal of Reproductive Immunology. 1984; 5: 56–60.

[33] Chereshnev VA, Pichugova SV, Beikin YB, Chereshneva MV, Iukhta AI, Stroev YI, *et al*. Pathogenesis of autoimmune male infertility: juxtacrine, paracrine, and endocrine dysregulation. Pathophysiology. 2021; 28: 471–488.

[34] Leathersich S, Hart RJ. Immune infertility in men. Fertility and Sterility. 2022; 117: 1121–1131.

[35] Haratian K, Faegh A, Mehrpoor G, Doustmohammadi M, Rezaeinasab R, MomeniAmjadi A. Potential causes and associated conditions with antisperm antibody production among infertile males: a systematic literature review. BMC Immunology. 2025; 26: 58.

[36] Kramer G, Mitteregger D, Marberger M. Is benign prostatic hyperplasia (BPH) an immune inflammatory disease? European Urology. 2007; 51: 1202–1216.

[37] Hoover P, Naz RK. Do men with prostate abnormalities (prostatitis/benign prostatic hyperplasia/prostate cancer) develop immunity to spermatozoa or seminal plasma? International Journal of Andrology. 2012; 35: 608–615.

[38] Naz RK, Butler TS. Antibodies to prostate-specific antigen in immunoinfertile women and men. Journal of Reproductive Immunology. 2013; 97: 217–222.

[39] Lotti F, Baldi E, Corona G, Lombardo F, Maseroli E, Degl'Innocenti S, *et al*. Epididymal more than testicular abnormalities are associated with the occurrence of antisperm antibodies as evaluated by the MAR test. Human Reproduction. 2018; 33: 1417–1429.

[40] Punab M, Poolamets O, Paju P, Vihljajev V, Pomm K, Ladva R, *et al*. Causes of male infertility: a 9-year prospective monocentre study on 1737 patients with reduced total sperm counts. Human Reproduction. 2017; 32: 18–31.

[41] Hussein TM, Elneily D, Eid AA, Abou-ElKhier H. Assessment of antisperm antibodies in a sample of Egyptian patients with hepatitis C virus infection. Andrologia. 2017; 49: e12664.

[42] Garolla A, De Toni L, Bottacin A, Valente U, De Rocco Ponce M, Di Nisio A, *et al*. Human papillomavirus prophylactic vaccination improves reproductive outcome in infertile patients with HPV semen infection: a retrospective study. Scientific Reports. 2018; 8: 912.

[43] Luttmer R, Dijkstra MG, Snijders PJ, Hompes PG, Pronk DT, Hubeek I, *et al*. Presence of human papillomavirus in semen in relation to semen quality. Human Reproduction. 2016; 31: 280–286.

[44] Napolitano L, Barone B, Crocetto F, Capece M, La Rocca R. The COVID-19 pandemic: is it a wolf consuming fertility? International Journal of Fertility & Sterility. 2020; 14: 159–160.

[45] Silva AF, Ramalho-Santos J, Amaral S. The impact of antisperm antibodies on human male reproductive function: an update. Reproduction. 2021; 162: R55–R71.

[46] Rojas M, Restrepo-Jiménez P, Monsalve DM, Pacheco Y, Acosta-Ampudia Y, Ramírez-Santana C, *et al*. Molecular mimicry and autoimmunity. Journal of Autoimmunity. 2018; 95: 100–123.

[47] Vatti A, Monsalve DM, Pacheco Y, Chang C, Anaya JM, Gershwin ME. Original antigenic sin: a comprehensive review. Journal of Autoimmunity. 2017; 83: 12–21.

[48] Eggert-Kruse W, Batschulat K, Demirakca T, Strowitzki T. Male immunity to the chlamydial 60 kDa heat shock protein (HSP 60)-associated with semen quality? Andrologia. 2015; 47: 66–76.

[49] Prabha V, Chaudhary N, Kaur S. Molecular mimicry between spermatozoa and bacteria. Journal of Urology. 2011; 186: 2442–2447.

[50] Weng SL, Chiu CM, Lin FM, Huang WC, Liang C, Yang T, *et al*. Bacterial communities in semen from men of infertile couples: metagenomic sequencing reveals relationships of seminal microbiota to semen quality. PLOS ONE. 2014; 9: e110152.

[51] Farsimadan M, Motamedifar M. Bacterial infection of the male reproductive system causing infertility. Journal of Reproductive Immunology. 2020; 142: 103183.

[52] Rose BI, Scott B. Sperm motility, morphology, hyperactivation, and ionophore-induced acrosome reactions after overnight incubation with mycoplasmas. Fertility and Sterility. 1994; 61: 341–348.

[53] Díaz-García FJ, Herrera-Mendoza AP, Giono-Cerezo S, Guerra-Infante FM. Mycoplasma hominis attaches to and locates intracellularly in human spermatozoa. Human Reproduction. 2006; 21: 1591–1598.

[54] Taylor-Robinson D, Manchee RJ. Spermadsorption and spermagglutination by mycoplasmas. Nature. 1967; 215: 484–487.

[55] Svenstrup HF, Fedder J, Abraham-Peskir J, Birkelund S, Christiansen G. Mycoplasma genitalium attaches to human spermatozoa. Human Reproduction. 2003; 18: 2103–2109.

[56] Arya D, Balasinor N, Singh D. Varicocoele-associated male infertility: cellular and molecular perspectives of pathophysiology. Andrology. 2022; 10: 1463–1483.

[57] Veräjänkorva E, Laato M, Pöllänen P. Analysis of 508 infertile male patients in south-western Finland in 1980–2000: hormonal status and factors predisposing to immunological infertility. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2003; 111: 173–178.

[58] Bozhedomov VA, Lipatova NA, Rokhlikov IM, Alexeev RA, Ushakova IV, Sukhikh GT. Male fertility and varicocoele: role of immune factors. Andrology. 2014; 2: 51–58.

[59] Falcone M, Bocu K, Keskin H, Solorzano Vazquez JF, Banthia R, Mahendran T, *et al*. Anti-sperm antibody positivity in men with varicocele: a systematic review and meta-analysis. World Journal of Men's Health. 2025; 43: 60–69.

[60] Zen M, Gatto M, Domeneghetti M, Palma L, Borella E, Iaccarino L, *et al*. Clinical guidelines and definitions of autoinflammatory diseases: contrasts and comparisons with autoimmunity—a comprehensive review. Clinical Reviews in Allergy & Immunology. 2013; 45: 227–235.

[61] Shiraishi Y, Shibahara H, Koriyama J, Hirano Y, Okazaki H, Minota S, *et al*. Incidence of antisperm antibodies in males with systemic autoimmune diseases. American Journal of Reproductive Immunology. 2009; 61: 183–189.

[62] Rabelo-Júnior CN, Freire de Carvalho J, Lopes Gallinaro A, Bonfá E, Cocuzza M, Saito O, *et al*. Primary antiphospholipid syndrome: morphofunctional penile abnormalities with normal sperm analysis. Lupus. 2012; 21: 251–256.

[63] Nukumizu LA, Gonçalves Saad C, Ostensen M, Almeida BP, Cocuzza M, Gonçalves C, *et al*. Gonadal function in male patients with ankylosing spondylitis. Scandinavian Journal of Rheumatology. 2012; 41: 476–481.

[64] Massarotti C, Sbragia E, Gazzo I, Stigliani S, Inglese M, Anserini P. Effect of multiple sclerosis and its treatments on male fertility: cues for future research. Journal of Clinical Medicine. 2021; 10: 5401.

[65] Fode M, Krogh-Jespersen S, Brackett NL, Ohl DA, Lynne CM, Sønksen J. Male sexual dysfunction and infertility associated with neurological disorders. Asian Journal of Andrology. 2012; 14: 61–68.

[66] Li B, Zhang L, Li Q, Zhang J, Wang W, Quan J. Multiple sclerosis and abnormal spermatozoa: a bidirectional two-sample mendelian randomization study. PLOS ONE. 2024; 19: e0308815.

[67] Marconi M, Weidner W. Site and risk factors of antisperm antibodies production in the male population. In Krause W, Naz R (eds.) Immune Infertility (pp. 133–147). 2nd edn. Springer: Cham. 2017.

[68] Lee R, Goldstein M, Ullery BW, Ehrlich J, Soares M, Razzano RA, *et al*. Value of serum antisperm antibodies in diagnosing obstructive azoospermia. Journal of Urology. 2009; 181: 264–269.

[69] Azizi G, Namaki S, Mirshafiey A, Hamid KM. HLA antigens and antisperm antibody production in Iranian vasectomized men. Journal of Biomedical Research. 2015; 29: 87–90.

[70] Fillion M, Deal CL, Van Vliet G. Normal minipuberty of infancy in boys with Prader-Willi syndrome. The Journal of Pediatrics. 2006; 149: 874–876.

[71] Napolitano L, Barone B, Morra S, Celentano G, La Rocca R, Capece M, *et al*. Hypogonadism in patients with Prader Willi syndrome: a narrative review. International Journal of Molecular Sciences. 2021; 22: 1993.

[72] Chung E, Brock GB. Cryptorchidism and its impact on male fertility: a state of art review of current literature. Canadian Urological Association Journal. 2011; 5: 210–214.

[73] Jiang H, Zhu WJ. Cryptorchidism is not a risk factor for antisperm antibody production in post-orchidopexy males with infertility. Urologia Internationalis. 2013; 90: 470–474.

[74] Niepiekło-Miniewska W, Kuśnierczyk P, Havrylyuk A, Kamieniczna M, Nakonechnyy A, Chopyak V, *et al*. Killer cell immunoglobulin-like receptor gene association with cryptorchidism. Reproductive Biology. 2015; 15: 217–222.

[75] Cameron JL. Advances in Surgery. 1st edn. Elsevier: New York. 2015.

[76] Srsen D, Druzijanić N, Pogorelić Z, Perko Z, Juricić J, Kraljević D, *et al*. Quality of life analysis after open and laparoscopic inguinal hernia repair–retrospective study. Hepatogastroenterology. 2008; 55: 2112–2115.

[77] Stula I, Družijanić N, Sršen D, Capkun V, Perko Z, Sapunar A, *et al*. Influence of inguinal hernia mesh repair on testicular flow and sperm autoimmunity. Hernia. 2012; 16: 417–424.

[78] Negri L, Romano M, Cirillo F, Grilli L, Morenghi E, Romualdi D, *et al*. Influence of inguinal hernia repair on sperm autoimmunity: the largest

single center experience. Andrology. 2022; 10: 105–110.
[79] Heidenreich A, Bonfig R, Wilbert DM, Strohmaier WL, Engelmann UH. Risk factors for antisperm antibodies in infertile men. American Journal of Reproductive Immunology. 1994; 31: 69–76.
[80] Verón GL, Molina RI, Tissera AD, Estofan GM, Marín-Briggiler CI, Vazquez-Levin MH. Incidence of sperm surface autoantibodies and relationship with routine semen parameters and sperm kinematics. American Journal of Reproductive Immunology. 2016; 76: 59–69.
[81] World Health Organization. WHO laboratory manual for the examination and processing of human semen. 5th edn. WHO Press: Geneva, Switzerland. 2010.
[82] Rajah SV, Parslow JM, Howell RJ, Hendry WF. Comparison of mixed antiglobulin reaction and direct immunobead test for detection of sperm-bound antibodies in subfertile males. Fertility and Sterility. 1992; 57: 1300–1303.
[83] Francavilla F, Santucci R, Barbonetti A, Francavilla S. Naturally-occurring antisperm antibodies in men: interference with fertility and clinical implications. An update. Frontiers in Bioscience. 2007; 12: 2890–2911.
[84] El-Sherbiny AF, Ali TA, Hassan EA, Mehaney AB, Elshemy HA. The prognostic value of seminal anti-sperm antibodies screening in men prepared for ICSI: a call to change the current antibody-directed viewpoint of sperm autoimmunity testing. Therapeutic Advances in Urology. 2021; 13: 1756287220981488.
[85] Bohring C, Klepper L, Krause W. Localization of binding sites of naturally occurring antisperm antibodies on human spermatozoa by immunofluorescence. Andrologia. 2004; 36: 286–290.
[86] Hjort T. Antisperm antibodies. Antisperm antibodies and infertility: an unsolvable question? Human Reproduction. 1999; 14: 2423–2426.
[87] Nikolaeva MA, Kulakov VI, Korotkova IV, Golubeva EL, Kuyavskaya DV, Sukhikh GT. Antisperm antibodies detection by flow cytometry is affected by aggregation of antigen–antibody complexes on the surface of spermatozoa. Human Reproduction. 2000; 15: 2545–2553.
[88] van Eekelen R, van Geloven N, van Wely M, Bhattacharya S, van der Veen F, Eijkemans MJ, *et al*. IVF for unexplained subfertility; whom should we treat? Human Reproduction. 2019; 34: 1249–1259.
[89] Lombardo F, Gandini L, Lenzi A, Dondero F. Antisperm immunity in assisted reproduction. Journal of Reproductive Immunology. 2004; 62: 101–109.
[90] Cline AM, Kutteh WH. Is there a role of autoimmunity in implantation failure after *in-vitro* fertilization? Current Opinion in Obstetrics & Gynecology. 2009; 21: 291–295.
[91] Adeghe AJ. Effect of washing on sperm surface autoantibodies. British Journal of Urology. 1987; 60: 360–363.
[92] Francavilla F, Sciarretta F, Sorgentone S, Necozione S, Santucci R, Barbonetti A, *et al*. Intrauterine insemination with or without mild ovarian stimulation in couples with male subfertility due to oligo/astheno- and/or teratozoospermia or antisperm antibodies: a prospective cross-over trial. Fertility and Sterility. 2009; 92: 1009–1011.
[93] Barbonetti A, Castellini C, D'Andrea S, Minaldi E, Totaro M, Francavilla S, *et al*. Relationship between natural and intrauterine insemination-assisted live births and the degree of sperm autoimmunisation. Human Reproduction. 2020; 35: 1288–1295.
[94] Ombelet W, Vandeput H, Janssen M, Cox A, Vossen C, Pollet H, *et al*. Treatment of male infertility due to sperm surface antibodies: IUI or IVF? Human Reproduction. 1997; 12: 1165–1170.
[95] Lu SM, Li X, Wang SL, Yang XL, Xu YZ, Huang LL, *et al*. Success rates of *in vitro* fertilization versus intracytoplasmic sperm injection in men with serum anti-sperm antibodies: a consecutive cohort study. Asian Journal of Andrology. 2019; 21: 473–477.
[96] Clarke GN. Association between sperm autoantibodies and enhanced embryo implantation rates during *in vitro* fertilization. Fertility and Sterility. 2006; 86: 753–754.
[97] Vujisić S, Lepej SZ, Jerković L, Emedi I, Sokolić B. Antisperm antibodies in semen, sera and follicular fluids of infertile patients: relation to reproductive outcome after *in vitro* fertilization. American Journal of Reproductive Immunology. 2005; 54: 13–20.
[98] Zini A, Lefebvre J, Kornitzer G, Bissonnette F, Kadoch IJ, Dean N, *et al*. Anti-sperm antibody levels are not related to fertilization or pregnancy rates after IVF or IVF/ICSI. Journal of Reproductive Immunology. 2011; 88: 80–84.
[99] Esteves SC, Schneider DT, Verza S III. Influence of antisperm antibodies in the semen on intracytoplasmic sperm injection outcome. International Brazilian Journal of Urology. 2007; 33: 795–802.
[100] Mercan R, Oehninger S, Muasher SJ, Toner JP, Mayer J III, Lanzendorf SE. Impact of fertilization history and semen parameters on ICSI outcome. Journal of Assisted Reproduction and Genetics. 1998; 15: 39–45.
[101] Nagy ZP, Verheyen G, Liu J, Joris H, Janssenswillen C, Wisanto A, *et al*. Andrology: results of 55 intracytoplasmic sperm injection cycles in the treatment of male-immunological infertility. Human Reproduction. 1995; 10: 1775–1780.
[102] Saragüeta P, Lanuza G, Miranda PV, Tezón JG, Barañao JL. Immunoglobulins from human follicular fluid induce the acrosome reaction in human sperm. Molecular Reproduction and Development. 1994; 39: 280–288.
[103] Zini A, Fahmy N, Belzile E, Ciampi A, Al-Hathal N, Kotb A. Antisperm antibodies are not associated with pregnancy rates after IVF and ICSI: systematic review and meta-analysis. Human Reproduction. 2011; 26: 1288–1295.
[104] Karim MY, Pisoni CN, Khamashta MA. Update on immunotherapy for systemic lupus erythematosus—what's hot and what's not! Rheumatology. 2009; 48: 332–341.
[105] Zaki AA, Aldahmashi FS, Madboli AEA, Attia KA, Almulhim FS, Albarrak SM. Therapeutic approaches for anti-sperm-antibodies in the testicular sperm aspiration rat model. Veterinary World. 2023; 16: 296–308.
[106] Taiyeb AM, Ridha-Albarzanchi MT, Taiyeb SM, Kanan ZA, Alatrakchi SK, Kjelland ME, *et al*. Improvement in pregnancy outcomes in couples with immunologically male infertility undergoing prednisolone treatment and conventional *in vitro* fertilization preceded by sperm penetration assay: a randomized controlled trial. Endocrine. 2017; 58: 448–457.
[107] Bals-Pratsch M, Dören M, Karbowski B, Schneider HP, Nieschlag E. Cyclic corticosteroid immunosuppression is unsuccessful in the treatment of sperm antibody-related male infertility: a controlled study. Human Reproduction. 1992; 7: 99–104.
[108] Curtis P, Preutthipan S, Gleeson K, Shaw RW. Effect of low-dose prednisolone on sperm fertilizing capacity in subfertile men with circulating antisperm antibodies. Archives of Andrology. 1994; 33: 111–118.
[109] Li TS. Sperm immunology, infertility, and fertility control. Obstetrics & Gynecology. 1974; 44: 607–623.
[110] Menge AC, Christman GM, Ohl DA, Naz RK. Fertilization antigen-1 removes antisperm autoantibodies from spermatozoa of infertile men and results in increased rates of acrosome reaction. Fertility and Sterility. 1999; 71: 256–260.
[111] Al-Daghistani HI. Staphylococcusaureus protein a as a means of assessing sperm penetrability in cervical mucus *in vitro*. Clinical and Experimental Reproductive Medicine. 2020; 47: 186–193.
[112] Jia L, Yang L, Zou H, Zhang Y, Zhao J, Fan C, *et al*. Protein a tangential flow affinity membrane cartridge for extracorporeal immunoadsorption therapy. Biomedical Chromatography. 1999; 13: 472–477.
[113] Tiktinskiĭ OL, Koren'kov DG, Aleksandrov VP, Mikhaĭlichenko VV, Marusanov VE. Immune male infertility: correction with efferent therapy. Urologiia. 2004; 52–56. (In Russian)
[114] Fu B, Lun X, Gong Y. Effects of the combined therapy of acupuncture with herbal drugs on male immune infertility—a clinical report of 50 cases. Journal of Traditional Chinese Medicine. 2005; 25: 186–189.
[115] Sun Z, Bao Y. TCM treatment of male immune infertility—a report of 100 cases. Journal of Traditional Chinese Medicine. 2006; 26: 36–38.

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