Immune infertility in men

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Male factors are implicated as the cause of roughly half of cases of infertility, and the presence of antisperm antibodies (ASA) may be responsible for some of these. Their presence is associated with a reduction in natural conception and live birth and impacts the success of assisted reproductive technologies. Interpretation of the data regarding ASAs and fertility is complicated by a lack of standardization in testing methodology and test thresholds and a lack of data on their prevalence in the healthy fertile population. Although their pathogenesis remains elusive, and many cases are idiopathic, a disruption in the immunologic blood-testis barrier (BTB) appears to contribute to the formation of ASA. As delineation of the specific antigen targets of ASA advances, it has been recognized that they may affect almost all aspects of sperm function, and ASA against different targets likely have specific mechanisms of impairing fertility. Intracytoplasmic sperm injection (ICSI) appears to be the most reliable method by which to overcome fertility impairment due to ASA, achieving similar outcomes to ASA-negative patients with regard to fertilization rates, embryonic development, clinical pregnancy rates, and live birth rates. The lack of consistency in testing for and reporting ASA remains a substantial barrier to achieving clarity in describing their role in infertility and the optimal management approach, and future research should use a unified approach to the detection and description of ASA. Determination of the specific antigens targeted by ASA, and their function and clinical relevance, would contribute to improving the understanding of ASA-mediated impacts on fertility and tailoring treatment appropriately to achieve the best outcomes for patients. (Fertil Steril® 2022;117:1121–31. ©2022 by American Society for Reproductive Medicine.)
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Infertility affects up to 15% of couples worldwide, with up to 186 million individuals living with infertility (1, 2). Male factors are implicated in roughly half of cases of couples with infertility. In addition to standard semen analyses, extended testing is possible, one aspect of which is the detection of antisperm antibodies (ASA). Male immune infertility is defined as infertility caused by ASA (3, 4). The most recent World Health Organization (WHO) laboratory manual for the examination and processing of human semen states that "the mere presence of sperm antibodies is insufficient for a diagnosis of sperm autoimmunity. It is necessary to demonstrate that the antibodies interfere severely with sperm function" (3). Furthermore, chronic inflammatory disorders, or even their treatment, may also impact semen quality and function (5).

Sperm-agglutinating antibodies were first reported in the serum and semen of humans in 1954 (6) and were correlated with infertility by the 1970s (7). Despite extensive research in the ensuing decades, the clinical impact of ASA, the indications for and utility of their testing, and the management of immune infertility still remain controversial.

The scope of the impact of ASA alone on fertility outcomes (natural and assisted) remains to be clearly elucidated. They can be detected in up to 16% of infertile men and approximately 2% of fertile men. To complicate matters further, ASA may also be detected in the serum and reproductive tract secretions of women (8). Globally, ASA have been demonstrated at similar rates in geographically and ethnically diverse infertile and fertile populations (1, 9–14).

Systemic autoimmune diseases and their treatments may also impact male reproductive health and fertility outcomes. This has recently been examined by a number of systematic reviews, with both autoimmune diseases and immunosuppressive medications altering fertility outcomes, hormonal levels, and semen characteristics (5, 15, 16).

Systematic reviews published in 2021 and 2022 report an association between systemic autoimmune diseases in men and abnormal semen parameters, sperm deoxyribonucleic acid (DNA) fragmentation, elevated gonadotropin levels, and the presence of varicocele (5, 15). Although both reviews found evidence that autoimmune diseases are likely to impact fertility in men, the data available are sparse, with substantial heterogeneity, small sample sizes, mixed treated and

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untreated populations, and limited information to guide treatment of these patients from a fertility perspective.

Immunosuppressive medications themselves were found to have variable effects on sperm quality, endocrine function, and reproductive outcomes, although high-quality evidence is lacking and there are many treatments for which no or very few studies exist with regard to their impact on reproductive function. Sulfasalazine and cyclophosphamide were found to have a detrimental effect on sperm quality, whereas the impact of colchicine, methotrexate, and sirolimus was unclear. Treatment with some immunosuppressants, such as tumor necrosis factor α inhibitors, may improve sperm quality (5, 16). Given these contemporary and comprehensive reviews of the current literature, this review will instead focus on immune infertility caused by ASA in men.

SEARCH STRATEGY

A search of Medline, PubMed, Web of Science, and Cochrane was performed on October 27, 2021, using the Medical Subject Heading terms ("antisperm antibodies" OR "ASA" OR "sperm antibodies") AND ("infertility" OR "subfertility" OR "time to conceive" OR "sperm parameters" OR "sperm motility" OR "sperm output" OR "sperm count" OR "sperm density" OR "semen analysis" OR "seminal parameters"). The search was limited to human clinical trials and observational studies of men published in the English language from 2000 onwards.

IMMUNOGLOBULIN SUBTYPES

Antisperm antibodies are detectable in men and women in serum, seminal fluid (either free or sperm-bound), and female reproductive tract secretions. Immunoglobulin G (IgG) predominates in serum, whereas IgA predominates in mucosal surfaces and secretions such as seminal plasma and cervical mucus. Both may be found bound to sperm surface antigens. Some have suggested that IgA may be more clinically relevant to fertility outcomes than IgG, although there is high (>95%) correlation between the 2, and many studies have tested only for IgG (3, 17).

TESTING FOR ASA

Antisperm antibodies may be detected by various methods with different targets, reference ranges, and possibly clinical implications. Much of the difficulty in interpreting and comparing the available data stems from the variation in detection techniques, which may test for seminal, serum, or reproductive tract antibodies. Clinically relevant reference ranges have not been universally accepted, and studies use varying thresholds. World Health Organisation-recommended thresholds have also changed over the years, as outlined below (3). Although ASA are detectable in cervical mucus and were formerly evaluated by the postcoital test, the most recent United Kingdom National Institute for Health and Care Excellence guidelines on infertility state that "the routine use of postcoital testing of cervical mucus in the investigation of fertility problems is not recommended because it has no predictive value on pregnancy rate" (18), citing data from a 1995 systematic review (19).

The recently released WHO guidelines (2021) suggest testing for seminal ASA in the extended sperm examination when sperm agglutination is present (3). A recent study suggested that ASA testing should be considered not just when sperm agglutination is present (37.5% positive compared with 2.6% in the absence of agglutination), but also with a history of testicular trauma or inguinal surgery (18.4% positive compared with 2.2% in the absence of such risk factors (20).

Recommended tests are either direct (detecting sperm-bound antibodies) or indirect (detecting free antibodies.) A positive test is not in itself sufficient to confirm a diagnosis of immune infertility, and demonstration of impaired sperm function is necessary (3).

Direct Tests

Direct tests include the mixed antiglobulin reaction (MAR) test and the direct immunobead binding test (IBT). Both tests use anti-Ig–coated particles to detect antibody-coated sperm. The MAR test is performed on unwashed spermatozoa, and the direct IBT is performed on washed spermatozoa. Binding of motile spermatozoa with the coated particles is a positive test. It is recommended that binding exclusively at the tail tip not be counted, as it is not associated with infertility (3, 21). There is not an agreed proportion of bound spermatozoa that constitutes a clinically relevant result, and the recent sixth edition of the WHO guidelines suggests that each laboratory should define its own reference range by testing healthy, fertile men (3). In contrast, the fourth and fifth editions recommended binding of $\geq$50% of spermatozoa as the criterion for a positive test.

Direct tests require motile spermatozoa; in the absence of adequate motile spermatozoa, an indirect test must be used. Therefore, cytotoxic ASA that cause necrospermia or severe asthenozoospermia cannot be detected by direct tests (3).

Although a $\geq$50% threshold has been suggested, there is evidence that higher thresholds (i.e., 100%) correlate better with spermiogram abnormalities, functional sperm abnormalities, and lower live birth rates (8, 22, 23).

Indirect Tests

In the indirect IBT, washed donor spermatozoa are incubated in the body fluid of interest, and free ASA are detected within the fluid. This test can be used to detect ASA in fluids other than semen, or when there is such severe necrospermia or oligoasthenozoospermia to make direct tests impossible (3).

Antisperm antibodies also can be detected with commercially available enzyme-linked immunoassays, the sperm immobilization test, and protein microarray chips; however, currently these are not widely used in clinical practice (24–27).

PREVALENCE OF ASA

Antisperm antibodies prevalence is dependent on test type, test threshold, and the population studied. Recent studies

using the MAR test with the previously WHO-recommended threshold of 50% report a prevalence of 2.6%–6.6% in infertile men and 0.9% in fertile men. Meta-analyses including older studies with lower thresholds have reported rates of 5%–16% in infertile men and 1%–2% in fertile men (28, 29). Detected prevalence is generally higher with the use of microarray chips or enzyme-linked immunoassays; however, the clinical implications of these remain understudied (26, 30). Women and fertile men are underrepresented in the literature, and the true population prevalence remains unknown.

PATHOGENESIS OF ASA

Semen is highly antigenic; ASA and infertility can be induced in both men and women following immunization with semen (31). In women, sperm antigens are foreign antigens. In men, self-tolerance to sperm surface antigens does not develop during immunologic maturation, as spermatogenesis begins at puberty, when tolerance to self-antigens has already been established. Normally, the sites of spermatogenesis, semen production, and semen transport are immunoprivileged. When the anatomic and immunologic barriers are disrupted, ASA may be formed (32). This is thought to occur secondary to trauma (accidental or surgical), infection, or congenital reproductive tract anomalies; however, many cases are idiopathic.

Immunologic homeostasis within the male reproductive tract is in a complex state of balance, with immune privilege allowing tolerance of antigenic haploid cells (i.e., spermatogonia and spermatozoa), whereas innate immunity protects the testis from microbial infection (33). Although the seminiferous tubules were previously thought of as an anatomic barrier isolating them from circulating immune cells, it is increasingly evident that both anatomic and immunologic mechanisms support maintenance of self-tolerance in the testes (32). Tight junctions between Sertoli cells and between epididymal cells form the basis of the barrier, isolating the site of spermatogenesis and sperm transport. Low-permeability capillaries reduce migration of lymphocytes and antibodies into the seminiferous tubules; however, this is insufficient to provide complete immune isolation. Local immunoregulation within the testis includes a lymphocyte population typically dominated by regulatory T cells, tolerogenic dendritic cells, and the production of anti-inflammatory and tolerogenic cytokines. Sertoli cells have been shown in some studies to suppress activated T lymphocytes and degrade abnormal spermatozoa without presenting their antigens (32). Although they are incompletely understood, together these mechanisms achieve immunologic tolerance of germ cells in normal men, the disruption of which underlies the formation of ASA.

Testicular Trauma or Surgery

Although testicular injury is often thought to be associated with the development of ASA, the data are variable in their findings. Testicular biopsy in cryptorchidism (34), orchiectomy, or orchidopexy for testicular torsion (35) and surgical repair of testicular rupture (36) are not associated with ASA. These studies were performed in pediatric populations, making it possible that the absence of spermatogenesis in this population may limit the sperm antigens against which antibody responses may develop. Conversely, adults with testicular trauma in the context of a varicocele have 1.9 times greater odds of having ASA (37). In a large observational study, Lotti et al. (24) reported an association between ASA and sonographic epididymal, but not testicular, abnormalities, suggesting that chronic epididymal inflammation may be more associated with ASA than testicular injury. There is no evidence that conventional testicular sperm extraction or microdissection testicular sperm extraction results in new ASA formation in men or their female partners up to 12 months postoperatively (38, 39).

Inguinal Hernia or Hernia Repair

Andrologic surgery and inguinal hernia repair have been associated with the development of ASA due to the potential disruption of the BTB, alterations in testicular blood flow, damage to or obstruction of the vas deferens, and the local inflammatory response. A retrospective cohort study of 2,258 infertile male patients found higher rates of seminal ASA among men who had a history of andrologic surgery or groin herniorrhaphy (3.48 and 2.45 times more prevalent than in the unselected infertile population, respectively) (40).

The method of hernia repair may be relevant. Open mesh hernioplasty is associated with a greater increase in serum ASA titers than laparoscopic or preperitoneal repairs; however, all procedures are associated with an improvement in semen parameters. The clinical significance of the increase in titers is unclear, since the absolute differences were small, and except for one patient, all titers remained within the normal range of $\leq$60 U/mL (41–44). These results suggest that although a history of inguinal hernia or hernia repair should be a trigger for evaluation for ASA in men presenting with infertility, the surgery itself is unlikely to stimulate a significant autoimmune response, as measured by serum ASA.

Varicocele

The presence of a varicocele is associated with infertility and abnormal semen parameters. The mechanism by which varicocele affects fertility is debated; theories include scrotal hyperthermia, circulatory dysfunction, or the formation of ASA (45). However, a large observational study found no correlation between seminal or serum ASA prevalence and the presence of varicocele (37). It was reported that the coexistence of varicocele and ASA may contribute to infertility in such patients. Among patients with varicocele, ASA-positive patients are more likely than ASA-negative patients to have abnormal semen analyses, abnormal sperm morphology and motility, increased premature acrosome reactions, reduced inducible acrosome reactions, and an increase in sperm DNA fragmentation (37).

Microsurgical treatment of varicocele is associated with improvement in seminal parameters in both ASA-positive and ASA-negative patients. Although they are equally likely to be improved compared with preoperatively, ASA-positive patients have poorer semen analyses than their ASA-

negative counterparts postoperatively, as well as lower spontaneous pregnancy rates in the subsequent 12 months (45–48). These results suggest that seminal ASA are predictive of poor sperm motility, but do not predict improvement in seminal parameters following varicocelectomy, and should not preclude surgical management of varicocele in the infertile patient. Contrary to these studies using a microsurgical approach, an increase in ASA has been reported following open varicocelectomy, suggesting that the surgical approach may affect immune fertility outcomes following varicocelectomy (49).

Cryptorchidism

Cryptorchidism is associated with infertility and azoospermia (50), although a clear association with ASA has not been demonstrated, suggesting that infertility associated with cryptorchidism is not immunologically mediated (51, 52). A number of older studies found an association between cryptorchidism and serum ASA compared with healthy controls, although whether this represents a true difference or a difference in detection techniques is unclear (53–56).

Obstructive Azoospermia

Lee et al. (57) used serum ASA quantification by indirect IBT to predict spermatogenesis in men with azoospermia on the basis that the development of ASA is dependent on spermatogenesis. Detectable IgG had a sensitivity of 85% and specificity of 97% for predicting obstructive azoospermia in men with azoospermic infertility (57).

Other Testicular Causes

Domagala et al. (58) reported detectable antibodies against mature spermatozoa in prepubertal boys with testicular failure, although there was substantial variation in the results from different methods (Western blotting and indirect IBT). It is possible that antibodies in this population may form against testicular or sperm antigens in the prepubertal gonads, although in the absence of longitudinal studies the impact on fertility remains uncertain (54). Testicular microlithiasis was not found to be associated with detectable ASA by IBT in 22 infertile men incidentally diagnosed with testicular microlithiasis (59).

Infection

Reproductive tract infections have been proposed as a cause of ASA due to disruption of the BTB and local inflammation, as well as epitope cross-reactivity with spermatozoa.

Chlamydia trachomatis infection was not associated with ASA in a retrospective study of 7,154 infertile men with a *C. trachomatis* prevalence of 5.8% (60). Similarly, a prospective study did not demonstrate an association between ASA and antibodies to chlamydial heat shock protein 60, one of the proposed candidates for sperm-bacteria cross-reactivity (61). A significant correlation has been reported between the presence of antichlamydial and ASA among patients with genital chlamydial infections, but not ocular infections, suggesting that ASA production in these patients is not due to antigenic cross-reactivity, but may instead be due to genital tract injury or inflammation and the associated disruption of the BTB (62).

Antigenic cross-reactivity between sperm and bacterial carbohydrate antigens has been reported and proposed as a cause of ASA formation following infection (63). Men with ulcerative colitis have higher rates of ASA than healthy controls, which may result from increased intestinal permeability and generation of antibodies against intestinal flora that cross-react with sperm antigens (64, 65).

A cross-reactive antigen between *Ureaplasma urealyticum* and human sperm is able to prevent mouse sperm-egg binding and fusion in vitro and induce infertility in female mice following inoculation, suggesting a possible cause for the epidemiologic link between reproductive tract *U. urealyticum* infection and subfertility (66). Furthermore, cross-reactive antibodies against sperm and *Streptococcus agalactiae*, *Staphylococcus aureus,* and *Enterococcus faecalis* have been detected in men with bacteriospermia, leukocytospermia, and ASA (67) and in men with *Gardnerella vaginalis* in the seminal microbiome (68).

There does not appear to be an association between ASA and benign prostatic hyperplasia or prostate cancer, or chronic prostatitis, epididymitis, or urethritis (69–71).

Human papillomavirus (HPV) infection has been associated with impaired sperm motility and the presence of seminal ASA in most of the published studies (72–74) and may be ameliorated by HPV vaccination (75), whereas others have found no association (76). The conflicting results may be due to failure to separate patients with HPV infection of the sperm from those with HPV present in other seminal components (77, 78), with the former correlated with higher ASA rates and reduced sperm motility (73).

An association has been observed between hepatitis C infection and ASA (79), whereas adeno-associated virus does not appear to be associated with abnormalities in semen analyses or the presence of seminal ASA (80).

There are theoretical concerns that coronavirus disease 2019 infection may impair reproductive function through viral binding to the angiotensin-converting enzyme 2 receptor, which is expressed in the testis. Viral infection of Sertoli cells may interrupt the BTB and result in formation of ASA, and future studies on the impact of coronavirus disease 2019 infection on fertility and ASA formation should be undertaken (81).

Inflammatory and Autoimmune Diseases

An increased incidence of ASA has been reported in men with some systemic autoimmune diseases, with rates up to 41% in those with systemic lupus erythematosus; however, the broad health impacts of these diseases are also likely to play a role in the associated infertility (82–85). Conversely, ankylosing spondylitis, juvenile dermatomyositis, and antiphospholipid syndrome do not appear to be associated with ASA (86–88).

Some men may be genetically predisposed to ASA formation, with associations documented between polymorphisms in either the programmed cell death-1 gene or HLA-DRB1

and ASA levels. These genes are also associated with autoimmune disease, and the association with ASA may be due to disruption of their role in down-regulating immune cell activation and promoting peripheral tolerance (89, 90).

Lifestyle Factors

Lifestyle is known to affect fertility. Regularly getting less than 6 hours of sleep per night is significantly associated with an increase in ASA and a reduction in sperm motility (91). In patients undergoing vasectomy reversal, increased body mass index has a significant association with the presence of ASA (92). Seminal plasma zinc levels do not appear to be associated with sperm autoimmunity (93).

Testicular Tumors

A possible link between testicular cancer and ASA was reported in early studies; however, these used detection techniques known to give higher false positive or negative results than current methods (94–96). Recent studies demonstrate no significant association between ASA and testicular cancer and no correlation between ASA and type of testicular surgery, tumor size, histologic subtype, or clinical stage (97, 98).

Sexual Practices

A small cross-sectional study found no association between sexual practices (anal or oral intercourse or vaginal intercourse during menstruation) and levels of ASA in men and women (99).

ASA TARGETS

In most individuals, detectable ASA represent polyclonal antibodies with different antigen targets. It has been shown that at least some ASA are sperm-specific, with some of these targets having been identified (100). The antigen specificity may determine the clinical implications of a given antibody, with documented roles of isolated antigens in sperm motility, agglutination, cervical mucus penetration, capacitation, zona pellucida binding, the acrosome reaction, oolemma binding. and sperm-egg fusion (101–130). This is particularly so given the detection of ASA in fertile patients, indicating that not all ASA cause infertility, with analysis of antibodies in fertile and infertile individuals revealing that specific are antibodies present only in infertile subjects. Isolation of specific ASA in a given patient may allow prediction of their biologic and clinical impact and facilitate selection of the most appropriate treatment option.

The antigenic profile of spermatozoa differs across their lifespan; membrane proteins may be of testicular, epididymal, or accessory gland origin and attach to the spermatozoa at different points in the reproductive tract. Others may be altered by functional changes in the sperm, such as fibronectin, which is only expressed after sperm capacitation, or acrosomal proteins that are exposed by the acrosome reaction (131). This may impact the pathophysiologic mechanisms by which antibodies relevant to different eras in the sperm lifespan develop and the role they have in infertility.

There is evidence that the physical site of antibody binding may affect the clinical impact, with sperm bound at the neck region or equatorial segment having a shorter migration distance in cervical mucus in vitro than those bound at the head or tail (132–134). Similarly, ASA bound to the head region can inhibit the acrosome reaction, whereas those bound to the tail or midpiece do not (109).

There may also be a protective effect of antibody-binding proteins in seminal plasma, which may play a role in inactivating ASA. This could be a possible underlying contributor to the diversity of effects that ASA positivity has on fertility outcomes (135).

Effect of ASA on Semen Parameters and Mechanisms of Infertility

Antisperm antibodies are theorized to affect fertility in different ways, and this may be evident in abnormalities on conventional semen analysis or functional deficits. The most widely reported impacts of ASA are impaired sperm motility, sperm agglutination, impaired cervical mucus penetration, impaired capacitation, alterations in the acrosome reaction, and interruption in sperm-egg interactions (136). Some studies have also reported reductions in sperm counts, reduced sperm membrane integrity, and phagocytosis of antibody-bound sperm (137–141).

Antisperm antibodies are also associated with oxidative injury, as evidenced by elevated reactive oxygen species (37, 139, 142, 143). These are known to be associated with sperm DNA fragmentation, which has been confirmed in the largest study evaluating ASA and DNA fragmentation (144), although a smaller study found no correlation (145, 146).

It has been recognized that even in men with normal conventional semen analyses, a high proportion of ASA-bound spermatozoa is associated with disorders in the acrosome reaction, sperm hyperactivation, DNA fragmentation, and reactive oxygen species generation, suggesting that even microscopically normal sperm may have impaired functional capacity (145).

Although the impact of ASA on fertility may be variable, it is known that at least some ASA are sufficient to cause infertility. Kaur et al. (147) generated antibodies to a sperm-specific receptor that resulted in sperm agglutination, impaired sperm motility, premature acrosomal reaction and apoptosis, and induced infertility in mice when administered vaginally. All of these effects were mitigated by the addition of purified receptor, demonstrating that antibody binding to the receptor was causative of the observed results (147).

Effect of ASA on Fertility

The impact of ASA on natural conception and live births has not been well evaluated, with subjects included in studies primarily drawn from an infertile population. Men with a 100% positive MAR test have a lower natural live birth rate than those with a 50%–99% positive test (4.5% vs. 30.0%), along with poorer postcoital test results (22), suggesting that the

currently suggested test threshold of ≥50% may be inadequate for identifying patients in whom ASA are sufficient to impair spontaneous conception. Similarly, a large prospective cohort study found that a MAR test ≥50% alone was not associated with a reduction in spontaneous ongoing pregnancy (148).

Patients with a 100% positive MAR test may be less likely to conceive by intrauterine insemination (IUI), suggesting that ASA may impair fertility not only by impeding progression of sperm through the cervical mucus, but also by altering other components of fertilization, such as oocyte recognition, fusion, capacitation, acrosome reaction, and zona pellucida binding (149). More recent studies have found conflicting results, which are discussed in the following section (22, 150).

There is some evidence that the presence of ASA may result in impaired embryonic development. High titers of ASA in ovarian follicular fluid have been associated with a decreased rate of good-quality embryonic development but no difference in fertilization rates with in vitro fertilization (IVF) (151, 152), whereas a 1995 study also reported poorer embryo quality following ICSI in couples with positive MAR tests (152). Conversely, more recent studies have not found a difference in embryo quality or fertility outcomes between couples with and without seminal ASA who are undergoing IVF with ICSI, suggesting there is likely to be little, if any, impact on embryo quality in this group (153–155).

TREATMENT

Intrauterine insemination can bypass the cervical mucus and is proposed as a treatment option to overcome poor cervical mucus penetration and migration by ASA-affected sperm. Barbonetti et al. (22) found a live birth rate of 36.8% using IUI in a population with 100% positive MAR test results (compared with a natural live birth rate of 4.5%), while finding no difference between IUI and natural live birth rates in couples with MAR test results that were 50%–99% positive (26.9% vs. 30.0%, respectively). This is at odds with a much earlier study by Francavilla et al. (149), reporting no successful conceptions in 110 IUIs for 19 patients with MAR test results of 100%. Interestingly, Francavilla et al. (150) published a report in 2009 of 10 patients with MAR test results ≥90% and found a live birth rate of 18% of cycles when undertaking IUI with or without mild ovarian hyperstimulation (150). Whether this reflects a change in clinical practice, a different method of ASA detection, or a genuine difference in the patient groups is unclear; however, it seems likely that IUI can overcome some of the mechanisms of ASA-mediated infertility and is a reasonable approach for selected patients.

Treatment by mixing ejaculate with chymotrypsin has been proposed as a method to improve IUI efficacy, with a study of 16 patients with 100% of sperm coated in ASA by the direct IBT randomized to chymotrypsin treatment of ejaculated sperm compared with albumin-treated sperm finding a pregnancy rate per cycle of 25% vs. 3%, respectively (156). However, a prospective nonrandomized study found that IVF with ICSI resulted in a higher pregnancy rate per cycle than chymotrypsin and IUI (44% vs. 29.4%) and is likely to be a more effective approach to treatment of these patients (157).

Intracytoplasmic sperm injection overcomes the steps at which sperm autoimmunity affects fertilization. Multiple studies have found that ASA have no influence on fertilization rates, high grade embryonic development, clinical pregnancy rates, and live birth rates when ICSI is used (30, 153, 155, 158, 159). Conversely, ASA have been associated with a reduction in success rates when IVF is used without ICSI (30), although this finding is not consistent across all studies (160, 161). However, Zini et al. (28) reported on a retrospective cohort in which ASA-positive patients were more likely to have been included in the ICSI group rather than the IVF group, raising concerns around selection bias, whereas Vujisić et al. (161) used a low threshold for ASA positivity (MAR test ≥20%). Although a 2011 meta-analysis found that IVF alone and IVF with ICSI resulted in equivalent pregnancy rates in couples with ASA, there was substantial heterogeneity in the study designs and ASA thresholds used, and the reported outcome was pregnancy rather than live birth (28). A subsequent prospective study comparing IVF and ICSI in a population with ASA found significantly higher pregnancy and live birth rates with ICSI compared with IVF without ICSI (30). Given the correlation between ASA positivity and greater success with ICSI, detection of ASA should be cause for consideration of ICSI as the first line of treatment (153).

Staphylococcus protein A binds the Fc portion of human IgG and has been used to treat autoimmune diseases. Addition of staphylococcus protein A to ASA-positive seminal fluid resulted in decreased ASA titers, increased sperm concentration, and an increase in mean migration distance using the capillary tube penetration method (133); however, the impact on fertility outcomes is unknown, and further investigation is required before this treatment is routinely used in clinical practice.

Corticosteroids have been investigated for their immunosuppressive role in the treatment of infertile men with ASA, with benefits in sperm motility and IVF (without ICSI) fertilization rates, embryo cleavage rates, and pregnancy rates reported. However, this study excluded patients with persistently elevated ASA titers, treated selected patients by ICSI, and transferred more embryos in the intervention arm, making the effect of corticosteroid treatment on ASA-related outcomes difficult to determine (162). Two studies have compared the use of traditional Chinese medicine, with or without acupuncture, to oral prednisolone and reported a significant improvement with traditional Chinese medicine compared with steroids, with reduced ASA titers, increased pregnancy rates, and reduced sperm agglutination (163, 164).

In conclusion, currently, IUI, IVF, and ICSI are all reasonable approaches to the treatment of infertility in couples with suspected immune infertility. There is a lack of proven alternative treatments to mitigate the effects of ASA on fertility, and proposed treatments, such as oral corticosteroids, carry substantial long-term risks with unclear benefits. Key to applying these appropriately is determining the appropriate test thresholds for the available investigations.

There are varied mechanisms of immune infertility caused by ASA, and the group identified by current testing likely represents a heterogeneous population. Some may have impaired cervical mucus ingression impairing natural fertilization, which can be overcome by IUI, whereas others may have impairments in sperm function or sperm-oocyte interactions, which can be treated by IVF/ICSI.

An increased understanding of the antigens targeted by ASA and their clinical relevance, along with universally agreed methods of testing and reporting, may facilitate the stratification of couples with immune infertility into groups that would predict their likelihood of a positive outcome with natural conception, IUI, IVF, or ICSI.

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