Review

Roles of Antiphospholipid Antibodies, Antithyroid Antibodies and Antisperm Antibodies in Female Reproductive Health

Boon Chin Heng^{a, b} Wenjin Huang^c Xiufang Zhong^c Ping Yin^c
Guo Qing Tong^c

^aDepartment of Biological Sciences, Faculty of Science and Technology, Sunway University, Bandar Sunway, Malaysia; ^bDepartment of Biosystems Science and Engineering, ETH Zurich, Basel, Switzerland; ^cReproductive Medicine Center, Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai, China

Key Words

Antibody · Female reproductive health · Phospholipid · Reproduction · Sperm · Thyroid

Abstract

Autoantibodies are implicated in various human diseases. In this review, the effects of three different types of autoantibodies (antiphospholipid antibody, antithyroid antibody, and anti-sperm antibody) on female reproductive health are critically examined. Antiphospholipid antibodies are being detected more frequently in women undergoing in vitro fertilization, but their presence does not appear to influence the outcome of pregnancy, miscarriage, or live birth rates. Available evidence makes it conclusive that antiphospholipid antibodies play negligible roles in recurrent miscarriage. Treatment with aspirin together with low-molecular-weight heparin appears to be effective for recurrent miscarriage. Although antithyroid antibodies are commonly found in women of reproductive age, implantation rates and miscarriage rates are unaffected when women have normal thyroid function. Women with thyroid dysfunction should be treated with L-thyroxine before conception or at early gestational stages to avoid pregnancy complications. Antisperm antibodies are uncommon but are most often associated with ovarian hypofunction. They are believed to cause fertilization failure when found at high titers in seminal plasma, or in the mucosal immune system of women. Intrauterine artificial insemination and in vitro fertilization/embryo transfer are effective treatment modalities for antisperm antibody-related infertility, although this remains a controversial topic in the field of female infertility.

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Prof. Guo Qing Tong, MD, PhD
Reproductive Medicine Center, Shuguang Hospital
Affiliated to Shanghai University of Traditional Chinese Medicine
528, Zhangheng Rd, Shanghai 201203 (China)
E-Mail tongguoqing@hotmail.com

Introduction

In recent years, much progress has been made in characterizing the etiology of infertility and identifying the various causative factors, i.e. sperm count abnormality, ovulatory problems, and obstructed fallopian tubes [1, 2]. Nevertheless, there are still many unknown and uncharacterized factors that undoubtedly play important roles in unexplained infertility and recurrent miscarriages. Autoantibodies are thought to be widely implicated in infertility [3–7]. These non-tissue-specific antibodies are highly prevalent in female infertility as well as other complicated endocrine disorders, such as endometriosis and polycystic ovary syndrome (PCOS) (table 1). Nevertheless, the correlation between autoantibodies and infertility is poorly understood at this stage. In this review, the roles of three different types of autoantibodies [antiphospholipid antibody (APA), antithyroid antibody (ATA), and anti-sperm antibody (ASA)] in the etiology of female factor infertility are critically examined.

Antiphospholipid Syndrome

Prevalence and Etiology

Antiphospholipid syndrome (APS) is increasingly being recognized as an important cause of recurrent pregnancy loss [8, 9] and preeclampsia [10]. Additionally, there is growing evidence that APS may cause infertility. This thrombophilic condition is often associated with preterm delivery, vascular thrombosis, intrauterine growth retardation, intrauterine death, and abruptio placentae [11–13]. The prevalence of APAs among women with idiopathic infertility (8%) and among women experiencing recurrent implantation failure (9%) is significantly higher than that in fertile women (1.5%) [14]. Additionally, APA levels are elevated in patients with recurrent abortions. The association of elevated titers of circulating APAs with reproductive health problems has been extensively documented since the 1990s.

The mechanism of thrombosis associated with APS is still not completely understood at this stage. APS-mediated recurrent pregnancy loss and other features of reproductive failure might arise from various autoimmune factors and inflammatory pathways involving different mechanisms [15]. Antibodies against a diverse array of phospholipids have been implicated in APS. These not only consist of antibodies against phospholipids per se, but also antibodies against phospholipid-protein complexes and phospholipid-binding proteins. Our current available knowledge of APS is inadequate to clearly implicate or pinpoint a subgroup of APAs or a particular pathophysiological mechanism as being responsible for reproductive failures. However, there is growing evidence that prevalent diagnostic tests for anticardiolipin antibodies (aCL) and lupus anticoagulant (LAC) are useful for identifying APS-associated infertility [16].

It has been demonstrated in both in vitro experimental models and animal studies that monoclonal or polyclonal autoantibodies, including antiphosphatidylserine antibody and aCL, can specifically destroy trophoblast, inhibit syncytium formation, suppress human chorionic gonadotropin production, and prevent trophoblast invasion. The antiphosphatidylserine antibody and aCL are often cross-reactive. Data from several independent laboratories document that antiphosphatidylethanolamine antibody (aPE) are significantly associated with very early (embryonic) recurrent pregnancy loss [17]. APAs have also been reported to affect implantation, placentation as well as early embryonic development. The binding of antiphosphatidylinositol antibody to β_2 -glycoprotein I may lead to a breakdown of phospholipid adhesion molecules between different elements of the trophoblast [18]. Antibodies against other phospholipids such as phosphatidylcholine and phosphatidylglycerol may also be relevant to APS-associated infertility [19]. It is necessary to ascertain that the embryo is

Table 1. Effects of autoantibodies on female reproductive health

Autoantibodies/effects	References
<i>APAs</i>	
Recurrent pregnancy loss	McIntyre [17] Iwasawa et al. [18] Backos et al. [19] Vinatier et al. [20] Malinowski et al. [21] De Carolis et al. [23] Ulcova-Gallova et al. [24]
IVF/ICSI outcome	Denis et al. [25] Eldar-Geva et al. [27] Sanmarco et al. [28] Buckingham et al. [29] Matsubayashi et al. [30] Lee et al. [31] Zou et al. [32]
<i>ATAs</i>	
Recurrent pregnancy loss	Dendrinis et al. [39] Bellver et al. [40] Chen and Hu [53] Toulis et al. [54] Poppe et al. [55]
IVF/ICSI outcome	Poppe and Velkeniers [56] Kilic et al. [57] Revelli et al. [58]
Endometriosis and PCOS	Poppe et al. [45]
<i>ASAs</i>	
IVF/ICSI outcome	Vujisic et al. [65] Esteves et al. [66] De Almeida et al. [67] Bahranejad et al. [68] Chang et al. [69] Kutteh et al. [70] Shibahara et al. [71] Naz [72] Zini et al. [74]

chromosomally normal to determine conclusively whether infertility or even pregnancy loss is associated with APS. As updated microarray-based preimplantation genetic diagnosis shows up to 30% of human cleavage embryos or blastocysts being chromosomally abnormal in human in vitro fertilization (IVF) treatment, this may confound our understanding of the association between APS and infertility, failed IVF or even pregnancy loss.

APS and Recurrent Miscarriage

It is estimated that around 60% of recurrent spontaneous abortions are unexplained. The proportion of abortions associated with APS is difficult to calculate for several reasons: the definition of recurrent abortion is variable, the assays for detecting APAs are not well standardized, and the inclusion of patients in the study group according to their antibody titer is highly subjective. Recent studies suggest an association of APS not only with recurrent abortions but also with infertility [4, 20].

In a study involving 268 women diagnosed with various causes of infertility, it was found that APAs are more prevalent in patients suffering from infertility compared to fertile women.

This strongly suggests a role of APS in the etiology of infertility. The occurrence of aCL in almost every second woman suffering from endometriosis suggests the existence of autoimmune disorders in this particular disease [21].

There may also be a correlation between ATAs and APS [22]. ATAs were found in 27% of APS patients examined. Patients with APAs alone had higher percentages of spontaneous pregnancies and live births, compared with patients positive for ATAs (alone or with APAs). Thyroid autoimmunity (TAI) is frequently present in APS patients with recurrent abortions and is often associated with either reduced fecundity or with poor pregnancy outcome. It is thus recommended that thyroid antibodies should always be evaluated in women with recurrent spontaneous abortions including those with APS [23].

In addition, endometriosis stages I–II are associated with higher serum and peritoneal fluid levels of APAs against inositol, cardiolipin, ethanolamine, and β_2 -glycoprotein I. About 40% of patients are positive for anti-zona pellucida antibodies. In general, patients with endometriosis stages I–II have more autoantibodies than those with stages III–IV, and may be immunologically more active. Such a result may have important implications for considering subsequent treatment modalities, such as IVF and embryo transfer (ET) [24].

APS and IVF

The association between APS and IVF outcome has been intensively investigated. In an early study conducted in the 1990s, it was shown that pregnancy rates were not significantly different between patients tested positive and negative for 21 different APAs. There was no correlation between pregnancy rates or outcome with any definable threshold levels of APAs. Elevated levels of APAs are not associated with any change in either pregnancy rates or pregnancy loss rates in patients attempting to conceive through IVF [25] or intracytoplasmic sperm injection (ICSI) [26].

Another independent study showed similar results. Serum samples from 173 IVF patients were tested for the presence of immunoglobulins IgG, IgM and IgA against cardiolipin, phosphatidylserine, phosphatidylethanolamine, phosphatidylinositol, phosphatidic acid, and phosphatidylglycerol. The results showed that cumulative pregnancy and live birth rates were not affected by the presence of any specific or any number of seropositive APAs. In 56 samples from patients who had had at least 2 failed IVF cycles, 54 showed absence of LAC. There was no association between multiple assisted reproduction treatment failures and APA seropositivity. No relationship was found between circulating APAs and assisted reproduction treatment outcomes. This suggests that APS does not affect the early process of implantation or maintenance of pregnancy amongst patients receiving assisted reproduction treatment [27]. aPE was reported to be the most prevalent APA in infertile women, with IgA being more common than IgG and IgM [28]. Among APAs, aPE exhibited a significantly higher prevalence compared with LAC, aCL, and anti- β_2 -glycoprotein I. Nevertheless, no significant association between the presence of APAs and IVF outcome was found [28].

Ambiguous results were reported in a study by Buckingham et al. [29], which showed that the presence of circulating APAs appears to adversely affect the IVF result. In 19.2% of 99 women undergoing IVF, at least 1 APA type was detected in their serum and/or follicular fluid. It was found that the antibody levels in follicular fluid were not higher than in serum. Women with APAs had a lower implantation rate (14%) than women without these antibodies (24.1%), but this difference was not significant ($p = 0.127$). There was also a nonsignificant reduction in the live birth rate for women with APAs. APAs do not appear to be selectively concentrated in follicular fluid and, when present, do not adversely affect the reproductive outcome of women undergoing IVF [29].

However, some studies reported contradictory results with regard to the association of APS with infertility. One study showed that follicular fluid IgG APAs appear as a risk factor

associated with IVF-ET outcomes. Blood from 44 patients with ≥ 3 IVF-ET failures were tested for the presence of immunoglobulins IgG, IgM and IgA APAs. Subsequently, 29 APA-positive and 15 APA-negative patients were subjected to additional APA detection in follicular fluid during their following IVF-ET attempt, and the presence of IgG APAs in follicular fluid was demonstrated to be significantly related to lower fertilization rates [30]. In another study conducted in Korea [31], it was reported that the presence of APAs in women undergoing IVF-ET was associated with poorer pregnancy outcome. The APA-positive and APA-negative group had abortion rates of 62.5 and 20.0%, respectively, and delivery rates of 37.5 and 80.0%, respectively [31]. There were no significant differences between the two groups in clinical characteristics such as age, infertility duration, and response to controlled ovarian hyperstimulation. In a Chinese study [32], it was found that although there were no significant differences in the rates of embryo implantation and clinical pregnancy between the APA-positive and APA-negative groups, the miscarriage rate was significantly higher while the ongoing pregnancy rate was significantly lower in the positive groups compared to the negative controls ($p < 0.05$). APAs, ATAs, human chorionic gonadotropin antibodies and endometrium antibodies may cause miscarriage in infertile women undergoing IVF and consequently reduce the rate of ongoing pregnancy [32].

APAs and Treatment

Interestingly, it was found that the prevalence of APAs in patients diagnosed with organic pelvic disease (53%) was much higher than that in patients without the pathology (14%). APA-seropositive patients received treatment with aspirin and heparin beginning on day 1 of controlled ovarian stimulation. The administration of heparin/aspirin to APA-seropositive patients significantly improved the clinical pregnancy rate (49%) compared to the untreated APA-seropositive group (16%). This suggested that all women who chose IVF should undergo APA testing prior to initiating ovarian stimulation and those with APA seropositivity should be treated with heparin/aspirin [33, 34].

Aspirin alone was found to be effective in improving IVF results in APA-positive women. It was reported that aspirin-triggered lipoxin prevents APA effects on human trophoblast migration and endothelial cell interactions [35]. Aspirin together with heparin was more effective at further improving IVF results. One study showed that APA-positive women have only a 10% live birth rate in pregnancies in which no pharmacological treatment was given. Pregnancy loss is often attributed to uteroplacental insufficiency subsequent to placental thrombosis. Treatment with low-dose aspirin improves the live birth rate amongst women with APAs to 40%, and it is further significantly improved to 70% when they are treated with aspirin together with low-dose heparin [36].

However, treatment of APA-positive IVF patients with aspirin and heparin still remains controversial. A randomized, double-blind crossover trial, involving transfer of fresh and cryopreserved embryos, gave contradictory results. It was demonstrated that heparin and aspirin did not improve pregnancy or implantation rates of APA-positive or ATA-positive patients with previous IVF implantation failure [37].

Antithyroid Antibody

Prevalence

Autoimmune thyroid disease is present in around 4% of young females. However, more young women are at risk because up to 15% are in fact thyroid antibody positive [38]. The incidence of thyroid autoantibodies in women of reproductive age with recurrent fetal loss and infertility appears to be higher compared to that in controls without previous abortions.

It was reported that the frequency of ATAs in women with recurrent spontaneous miscarriage was 37% compared to 13% for controls [39]. It was shown that the prevalence of TAI in women with implantation failure and unexplained infertility was significantly increased in comparison to those women with recurrent spontaneous abortions. There was also a trend towards a higher prevalence of TAI in the unexplained infertility and implantation failure groups compared to the controls [40].

TAI has been implicated as the most common cause of hypothyroidism in the general population, especially in women. Many studies revealed a strong association of infertility with TAI [41–48]. In infertile women suffering from PCOS, antithyroid peroxidase antibody values exceeding the upper normal threshold levels were found in significantly more clomiphene citrate-resistant patients, as compared to clomiphene citrate responders and metformin responders [49]. Thus, elevated ATA levels are associated with poor treatment response in infertile women who also suffer from PCOS [50–52].

Association with Recurrent Spontaneous Miscarriage

When infertility is due to well-defined female causes, TAI most likely underlines immunological abnormality, independently of thyroid function disorders. Many studies demonstrated that TAI is frequently present in recurrent aborters with APS and is often associated with either poor pregnancy outcome or reduced fecundity [53, 54]. In infertile women, the prevalence of TAI is significantly higher compared to that in parous age-matched women. This is particularly the case for women with endometriosis and PCOS. This suggests that thyroid antibodies should always be evaluated in women with recurrent spontaneous abortions including those with APS.

Association with Endometriosis and PCOS

In infertile women, especially those diagnosed with endometriosis and PCOS, the prevalence of TAI is significantly higher than that in parous age-matched women [45]. TAI does not interfere with normal fetal implantation, and comparable pregnancy rates have been observed after assisted reproduction treatment in women with and without TAI. However, during the first trimester, pregnant women with TAI carry a significantly increased risk of miscarriage compared to women without TAI, even when euthyroidism was present before pregnancy [55].

TAI and IVF

It has been shown that in euthyroid women undergoing assisted reproduction treatment, the pregnancy and delivery rates were not affected by the presence of thyroid peroxidase antibodies. In a case-control study [56], it was shown that the relative risk of positive thyroid peroxidase antibodies in infertility due to female cause and related to endometriosis in particular is significantly increased. In addition, thyroid dysfunction may interfere with normal ovarian function and is more prevalent in women positive for anti-thyroid peroxidase antibodies.

A prospective follow-up of a cohort of infertile women undergoing assisted reproduction showed a significantly elevated risk of miscarriage in women with positive anti-thyroid peroxidase antibodies compared to that in women without TAI after the establishment of clinical pregnancy by assisted reproduction treatment procedures [56].

Another study showed that the clinical pregnancy rate was lower in women undergoing IVF treatment who were positive for thyroid autoantibodies, as compared to women with negative thyroid autoantibodies. Although the embryo grades and endometrium volume did not differ among these two groups, the clinical pregnancy rate differs and it was conclusive that ATA levels above the cutoff point will affect the clinical pregnancy rate [57].

ATA-positive patients who did not receive any adjuvant treatment showed significantly less ovarian responsiveness to stimulation and poorer IVF results than controls. For ATA-positive patients, the group that received levothyroxine + ASA + prednisolone displayed significantly higher pregnancy and implantation rates, as well as better overall IVF results, compared to the untreated group [58].

A recent meta-analysis provided conclusive evidence that women with subclinical thyroidism should be treated with levothyroxine before or at early gestational stages to avoid further pregnancy complications [59]. Whether thyroid hormones should be given prior to or during pregnancy in euthyroid women with TAI remains controversial and needs further investigation [55].

TAI Affects Infant Health

Any disturbance in the functional state of the thyroid gland within the mother could have an adverse influence on the course of pregnancy [60]. Thyroid dysfunction is associated with adverse consequences on fetal development. In particular, hypothyroidism should be avoided during pregnancy due to the increased risk of affecting neurocognitive development in the offspring [61]. Recent studies suggest that maternal thyroid dysfunction, even when considered as mild (or subclinical), is associated with impairment of fetal brain development [44].

ASA and Infertility

Prevalence

The prevalence of ASAs in the general population ranges from 0 to 2%. The prevalence in infertile men is, however, much higher at 7–26%. Several risk factors for ASA development in men have been identified (such as testicular torsion, varicocele, cryptorchidism, vasectomy, and genital tract infection), even though there are no specific indications for ASA testing. In a retrospective study on Polish infertile couples, 4.1% of the serum samples and 3.2% of the cervical mucus samples from infertile women were tested positive for ASA, while 7% of the serum samples from infertile men were ASA positive. Moreover, 10.4% of the semen samples had spermatozoa-coated antibodies [62].

How do ASAs adversely affect fertility? It was demonstrated that antispermatozoal antibodies damage fertility by a number of different mechanisms: (a) ASAs cause spontaneous agglutination during ejaculation and prevent their progression into the female genital tract, (b) free spermatozoa, bound to antibodies, are retained at the level of the cervical secretion, (c) the antispermatozoal antibodies may mask some antigens which are important for the penetration of the spermatozoa into the ovule, and (d) spermatozoa and antibody may form complexes on uterine tissue, which triggers the secretion of histamine and induces the expulsion of the implanted embryo. It is estimated that around 5% of infertility cases are of immunological origin and associated with the presence of ASAs in men and/or women.

Serum ASAs were absent in children but appeared and increased in teenage boys (10%) and in adult men (20%) and women (30%). A lower prevalence of serum ASAs was noted for older individuals of both sexes (6–10%) [63]. Among individuals with a history of infertility, a significantly higher frequency of men positive for ASAs ($p < 0.001$ and $p < 0.05$) was found, as compared to fertile controls. The presence of IgA antibodies bound to the equatorial segment of spermatozoa was associated with impaired sperm penetration capacity in vitro. No IgG or IgM ASAs bound to the equatorial segment of spermatozoa were ever found [63].

A comprehensive online search of the English-language scientific literature published between January 1966 and December 1997 was performed on MEDLINE [64]. There is suffi-

cient evidence that ASAs impair fertility in couples with idiopathic infertility. Although there is not enough evidence to support systemic treatment for ASAs, application of a variety of assisted reproductive technologies improves outcome.

ASAs and IVF

Currently, available clinical data on the effect of ASAs on IVF/ICSI outcome is rather ambiguous, with conflicting results being reported by different studies. Vujisic et al. [65] reported that the presence of ASAs on sperm or in the serum and follicular fluid was not associated with poorer IVF outcomes in couples with good quality semen characteristic. Esteves et al. [66] demonstrated that ICSI outcomes are not influenced by ASA levels [66].

In another study, 13 infertile women with high titers of sperm-agglutinating antibodies in their serum and/or in cervical mucus underwent IVF-ET [67]. Fertilization occurred in 68% of the oocytes within serum-free medium. Eight pregnancies were obtained in 22 IVF cycles (36.4%). ASAs were also found in the follicular fluids of 5 out of 11 women with circulating ASAs. Fertilization results were independent of both the localization and the level of ASAs. From these results, it was concluded that IVF-ET is a suitable treatment modality for long-term female infertility linked to anti-sperm immunity.

Surprisingly, it was reported that ASA prevalence (43.1%) was quite high among prostitutes [68]. It was found that the ASA-positive incidence in 27 prostitutes who had never used any contraceptive method and who became infertile within 9.3 years (average) was 61.3%. Repeated exposure to multiple sperm antigens and/or microorganisms may explain the high incidence of ASAs and reproductive failure among prostitutes in these cases.

It was also shown that couples with ASAs on spermatozoa had lower fertilization rates and lower numbers of transferred embryos, with IgG being the major immunoglobulin involved [69]. Couples with ASAs in female sera showed significant reductions in the rates of fertilization, cleavage, and numbers of transferred embryos only when IgM was detected, but not IgG or IgA.

However, the presence of IgA ASAs in female sera was only associated with a decrease in the pregnancy rate, but not a reduction in the numbers of transferred embryos [69]. These findings suggest that ASAs can influence IVF results and that the specific effect is dependent upon the subtypes of ASAs.

In a study of intrauterine insemination treatment for unexplained infertility, it was found that about 15.0% (or 23/153) of all the cervical mucus samples were positive for ASAs [70]. Of the ASA-positive samples, a large fraction (9/23, 39.1%) was only positive for IgA antibodies, while 11/23 (47.8%) samples were only positive for IgG antibodies, and a small fraction (3/23, 13.0%) was positive for both IgA and IgG antibodies. Insemination resulted in pregnancy in 6/23 (26.1%) of women with cervical mucus ASAs after 1–3 cycles. Based on these results, the authors suggested that testing for cervical mucus ASAs should be performed in patients with ‘unexplained’ infertility, and that intrauterine insemination may be an effective treatment modality to achieve relatively good pregnancy rates.

In another study, 44 couples with infertility of immunological origin were investigated. Because of failed or very low fertilization rates after standard IVF in the previous treatment, ICSI had to be used in 5 out of 15 cases with ASAs (33.3%). Clinical pregnancy rate with ICSI was successfully achieved in 60% of cases with ASAs. This result indicated that immunological infertility could be treated by conventional assisted reproduction treatment procedures with very good outcomes. It was also recommended that women with ASAs should be treated with ICSI without any delay [71–73].

However, contrary results were reported in the study by Zini et al. [74], which showed that there was no significant correlation between direct ASA levels and reproductive outcomes after IVF and IVF/ICSI. In particular, there was no significant difference in clinical pregnancy

rates between ASA-positive (>50% of sperm coated with ASAs) and ASA-negative patients (42 vs. 52%, respectively, odds ratio 1.45, 95% CI 0.63–3.30, $p > 0.05$). These data indicate that ASAs in semen are not associated with reproductive outcomes (fertilization and clinical pregnancy rate) after IVF/ICSI.

Conclusion

In conclusion, APAs, ATAs and ASAs are highly prevalent in patients with recurrent miscarriages and infertility. However, the presence of these antibodies do not adversely affect assisted reproduction treatment outcome, even though there is increasing evidence of their role in recurrent miscarriages. Assisted reproduction techniques such as IVF and ICSI are effective treatment modalities for patients expressing these antibodies with unexplained infertility.

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