Lupus (2019) 0, 1–13
journals.sagepub.com/home/lup

REVIEW

Antiphospholipid syndrome and infertility

G El Hasbani[1], M Khamashta[2] and I Uthman[1]
[1]Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon; and [2]London Lupus Centre, London, UK

Antiphospholipid syndrome is a systemic autoimmune disease associated with obstetric complications along with vascular events affecting multiple organ systems in patients having positive titers of antiphospholipid antibodies. Eight to 20% of infertility cases have an unknown cause, part of which could be due to antiphospholipid syndrome. Although still debatable, many studies have addressed the relation between reproductive failure and antiphospholipid antibodies through the relation between antiphospholipid antibodies and unexplained infertility as well as the effect of antiphospholipid antibodies on the outcome of in vitro fertilization–embryo transfer. Few studies and cases have associated the presence of antiphospholipid antibodies with male infertility, describing morphofunctional penile abnormalities and testicular infarction. There are not enough data to support the routine practice of testing antiphospholipid antibodies in patients with infertility. *Lupus* (2019) **0,** 1–13.

Key words: Antiphospholipid syndrome; antiphospholipid antibodies; obstetric complications; infertility

Introduction

Anti-phospholipid syndrome (APS), a systemic autoimmune condition, is characterized by vascular thrombosis and/or pregnancy morbidity in the presence of anti-phospholipid antibodies (aPL). A patient with APS must manifest at least one of the two clinical criteria (vascular thrombosis or pregnancy morbidity) and at least one of three laboratory criteria: positive lupus anticoagulant (LA), or medium- to high-titer IgG or IgM anticardiolipin antibody (aCL), or medium- to high-titer B2 glycoprotein I (B2GPI) IgG or IgM antibody confirmed on two separate occasions, at least 12 weeks apart.[1] aPL can inhibit the function of the regulators of hemostasis such as beta-2 glycoprotein 1, protein C, and protein S by binding to phospholipids and phospholipid-binding proteins, which mediates vascular events and pregnancy complications.[2] They can also activate endothelial cells to increase the production of arachidonic acid metabolites, adhesion molecules, and cytokines. In either way, aPL can enhance the potential for thromboembolism.[3]

Infertility is defined as the failure of conceiving after 12 months of regular unprotected intercourse.[4] Eight to 20% of infertility cases are unexplained and referred to as "idiopathic infertility," which requires an etiologic assessment. Although still debatable, serum autoantibodies might contribute to idiopathic infertility. A tolerance mechanism involving a Th1 to Th2 shift allows the implantation of the embryo into the maternal endometrium favoring autoantibody production.[5] There has been a considerable interest in exploring the relationship between unexplained infertility and aPL as well as the effect of aPL on the outcome of in vitro fertilization-embryo transfer (IVF-ET).

This review is intended to discuss the available evidence on the relationship between APS and infertility in females and males.

Clinical picture and pathogenesis of APS

APS is an autoimmune condition characterized by the presence of one or more aPL combined with certain clinical features related to

Correspondence to: Imad Uthman, Division of Rheumatology, Department of Internal Medicine, American University of Beirut Medical Center, Beirut, Lebanon.
E-mail: iuthman@aub.edu.lb
Received 18 July 2019; accepted 18 November 2019

10.1177/0961203319893763

thromboembolism.[6] Thrombotic events may occur in any vascular bed, with the cerebral circulation being most commonly affected. Recurrent early miscarriage, usually before 10 weeks of gestation, is the most common obstetric manifestation of APS.

aPL can lead to a disordered placental function by several mechanisms. aPL can block the trophoblastic migration in-vitro, thereby inhibiting the formation of giant multinucleated cells that are essential for placental function before the formation of spiral arterioles.[7] In addition, aPL can inhibit certain trophoblast cell adhesion molecules such as alpha I and V integrins as well as cadherin E and vascular endothelial cadherin. Moreover, inflammatory responses have been suggested in the action of aPL that activate the complement system on the trophoblast surface.[8] Additionally, aPL has the ability to bind to placental anticoagulant proteins, facilitating coagulation in the placenta.[3,9]

The pathogenic mechanisms of infertility in APS

Although the precise pathogenic mechanisms by which aPL might influence the fertility of a couple have not yet been characterized, some studies have addressed the role of complement as well as neutrophils. It has been hypothesized by in vivo studies that aPL can interfere with oocyte development and uterine decidualization.[10] Decidual necrosis has been observed in mice models upon treatment with aPL IgG.[2] Moreover, the treatment of pregnant mice with aPL IgG facilitated the extensive deposition of complements fragments C3 and C5 at the uterine decidua.[11,12] An mRNA expression study by Francis and colleagues revealed that APS women express lower levels of decidual markers such as prolactin, tissue factor, and DAF/CD55, which is a complement regulatory protein conferring cellular protection against complement-mediated lysis.[13]

Neutrophils have been implicated in the pathways of APS infertility. Girardi and colleagues showed that aPL activate C5a, which activates numerous neutrophils leading to fetal injury and death.[12] It has been hypothesized that the presence of neutrophil extracellular traps (NETs) promotes coagulation.[14] The mechanism might involve an activation of platelets to induce the process of NETosis.[15] Maternal cell-free DNA has been marked as an isolated form of NET components, which increases in concentration during labor and immediately post-partum when the risk of thrombosis is significantly higher. The association between cell-free DNA as a form of NETs and placental dysregulation leading to infertility is still questionable.[16] Another role for NETs in mediating infertility was proposed by Zamrano and colleagues. Isolated human polymorphonuclear neutrophils from humans was incubated with fresh human sperm to trigger the generation of NETs. Sperm motility were impeded by NET formation, which might reduce the chance of successful fertilization.[17]

APS and female infertility

APS and unexplained infertility

A review of the literature yielded 16 studies that have assessed aPL positivity rates in infertile women and control populations. In total, 10 studies showed an elevation of ome or more aPL in women with unexplained infertility compared with healthy controls. Six studies showed no significant differences of measured aPL between patients with unexplained infertility and healthy controls.

APS related to unexplained infertility

The initial evidence linking aPL and infertility came from retrospective serologic studies of women with unexplained infertility. In 1989, Gleicher and colleagues performed 33 separate assays consisting of antibodies against two phospholipids, five histone, and four polynucleotide antigens, using blood samples from women with unexplained infertility as well as from patients with unexplained pregnancy loss. A greater proportion of those with unexplained infertility were positive for at least one of the 33 antibodies.[18] Another study by the same group tested multiple aPL in women with unexplained infertility and other women with endometriosis, and compared the results with women diagnosed with infertility from a known cause without a history of recurrent pregnancy loss. The group of women with unexplained infertility and endometriosis had a higher number of subjects who were positive for two or more of either aCL, antiphosphatidylserine (aPS), or antiphosphatidyinositol (aPI) than the controls.[19] Around that time, serum samples from patients with unexplained infertility and normal pregnant women were assayed for a range of autoantibodies by Taylor and colleagues. The prevalence of autoantibodies in smooth muscle, phospholipids, and nuclear antigens was elevated in women with infertility compared with normal pregnant women.[20]

Later, Roussev and colleagues determined the frequency of abnormal immunologic tests among women suffering from reproductive failure. aPL was more prevalent in women with unexplained infertility than in controls.[21] While studying the effects of immunotherapy with corticosteroids on the pregnancy rate in infertile patients with an ovulatory factor and in patients with unexplained infertility referred to superovulation with intrauterine insemination, Kim and colleagues measured the prevalence of autoantibodies in both groups of patients. The prevalence of LA and aCL was elevated significantly in patients with unexplained infertility compared with patients with ovulatory infertility.[22] Coulam and colleagues had the purpose of determining the specific aPL that must be evaluated to identify individuals at risk of implantation failure. All of the aPL tested had a significantly higher frequency among women with autoimmune implantation failure compared with controls.[23] The purpose of Cubillos and colleagues' study was to determine the incidence of autoantibodies in patients with no term pregnancies. A high incidence of autoantibodies including LA and aCL was found in patients with primary infertility.[24] Kutteh and colleagues measured the serum levels of antibodies for five different phospholipids in women with infertility before undergoing an IVF cycle and in healthy women. aPL was significantly higher in patients undergoing IVF.[25] Radojcic and colleagues assessed the presence of non-organ specific autoantibodies in fertile, infertile, and cases of unexplained infertility. Increased incidence of aCL in infertile women was observed.[26] Sera from patients who had unexplained infertility and healthy females were age matched to the study patients and assessed for aPL, which were found to be higher in infertility patients in the study of Shoenfeld and colleagues.[27] The prevalence of aPL among a large group of patients and controls were measured in the study by Sauer and colleagues. A significantly higher proportion of women with a history of unexplained infertility had more than one positive aPL compared with fertile negative control women.[28] Table 1 lists all the studies that concluded aPL are associated with unexplained infertility.

APS not related to unexplained infertility

Most of the early studies had problems of interassay variation between the patient group and the control group. Taking into consideration the critics, Hatasaka and colleagues[29] studied the seroprevalence of aPL antibodies in women with unexplained infertility. The investigators in this study were blinded. The control group constituted of women with documented fertility. A standardized assay was used. Contrary to what has been concluded in previous studies, no difference between infertile and fertile women in mean normalized aPL antibodies was observed. The sera of normal non-pregnant women along with the sera and follicular fluids of women with unexplained infertility, endometriosis, and tubal infertility were tested for the prevalence of antibodies to phospholipid and sperm antigens by Nip and colleagues. The comparison between the sera and the follicular fluid of the two groups showed the titers of specific antibodies were different.[30] Ruiz and colleagues prospectively studied women with unexplained infertility. Maternal antipaternal lymphocyte antibodies and aPL were tested. The prevalence of aPL was not different between patients and controls.[31] Because there were numerous studies at the time suggesting that aCL might serve as possible markers for the failure of reproduction, Azem and colleagues studied women with either unexplained infertility or infertility due to tubal factors. No statistically significant differences were found.[32] A case control study was performed by Martinelli and colleagues in women referred for IVF and in women who conceived naturally. aPL were not detected in any of the women.[33] Table 2 lists all the studies that concluded aPL are not associated to unexplained infertility.

APS and IVF outcome

The association of aPL-mediated infertility has been proposed as a cause of IVF outcome. Our literature review showed 33 studies that tested the relationship between titers of certain aPL in women who underwent at least one cycle of IVF. In total, 15 studies showed that aPL contribute to IVF failure, whereas 18 studies showed no association between aPL and IVF failure.

APS related to infertility

El-Roeiy and colleagues reported in 1987 that the aPL present in the serum of infertile women being treated with IVF could be transferred into follicular fluid, resulting in failed subsequent implantation.[34] A prospective study by Fisch and colleagues in 1991 assessed the possible effects of stimulating the ovaries during IVF treatment cycles on circulating levels of aPL. Sera from patients were collected at three time points along the IVF treatment cycle, and the levels of autoantibodies were compared with age- and sex-matched controls. The mean levels of aPL in sera of patients treated by IVF

Table 1 Studies linking aPL to unexplained infertility

Study	*Patient population*	*Control population*	*Results*
Gleicher et al.[19]	26 infertile patients due to an idiopathic cause	24 controls with unexplained pregnancy loss	A greater proportion of those with unexplained infertility were positive for at least one of the 33 antibodies measured.
Aoki et al.[20]	65 patients with unexplained infertility and 64 patients diagnosed with endometriosis	97 patients with infertility due to a known cause	More patients in the unexplained infertility and endometriosis group were positive for two or more of either aCL, aPS, or aPI.
Taylor et al.[21]	41 patients with unexplained infertility	351 normal pregnant women	The prevalence of autoantibodies to smooth muscle, phospholipids, and nuclear antigens was significantly elevated in women with infertility compared with normal pregnant women.
Roussev et al.[22]	108 patients: 45 with recurrent pregnancy loss; 45 with unexplained infertility including 10 who failed IVF; 10 with endometriosis; five with ovarian failure; and three with polycystic ovaries	15 normal controls	65% of women from the patient group had at least one positive test. The most frequent abnormal result among women with unexplained infertility was the presence of aPL (42%).
Kim et al.[23]	78 patients with unexplained infertility	91 infertile controls with ovulatory factors	The prevalence of autoantibodies (antinuclear antibody, lupus anticoagulant, anticardiolipin antibody, antidouble-stranded DNA antibody) was elevated significantly in patients with unexplained infertility compared with patients with ovulatory infertility (20.5% versus 3.3%).
Coulam et al.[24]	312 patients with autoimmune implantation failure	100 fertile control women	All of the aPL tested (IgG, IgM, and IgA anticardiolipin, antiphosphatidyl ethanolamine, antiphosphatidyl inositol, antiphospatidic acid, anti-phosphatidyl glycerol, antiphosphatidyl choline, and antiphosphatidyl serine) had a significantly higher frequency among women with implantation failure.
Cubillos et al.[25]	43 patients with primary infertility	35 healthy controls with proven fertility and no history of pregnancy loss or autoimmune disease	The incidence of APA and aPL was 37.2% ($p < 0.05$) and 53.5% ($p < 0.05$), respectively in the patient group. The incidence of ANA was 5.7% and 11.4% for aPL in the control population.
Kutteh et al.[26]	191 patients with a history of infertility before undergoing IVF cycle	200 normal controls	aPL were detected in 18.8% of patients undergoing IVF compared with only 5.5% in the 200 normal controls.
Radojcic et al.[27]	65 infertile women, and 42 cases of unexplained infertility	27 fertile controls	In fertile women, aCL was below the negative cut-off value (100%), whereas women with unexplained infertility were positive in 23.8%. aCL antibodies were detected in 21.5% of infertile patients, most of them with unexplained infertility (15.4%). TgAt incidence was increased in infertile (20%) and unexplained infertility group (21.4%) compared with the fertile controls (18.5%).
Shoenfeld et al.[28]	69 patients with unexplained infertility	120 healthy controls	aPL and anti-prothrombin antibodies were found to be raised in infertility patients compared with controls.
Sauer et al.[29]	1325 patients with a history of unexplained infertility	205 fertile control women	8% of women with a history of unexplained infertility had more than one positive aPL compared with 1.5% of fertile control women.

aCL: anticardiolipin antibody; APA: all anti-phospholipid antibodies; aPS: anti-phosphatidylserine; aPI: antiphosphatidyinositol; aPL: anti-phospholipid antibodies; IVF: in vitro fertilization; tgAT: antithyroglobulin.

were found to be significantly higher than the corresponding levels of the control group.[35] To investigate the role of autoimmune factors as a possible cause for implantation failure as manifested by chemical pregnancy after IVF and ET, Geva and colleagues examined patients who had one or more chemical pregnancies and no deliveries for serum levels of many autoantibodies including aCL and

Table 2 Studies showing no link between aPL and unexplained infertility

Study	*Patient population*	*Control population*	*Results*
Porter et al.[22]	48 patients with isolated tubal factor infertility and 55 patients with unexplained infertility	122 healthy, non-pregnant controls of reproductive age	For each of the seven aPL tested (aCL, aPS, phoshatidic acid (PA), p-inositol (PI), p-glycerol (PG), p-choline (PC), and pethanolamine (PE)), no differences were observed among the study groups.
Nip et al.[31]	30 patients with unexplained infertility, 20 with endometriosis, and 50 with tubal infertility	20 normal non-pregnant controls	There was no relation between presence of specific antibodies in serum or between serum and follicular fluids of patients and controls.
Ruiz et al.[32]	36 patients with unexplained infertility	124 controls with three or more recurrent spontaneous abortions	The prevalence of autoantibodies to phospholipids and nuclear components was not different.
Azem et al.[33]	63 patients with unexplained infertility	54 controls with infertility due to tubal factors	aCL was present in 36.5% of patients in contrast to 29.6% of controls, which is not significant.
Martinelli et al.[34]	234 patients referred to IVF or ICSI	234 controls who conceived naturally	The prevalence of factor V, prothrombin, and methylene-tetrahydrofolate reductase mutations was similar. aPL were not detected in any of the women.

aCL: anticardiolipin antibody; aPS: anti-phosphatidylserine; aPI: antiphosphatidyinositol; aPL: anti-phospholipid antibodies; ICSI: intracytoplasmic sperm injection; IVF: in vitro fertilization.

LA, and compared the levels of those autoantibodies to patients for whom IVF-ET treatment was successful. Unlike the study group, autoantibodies were not detected in any of the control group.[36] The purpose of another early study performed by Birkenfeld and colleagues was to investigate the possible role of autoantibodies including aCL and LA as a cause of implantation failure following IVF-ET. Three groups were studied: one group contained patients who failed to conceive following ET; another group with patients who conceived following IVF-ET or are currently pregnant; and another group with patients who were new candidates for IVF-ET. None of those who had successful IVF tested positive for autoantibodies, in contrast to the other two groups. The study suggested that peri-implantation events may be affected by autoantibodies including aPL.[37]

A few years later, Geva and colleagues measured the serum levels of aCL and LA in IVF patients with three or more previously failed cycles and in controls. aCL was significantly higher in the patient group compared with the control group. LA was absent in both groups.[38] Focusing on routine screening for circulating aPL, Balasch and colleagues concluded their results favor a possible role of aPL in failure of implantation after IVF-ET.[39] The purpose of Kaider and colleagues' study was to establish the prevalence of aPL in women who have had at least 12 embryos transferred during several IVF cycles without a successful pregnancy. The difference between IVF failure and IVF successful groups was significant.[40] In 1998, a prevalence study was performed by Stern and colleagues to investigate that autoantibodies were associated with IVF implantation failure.[41] Kaider and colleagues had a large group of patients with reproductive failure. The presence of aPL in those patients was compared with healthy women. Most women with IVF failure had at least one abnormal immunologic test. Also, a majority of patients diagnosed with unexplained infertility had at least one abnormal test. Of normal fertile controls, a minority showed at least one abnormal test result.[42] Ulcova-Gallova concluded in their study that aPL can reduce the success of spontaneous and artificial IVF-ET implantation by being directed against negatively charged phopsholipids.[43] Sanmarco and colleagues determined the percentage of infertile women with at least three unsuccessful IVF attempts who were positive for aPL, and compared it with controls. aPL prevalence was significantly higher in the patients group.[44] Blood samples from patients with three or more IVF-ET failures were tested for the presence of aPL to be followed by measurement of aPL in the follicular fluid in Matsubayashi and colleagues' study. Patients with no aPL in their blood had no aPL in their follicular fluid. Patients with aPL in their blood specifically had IgG aPL in their respective follicular fluid. The presence of IgG aPL in the follicular fluid and increased infertility length

were associated to lower fertilization rates, independently.[45] Blood samples taken from women referred for IVF were tested for the presence of aPL by Lee and colleagues. The autoantibody positive group had significantly higher abortion rate and lower delivery rate than autoantibody negative group.[46] The IVF success rate, pregnancy rate, and implantation rate were markedly lower in the aCL positive group compared with the aCL negative group in Zhong and colleagues' study.[47] Chen and colleagues performed a prospective study on a large number of women undergoing IVF. The comparison between the aPL positive and aPL negative groups yielded a lower pregnancy rate and live birth rate in the aPL positive group whenever only selected antibodies were taken into consideration.[48] Recently, Khizroeva and colleagues examined the relation between the presence of aPL and the outcomes of IVF treatment. The IVF failure group had significantly higher levels of aPL compared with IVF success group.[49] Table 3 lists all the studies that concluded aPL can be related to IVF failure.

APS not related to infertility

At the time when several studies were describing the effect of aPL on the outcome of IVF-ET, Sher and colleagues compared the prevalence of certain isotypes of six different aPL in women on whom IVF-ET had failed, and in women who had successful outcomes of IVF-ET. The prevalence of aPL in patients with organic pelvic disease was much higher than in those without reproductive tract pathology. The study group combined the data for women positive for aPS with the women positive for anti-phosphatidylethanolamine, and reported that those women had a lower live birth rate than women who were negative for either one of the antibodies. However, there was no difference in birth rates between women positive for any aPL individually.[50] At the same time, Gleicher and colleagues measured the levels of six different anti-phospholipid antibodies in infertile patients who had undergone IVF. Autoantibody and immunoglobulin abnormalities alone or in combination did not predict pregnancy success.[51] Birdsall and colleagues took a large group of women undergoing IVF treatment who had attempted fewer than three previous IVF cycles. Comparing women with previous attempts at IVF and women having their first cycle, the percentage of aPL positive women was similar.[52] Antibodies against seven different types of phospholipids were measured in serum samples collected from women undergoing IVF who were followed up for their pregnancy rate by Denis and colleagues. Pregnancy rates were equal among patients with or without aPL.[53]

To determine the prevalence of aCL in the IVF population and explain their presence and specific isotype with IVF cycle outcome, Kowalik and colleagues assessed the midfollicular sera of non-conceiving women after IVF and women who successfully underwent IVF. There was no statistically significant difference in the prevalence of antibodies between the two groups. The study group concluded that aCL do not predict the outcome of an IVF cycle, and that routine testing of IVF patients for the presence of these antibodies is of limited clinical utility.[54] In Egbase and colleagues' study, the prevalence of aPL was similar between the group of women having consecutive miscarriage after IVF or intracytoplasmic sperm injection (ICSI) and the group of fertile women with three or more miscarriages.[55] Eldar-Geva and colleagues aimed to investigate the influence of aPLs on the pregnancy and live-birth rates in patients undergoing assisted reproductive treatment. They assessed 18 different antibodies for phospholipids in women before starting IVF cycles, women who had at least failed two cycles, women who failed five or more IVF cycles, and women who became pregnant within their first two IVF cycles. There was no relationship between circulating aPL and IVF outcome.[56] Martinuzzo and colleagues evaluated aPL in women with recurrent IVF failures and compared the serum levels to controls. No significant difference was observed.[57] According to Qublan and colleagues, the percentage of LA and aCL positive women with three or more previously failed IVF-ET cycles was not statistically different from that in women who have had successful pregnancy after their first IVF-ET cycle, and from women who conceived without any reproductive assistance.[58] Buckingham and colleagues also aimed to investigate the finding that aPLs are concentrated in follicular fluid and establish if this is associated with a poorer outcome for IVF. They determined the number of women who were seropositive for at least one aPL before undergoing IVF. Women positive for aPL had a lower implantation rate, but the difference was not significant.[59] In 2008, the American Society for Reproductive Medicine published a systematic review on the presence of aPL and IVF outcome. Based on the available data at the time, the review concluded that no association exists between aPL and IVF failure.[60]

In the study by Caccavo and colleagues, aCL was measured in women undergoing IVF-ET before starting treatment on the day of oocyte retrieval, and 14 days after ET and compared with fertile

Table 3 Studies showing that aPL is related to IVF failure

Study	*Patient population*	*Control population*	*Results*
Fisch et al.[36]	35 patients who underwent at least one previous IVF attempt	36 age- and sex-matched controls	The mean levels of aPL (but not ANA) in sera of IVF-treated patients were found to be significantly higher than the corresponding values of the control group.
Geva et al.[37]	21 patients who had one or more chemical pregnancies and no deliveries	21 controls who had conceived and delivered after IVF-ET treatment	The incidence of circulating autoimmune antibodies in the study group was 33.3% (7/21) with three patients (14.2%) positive for aCL. Autoimmune antibodies were not detected in any control.
Birkenfeld et al.[38]	56 patients who failed to conceive following ET	14 patients who have conceived following IVF-ET and delivered or are carrying an uncomplicated ongoing pregnancy	18 out of 56 (32.1%) of patients tested positive for one or more of the autoimmune antibodies including LA and aCL. None of the 14 controls tested positive for any of the autoimmune antibodies.
Geva et al.[39]	50 IVF patients with three or more previously failed cycles	80 controls; 40 who had conceived and delivered following three or fewer IVF and embryo transfer cycles, and 40 who were healthy nulligravidas	The incidence of autoantibodies in the patient group was 22%, compared with 2.5% in the IVF control group ($p < 0.05$) and 7.5% in the nulligravida group ($p < 0.05$). aCL was present in 6% of the patients compared with 0% of controls. LA was absent in both groups.
Balasch et al.[40]	822 patients, notably 498 infertile women and 40 with repeated failure of embryo transfer	451 controls who had never been pregnant, or had been pregnant with no previous abortions, or had a successful IVF-ET after their first treatment	aPL positivity among women with repeated failure of IVF-ET was 10% compared with 0% in infertile women achieving a live birth with their first IVF-ET.
Kaider et al.[41]	42 patients with IVF failure	42 controls who successfully conceived after IVF	11/42 (26.2%) IVF failure patients were positive for any aPL in comparison with 2/42 (4.8%) of IVF successful controls.
Stern et al.[42]	105 patients undergoing IVF who had at least 10 embryos transferred without a successful outcome	106 fertile controls	Autoantibodies, particularly anti-β2GPI antibodies, were associated with IVF implantation failure along with recurrent spontaneous abortion.
Kaider et al.[43]	122 patients with a history of IVF-ET failure; 97 women had a history of unexplained infertility	100 healthy women	70% of women with IVF failure had at least one abnormal test; approximately 81% of patients diagnosed with unexplained infertility had at least one abnormal test. 10% of normal fertile controls showed at least one abnormal test result.
Ulcova-Gallova et al.[44]	1073 patients after one IVF, 853 women after two and more IVF cycles	391 healthy fertile women	Patients after two and more IVF cycles were associated with significantly higher serum levels of aPLs.
Matsubayashi et al.[46]	44 patients with three or more IVF-ET failures (29 aPL positive and 15 aPL negative patients)	No control group	The presence of aPL in follicular fluid was significantly related to a lower fertilization rate.
Sanmarco et al.[45]	101 infertile patients with at least three unsuccessful IVF attempts	160 healthy fertile controls	40 infertile patients were persistently positive for aPL, showing a prevalence significantly higher than in controls (39.6% versus 5%, $p < 0.0001$).
Lee et al.[47]	54 patients referred for IVF	No control group	Nine patients (16.7%) were positive and 45 (83.3%) were negative for aPL. The aPL positive group and aPL negative group had abortion rates of 62.5% and 20.0%, respectively. Delivery rates were 37.5% and 80.0%, respectively.

(continued)

Table 3 Continued

Study	*Patient population*	*Control population*	*Results*
Zhong et al.[48]	76 infertile patients diagnosed as having pure tubal factor infertility undergoing IVF-ET	No control group	The IVF rate, pregnancy rate, and implantation rate in the aCL positive group were markedly lower than those in the aCL negative group (75.5% versus 78.9%, 31.3% versus 48.6% and 16.1% versus 28.1%, respectively).
Chen et al.[49]	193 patients undergoing IVF who were positive for any aPL	844 controls undergoing IVF who were negative for any aPL	The clinical pregnancy rate was significantly lower in the anti β2GPI antibody group than in the negative group. The live birth rates were significantly lower in the aCL and anti β2GPI antibody group than in the negative group. The miscarriage rates were markedly higher in the aCL and anti β2GPI antibody group than those in the negative group.
Khizroeva et al.[50]	178 infertile patients with IVF failure	89 controls with pregnancy after the IVF program	A high frequency of aPL in the group of women with IVF failures was illustrated. 42.1% IVF failures had elevated aPL levels. Among IVF success women, the rate of aPL was 19.1%.

aCL: anticardiolipin antibody; APA: all anti-phospholipid antibodies; aPL: anti-phospholipid antibodies; IVF-ET: in vitro fertilization-embryo transfer; LA: lupus anticoagulant.

controls. No relationship was found between aCL and pregnancy outcome.[61] In the study by Steinvil and colleagues, LA positive women had significantly higher live birth rates in comparison with women who tested negative.[62] In 2014, the participants in the congress of the Task Force on obstetric Antiphospholipid Syndrome agreed there are not enough data to support the inclusion of "infertility" as criteria for APS. They rejected the routine practice of investigating aPL in patients with infertility. Also, they concluded there are no well-designed studies to show that patients with infertility and positive aPL require treatment.[63]

Ying and colleagues studied infertile women positive for aCL and those who were negative for aCL. The overall IVF results in the aCL positive group were comparable with patients negative for aCL.[64] The presence of LA and aCL did not affect the pregnancy rate nor did it increase the risk for IVF cycle failure or ovarian hyperstimulation syndrome in a Jamaican retrospective study performed by DaCosta and colleagues.[65] The relationship between implantation failure and aPL was assessed by Paulmyer-Lacroix and colleagues through the measurement of different phospholipids in women presenting with at least two implantation failures after IVF. No significant difference existed between the total number of IVF attempts including those that succeeded between aPL positive and negative IVF patients.[66] Similarly, Orquevaux and colleagues assessed aPL in women undergoing IVF and associated the presence of aPL to IVF outcome. Pregnancy rate in both groups was similar.[67] To investigate the prevalence of aPL among women undergoing their first IVF treatment and evaluate the influence of aPL on the subsequent IVF outcomes, Hong and colleagues measured the plasma concentration of different aPL before starting the cycle. The clinical pregnancy rate, ongoing pregnancy rate, and miscarriage rate were all similar between the aPL positive and aPL negative group.[68] Di Nisio and colleagues showed no statistically significant associations between thrombophilic defects and IVF outcomes in women undergoing IVF after following-up prospectively seropositive and seronegative women undergoing IVF.[69] Table 4 lists all the studies that concluded aPL have no relation to IVF outcome.

aPL and male infertility

Male infertility can have several causes such as abnormal sperm function, blockages that prevent the delivery of sperm, or varicocele.[5] About 8% to 18% of APS patients are males, and most organ systems in the human body, including

Table 4 Studies showing no effect of aPL on IVF outcome

Study	*Patient population*	*Control population*	*Results*
Sher et al.[51]	429 patients with organic pelvic disease undergoing IVF	64 infertile patients with isolated male factor	53% of patients with organic pelvic disease had aPL, which was much higher than in those without a pathology (14%). aPL positive patients had a lower live birth rate although no difference in birth rates existed between women positive for any aPL antibody individually compared with women who tested negative.
Gleicher et al.[52]	105 infertile patients who had undergone IVF	Not applicable	The patients had low autoantibody and total immunoglobulin levels, which did not explain the low clinical pregnancy rates.
Birdsall et al.[53]	240 patients who had attempted fewer than three previous IVF cycles	No control group	aCL and aPS were present in 36 out of 240 (15%) patients but were not associated with a failed IVF cycle or miscarriage. aPL were not significantly higher in women with previous attempts at IVF compared with women having their first cycle.
Denis et al.[54]	793 patients attempting to conceive by IVF	No control group	66% of patients successfully conceived by IVF. Pregnancy rates were equal among patients with positive and negative aPL.
Kowalik et al.[55]	222 patients non-conceiving after IVF	307 controls who successfully underwent IVF	The overall prevalence of aCL in IVF patients was 7%. There was no statistically significant difference in the prevalence of these antibodies in the groups of controls, spontaneous miscarriage, ongoing pregnancy, and patients who failed to conceive. There was no association between the outcome and the antibody isotype expressed.
Egbase et al.[56]	60 patients with primary infertility undergoing IVF or ICSI and 16 patients with miscarriage before 20 completed weeks after IVF or ICSI cycle	42 fertile women with three or more miscarriages	Seropositivity was similar between women with miscarriage before 20 weeks after IVF or ICSI (25%) and fertile women with three or more miscarriages (21.4%).
Elder-Geva et al.[57]	67 patients with two to four failed assisted reproductive treatment cycles, and 29 women with five or more failed assisted reproductive treatment cycles	45 controls who became pregnant within their first two IVF cycles	Neither the serum concentration of any of the 18 aPL nor the number of positive subjects for aPL was related with the number of assisted reproductive treatment failed cycles or affected the probability of pregnancy.
Martinuzzo et al.[58]	48 patients with recurrent IVF failures	80 fertile controls who had only successful pregnancies	Of the 80 control women, aCL was found in only one subject (1.2%). Only two out of 48 (4.2%) patients with IVF failures had aCL. Neither the patients nor the controls had a positive LA.
Qublan et al.[59]	90 patients with three or more previously failed IVF-ET cycles	90 controls who have had successful pregnancy after their first IVF-ET cycle, and other 100 controls who conceived spontaneously with at least one uneventful pregnancy and no previous history of miscarriage	Seropositivity for LA and aCL was not statistically significant between patients and controls. Eight out of 90 patients (8.9%) were positive for LA in comparison with two out of 190 (2.2%) for controls ($p = 0.2$). Nine out of 90 patients (10%) were positive for aCL in comparison with five out of 190 controls (2.6%) ($p = 0.294$).
Buckingham et al.[60]	99 patients undergoing IVF	No control group	In 19.2% of patients, at least one aPL was detected in their serum and/or follicular fluids. Subjects with positive aPL had a lower implantation rate (14%) than subjects without these antibodies (24.1%), but this difference was not significant ($p = 0.127$).

(continued)

Table 4 Continued

Study	*Patient population*	*Control population*	*Results*
Caccavo et al.[62]	50 patients undergoing IVF-ET	31 age-matched fertile controls	aCL levels detected before the treatment in patients were not significantly different compared with the control group. aCL measured 14 days after the embryo transfer was significantly higher than before starting treatment and on the day of oocyte retrieval. However, no relationship was found between aCL and pregnancy outcome.
Steinvil et al.[63]	594 patients undergoing IVF	Total of 67 fertile controls plus women with a history of DVT	Those who had LA had significantly higher live birth rates (12.3%) in comparison with women who tested negative (9.7%).
Ying et al.[65]	116 infertile women positive for aCL	518 infertile women negative for aCL	The overall IVF results in the aCL positive group were comparable with patients negative for aCL.
DaCosta et al.[66]	34 aPL positive patients	205 aPL negative controls	Of the 30 patients who were LA and/or aCL positive, eight (26.7%) had a positive pregnancy test. Of the controls, 61 out of 181 (33.7%) were LA and/or aCL negative ($p = 0.5787$).
Paulmyer-Lacroix et al.[67]	Eight aPL positive patients presenting with at least two implantation failures after IVF	32 aPL negative controls presenting with at least two implantation failures after IVF	β2GPI IgA antibodies were significantly higher in patients who underwent IVF (12.5%, 5/40) than in those who did not (1%, 1/100) ($p = 0.01$). No difference according to the number of IVF attempts and success of embryo implantation was found between aPL positive and negative IVF patients.
Orquevaux et al.[68]	12 patients who were aPL positive and underwent IVF	15 controls who underwent IVF and were aPL negative	Pregnancy rate in both groups was similar (25% for aPL positive group and 32.43% for women who were aPL negative).
Hong et al.[69]	12 aPL positive patients undergoing their first IVF	181 aPL negative controls undergoing their first IVF cycle	The clinical pregnancy rate, ongoing pregnancy rate, and miscarriage rate were all similar between aPL positive and aPL negative groups.
Di Nisio et al.[70]	57 aPL positive patients undergoing IVF	598 aPL negative controls undergoing IVF	There were no statistically significant associations between thrombophilic defects and clinical pregnancy or pregnancy test results.

aCL: anticardiolipin antibody; aPS: anti-phosphatidylserine; aPL: anti-phospholipid antibodies; IVF-ET: in vitro fertilization-embryo transfer; DVT: deep vein thrombosis; LA: lupus anticoagulant; ICSI: intracytoplasmic sperm injection.

testicles, can be affected.[70] Rabelo-Júnior and colleagues conducted a cross-sectional study to perform global testicular and sexual function assessments in male patients with primary APS, evaluating its possible association with clinical and laboratory parameters. Although APS males had more morphofunctional penile abnormalities than control males, both groups had normal testicular function. This study raised an issue about fertility or fear of impaired sexual function in male patients with rheumatologic diseases.[71] In another cross-sectional study, Rabelo-Júnior and colleagues compared the median penis circumference, sperm concentration, and total sperm count between APS males and healthy controls. The authors observed an association between reduced penile size with erectile dysfunction and previous arterial thrombosis in APS patients.[72]

There have been case reports in the literature describing the existence of testicular vein thrombosis in patients with high titers of aPL, which might affect fertility. Wu and colleagues reported the case of a male diagnosed with APS who presented for left scrotal pain secondary to a thrombosis of the left testicular vein and pampiniform plexus, which led to an extensive intra-parenchymal hemorrhage of the testis and epididymis with congestion of the spermatic cord and vessels.[73] Another case report by Leder and colleagues demonstrated testicular thrombosis necessitating orchiectomy in a patient with high

levels of aCL associated with acute HIV infection.[74] Similarly, Gobel and colleagues presented the case of a man with left testicular thrombosis who underwent unilateral orchiectomy, and was found to have high titers of aCL.[75] Fernandez Rosado and colleagues also described a relationship between APS and male infertility.[76] Srivastava and colleagues reported the case of a patient who presented for left testicular pain to undergo unilateral orchiectomy, and was found to have high titers of LA, aCL, and anti-β2GPI antibodies on two separate tests.[77] Further data are required to assess male infertility in APS.

Conclusion

APS is characterized by a variety of clinical manifestations induced by aCL, anti-β2GPI, and LA. Controversy continues to exist regarding a possible association between aPL and infertility. Although an association between aPL and IVF failure has been suggested in some retrospective studies, no association was present in most of the prospective studies published so far. There are not enough data to support the routine practice of testing aPL in patients with infertility. Furthermore, there are no well-designed studies to show that patients with infertility and positive aPL require treatment. With regards to male fertility, some cross-sectional studies have described an association between APS and male infertility and some case reports have described testicular thrombosis as a result of APS followed by orchiectomy, which could affect future fertility.

Declaration of conflicting interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

G El Hasbani https://orcid.org/0000-0003-2571-1450

References

1 Miyakis S, Lockshin MD, Atsumi T, *et al*. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4: 295–306.
2 Chighizola CB, Raimondo MG, Meroni PL. Does APS impact women's fertility? *Curr Rheumatol Rep* 2017; 19: 33.
3 Pattison NS, Chamley LW, Birdsall M, Zanderigo AM, Liddell HS, McDougall J. Does aspirin have a role in improving pregnancy outcome for women with the antiphospholipid syndrome? A randomized controlled trial. In: *Am J Obstetrics Gynecol* 2000; 183: 1008–1012.
4 Kovács M, Hartwig M, Aleksza M, *et al*. Antiphospholipid antibodies in relation to sterility/infertility. *Hum Immunol* 2012; 73: 726–731.
5 Deroux A, Dumestre-Perard C, Dunand-Faure C, Bouillet L, Hoffmann P. Female infertility and serum auto-antibodies: A systematic review. *Clin Rev Allergy Immunol* 2017; 53: 78–86.
6 Chighizola CB, de Jesus GR, Branch DW. The hidden world of anti-phospholipid antibodies and female infertility: A literature appraisal. *Autoimmun Rev* 2016; 15: 493–500.
7 Out HJ, Kooijman CD, Bruinse HW, Derksen RHWM. Histopathological findings in placentae from patients with intrauterine fetal death and anti-phospholipid antibodies. *Eur J Obstet Gynecol Reprod Biol* 1991; 41: 179–186.
8 Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. *Nat Med* 2004; 10: 1222–1226.
9 Lim W. Complement and the antiphospholipid syndrome. *Curr Opin Hematol* 2011; 18: 361–365.
10 Cervera R, Balasch J. Bidirectional effects on autoimmunity and reproduction. *Hum Reprod Update* 2008; 14: 359–366.
11 Branch DW, Dudley DJ, Mitchell MD, *et al*. Immunoglobulin G fractions from patients with antiphospholipid antibodies cause fetal death in BALB/c mice: A model for autoimmune fetal loss. *Am J Obstet Gynecol* 1990; 163(1 Pt 1): 210–216.
12 Holers VM, Girardi G, Mo L, *et al*. Complement C3 activation is required for antiphospholipid antibody-induced fetal loss. *J Exp Med* 2002; 195: 211–220.
13 Girardi G, Berman J, Redecha P, *et al*. Complement C5a receptors and neutrophils mediate fetal injury in the antiphospholipid syndrome. *J Clin Invest* 2003; 112: 1644–1654.
14 Francis J, Rai R, Sebire NJ, *et al*. Impaired expression of endometrial differentiation markers and complement regulatory proteins in patients with recurrent pregnancy loss associated with antiphospholipid syndrome. *Mol Hum Reprod* 2006; 12: 435–442.
15 Fuchs TA, Brill A, Duerschmied D, *et al*. Extracellular DNA traps promote thrombosis. *Proc Natl Acad Sci USA* 2010; 107: 15,880–15,885.
16 Pfeiler S, Stark K, Massberg S, Engelmann B. Propagation of thrombosis by neutrophils and extracellular nucleosome networks. *Haematologica* 2017; 102: 206–213.
17 Hahn S, Hasler P, Vokalova L, et al. The role of neutrophil activation in determining the outcome of pregnancy and modulation by hormones and/or cytokines. *Clin Exp Immunol* 2019; 198: 24–36.
18 Zambrano F, Carrau T, Gärtner U, *et al*. Leukocytes coincubated with human sperm trigger classic neutrophil extracellular traps formation, reducing sperm motility. *Fertil Steril* 2016; 106: 1053–1060.
19 Gleicher N, el-Roeiy A, Confino E, Friberg J. Reproductive failure because of autoantibodies: Unexplained infertility and pregnancy wastage. *Am J Obstet Gynecol* 1989; 160: 1376–1380; discussion 1380–1385.
20 Aoki K, Dudkiewicz AB, Matsuura E, Novotny M, Kaberlein G, Gleicher N. Clinical significance of beta 2-glycoprotein I-dependent anticardiolipin antibodies in the reproductive autoimmune failure syndrome: Correlation with conventional antiphospholipid

antibody detection systems. *Am J Obstet Gynecol* 1995; 172: 926–931.
21 Taylor PV, Campbell JM, Scott JS. Presence of autoantibodies in women with unexplained infertility. *Am J Obstet Gynecol* 1989; 161: 377–379.
22 Roussev RG, Kaider BD, Price DE, Coulam CB. Laboratory evaluation of women experiencing reproductive failure. *Am J Reprod Immunol N Y N 1989* 1996; 35: 415–420.
23 Kim CH, Cho YK, Mok JE. The efficacy of immunotherapy in patients who underwent superovulation with intrauterine insemination. *Fertil Steril* 1996; 65: 133–138.
24 Coulam CB, Kaider BD, Kaider AS, Janowicz P, Roussev RG. Antiphospholipid antibodies associated with implantation failure after IVF/ET. *J Assist Reprod Genet* 1997; 14: 603–608.
25 Cubillos J, Lucena A, Lucena C, *et al*. Incidence of autoantibodies in the infertile population. *Early Pregnancy Biol Med Off J Soc Investig Early Pregnancy* 1997; 3: 119–124.
26 Kutteh WH, Yetman DL, Chantilis SJ, Crain J. Effect of antiphospholipid antibodies in women undergoing in-vitro fertilization: Role of heparin and aspirin. *Hum Reprod Oxf Engl* 1997; 12: 1171–1175.
27 Radojcić L, Marjanović S, Vićovac L, Kataranovski M. Anticardiolipin antibodies in women with unexplained infertility. *Physiol Res* 2004; 53: 91–96.
28 Shoenfeld Y, Carp HJA, Molina V, *et al*. Autoantibodies and prediction of reproductive failure. *Am J Reprod Immunol N Y N 1989* 2006; 56: 337–344.
29 Sauer R, Roussev R, Jeyendran RS, Coulam CB. Prevalence of antiphospholipid antibodies among women experiencing unexplained infertility and recurrent implantation failure. *Fertil Steril* 2010; 93: 2441–2443.
30 Porter T. Antiphospholipid antibodies and infertility. *Clin Obstet Gynecol* 2001; 44: 29–35.
31 Nip MMC, Taylor PV, Rutherford AJ, Hancock KW. Autoantibodies and antisperm antibodies in sera and follicular fluids of infertile patients; relation to reproductive outcome after in-vitro fertilization. *Hum Reprod* 1995; 10: 2564–2569.
32 Ruiz AM, Kwak JY, Kwak FM, Beer AE. Impact of age on reproductive outcome in women with recurrent spontaneous abortions and infertility of immune etiology. *Am J Reprod Immunol* 1996; 35: 408–414.
33 Azem F, Geva E, Amit A, *et al*. High levels of anticardiolipin antibodies in patients with abnormal embryo morphology who attended an in vitro fertilization program. *Am J Reprod Immunol* 1998; 39: 161–163.
34 Martinelli I, Taioli E, Ragni G, *et al*. Embryo implantation after assisted reproductive procedures and maternal thrombophilia. *Haematologica* 2003; 88: 789–793.
35 el-Roeiy A, Gleicher N, Friberg J, Confino E, Dudkiewicz A. Correlation between peripheral blood and follicular fluid autoantibodies and impact on in vitro fertilization. *Obstet Gynecol* 1987; 70: 163–170.
36 Fisch B, Rikover Y, Shohat L, *et al*. The relationship between in vitro fertilization and naturally occurring antibodies: Evidence for increased production of antiphospholipid autoantibodies. *Fertil Steril* 1991; 56: 718–724.
37 Geva E, Yaron Y, Lessing JB, *et al*. Circulating autoimmune antibodies may be responsible for implantation failure in in vitro fertilization. *Fertil Steril* 1994; 62: 802–806.
38 Birkenfeld A, Mukaida T, Minichiello L, Jackson M, Kase NG, Yemini M. Incidence of autoimmune antibodies in failed embryo transfer cycles. *Am J Reprod Immunol* 1994; 31: 65–68.
39 Geva E, Amit A, Lerner-Geva L, Azem F, Yovel I, Lessing JB. Autoimmune disorders: Another possible cause for in-vitro fertilization and embryo transfer failure. *Hum Reprod Oxf Engl* 1995; 10: 2560–2563.
40 Balasch J, Creus M, Fábregues F, *et al*. Antiphospholipid antibodies and human reproductive failure. *Hum Reprod Oxf Engl* 1996; 11: 2310–2315.
41 Kaider BD, Price DE, Roussev RG, Coulam CB. Antiphospholipid antibody prevalence in patients with IVF failure. *Am J Reprod Immunol* 1996; 35: 388–393.
42 Stern C, Chamley L, Hale L, Kloss M, Speirs A, Baker HW. Antibodies to beta2 glycoprotein I are associated with in vitro fertilization implantation failure as well as recurrent miscarriage: Results of a prevalence study. *Fertil Steril* 1998; 70: 938–944.
43 Kaider AS, Kaider BD, Janowicz PB, Roussev RG. Immunodiagnostic evaluation in women with reproductive failure. *Am J Reprod Immunol 1989* 1999; 42: 335–346.
44 Ulcova-Gallova Z, Krauz V, Novakova P, *et al*. Anti-phospholipid antibodies against phosphatidylinositol, and phosphatidylserine are more significant in reproductive failure than antibodies against cardiolipin only. *Am J Reprod Immunol* 2005; 54: 112–117.
45 Sanmarco M, Bardin N, Camoin L, *et al*. Antigenic profile, prevalence, and clinical significance of antiphospholipid antibodies in women referred for in vitro fertilization. *Ann N Y Acad Sci* 2007; 1108: 457–465.
46 Matsubayashi H, Sugi T, Arai T, *et al*. IgG-antiphospholipid antibodies in follicular fluid of IVF-ET patients are related to low fertilization rate of their oocytes. *Am J Reprod Immunol* 2006; 55: 341–348.
47 Lee S-R, Park E-J, Kim S-H, Chae H, Kim C-H, Kang B-M. Influence of antiphospholipid antibodies on pregnancy outcome in women undergoing in vitro fertilization and embryo transfer. *Am J Reprod Immunol* 2007; 57: 34–39.
48 Zhong Y-P, Ying Y, Wu H-T, *et al*. Impact of anticardiolipin antibody on the outcome of in vitro fertilization and embryo transfer. *Am J Reprod Immunol* 2011; 66: 504–509.
49 Chen X, Mo M-L, Huang C-Y, *et al*. Association of serum autoantibodies with pregnancy outcome of patients undergoing first IVF/ICSI treatment: A prospective cohort study. *J Reprod Immunol* 2017; 122: 14–20.
50 Khizroeva J, Makatsariya A, Bitsadze V, Makatsariya N, Khamani N. In vitro fertilization outcomes in women with antiphospholipid antibodies circulation. *J Matern-Fetal Neonatal Med Off J Eur Assoc Perinat Med Fed Asia Ocean Perinat Soc Int Soc Perinat Obstet* October 2018; 12: 1–11.
51 Sher G, Feinman M, Zouves C, *et al*. High fecundity rates following in-vitro fertilization and embryo transfer in antiphospholipid antibody seropositive women treated with heparin and aspirin. *Hum Reprod Oxf Engl* 1994; 9: 2278–2283.
52 Gleicher N, Liu HC, Dudkiewicz A, *et al*. Autoantibody profiles and immunoglobulin levels as predictors of in vitro fertilization success. *Am J Obstet Gynecol* 1994; 170: 1145–1149.
53 Birdsall MA, Lockwood GM, Ledger WL, Johnson PM, Chamley LW. Antiphospholipid antibodies in women having in-vitro fertilization. *Hum Reprod Oxf Engl* 1996; 11: 1185–1189.
54 Denis AL, Guido M, Adler RD, Bergh PA, Brenner C, Scott RT. Antiphospholipid antibodies and pregnancy rates and outcome in in vitro fertilization patients. *Fertil Steril* 1997; 67: 1084–1090.
55 Kowalik A, Vichnin M, Liu HC, Branch W, Berkeley AS. Midfollicular anticardiolipin and antiphosphatidylserine antibody titers do not correlate with in vitro fertilization outcome. *Fertil Steril* 1997; 68: 298–304.
56 Egbase PE, Al Sharhan M, Diejomaoh M, Grudzinskas JG. Antiphospholipid antibodies in infertile couples with two consecutive miscarriages after in-vitro fertilization and embryo transfer. *Hum Reprod Oxf Engl* 1999; 14: 1483–1486.
57 Eldar-Geva T, Wood C, Lolatgis N, *et al*. Cumulative pregnancy and live birth rates in women with antiphospholipid antibodies undergoing assisted reproduction. *Hum Reprod Oxf Engl* 1999; 14: 1461–1466.
58 Martinuzzo M, Varela MLI, Adamczuk Y, Broze GJ, Forastiero R. Antiphospholipid antibodies and antibodies to tissue factor pathway inhibitor in women with implantation failures or early and late pregnancy losses. *J Thromb Haemost* 2005; 3: 2587–2589.
59 Qublan HS, Eid SS, Ababneh HA, *et al*. Acquired and inherited thrombophilia: implication in recurrent IVF and embryo transfer failure. *Hum Reprod* 2006; 21: 2694–2698.
60 Buckingham KL, Stone PR, Smith JF, Chamley LW. Antiphospholipid antibodies in serum and follicular fluid: Is there a correlation with IVF implantation failure? *Hum Reprod* 2006; 21: 728–734.

61 Practice Committee of American Society for Reproductive Medicine. Anti-phospholipid antibodies do not affect IVF success. *Fertil Steril* 2008; 172–173.
62 Caccavo D, Pellegrino NM, Lorusso F, *et al*. Anticardiolipin antibody levels in women undergoing first in vitro fertilization/embryo transfer. *Hum Reprod Oxf Engl* 2007; 22: 2494–2500.
63 Steinvil A, Raz R, Berliner S, *et al*. Association of common thrombophilias and antiphospholipid antibodies with success rate of in vitro fertilisation. *Thromb Haemost* 2012; 108: 1192–1197.
64 de Jesus GR, Agmon-Levin N, Andrade CA, *et al*. 14th International Congress on Antiphospholipid Antibodies Task Force Report on Obstetric Antiphospholipid Syndrome. *Autoimmun Rev* 2014; 13: 795–813.
65 Ying Y, Zhong Y, Zhou C, *et al*. A retrospective study on IVF outcome in patients with anticardiolipin antibody: Effects of methylprednisolone plus low-dose aspirin adjuvant treatment. *J Reprod Immunol* 2012; 94: 196–201.
66 DaCosta V, Chin L, Wynter S, *et al*. Anticardiolipin antibodies and lupus anticoagulants among women undergoing in vitro fertilization in Jamaica. *West Indian Med J* 2012; 61: 789–794.
67 Paulmyer-Lacroix O, Despierres L, Courbiere B, Bardin N. Antiphospholipid antibodies in women undergoing in vitro fertilization treatment: Clinical value of IgA anti-β2glycoprotein I antibodies determination. *BioMed Res Int* 2014; 2014: 314704.
68 Orquevaux P, Masseau A, Le Guern V, *et al*. In vitro fertilization in 37 women with systemic lupus erythematosus or antiphospholipid syndrome: A series of 97 procedures. *J Rheumatol* 2017; 44: 613–618.
69 Hong YH, Kim SJ, Moon KY, *et al*. Impact of presence of antiphospholipid antibodies on in vitro fertilization outcome. *Obstet Gynecol Sci* 2018; 61: 359–366.
70 Di Nisio M, Ponzano A, Tiboni GM, Guglielmi MD, Rutjes AWS, Porreca E. Effects of multiple inherited and acquired thrombophilia on outcomes of in-vitro fertilization. *Thromb Res* 2018; 167: 26–31.
71 Mehdi AA, Salti I, Uthman I. Antiphospholipid syndrome: Endocrinologic manifestations and organ involvement. *Semin Thromb Hemost* 2011; 37: 49–57.
72 Rabelo-Júnior CN, Freire De Carvalho J, Lopes Gallinaro A, *et al*. Primary antiphospholipid syndrome: Morphofunctional penile abnormalities with normal sperm analysis. *Lupus* 2012; 21: 251–256.
73 Rabelo-Júnior CN, Bonfá E, Carvalho JF, *et al*. Penile alterations with severe sperm abnormalities in antiphospholipid syndrome associated with systemic lupus erythematosus. *Clin Rheumatol* 2013; 32: 109–113.
74 Wu VH, Dangman BC, Kaufman RP. Sonographic appearance of acute testicular venous infarction in a patient with a hypercoagulable state. *J Ultrasound Med* 1995; 14: 57–59.
75 Leder AN, Flansbaum B, Zandman-Goddard G, Asherson R, Shoenfeld Y. Antiphospholipid syndrome induced by HIV. *Lupus* 2001; 10: 370–374.
76 Göbel U, Kettritz R, Schneider W, Luft FC. A particularly private pain. *Nephrol Dial Transplant* 2002; 17: 516–518.
77 Fernández Rosado E, Sánchez Rodríguez-Losada J, Alvarez Castelo L, *et al*. Urologic damage of the primary antiphospholipid syndrome. *Arch Esp Urol* 2004; 57: 707–723.
78 Srivastava A, Ko J, Ogunsile J, Moliterno A, Westra WH, Semerjian A. Patient with antiphospholipid syndrome presenting with testicular torsion-like symptoms. *Urol Case Rep* 2017; 15: 26–27.