

# Antiphospholipid Antibody Syndrome and Infertility

## *Síndrome Anticorpo Antifosfolípide e Infertilidade*

Vivian de Oliveira Rodrigues<sup>1</sup> Adriana de Góes e Silva Soligo<sup>2</sup> Gabriel Duque Pannain<sup>1</sup> 

<sup>1</sup> Gynecology Department, Faculdade de Medicina, Universidade Federal de Juiz de Fora, Juiz de Fora, MG, Brazil

<sup>2</sup> Post Graduate Department, Associação Instituto Sapientiae, São Paulo, SP, Brazil

Address for correspondence Vivian de Oliveira Rodrigues, MD, Campus Universitário, Rua José Lourenço Kelmer, s/n, 36036-900, São Pedro, MG, Brazil (e-mail: vivian.orodrigues@outlook.com).

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### Abstract

Antiphospholipid antibody syndrome (APS) is a systemic, autoimmune, prothrombotic disease characterized by persistent antiphospholipid antibodies (aPLs), thrombosis, recurrent abortion, complications during pregnancy, and occasionally thrombocytopenia. The objective of the present study was to review the pathophysiology of APS and its association with female infertility. A bibliographic review of articles of the past 20 years was performed at the PubMed, Scielo, and Bireme databases. Antiphospholipid antibody syndrome may be associated with primary infertility, interfering with endometrial decidualization and with decreased ovarian reserve. Antiphospholipid antibodies also have direct negative effects on placentation, when they bind to the trophoblast, reducing their capacity for invasion, and proinflammatory effects, such as complement activation and neutrophil recruitment, contributing to placental insufficiency, restricted intrauterine growth, and fetal loss. In relation to thrombosis, APS results in a diffuse thrombotic diathesis, with global and diffuse dysregulation of the homeostatic balance. Knowing the pathophysiology of APS, which is closely linked to female infertility, is essential for new therapeutic approaches, specialized in immunomodulation and inflammatory signaling pathways, to provide important advances in its treatment.

### Keywords

- ▶ antiphospholipid antibody syndrome
- ▶ infertility
- ▶ recurrent abortion
- ▶ antiphospholipid antibody

### Resumo

A Síndrome do anticorpo antifosfolípide (SAF) é uma doença sistêmica, autoimune e pró-trombótica caracterizada por anticorpos antifosfolípidos, trombose, aborto recorrente, complicações durante a gestação, e, ocasionalmente, trombocitopenia. O objetivo do presente estudo foi revisar a fisiopatologia da SAF e sua associação com a infertilidade feminina. Foi feita uma revisão bibliográfica dos últimos 20 anos nas bases de dados PubMed, Scielo e Bireme. A SAF pode estar associada à infertilidade primária, interferindo na decidualização endometrial e com baixas reservas ovarianas. Os anticorpos antifosfolípidos também apresentam efeito negativo direto na placentação, se ligando ao trofoblasto e diminuindo sua capacidade de invasão, além de efeitos pró-inflamatórios, tais como ativação do sistema de complemento e recrutamento de neutrófilos, contribuindo para a insuficiência placentária, crescimento intrauterino restrito e perda fetal. Quanto a trombose, a SAF resulta em distúrbios trombóticos difusos, com uma desregulação do balanço homeostático. Conhecer a fisiopatologia da SAF, que apresenta associação importante com a infertilidade feminina, é essencial para novas abordagens terapêuticas, principalmente no que tange imunomodulação e os caminhos de ativação inflamatórios.

### Palavras-chave

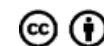
- ▶ síndrome do anticorpo antifosfolípide
- ▶ infertilidade
- ▶ aborto de repetição
- ▶ anticorpo antifosfolípide

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## Introduction

Antiphospholipid antibody syndrome (APS) was first described in 1983. It is defined as a prothrombotic autoimmune disease, characterized by the presence of persistent antiphospholipid antibodies (aPLs), thrombosis, recurrent abortion, and, occasionally, thrombocytopenia. It can manifest itself in isolation (primary APS) or associated with another autoimmune disease (secondary APS). The most common association is with systemic lupus erythematosus (SLE).<sup>1,2</sup>

Antiphospholipid antibody syndrome, an acquired thrombophilia, is associated with arterial and venous thrombosis, which can occur in unusual sites, such as hepatic veins, visceral veins, and in the cerebral venous circulation. Any signs of thrombosis in these sites require investigation of APS.<sup>3</sup>

The prevalence of the disease is unknown; however, it is estimated to affect ~ 0.5% of the population. The average age at the time of diagnosis is ~ 35 years old, since it is rare in children.<sup>1</sup>

The aPLs are a heterogeneous group of antibodies directed against phospholipids, situated in the endothelial cell membrane, platelets, and other cells involved in the coagulation cascade. Its discovery began with the discovery of cardiolipin in 1906, when Wassermann described it as a marker for syphilis. In 1941, Pangborn isolated and identified the antigen component in heart fragments of cattle, such as cardiolipin (diphosphatidylglycerol). Cardiolipin is a unique phospholipid of biomembranes which have coupled phosphorylation and electron transport, such as mitochondria. There are currently > 10,000 publications on these antibodies, and the most researched in reproductive immunology are lupus anticoagulant, anti- $\beta$ -2-glycoprotein, and anticardiolipin.<sup>4-6</sup>

According to the revised Sapporo criteria, 2006, the diagnosis of APS occurs when patients present at least one clinical criterion associated with a laboratorial one, **which should be performed with a minimum interval of 12 weeks of the clinical event.**<sup>7,8</sup> Clinical criteria include (**Table 1Q4**):  $\geq 1$  previous thrombosis cases confirmed by histological or imaging tests, or cases of obstetric morbidity,

**Table 1** Clinical Criteria of Antiphospholipid Antibody Syndrome

|   |
|---|
| 1 Vascular thrombosis   |
| One or more episodes of arterial or venous thrombosis in any tissue or organ, confirmed by validated objective criteria (imaging exams or histopathology).                                |
| 2 Obstetrics morbidity  |
| (a) One or more unexplained of morphologically normal fetuses with gestational age $\geq 10$ weeks (normal morphology documented by ultrasonography or direct fetus examination).         |
| (b) One or more premature births of morphologically normal neonates with < 34 weeks of gestational age due to severe pre-eclampsia or pre-eclampsia, or signs of placental insufficiency. |
| (c) Three or more unexplained spontaneous abortions with < 10 weeks of gestational age, excluding anatomic maternal, hormonal, and chromosomal causes.                                    |

Source: Adapted from Kovács et al.<sup>9</sup>

**Table 2** Laboratory Criteria of Antiphospholipid Antibody Syndrome

|  |
|--|
| 1 Lupus anticoagulant present on plasma, $\geq 2$ occasions, with 12 weeks of difference, detected according to the guidelines of the International Society of Thrombosis and Hemostasis.                        |
| 2 Anticardiolipin (IgG or IgM) detected on serum or plasma, and medium or higher titles ( $> 40$ GPL or MPL, or $> p 99$ ), in $\geq 2$ occasions, with 12 weeks of difference, through ELISA standardized exam. |
| 3 Anti- $\beta$ -2-glycoprotein I (IgG or IgM), detected on serum or plasma (titles $> 99$ percentile), in $\geq 2$ occasions, with 12 weeks of difference, through ELISA standardized exam.                     |

Abbreviation: ELISA, Enzyme-Linked Immunosorbent Assay.

Source: Adapted from Kovács et al.<sup>9</sup>

which include: unexplained death of  $\geq 1$  morphologically normal fetuses with  $\geq 10$  weeks of gestation;  $\geq 1$  normal fetuses born before 34 weeks of gestation (due to pre-eclampsia [PE], eclampsia, or placental insufficiency); or  $\geq 3$  spontaneous miscarriages before 10 weeks of gestation.

The laboratory criteria (**Table 2**) includes the positivity (on 2 occasions in a range of at least 12 weeks) of  $\geq 1$  of the following aPLs: lupus anticoagulant; anti- $\beta$ -2-glycoprotein (immunoglobulin M [IgM] and/or immunoglobulin G [IgG]); and anticardiolipin (IgM and/or IgG). Although the Sapporo criteria are widely used in medical practice, it should be noted that they were initially developed to define a uniform cohort of patients with APS for clinical trials, rather than providing a practical system for clinical diagnosis.<sup>3,7</sup>

Antiphospholipid antibodies can also be present even if the patient does not fulfill the clinical criteria for the syndrome (nonspecific autoimmunity).<sup>8</sup>

It is known that the presence of these antibodies is associated with primary infertility. They are more frequent in infertile patients and interfere with the endometrial decidualization and, consequently, with the embryo implantation rates. Others suggest that it can also be associated with decreased ovarian reserve. The ovarian reserve can be evaluated by the dosages of the antimullerian hormone or by the count of antral follicles on the ultrasonography. The antimullerian hormone is produced by growing follicles from granulosa cells that harbor the oocytes until their maturation, and its levels remain stable throughout the whole menstrual cycle.<sup>9,10</sup>

The pathogenesis of obstetric morbidity on APS is not yet fully understood; however, it may happen due to the negative effect that the antiphospholipid antibodies exert on the placental function, decreasing the trophoblastic viability and its invasiveness. Furthermore, recent evidence suggest that the inflammatory factor can also justify the poor obstetrics prognosis. There are experimental studies on animals that confirm the ability of large quantities of antiphospholipid antibodies to induce fetal reabsorption and growth retardation through the placental deposition of IgG and complement, neutrophilic infiltration, and local secretion of tumor necrosis factor alpha (TNF- $\alpha$ ).<sup>1,11</sup>

The primary treatment of the syndrome, whose main objective is to prevent thrombosis, presents only partial success rates. Nowadays, ~ 80% of the gestations with APS result in live births. However, these gestations have a higher risk of developing PE, ranging from 18 to 40%, a higher risk of restricted intrauterine growth in 5 to 15%, besides a higher risk of premature birth.<sup>12</sup>

Therefore, APS is a syndrome with high prevalence rates, since 15 to 20% of the women with recurrent miscarriage are APS carriers.<sup>13</sup> It is necessary to expand the investigations about APS in order to understand its pathogenic mechanisms and its association with female infertility.

## Methods

The present study consists of a bibliographic review of articles found in databases, such as PubMed, Scielo, and Bireme, from 1998 to 2018. Two articles, one from 1990 and another from 1995, were also included because of their relevance to the theme of the study. The scientific articles related to the keywords were selected, as well as the others related to the pathophysiology of APS. The used keywords were: *síndrome do anticorpo antifosfolípideo, infertilidade, aborto recorrente, anticorpo antifosfolípideo, antiphospholipid syndrome, infertility, recurrent pregnancy loss, antiphospholipid antibody.*

## Results

### Antiphospholipid antibody syndrome and primary infertility

Primary infertility is defined as the absence of gestation after 12 months of intercourse without the use of contraceptives. The global prevalence of infertility is 9%, while the 60-month prevalence of infertility in Europe is estimated to be 1.5%.<sup>10</sup>

A recent literary evaluation analyzed 31 studies, all of which showed a high and important association between aPLs and female infertility. A total of 45% of these studies confirmed the association between anticardiolipin antibody and infertility; however, this rate dropped to 31% when the association with lupus anticoagulant was analyzed. Only 4 studies evaluated anti- $\beta$ -2-glycoprotein, and yet, 75% of them revealed a positive association with infertility. There was a significant difference of the positivity of anticardiolipin antibody in infertile women, but the frequencies of anti- $\beta$ -2-glycoprotein and lupus anticoagulant antibodies were similar both in infertile and fertile women. It must be highlighted that < 25% of the studies utilized a medium-high limit to define the positivity of anticardiolipin and/or of anti- $\beta$ -2-glycoprotein, as recommended by international guidelines. ► **Table 3** reveals the estimated positivity rates of aPLs.<sup>10,14</sup>

### Antiphospholipid antibody syndrome and obstetrics morbidity

The abortion rate, when aPL levels are > 90% of the normal population values, is estimated to be 52%. In addition, positive aPLs patients who already had an abortion have a higher risk of obstetric morbidity in future pregnancies.<sup>15</sup>

**Table 3** Positivity rates of Antiphospholipid antibodies in infertile women and in the control group

| aPL                           | Number of studies | Infertile women Positivity  | Control group Positivity       |
|-------------------------------|-------------------|-----------------------------|--------------------------------|
| Lupus anticoagulant           | 13                | 0% (0-2-5)<br>7% (3-7-13-3) | 0% (0-0)<br>1-6% (0-3)<br>2-8% |
| Anticardiolipin               | 29                |                             |                                |
| Anti- $\beta$ -2 glycoprotein | 4                 | 7-6%                        |                                |

Source: Adapted from Chighizola et al.<sup>10</sup>

Although all three antibodies (lupus anticoagulant, anticardiolipin, and anti- $\beta$ -2 glycoprotein) are associated with recurrent miscarriage, the risk varies according to the positivity of different types of antibodies. For example, the presence of anticardiolipin antibody is associated with an odds ratio (OR) of 22.6% (95%CI [confidence interval]) for recurrent miscarriage. The presence of anti- $\beta$ -2 glycoprotein antibodies increases the chance of recurrent miscarriage from 6.8% to 22.2% when compared with women positive for lupus anticoagulant or anticardiolipin.<sup>16</sup>

Fetal complications in APS include prematurity, intrauterine growth restriction (IUGR) (due to placental insufficiency) and stillbirth. The "Euro-Phospholipid Project" cohort study analyzed the clinical characteristics of 1,000 patients with APS during a 5-year period, and concluded that these events complicate 28%, 11% and 7% of APS pregnancies, respectively.<sup>17</sup>

A meta-analysis of 2006 revealed a positive association between the presence of anticardiolipin IgG (between high and low titles) and recurrent abortion at < 13 weeks of gestational age (OR 3.56; 95%CI: 1.48-8.59). Other studies suggest that circulating aPLs are the main risk factor for 7 to 25% 1<sup>st</sup>-trimester gestational losses, whereas prevalence studies showed that 1 in 5% of these patients are lupus anticoagulant-positive. A cohort of 500 women with a history of recurrent abortion revealed that 9.6% were lupus anticoagulant-positive, whereas anticardiolipin IgG and IgM were found on 3.3% and 2.2% of them, respectively.<sup>18,19</sup>

Other obstetrics morbidities, such as PE and/or placental insufficiency and IUGR are also associated with APS. Preeclampsia can occur in between 2 to 8% of 1<sup>st</sup> gestations, whereas severe preeclampsia can be seen in 0.5% of the gestations in developed countries. Most of these prospective observational studies corroborate the association between aPL with PE and placental insufficiency. A meta-analysis of 2010 exposed that moderate to high titles of anticardiolipin are associated with preeclampsia. Prospective and retrospective studies have shown that the persistence of high titles of aPLs are associated with IUGR and premature birth. Data from case-control studies indicate that aPLs were found in 50% of the patients with a history of PE or IUGR, and in 7% of women without these morbidities.<sup>20-22</sup>

### Antiphospholipid antibody syndrome and thrombosis

The association between aPLs and thrombosis is significant. Antiphospholipid antibodies are found in ~ 13% of the

patients with history of stroke, 11% of the patients with acute myocardial infarction, and 9.5% of the patients with a history of deep vein thrombosis.<sup>2</sup> The annual rate of a first thromboembolic event on patients between 35 and 55 years old who are not APS carriers is of ~ 0.4%. On APS carriers, the rates are around 3.8%. The incidence of thrombosis in patients positive for a single antiphospholipid antibody is 1.36%, and increases to 5.3% in patients positive for all 3 antibodies. Therefore, triple positivity presents a higher risk of occurrence and recurrence of thromboembolic events.<sup>23</sup>

## Discussion

### Antiphospholipid antibody syndrome and primary infertility

The pathogenic mechanism that explains how aPLs induce infertility is not yet fully understood. Some authors believe that aPLs may alter the development of the oocyte after its secretion into the follicular fluid, since gametes or preimplantation embryos do not come into contact with maternal blood.<sup>10</sup>

An alternative theory relies on the fact that the antibodies interfere on uterine decidualization, compromising implantation. Decidualization is the transformation of the endometrial stromal fibroblasts into specialized decidual secretory cells, which provide a nutritional and immunoprivileged matrix that is essential to embryonic implantation and placental development. In vitro studies also observed the connection between aPLs and endometrial endothelial cells, impairing angiogenesis.<sup>10,24,25</sup>

Evidence on the interaction between aPLs and decidua has been obtained by in vivo studies. A 1990 study showed that mice treated with IgG aPLs showed, on histological examination, decidual necrosis associated with intravascular deposits of IgG and fibrin. In other studies, through the immunohistochemical analysis of the decidua of pregnant mice, it was observed that the decidua is a preferential target for complement deposition after treatment with IgG aPLs.<sup>26-28</sup>

Otherwise, in addition to inflammatory changes in the decidua and its interference with embryo implantation, there is another mechanism by which APS is associated with infertility. It also can decrease ovarian reserve.<sup>29</sup>

The term ovarian reserve, traditionally, has been used to describe the reproductive potential of a woman; in other words, the quantity and quality of the oocytes she possesses. However, ovarian reserve markers serve as a substitute for oocyte quantity, but are poor indicators of oocyte quality. Therefore, the modern use of the term applies to the quantity of remaining oocytes, not to oocyte quality.<sup>30</sup>

Thus, the ovarian reserve can be evaluated by the dosages of the antimüllerian hormone or the count of antral follicles on the ultrasonography. Both present the same sensitivity and specificity as predictors of follicular reserve.<sup>10</sup>

A 2014 study assessed the ovarian reserve of patients with APS and observed that these women had a lower count of antral follicles than those in the control group. Vega et al, in 2016,<sup>29</sup> demonstrated a strong association between aPL positivity and decreasing levels of antimüllerian hormone. Thus, antiphospholipid antibodies may represent the 1<sup>st</sup> laboratory

markers for early ovarian failure associated with autoimmunity. This suggests that the presence of aPLs in women of reproductive age should be considered a risk factor for the development of premature ovarian failure. The confirmation of this association in future studies, therefore, could lead to the early diagnosis of this condition in many women.<sup>29,31</sup>

### Antiphospholipid antibody syndrome and obstetric morbidity

The pathogenesis of obstetric morbidity in APS is still not completely understood. Initially, intraplacental thrombosis was considered to be the main mechanism of poor obstetric prognosis. However, most subsequent studies have not been able to find blood clots in most placentas from carriers. Other hypotheses, therefore, have been suggested, such as that aPLs induce a direct negative effect on placentation, interfering in both trophoblastic invasion and endometrial angiogenesis.<sup>32</sup>

Immediately after placental implantation, the mononuclear trophoblast (cytotrophoblast) invades the decidua of the uterus, differentiating itself into an extravillous trophoblast. A part of this trophoblast invades the uterine spiral arteries, which supply blood to the decidua, digesting the musculature and replacing the endothelial cells lining these vessels. This invasion is capable of remodeling the spiral arteries and transforming them into nonvasoactive conduits of greater caliber. Up to half of the gestational period, the spiral arteries are remodeled throughout the decidua depth, up to one-third of the depth of the myometrial segments. This remodeling allows a large and uninterrupted blood supply to the fetus during the second half of the gestation, when the demand is greater.<sup>33-35</sup>

The majority of obstetric manifestations of APS, such as preeclampsia and restricted intrauterine growth, present failure of the extravillous trophoblast to adequately remodel the spiral arteries. As a consequence, there is a significant decrease in maternal blood flow to the placenta, causing ischemic injury, lack of nutrients to the fetus, and increased blood flow velocity, which can damage the placenta.<sup>34,35</sup>

A recent meta-analysis of the histopathological findings of placentas affected by aPLs showed five changes associated with aPLs: placental infarction, inadequate remodeling of spiral arteries, decidual inflammation, increased number of syncytial nodes, and decreased synovial vascular membranes. It is important to note that placentas with aPLs rarely present evidence of intravascular or intravillous clots.<sup>35,36</sup>

The negative effect that aPLs exert on human placentation begins with the binding of the antibodies to the trophoblast. It is known that polyclonal IgG antibodies from APS patients and monoclonal antibodies with anti- $\beta$ -2-glycoprotein activity are able to adhere to the trophoblast and endometrial endothelial cells in vitro. The pathogenic mechanisms by which antiphospholipid antibodies alter placentation will be described in detail below<sup>37</sup>:

1–Antiphospholipid antibodies are able to stimulate the trophoblast to secrete inflammatory interleukins, such as IL-1 and IL-8, through the activation of the toll-like receptor (TRL4)<sup>35</sup>;

2–Antiphospholipid antibodies limit the migration of trophoblast via mediation of apolipoprotein E receptor 2 (ApoER2), which is expressed in human trophoblast and targets the anti- $\beta$ -2-glycoprotein complexes. In addition, ApoER2 has been associated with restricted intrauterine growth and fetal loss<sup>35,38</sup>;

3–Antiphospholipid antibodies increase the production of extracellular vesicles of the syncytiotrophoblast. In placentas affected by aPLs, there is an increase in syncytial nodes, which are aggregates of syncytiotrophoblast nucleoli and aging markers of them. They are expelled from the placenta in large vesicles as syncytial nuclear aggregates and are responsible for activating the maternal vasculature<sup>36,39</sup>;

4–Syncytiotrophoblast produces human chorionic gonadotropin (hCG). Antiphospholipid antibodies reduce the growth of the syncytiotrophoblast in vitro, reducing the production of hCG. As they prevent the formation of new syncytiotrophoblast and induce cell death, they also cause a reduction in transplacental transport, evidenced by decreased levels of the cholesterol transporter ABCA1 in placentas affected by APS<sup>40,41</sup>;

5–These antibodies are also capable of blocking endometrial angiogenesis both in vitro and in vivo. One mechanism is the inhibition of the production of factors regulated during angiogenesis, such as vascular endothelial growth factor (VEGF). A study of  $\beta$ -2-glycoprotein involvement has shown that, in contrast to its previously reported anti-angiogenic properties, the cleaved form of  $\beta$ -2-glycoprotein is able to block the activity of angiostatin, a known angiogenesis inhibitor. The inhibitory effect of angiogenesis is demonstrated, but it is not yet known whether it is caused by the imbalance between the cleaved and intact forms of  $\beta$ -2-glycoprotein.<sup>32</sup>

In addition to the changes described above, the inflammatory effects that the antiphospholipid antibodies induce on the trophoblast are significant. According to Hokers et al,<sup>11</sup> passive IgG transfer from patients with high aPL titles to pregnant mice resulted in fetal resorption and restricted growth.

Mice models have confirmed a critical role of neutrophils in fetal developmental abnormalities. Pregnant mice treated with aPLs had placental neutrophil infiltration, and the deleterious effects of aPLs on fetal survival and growth were abolished by neutrophil depletion. Neutrophil recruitment is triggered by complement activation at the maternal-fetal interface and leads to elevated TNF- $\alpha$  levels, VEGF reduction and, finally, to abnormal placentation and fetal death.<sup>35,42</sup>

Studies in women support the role of complement in the complications of APS pregnancies. The C4d complement fragment, a classic pathway activation marker, is present in placentas of women with APS and PE. Hypofunctional variants inherited from complement regulators provide a higher risk of PE in women with APS. It is possible to suggest that complement-mediated injury is a common pathogenic mechanism that causes abnormal placentation, fetal loss, and restricted intrauterine growth.<sup>35,43</sup>

**Table 4** Coagulation process modified by antiphospholipid antibodies

|   |
|---|
| Inhibition of protein C activity  |
| Inhibition of protein S activity  |
| Inhibition of antithrombin activity                                       |
| Induction of tissue factor in endothelial cells and monocytes             |
| Inhibition of Tissue Factor Pathway Inhibitor (TPFI)                      |
| Increased prothrombin deposition, leading to increased thrombin formation |
| Inhibition of fibrinolysis  |
| Activation of factor XI   |
| Induction of platelet aggregation   |
| Induction of endothelial cell adhesion receptors                          |

Source: Adapted from Salmon et al.<sup>46</sup>

### Antiphospholipid antibody syndrome and thrombosis

Alterations in the complement system may contribute to aPL-induced thrombosis, and coagulation factors may activate the complement cascade.<sup>44</sup> The pathophysiology of thrombosis associated with APS is different from other hypercoagulability known conditions. In APS, thrombosis can occur in virtually all vessels, in arteries and veins, as well as in large vessels and in microcirculation. The presence of aPLs is able to interfere with virtually all known homeostatic reactions, as shown in **Table 4**. Their presence results in diffuse thrombotic diathesis, suggesting global and general deregulation of the hemostatic equilibrium.<sup>45,46</sup>

It is true that there are many paths by which aPLs induce thrombosis. The other main path, besides the alteration of the homeostatic equilibrium, is the activation of the complement system. Studies have shown that aPL-treated mice showed increased leukocyte adhesion to endothelial cells and were able to conclude that mice deficient in C3, C5 or C5a complement components were resistant to aPL-induced thrombophilia and endothelial cell activation.<sup>47</sup>

### Conclusion

Antiphospholipid antibody syndrome is an autoimmune and inflammatory disease associated with a substantial incidence of thrombosis, obstetric morbidity, and infertility. In recent times, aPLs have been recognized as triggers of innate immune inflammatory pathways within the trophoblast and at the maternal-fetal interface. No longer considered simple prothrombotic antibodies that activate the endothelial cells and platelets, aPLs are directly responsible for the connection to the trophoblast and the alteration of its function. The study of the pathophysiology of APS should be encouraged, since innovative therapeutic approaches, focused on immunomodulation and inflammatory signaling pathways, may provide important therapeutic advances for this disease, which has such a significant impact on female fertility.

## Conflicts of Interests

No loan, equipment or drugs support were given for the present work, nor was it presented at any congress.

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