



## ARTIGO DE REVISÃO

### Antiphospholipid Syndrome

#### Síndrome do Anticorpo Antifosfolipídico

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#### ABSTRACT

Antiphospholipid syndrome (APS) is an autoimmune disease characterized by the production of antiphospholipid antibodies (aPL) and is associated with thrombosis and morbidity in pregnancy. The prevalence of aPL in the population ranges from 1 to 5%. The hypotheses regarding pathophysiological mechanisms are strongly related to binding proteins and antiphospholipid antibodies. The exact mechanisms that lead to clinical manifestations appear to be heterogeneous, but it is believed that aPL contribute to the cellular activation of coagulation cascade, leading to thrombotic events. The treatment of APS should be at an individual basis, and several factors should be taken into account, such as antibodies, the age of the patient and the history of thrombotic events.

#### RESUMO

A síndrome do anticorpo antifosfolipídico (SAF) é uma doença autoimune caracterizada pela produção de anticorpos antifosfolipídeos (AAF) e está associada a eventos tromboembólicos e morbidade na gravidez. A prevalência de AAF na população varia de 1 a 5%. As hipóteses sobre os mecanismos fisiopatológicos estão fortemente relacionadas a proteínas de ligação e aos AAF. Os mecanismos exatos que levam a manifestações clínicas parecem ser heterogêneos, mas acredita-se que os AAF contribuem para a ativação celular e da cascata da coagulação, provocando eventos tromboembólicos. O tratamento da SAF deve ser de caráter individual e vários fatores devem ser levados em consideração, como número de anticorpos presentes, idade do paciente e histórico pessoal.

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## Introduction

The antiphospholipid syndrome (APS) is an autoimmune disease that is characterized by the presence of antiphospholipid antibodies (aPL) and is associated with thrombosis and morbidity in pregnancy<sup>1</sup>. The aPL are autoantibodies that target the cell membrane phospholipids and/or phospholipid-associated proteins, such as  $\beta$ -2-glycoprotein I ( $\beta$ 2-GPI) and prothrombin.

However, the pathogenic mechanisms underlying the syndrome are not fully elucidated<sup>2</sup>.

The major aPL found in APS are lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti- $\beta$ 2-glycoprotein I antibodies (a $\beta$ 2-GPI) and are part of the diagnosis of APS, composing the international classification criteria<sup>3</sup>.

The epidemiological data described for APS show that the prevalence of aPL in the general population varies between 1 and 5%, although few individuals will present clinical manifestations. The incidence of APS is estimated at five new cases per

100,000 people/year and the prevalence is about 40-50 cases per 100,000 people<sup>4</sup>. Recently, estimates of the prevalence of autoantibodies in APS in general population have shown that aPL occurs in approximately 13% of patients with stroke, 11% of myocardial infarctions, 9.5% in patients with deep venous thrombosis and 6% of patients with complications during pregnancy<sup>5</sup>. The APS is predominant in women, especially in patients who also have systemic lupus erythematosus (SLE). Concerning age, young and adult commonly present aPL, but children and older people may also have these autoantibodies<sup>6</sup>.

Thrombotic events are the main manifestations that affect APS patients<sup>7</sup>. It is believed that is necessary more than the simple occurrence of aPL to trigger coagulation cascade and provoke thrombotic events. Additional factors that contribute to thrombotic events include age, risk factors for cardiovascular disease, hereditary thrombophilia, use of oral contraceptives, nephrotic syndrome, malignant disease, prolonged immobilization, and surgeries<sup>3</sup>. Also, there are indications of genetic predisposition to APS in populations associated with human leukocyte antigen (HLA) and its polymorphisms<sup>8</sup>.

Most studies confirm the association between aPL and complications during pregnancy. The main obstetric manifestations related to the disease are recurrent abortions, prematurity, eclampsia, preeclampsia, and intrauterine growth restriction<sup>1,9</sup>. A meta-analysis that studied couples who presented recurrent miscarriage showed an incidence of APS from 15% to 20% compared to approximately 5% in non-pregnant women without obstetric history<sup>1</sup>. After treatment, live birth rates among APS patients increase considerably<sup>10</sup>.

## Development

### History

Antiphospholipid syndrome was originally described by Hughes in 1983<sup>11</sup>, but in the early twentieth century (1906), Wassermann, Neisser, and Bruck were the first to identify aPL in individuals diagnosed with syphilis<sup>12</sup>. The antigen from the reaction was only identified by Pangborn in 1941 as being cardiolipin, a negatively charged mitochondrial phospholipid<sup>13</sup>. The Wassermann test was modified several times to improve the detection of syphilis and was renamed as *Venereal Disease Research Laboratory* (VDRL), a combination of cardiolipin with lecithin and cholesterol, used until today as a screening test for detection of syphilis. However, when more specific methods, such as the immobilization test for *Treponema pallidum*, were used for syphilis diagnosis<sup>14</sup>, it was found that not all VDRL-positive individuals had syphilis. Therefore, positive VDRL started to be considered in other diseases as autoimmune disease<sup>15</sup>.

Conley and Hartmann, in 1952<sup>16</sup>, were the first investigators to identify circulating anticoagulant proteins (lupus anticoagulant) in two patients with SLE who had a false positive serological test for

syphilis and hemorrhagic disorders due to prolonged prothrombin time *in vitro*. Although Feinstein and Rapaport<sup>17</sup> first coined the term Lupus Anticoagulant (LA) in 1972, it was already known that the majority of LA-positive patients had no SLE<sup>18</sup>. Laurell and Nilsson, in 1957<sup>19</sup>, were the first investigators to recognize that individuals suspected of having SLE with false-positive VDRL had a high incidence of LA, thus establishing a relationship of LA to cardiolipin. Thus, strong perception in the scientific community pronounced that the disease was not a subset of SLE, but a single disease<sup>20</sup>. Hughes, in 1983, described several cases of arterial and/or venous thrombosis with positive direct antiglobulin test, thrombocytopenia, *livedo reticularis*, and obstetric complications related to LA, the first description of APS<sup>11</sup>.

### Pathophysiology

The molecular and cellular mechanisms by which APS promotes thromboembolic events are not yet fully elucidated. Changes in coagulation, hypotheses on procoagulant effects, and/or inhibition of anticoagulant effects are recognized<sup>21</sup>. Several theories of the pathophysiological mechanisms are strongly related to binding proteins and the aPL. There is evidence that aPL interferes with various levels of regulation of blood hemostasis<sup>22</sup>, such as endothelial cell activity (inhibition of prostacyclin release and increase of tissue factor)<sup>23</sup>, platelet activation<sup>22</sup>, fibrinolysis regulation<sup>24</sup> and its regulatory proteins (pathways of C and S proteins)<sup>25</sup>.

The main functions of activated platelets in blood coagulation are to provide intrinsic coagulation proteins and to expose external anionic phospholipids of the cell membrane (mainly phosphatidylserine) to catalytic formation for procoagulant factors<sup>22,25</sup>. There is evidence that the physiopathology involves activation and induction of platelet degranulation after binding to proteins located on their cell membrane. The main protein present in platelets membrane is  $\beta 2$ -GPI, which binds to aPL as a cofactor and antibodies. When  $\beta 2$ -GPI is absent, anticardiolipin does not inhibit the activity of prothrombinase complex on platelets, inducing a pro-coagulant state and resulting in thrombosis<sup>25</sup>. Other studies indicate that the aPL binds  $\beta 2$ -GPI and promotes, within activated platelets, the production of thromboxane A<sub>2</sub>, an eicosanoid responsible for vasoconstriction and coagulation<sup>26</sup>.

Endothelial cells (EC) play an essential role in hemostasis by balancing coagulation and anticoagulation through mediators, such as heparin-like molecules, thrombomodulin, protein C (PC), prostacyclins, and other<sup>25</sup>. Evidence suggests that aPL may promote a pro-coagulant phenotype in EC<sup>27</sup>. When aPL binds the exposed membrane of EC, a reduction in the contact area for binding clotting factors occurs, causing a paradoxical anticoagulant effect (increased coagulation time in the test). However, a procoagulant effect also occurs by inhibition of activation of proteins and messengers indirectly responsible for the synthesis of prostacyclins<sup>25</sup>. Prostacyclins are eicosanoids secreted by EC<sup>27</sup>, considered as natural antiplatelet

agents. With the reduction of prostacyclin levels, there is an increase in platelet aggregation and eventual thrombosis<sup>25</sup>. It is believed that aPL also increases the procoagulant activity of EC by increasing the synthesis of platelet-activating factor (PAF) and tissue thromboplastin (tissue factor) activity, which consequently would increase the extrinsic pathway of coagulation<sup>23</sup>.

Other phospholipid-binding proteins like  $\beta$ 2-GPI may be cofactors, such as prothrombin, PC, protein S (PS), and annexin V (AV). The activated serine protease PC uses PS as a cofactor to degrade the factors Va and VIIIa of the coagulation cascade, thus acting as an anticoagulant<sup>28</sup>. The aPL may modify various components of the PC pathway, such as thrombin inhibition (via prothrombinase), reduction of thrombin-thrombomodulin complex, inhibition of activity and assembly of activated PC complex, binding aPL with factors Va and VIII (hindering their degradation by PC), and direct binding to PC and PS<sup>29</sup>. PC may also affect the fibrinolytic system because its activated form reduces the action of inhibitor plasminogen activator (PAI), acting indirectly on fibrinolysis<sup>25</sup>.

AV presents anticoagulant activity by interfering in pro-coagulant factors of cell membranes. The likely suggested mechanism of anticoagulant action by AV is the formation of a shield, crystallizing along with the anionic phospholipids, inhibiting their pro-coagulation action<sup>30</sup>. It is believed that aPL can disorganize this shield and increase thrombin<sup>31</sup>.

Fibrinolysis is the process of fibrin degradation, the final product of the coagulation cascade. Fibrin is degraded by the action of plasmin, a plasminogen-derived enzyme that is activated by the action of tissue plasminogen activator (tPA). Another important mediator and regulator of fibrinolysis is the PAI<sup>27</sup>. Research indicated that fibrinolysis is impaired by high levels of PAI in patients positive for LA compared to controls<sup>32</sup>. The presence of antibodies to tPA has also been demonstrated in APS patients. These antibodies act on the catalytic domain of the molecule and decrease fibrinolysis activity by action against tPA<sup>24</sup>. Kallikrein, another serine protease, converts plasminogen to plasmin and may also impair fibrinolysis when its activity is altered. Prekallikrein has been shown to have low activity in LA-positive patients<sup>33</sup>.

Obstetric complications in APS are presumed to be related to changes in the mechanisms of coagulation, causing placental and/or endometrial spiral arteries thrombosis<sup>34</sup>. Micro and macroscopic examinations demonstrated infarction in more than 50% of placental tissue, fibrinoid necrosis of spiral arteries, acute atherosclerosis, and intraluminal thrombosis<sup>35</sup>. APL, such as anticardiolipin, also appears to inhibit chorionic gonadotrophin secretion, which affects embryonic development<sup>36</sup> and interferes with the regulation of placental anticoagulant protein (PAP). PAP is a natural anticoagulant with affinity for anionic phospholipids, and aPL is his competitive inhibitor. Thus, elevated

titers of serum aPL can be associated with placental thrombosis and abortion<sup>23,25</sup>. Fetal loss may result from the uteroplacental circulation deficit caused by reduced fetal blood supply, severe hypoxia, and fetal death<sup>37</sup>.

One of the clinical manifestations of APS is preeclampsia. Its physiopathology may be related to the association of aPL in the metabolism of prostaglandins, which results in high levels of thromboxane A2, leading to vasoconstriction and increased blood pressure. Another frequent clinical manifestation of APS is the intra-uterine growth restriction (IUGR), resulting from placental insufficiency. The low supply of nutrients increases hepatic glycogen consumption and, eventually, causes a reduction in fetal liver size and abdominal circumference. Another consequence to the fetus resulting from placental thrombotic obstruction is hypoxemia, which may impair fetal development, mainly related to neurological damage<sup>37</sup>.

The physiopathology of fetal loss in APS also seems to involve placental insufficiency with decidua shrinkage, infiltration of inflammatory cells, and deficiency in the trophoblastic invasion by the spiral arteries<sup>38-40</sup>. After these observations, the hypothesis of the direct action of aPL in trophoblast was investigated. It was observed a higher amount of  $\beta$ 2-GPI in the placenta of women with APS and recurrent miscarriage when compared to healthy individuals. As the trophoblast expresses potential targets for aPL, there may be insufficiency in the formation and proliferation of the syncytiotrophoblast, a decrease in the production of human chorionic gonadotropin and a reduction in the invasive capacity of the trophoblast<sup>41</sup>. In addition, the interaction between AV and aPL is related to intrauterine thrombosis mechanisms. AV is expressed in large quantities on the surface of syncytiotrophoblast and has a potent anticoagulant effect, contributing to the integrity of the placenta<sup>42</sup>. In that sense, the expression of AV has been shown to be decreased in the placentas of women with APS and that aPL can reduce AV in cultures of trophoblast cells<sup>43</sup>.

### Diagnosis

Due to the difficulty in definition and the diversity of clinical and laboratory presentation of APS, a consensus diagnostic criterion was developed. Proper diagnosis requires both clinical and laboratory prerequisites, and individuals may present one or more conditions that are not listed in the consensus criteria<sup>3</sup>.

Vascular thrombosis is within the clinical criteria of APS and is defined as one or more episodes of thrombosis (arterial and/or venous) that occur in any tissue or organ. Complications in pregnancy that are considered clinical criteria for APS include: one or more unexplained (morphologically normal) fetal deaths older than ten weeks of gestation; one or more preterm births (morphologically normal) before the 34th week of gestation due to complications such as eclampsia, preeclampsia, or placental insufficiency; three or more consecutive unexplained miscarriages before the 10th

week of gestation<sup>3</sup>.

Laboratory criteria are required for confirmation of APS, especially for detection of aPL. The laboratory criterion for the diagnosis of APS only considers aCL (IgG and IgM), a $\beta$ 2-GPI (IgG and IgM), and LA. Other aPL, such as antiphosphatidylserine, antiprothrombin, antiphosphatidylserine-prothrombin complex, anti-phosphatidylethanolamine, aCL IgA and a $\beta$ 2-GPI IgA, are also available but are not yet recommended due to lack of clinical evidence<sup>3</sup>.

For aCL and a $\beta$ 2-GPI, screening is performed by enzyme-linked immunosorbent assay (ELISA), and for LA, phospholipid-dependent coagulation assays are used. The ELISA technique for aPL is internationally standardized, and for results to be considered positive, must have moderate to high titers of aCL (> 40 GPL or MPL units), while for a $\beta$ 2-GPI, it is considered positive when the titer is higher than the 99th percentile. For LA research, it is necessary to use at least two coagulation tests with different principles. The aCL research is the most sensitive and positive in about 80-90% of patients, whereas a $\beta$ 2-GPI and LA are more specific. However, screening for three antibodies is recommended for a reliable diagnosis of APS<sup>3</sup>.

Low aCL test specificity is due to its positivity in other diseases, such as syphilis, viral and parasitic diseases, and other autoimmune diseases. To exclude transient antibodies, the laboratory criterion establishes that a new test should be performed in an interval of at least 12 weeks after first positive results. This interval between tests avoids false positives; however, a test with an extended interval between clinical manifestations may compromise the diagnosis. The international criteria do not advise the diagnosis with an interval of more than five years between clinical and laboratory criteria, whatever of which occurred first<sup>3</sup>.

### Treatment

Treatment of APS should be at an individual basis, and many factors should be taken into account, as the number of antibodies, the patient's age, and history of thromboembolic events. The type of anticoagulation should be defined according to the site of thrombosis, and secondary prevention should last for long periods. The treatment of choice for pregnant women with APS is the combination of unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) given subcutaneously, with or without additional low-dose acetyl-salicylic acid (ASA)<sup>44,45</sup>. The frequency of use is important because discontinuation may contribute to the risk of thrombosis or abortion recurrence, except for rare cases when levels of aPL have become negative for more than three months<sup>46</sup>.

The therapeutic regimens suggested for the treatment of APS in pregnancy are different according to the severity of the woman's medical history. APS without previous thrombosis or recurrent early miscarriage suggests the use of low-dose ASA alone or together with either LMWH or UFH. In cases of APS with prematurity due to severe pre-eclampsia or placental insufficiency and cases of previous

thrombosis or fetal death, low-dose ASA plus LMWH or UFH is suggested<sup>45</sup>.

The treatment of APS in pregnant women aims maternal-fetal health through the prevention of abortion, placental insufficiency, preterm delivery, and preeclampsia. There is also a need to control the risk of gestational thromboembolism<sup>47</sup>. The use of ASA is normally recommended in preconception because of possible benefits in embryo implantation, and the use of heparin is begun after ultrasonography, with the confirmation of a viable embryo (first trimester)<sup>48</sup>. However, a Cochrane Systematic Review (2005) concluded that the treatment of choice of APS's patients with recurrent miscarriage would be the combined use of LMWH and low-dose ASA<sup>44</sup>. However, expert guidelines also recommend the combined use of ASA with UFH as an alternative<sup>49</sup>. The use of only ASA in certain cases cannot be ruled out<sup>45</sup>.

### Conclusion

Despite the complexity of APS and its obstetric and thrombotic complications, some advances have been achieved in the understanding of its pathogenesis. Therefore, it is known that the disease is a coagulation disorder, with procoagulant effects and/or inhibition of anticoagulant pathways. These hypotheses regarding physiopathological mechanisms are strongly related to binding proteins and aPL. Pregnancy loss also seems to involve placental insufficiency with decreased decidua, inflammatory cell infiltration, and impaired trophoblastic invasion of the spiral arteries.

Considering the difficulty of APS diagnosis, due to the diversity of clinical and laboratory presentation, confirmatory diagnosis requires both clinical criteria and laboratory evidence.

Treatment should be at an individual basis, and several factors should be taken into account, such as the detected antibodies, patient's age and history of thromboembolic events. The periodicity of medication usage is important, especially during pregnancy, once discontinuation may contribute to the risk of thrombosis or miscarriage recurrence. Treatment in pregnant women aims maternal-fetal health through the prevention of abortion, placental insufficiency, preterm delivery, preeclampsia, and gestational thrombosis.

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