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Chapter

Antiphospholipid Syndrome and Pregnancy-Diagnosis, Complications and Management: An Overview

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Abstract

Antiphospholipid syndrome which is also known as APS is an autoimmune disease which represents an acquired form of thrombophilia. The etiology of APS remains unknown. This disorder occurs when the immune system mistakenly attacks some of the normal human proteins and manifests itself as recurrent arterial or venous thrombosis and it could emerge after abortions or in recurrent pregnancy loss. In APS, the body produces the wrong antibodies against phospholipid-binding proteins, that is present in the blood and plays an important role in coagulation. Antibodies are specific proteins that usually target and neutralize the body's invaders, such as viruses and bacteria. When antibodies attack phospholipid-binding proteins, blood clots abnormally. Specifically, it could cause blood clots in veins or arteries leading to stroke and various pregnancy complications such as: endometrial death, miscarriage, preeclampsia, intrauterine growth restriction and prematurity. APS is divided into primary and secondary, which is associated with autoimmune diseases and more often with systemic lupus erythematosus (SLE), while antibodies against cardiolipin are detected in many other conditions (infections, malignancies, drugs, etc.). The symptoms of APS, in addition to arterial and/or venous thrombosis and pregnancy complications, are multisystemic and the differential diagnosis of the primary APS from the secondary, in the context of SLE, is of particular clinical interest and is subject of this literature review.

Keywords: antiphospholipid syndrome, pregnancy, management neonatal outcome

1. Introduction

APS characterized by thrombosis of the arteries, veins and microvessels and/or with pregnancy morbidity, with persistently elevated antiphospholipid antibody (aPLs) titers. The syndrome was first described in 1983 by Professor G. Hughes, at Hammersmith Hospital (Hughes Syndrome) [1, 2]. APS is a prothrombotic condition (with related complications such as deep vein thrombosis, pulmonary embolism, etc.), belonging to autoimmune diseases of unknown cause, and is strongly associated with pregnancy [1–3]. Generally, autoimmune diseases namely Sjorgen's syndrome, Spondylanthritis, rheumatoid arthtritis RA have an incidence of 5–8% in the general population organoid or systemic, and represent the 2nd cause of hospitalization in Internal Medicine Departments and the 3rd cause of morbidity/mortality [1–4]. APS occurs as primary in the absence of findings of other autoimmune diseases or as secondary in 36% of cases in the context of another autoimmune disease (SEL, Sjogren's disease, inflammatory bowel disease, etc.), while it is present in about 5% of patients with subclinical SEL or coexists with another underlying systemic autoimmune disease in 6% of cases [5, 6].

2. Epidemiology

The incidence of the syndrome is increased with age. During pregnancy, aPLs detection ranges from 0 to 11%, with an average incidence of about 2%. On the contrary, the syndrome is detected in up to 37% of the patients with systemic erythematosus lupus (SEL). In the nonpregnancy setting, venous thromboses are more common than arterial ones and can be diagnosed by imaging techniques and/or histologic evidence [5–7].

3. Frequency

According to literature APS is the cause for 1 out of 5 Deep Vein Thrombosis ('DVTs'), 1 out of 5 cases of SLE (arterial stroke) in young patients (age <45 years) and 1 out of 5 miscarriages. Especially for Obstetrics Hughes Syndrome is currently recognized as the leading cause for the miscarriages [5–7]. In addition, APS is diagnosed as the underlying diagnosis in a still unknown percentage of cases previously misdiagnosed as migraine, Alzheimer's disease, and Multiple MS. It is estimated that the true incidence of the syndrome can be up to 1–2% or more in the general population [5–7]. Correlations-Percentages The mean age of APS onset is >30 years, with a female to male ratio of 5:1 and relapses usually take place at the same or similar area of the body. There is no apparent racial preference, but an increased incidence of SEL is reported in African Americans and Spaniards. Patients with SEL have positive aPLs in a percentage of 15–35%, but only about 50% of these patients will develop APS symptoms [5–7].

4. Clinical subtypes

Special categories of APS are described usually correlated to the target-organ or the severity of the manifestations. The following are included: Generalized APS, Arterial APS, APS and heart, APS and kidneys, Cerebral APS, Pediatric APS, Neonatal APS, Catastrophic CAPS and Obstetric APS [5–7].

5. Catastrophic APS

The 0.8% of the cases is characterized as Catastrophic Antiphospholipid Syndrome (CAPS). It is a very rare and severe form of APS. There are diffuse clots in the small vessels throughout the body. Sometimes it can appear as the first manifestation of APS and even without clinical or serological confirmation of SEL. Early diagnosis is necessary and immediate start of an aggressive treatment is inevitable [5, 7–9]. CAPS is caused when at least 3 different systems are affected at intervals of days or weeks, with multiple thrombosis in large and small vessels. The organs that are usually affected are: a) kidneys, b) lungs, c) heart, d) small-large vessels with consequences as peripheral limb ischemia, stroke, myocardial infarction, thrombosis of blood vessels of abdominal organs with a mortality rate of 50% [5, 7–9]. The observed thrombocytopenia is usually mild between $100-150 \times 10^9/L$ but severe thrombocytopenia can be also observed. The prevalence of the syndrome in the general population ranges between 2% and 4% meaning 40–50 patients in 100,000 based on the criteria (mean age of diagnosis 34 years) and 7: 1 in the SEL/APS combination [5, 7–9].

6. Therapeutic interventions for catastrophic APS

Anticoagulant therapy + corticosteroids.
Anticoagulant therapy + corticosteroids + plasmapheresis.
Anticoagulant therapy + corticosteroids + IV γ-globin.
Anticoagulant therapy + corticosteroids + plasmapheresis + IV γ-globulin.

Diffuse intravascular coagulation is not usually seen in primary or secondary APS but it occurs in about 25% of patients with catastrophic APS. It is estimated that more than 53% of cases are related to the primary syndrome. It is estimated that approximately 10% of patients with primary APS will be diagnosed with another autoimmune, disorder, such as SEL, at some point in their lives which is estimated to coexist in up to 37% of patients with APS. Patients with primary APS and a female/male ratio incidence of 3.5: 1 should not be classified as SEL patients, as they are two different disease entities [5, 7–9]. Also, aPLs found in a variety of rheumatic and autoimmune diseases should not be confused with APS. The latter includes autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, rheumatoid arthritis and cutaneous manifestations such as edema. Also, the same antiphospholipid antibodies are detected either temporarily or permanently after various infections, such as hepatitis A, hepatitis B, acquired immune deficiency (AIDS), mumps, toxoplasmosis, erythema etc. The use of certain medicines, such as hydralazine, procainamide, and amoxicillin, phenothiazines may cause a serious differential diagnosis with APS, which requires immediate diagnostic and therapeutic treatment to reduce the increased maternal risk, and in particular perinatal morbidity and mortality due to placental infarction [5, 7–9].

7. Pathophysiology

Dysfunction of the vascular epithelium as well as oxidative damage and modifications of phospholipid-bound proteins that interfere with the regulation of coagulation are possible. It occurs when the immune system mistakenly attacks some of the normal proteins in the blood. The mechanism by which aPLs causes thrombosis is not fully understood. APLs consist of a heterogeneous group of

autoantibodies that react primarily with plasma proteins associated with negatively charged phospholipids (epitope formation). Moreover, also react directly with both phospholipid-binding proteins and phospholipids [10–12].

However, aPLs have been shown to target not only cell membrane phospholipids, but also plasma proteins. Initially aPLs are directed directly against negative cell membrane phospholipids and autoantibodies are directed against plasma proteins with high affinity for these anionic phospholipids [10–14]. Phospholipids are like building blocks of cell membranes and the appearance of aPLs is due to the "projection" of their anions to the extracellular space [10–14]. This phenomenon is usually happening due to various causes, such as trauma, ischemia, inflammation, infections, or drug interactions. They were first observed in 1906 in 1–5% of the normal population.

The prevailing theory is that APS initially causes a disorder in cell apoptosis procedure resulting in the exposure of cell membrane phospholipids and their subsequent binding to various plasma proteins, such as β2-glycoprotein I. This binding leads, through activation, to generation of intracellular mediators (such as nuclear factor kappa B and mammalian target of rapamycin), and the formation of a phospholipid-protein complex resulting in the discovery of a new epitope, which then becomes target of autoantibodies [10–14].

Recent studies suggest that oxidized β2-glycoprotein I is capable of binding to and subsequently activating dendritic cells in a similar pathway to the one induced by activation via the Toll-like receptor 4 (TLR-4), resulting in its induction and the production of autoantibodies.

A total of 4 types of aPLs have been isolated [14–18].

1. Antibodies that give a false positive serological test for syphilis.

2. Lupus anticoagulants, which are antibodies to plasma proteins that bind to anionic phospholipids and cause prolonged results in laboratory methods of coagulation control, such as activated partial thromboplastin time (aPTT), kaolin clotting time (Kaoline Clotting)-KCT) and dilute Russell Viper Venom Time (dRVVT). These proteins are prothrombin or annexin V [14–18].

3. Antibodies to cardiolipin and phosphatidylserine. These antibodies may be IgA, IgG or IgM and may cross-react with lupus anticoagulants.

4. Antibodies to β2-glycoprotein-I, which are detected in a significant percentage of patients with primary or secondary antiphospholipid syndrome, while in 11% of patients it is the only laboratory finding [14–18]. This association results in either the discovery of "hidden" antigenic epitopes or the creation of new or simply increasing the concentration of weak antigenic sites in such quantities as to elicit an immune response.

Types of anti-b2 GPI antibodies [14–18]. There are several types of anti-β2 glycoprotein I antibodies, but not all of them are harmful. Those that target specific β-2 glycoprotein epitopes, such as the epitope in the N-terminal I domain of the molecule, are associated with the onset of clinical manifestations of the syndrome [14–18].

8. Correlation between APS clinical events and the type of anti-β2GPI antibodies

Patients with triple positivity in aPLs: have higher anti-β2GPI – domain I antibody titers, compared to patients with single or double positivity. Almost all

anti-β2GPI – domain I IgG antibodies tested positive after 12 weeks, in contrast to innocent transient aPLs, which appear to be immune to infections. Although anti-β2GPI-Domain 1 (β2GPI-D1) IgG antibodies have been associated with thrombosis and pregnancy morbidity in APS patients, these antibodies are found in only one third of the patients [14–18].

9. Cell β2GPI/anti-β2GPI antibody receptors

Annexin A2 and Toll-like receptor (TLR) 4 are receptors for the entire β2GPI molecule. However, the absence of both of these receptors does not lead to the complete inhibition of the binding of the anti-β2GPI antibody, a finding that supports the view that there are additional surface adhesion molecules that play a role. TLR1, TLR2 and TLR6 are potential cell receptors [14–18].

10. Association of APS with pathogenic intestinal bacteria

B2GPI binds to LPS via domain V. Presence of a large amount of LPS probably increases the vascular distribution of APLs, by increasing the expression of TLR2 and especially TLR4. Because the main source of LPS in healthy people is the gut, it is possible that the presence of gut microbes in the gut increases them. Administration of intestinal flora-specific antimicrobial therapy to experimental animals showed a reduction in the thrombotic manifestations of APS [14–18].

11. The role of the complement in the pathogenesis of APS

Immediate evidence: In experimental models with C6-deficient rats and C5-depleted mice, it was shown that the addition of monoclonal anti-domain I MBB2 did not induce thrombosis or miscarriage. C4d and C3b sections have also been found in deposits on the placenta of women with APS [14–18].

Indirect evidence: In-vivo studies of the efficacy of drugs with C5 action. The non-complement-fixing anti-domain I monoclonal MBB2 [DELTA] Ch2 and the complement inhibitor C5-inhibitor rEV576 prevented the thrombotic complications of APS in vivo in experimental animals.

12. APL action mechanisms

APLs activate endothelial cells resulting in the expression of adhesion molecules (such as intercellular cell adhesion molecule-1 ICAM-1, vascular cell adhesion molecule-1 VCAM-1, E-selectin), and ultimately the overproduction of tissue factor TF.

APLs activate monocytes and cause increased tissue factor expression.

APLs activate platelets resulting in increased glycoprotein 2b-3a expression and thromboxane A2 synthesis. It has also recently been shown that aPLs induce the release of NETs from endothelial cells and these in turn further activate platelets. Their presence is enhanced by other conditions such as neoplasms, myelodysplastic syndromes, paraproteinemias, etc. [14–18].

These proteins (aPLs) normally bind to the phospholipid components of membranes and protect against activation of coagulation mechanisms. Autoantibodies displace these "protective" proteins and promote the formation of clots in the cells of the vascular endothelium resulting in arterial and venous thrombosis.

In particular, aPLs antibodies include antibodies to Lupus Anticoagulant (LA), antibodies to cardiolipin (aCL), antibodies to β2GPI (αβ2GPI) and antibodies to other phospholipid-binding proteins and other phospholipids. LA, aCL and αβ2GPI antibodies are important in the diagnosis of antiphospholipid syndrome [12–18].

13. The most likely explanation for the pathogenesis of APS

They occur in people with a genetic predisposition after accidental exposure to infectious agents or in a rheumatic disease environment such as SEL. It is the "second hit" theory required for the full development of the syndrome. Of course, not all people with antiphospholipid antibodies have thrombosis or obstetric complications.

The "two-hit theory" has been proposed, i.e. that in the manifestation of the disease only the presence of antiphospholipid antibodies is not sufficient but a second thrombotic risk factor must coexist (e.g. age, hypertension, infection, inflammation, diabetes mellitus, obesity, smoking, pregnancy and obstetrics, surgery, etc.) [14–18].

Regarding the pathophysiology of obstetric complications, trophoblast and perishable blood vessel thrombosis is at the heart of this process. Various mechanisms have been proposed that lead to this result:

1. aPLs bind to Annexin V molecules and reduce the active levels of the protein in the blood. Annexin V is a protein that covers the negatively charged phospholipids of the cell membrane when exposed to the extracellular space, thus making it impossible to activate the thrombosis mechanism, which would occur under other conditions. The reduction of the levels of this protein activates the thrombosis of the small vessels of the trophoblastic villi and consequently the abnormal penetration of the trophoblast into the myometrium.

2. aPLs may reduce the levels of endogenous anticoagulant proteins C and S.

3. aPLs can bind to and activate endothelial cells. This results in the production of cellular inflammatory agents (VCAM-1, ICAMP1, E-selectin), which eventually attract monocytes to the area, which contribute to the production of clots and the apoptosis of endothelial cells.

4. Binding of aPLs to the cell membrane β2-glycoprotein-1 complex and phospholipids reduces the efficacy of this complex, as an anticoagulant.

5. Binding of aPLs to platelet cell membrane components, such as phosphatidylserine, results in their injury, which promotes their adhesion and activation of the prothrombotic chain. Finally, the activation of the complement seems to play an important role in the pathophysiological chain of events, which may be necessary in those processes that lead to fetal death or intrauterine growth retardation [14–18].

14. Diagnostic criteria

"APL profile" includes: the type of autoantibodies and the presence of 2–3 types of autoantibodies. The title of aPLs is mid-high instead of low and their persistent positivity is certified by multiple tests. APS is characterized by the following lab test results [19–22].

Persistent presence of antiphospholipid antibodies (at least 2 positive results during a period of >12 weeks) including lupus anticoagulant, anticardiolipin antibodies and b2-glycoprotein 1$^\alpha$ antibodies [19–22].

Risk factors: pregnancy, labour, contraceptives, malignancy, infection (E-coli, Shigella, Salmonella, Streptococcus, Staphylococcus etc), injury, surgical procedures, operations, fractures, drugs, no compliance to the anticoagulant therapy and many other factors [19–22].

15. Laboratory findings

Usually there is severe thrombocytopenia, positive direct Coombs, microangiopathic hemolytic anemia, DIC findings in some patients and the presence of a heterogeneous group of antiphospholipid antibodies.

Laboratory confirmation is done with clotting assays for the detection of lupus anticoagulant and with solid phase assays-Elisa for the detection of anti-cardiolipin and anti-β2 glycoprotein antibodies [19–24].

1. The positive ACA IgG, Wolf Anticoagulant, ANA, ds-DNA, ENA (Ro, La) etc. are a heterogeneous group of IgG/IgM antibodies directed against plasma proteins involved in coagulation cataract activation. They are attached to PLs of the outer membrane of cells. While these antibodies cause thrombosis in vivo, in vitro prolong phospholipid-dependent coagulation tests. Detection of lupus anticoagulant (coagulation tests – 3-step procedure) prolongs the phospholipid-dependent coagulation time. Lupus anticoagulant is considered positive when it is detected in at least one of the two methods with the following diagnostic criteria – steps:

15.1 The screening test

a. Screening procedure when prolongation is observed in at least one of the phospholipid-dependent coagulation methods

- Activated partial thromboplastin time (aPTT),

- Russel snake venom dilution time (dRVVT)

b. Mixing patient plasma 50:50 with normal plasma fails to correct prolonged screening test time

- Confirmation of the presence of coagulation inhibitor and not the absence of coagulation factor mixing test: Proof that the prolongation is due to the presence of coagulation inhibitor.

c. The addition of extra phospholipids corrects the prolonged clotting time. Confirmation test: Evidence that this inhibitor is directed against phospholipids [19–24].

15.2 Anti-cardiolipin antibodies (aCL) (IgG-IgM)

Presence of antibodies against cardiolipin (aCL) – IgG moderately to strongly positive (>15–20GPL) – IgM(> 15 – 20MPL) moderate to strongly positive, but with the simultaneous presence of LA [19–24].

They are directed against epitopes resulting from modulatory changes in the β2GPI (domains-V) molecule after binding to cardiolipin. They are directed directly against cardiolipin (CL). They are associated with infections, syphilis, in healthy individuals and are not related to APS [19–24].

15.3 Antiβ2 GPI antibodies (IgG-IgM)

Antibodies against β2GPI (anti-β2GPI), β2-glycoproteinI (β2 GPI) natural anticoagulant plasma protein associated with negatively charged molecules: phospholipids, heparin, lipoproteins (oxLDL), activated PLTs/Ecs, apoptotic cell membranes.

They turn directly against β2-GPI and are a heterogeneous population that recognizes epitopes in different regions (I-V) of the protein.

Antigen: purified human β2GPI with tight adhesion to plates for low avidity binding of antibodies and detection of domain I in situ.

Anti-LA/β2GPIs are positively associated with a particularly increased risk of thromboembolic complications and detection with new methods offers new opportunities for risk assessment [19–22].

ELISA: αCL/β2GPI detects various antibody specificity es with relatively low clinical utility – their exclusion from the criteria has been widely discussed, they are still a diagnostic criterion but current screening guidelines should be followed faithfully [19–22].

aβ2GPI antibodies: correlate very well with the clinical manifestations of APS – They are positive in patients with thrombosis who have negative LA and aCLs.

If aPL title > 40 GPL or IU at least 2 times in 12 week interval then APS is diagnosed. The most important are Abs against β2GPI and against prothrombin which show LA activity. Lupus anticoagulant is part of the APS antibody spectrum, reacting in the liquid phase. In contrast, other aPLs such as anti-CL and anti-β2-glycoprotein (β2-GPI-1) antibodies are detected by solid-phase immunoassay. For the APS diagnosis it is necessary to use both solid phase methods and coagulation tests for LA [19–24].

16. Other aPLs

Prothrombin antibodies: They have good association with LA, use in seronegative APS.

Antibodies to Annexin V, II Associated with thrombosis in APS.

Proteins against protein C and S: Lower sensitivity and specificity than aCLs/IgG.

Antibodies against vimentin (anti-Vim/CL: Positive (55%) in seronegative SN-APS, their use needs documentation.

The diagnosis of the syndrome should be avoided when a period of <12 weeks or > 5 years separates the clinical from the laboratory characteristics (regardless of the most presented first) [24–26].

17. Secondary antibodies in APS

- IgA anticardiolipin antibodies

- anti-β2 glycoprotein I IgA antibodies

- antiphosphatidylserine antibodies

- anti-phosphatidylethanolamine antibodies

- anti-prothrombin antibodies

- antibodies against the phosphatidylserine-prothrombin complex

APLs are a very heterogeneous family of antibodies and more than 30 different antibodies have been reported in patients with APS called 'antibody burst'. Their positivity does not offer much in the absence of clinical findings although confirmation is necessary for the duration of the symptoms. Ultimately the history and clinical picture determine the treatment [24–28].

- Presence of positive lupus anticoagulant (LA) in plasma, in at least two tests with an interval of at least 12 weeks between them offers reliable criteria for diagnosis.

- Moderate presence of high title of anticardiolipin antibodies (aCL) IgG or IgM in serum or plasma (eg> 40 IgG phospholipid units-GPL/mL or IgM phospholipid units-MPL/mL or> 99th percentile) in at least two intervals between them for at least 12 weeks.

- Moderate presence of high titer anti-beta-2 glycoprotein I IgG or IgM antibodies in plasma or serum (> 99th percentile) in at least two tests with an interval of at least 12 weeks [19–26].

- Extension Activated partial thromboplastin time (aPTT)

- Falsely positive test for syphilis

- Low levels of total protein S

- Hemolytic anemia. It occurs quite frequently and is particularly associated with the presence of anticardiolipin IgM antibodies

- Thrombopenia. It is quite common in patients with APS (22% at diagnosis, 30% overall) and is associated with paradoxical thrombosis even with low platelet counts. It is of course possible that when their number is <50,000/μL there is a coexistence risk of bleeding, making the treatment of these patients particularly difficult and urgent.

Positive antinuclear antibodies are often found at low titers, without necessarily being associated with the presence of SLE [19–26].

Coagulation methods for detecting anticoagulant lupus are affected by oral anticoagulant therapy (coumarin, newer anticoagulants), but also by therapeutic doses of standard heparin. For this reason, testing should be done before starting or after cessation of these drugs. In contrast, administration of low molecular weight heparin in prophylactic doses of aspirin or clopidogrel does not appear to significantly affect the detection of anticoagulant lupus.

18. APS-pregnacy

18.1 Clinical findings

APS is diagnosed in up to 40% of women with a history of miscarriage, intra-uterine fetal death (> 18th week of gestation) or placental vascular disease, ie preeclampsia, intrauterine fetal growth retardation, placental abruption. However, in a percentage of 50–60% the causes remain unclear [26–34].

18.2 Manifested clinically with

- recurrent vascular thrombosis (venous and/or arterial, and/or capillary), and/or with

- obstetric vascular complications:

- abortions <10th week of pregnancy

- delayed miscarriages

- endometrial death

- preeclampsia and/or eclampsia, or HELLP syndrome

- intrauterine growth restriction (IUGR) [26–38]

18.3 Obstetric antiphospholipid syndrome triggered in pregnancy

The findings of some studies raise the suspicion of a subtype triggered by gestational APS, with a transient increase in antiphospholipid antibodies only during pregnancy.

18.4 Pregnancy morbidity

The morbidity of pregnancy is certified by the following parameters:

1. ≥1 unexplained fetal death > 10th week (morphologically healthy fetus)

2. ≥1 preterm birth <34th week (preeclampsia or severe placental insufficiency)

3. ≥3 consecutive miscarriages <10th week after exclusion of other pathologies such as anatomical, hormonal, chromosomal abnormalities, history of thromboembolic episodes

   - at least 1 unexplained fetal death in the 2nd or 3rd quarter (> 10 W)

   - at least 1 birth at gestational age <34 W, due to preeclampsia or placental insufficiency

According to the International Consensus Criteria of 2006, any of these antibodies, if tested positive in at least two laboratory tests at least 12 weeks apart, in combination with a clinical thrombosis or obstetric complication, leads to the diagnosis of APS.

There must be at least one laboratory and one clinical criterion for the diagnosis of primary APS. Antiphospholipid antibodies are detected by the enzyme-linked immunosorbent assay (ELISA) in which the phospholipid cardiolipin is used as the antigen. It is actually a complex of cardiolipin with a serum protein called β2-glycoprotein I (β2-GPI). The above protein plays an inhibitory role in blood clotting, and when the complex binds to antiphospholipid antibodies, its effectiveness as an anticoagulant decreases [26–42].

Laboratory findings usually show high titers of IgG or IgM antibodies against cardiolipin or lupus anticoagulant, which must be detected in the same patient in two different samples taken at least 6 weeks apart. The above mechanism is due to the frequent recurrent thrombi that affect both the large and small vessels of the arterial or venous limb. In addition, mild cytopenia occurs quite often, which usually subsides with the end of pregnancy.

18.5 The diagnosis of the syndrome can be suspected in

Arterial or venous thrombosis.

Presence of anticardiolipin antibodies, IgG, IgM, Anti-beta2-GPI and Lupus anticoagulant [26–42].

Adverse outcomes of pregnancy.

APS can be diagnosed, if one or more of the clinical criteria and one or more of the laboratory criteria are met.

Although a causal association between obstetric complications and antibody detection is difficult to identified, however the lupus anticoagulant is the major predictor of labor adverse events including both mother and fetus. Although spontaneous abortions before the 10th week are relatively common in the general population, it seems that this risk is higher in patients with the syndrome. Fetal demise due to insufficient blood flow is most probably caused by placental insufficiency triggered by placental infarctions [26–42].

This placental insufficiency is likely to be associated with delayed intrauterine fetal development, severe preeclampsia, premature rupture of the membranes, premature placental abruption, and preterm fetal death (preterm and preterm death) in the 20th week of pregnancy, which usually has the worst outcome, as well as the increased risk of premature ejaculation [26–42].

Regarding the relationship of aPLs with preeclampsia, their detection seems valuable only in cases of severe preeclampsia before the 34th week of pregnancy. For cases of severe intrauterine fetal growth retardation, there are studies that report its relationship to the presence of antibodies, while other studies do not seem to reach this conclusion.

19. Discussion

The risk of miscarriage in women with antiphospholipid antibodies is higher from the 10th week of pregnancy onwards. But also in women with a history of six miscarriages before the 10th week of pregnancy, antiphospholipid antibodies are detected in rates of 10 to 20% without the presence of other clinical manifestations [42–44].

Pregnancy complications in women with APS are due to decreased placental perfusion based on local thrombosis, which is probably caused by the interaction of aPL with annexin V of the trophoblast resulting in inhibition of its anticoagulant activity. Other manifestations of aPL include thrombocytopenia (40–50%), hemolytic anemia (14–23%), renal disease that has only recently been recognized

as a consequence of APS, and Liveto redicularis [42–48]. Female patients with APS and kidney disease from antiphospholipid antibodies typically have high blood pressure, which is an additional serious risk to their pregnancy and can lead to the complications mentioned above [42–48].

20. When will we check a patient for aPLs

1. Spontaneous venous thrombosis at age <45 years (deep vein thrombosis, pulmonary embolism)

2. Arterial thrombosis in a person <45 years of age (myocardial infarction), without risk factors

3. Recurrent pregnancy loss

4. Thrombosis and vascular diseases associated with SLE

5. Recurrent thrombocytopenia of unknown etiology

6. Neurological manifestations

7. Acquired heart valve disease

8. Liveto redicularis

9. Patients with a false positive RPR test

10. Prolongation of any coagulation test [42–54].

Finally, for the presence of antiphospholipid syndrome, women of reproductive age who have any of the following characteristics should be screened (other than those mentioned above): False positive test for syphilis, stroke and venous thrombosis without other predisposing prolongation of aPTT, SLE and autoimmune hemolytic anemia [48–58].

Of course, from the medical history of the pregnant woman should always be sought the episodes of venous thrombosis that are usually observed in the veins of the lower extremities, which are not necessarily accompanied by episodes of pulmonary embolism, but also in rarer localizations, such as the sphenoid sinuses of the skull and the small visceral vessels. Autoantibodies and microthrombotic mechanisms could affect the normal implantation, the trophoblasts' expansion and the development of effective fetoplacental circulation leading to abortions of the first trimester [48–58].

At older gestational ages endometrial death is attributed to massive placental thrombosis while the mechanisms associated with other complications (preeclampsia) are unknown. In terms of laboratory findings, moderate to high IgG or IgM antibodies to cardiolipin (20–50 GPL, 20–80 MPL respectively) or lupus anticoagulant should be detected [48–58].

Patients who present with clinical manifestations of APS could be permanently negative for the three main autoantibodies. Women with positive aPLs are more likely to have thromboembolic events, miscarriage or fetal death, intrauterine growth retardation, severe preeclampsia, and placental abruption. However, the presence of these antibodies cannot exclude the possibility of a successful

pregnancy and/or estimate the risk of potential complications. The existence of a burdensome obstetric or pathological history seems to play a more important role, since the reporting of thrombotic episodes, SLE or fetal death is associated with a 40% chance of premature birth and a greater than 30% chance of intrauterine growth retardation. From the beginning of pregnancy until the 20th week, visits should be made every 15 days and then every week until delivery [52–60].

Ultrasound examination of fetal development, but also the evaluation of the amount of amniotic fluid, should begin in the 16th week and be repeated every month unless there is a pathological finding. There is evidence that bilateral presence of notches in the uterine arteries, on Doppler screening at 24 weeks, can detect with satisfactory sensitivity those patients who develop preeclampsia and IUGR if they have a positive lupus anticoagulant. The umbilical artery test with Doppler from the 26th week until childbirth offers great help, while for the same period of time a weekly cardiotocographic test (non-stress test) should be performed, as well as an ultrasound control of the amount of amniotic fluid. The most commonly used regimen involves the administration of aspirin (80 mg daily) and heparin, either crystalline or low molecular weight, in prophylactic doses [60–64].

The patient's health condition before pregnancy will determine the resumption of therapy after childbirth. Thus, two to three days after delivery, women taking coumarin derivatives before pregnancy (due to a history of a thromboembolic event) should discontinue heparin (after an INR of 2–2.5) and resume taking these drugs. To decrease the possibility of a new thromboembolic event, women with a thrombotic history during the late pregnancy should be treated with prophylactic doses of heparin or coumarin derivatives for 6 weeks postpartum. For women without a thrombotic history, the anticoagulant therapy could be continued for the first five postpartum days at most. Compared to conventional heparin, less complications were related to low molecular weight heparins. Regarding the duration of the treatment, some recommend the prophylactic administration until the completion of the 37th week, then proposing induction of labor and others the administration until the automatic onset of labor with the simultaneous administration of vitamin K antagonists.

Hyperimmune γ-globin is no longer recommended because there is no clear evidence of improved perinatal outcome. Coumarin is not administered particularly in the 1st and 3rd trimesters as potential teratogens and due to easy passage through the placenta coagulation disorders in the fetus and because they are associated with greater maternal morbidity. Their administration is indicated only in rare cases of contraindication to heparin or aspirin [60–68].

Complications of anticoagulant therapy in pregnancy include embryopathy (nasal hypoplasia, spotted epiphyses), CNS abnormalities (Dandy-Walker syndrome, visual atrophy), fetal bleeding, hemorrhagic manifestations, skin allergies, thrombocytopenia and osteoporosis [60–72].

The basic principles of APS treatment include the systematic monitoring of the pregnant woman, the continuous assessment of the condition of the fetus, the administration of medication and the selection of the most appropriate time and manner of delivery. Despite the lack of large cross investigations, the usual therapeutic directions includes the corticosteroids, the aspirin, heparin, hyperimmune gamma globulin synd coumarins.

Treatment should be applied only when the risk of complications is considered to be higher and after a thorough discussion with the pregnant woman. The prognostic factors of poor outcome are the title of anticardiolipin antibodies and the obstetric history [60–72].

Aspirin significantly reduces the risk of thrombosis by blocking platelet aggregation. It is considered safe during pregnancy. Until now, there are no

final conclusions regarding the efficacy of the above therapy as monotherapy. Hydroxychloroquine inhibits aPL-B2GPI complexes on phospholipid surfaces, annexin A5, TF tissue factor, TLPs *Toll-like receptors*, statins such as pravastatin inhibition of *Nuclear factor kappa B* (*NF-κB*) is protein transcription factor, *Anti-CD20* monoclonal antibodies (mAbs) resistant APS and aspirin are recommended to prevent and treat preeclampsia [60–72].

The choice of time and method of delivery depends mainly on the presence or absence of complications of the disease during pregnancy. In any case of intra-uterine suffocation of the fetus, induction of labor is required with all the possible harmful consequences of prematurity. In asymptomatic forms of the disease and when there are no signs of fetal difficulty, childbirth is preferred as much as possible at the end of pregnancy.

Worldwide, the route of delivery has been the subject of intense controversy and it is not clear if vaginal delivery or cesarean (c-)section is safer for the mother. Thus, prelabour c-section or vaginal delivery should be guided by obstetric criteria [60–72].

APS (primary or secondary) is a chronic systemic autoimmune disorder that mainly affects young women of childbearing age. APL can impair trophoblast function and can cause implantation failure by not allowing fusion of the cytotrophoblast and can also developing small thrombophilia increase abortion rate. Natural killer cells attach to the cytotrophoblast of the embryo. However, the mechanisms by which such cells may or may not affect the embryo is not proven. Moreover, after the implantation, there is a slight inflammatory response. Patient with recurrent miscarriages and infertility develop less prominent reaction that may prevent the fetus from implantation [72–74].

21. Conclusion

The effect of the syndrome on pregnancy is accompanied by a multitude of serious complications that significantly increase the rates of maternal and especially perinatal morbidity and mortality.

There is an urgent need to create a new laboratory method, which will detect with great sensitivity and specificity all antiphospholipid antibodies and for this purpose large multicenter studies are already being done, the results of which are awaited.

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