Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 8 (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

The Impact Of Antiphospholipid Syndrome On Pregnancy Complications At Different Gestational Stages And The Influence Of Combined Therapeutic Approaches

Humbatova Leyla Ilgarovna[1], Shulcheva Anastasia Sergeevna[2], Anufrieva Alina Aleksandrovna[3], Yudichev Nikita Andreevich[4], Korshunova Arina Ivanovna[5], Bryksina Elena Sergeevna[6], Khuzhakulov Dzhonibek Khoshimzhonovich[7], Pavlov Bogdan Vladimirovich[8]

[1]Student of the Federal State Budgetary Educational Institution of Higher Education "Ryazan State Medical University named after Academician I.P. Pavlov" Ministry of Health of the Russian Federation, Ryazan

[2]Nurse of the Neonatal Department, 2nd year student specializing in Pediatrics at the G. R. Derzhavin Institute of Medicine and Health Care, Russian Federation.Tambov

[3]District nurse of the children's polyclinic, a 2nd-year student specializing in Pediatrics at the G.R. Derzhavin Institute of Medicine and Health Care, Tambov, Russian Federation

[4]Student of the Federal State Budgetary Educational Institution of Higher Education "Ryazan State Medical University named after Academician I.P. Pavlov" Ministry of Health of the Russian Federation, Ryazan

[5]5th year student of the Faculty of Dentistry of the Russian State Medical University (formerly MGMSU), Russian University of Medicine, Moscow

[6]Senior Lecturer of the Department of Human Morphology of the Institute of Medicine and Health Care TSU named after G.R. Derzhavin, Russian Federation, Tambov

[7]Student, specialty "Medical Science" of the G. R. Derzhavin Institute of Medicine and Health Care, Russian Federation. Tambov

[8]Endocrinologist, assistant of the Department of Propaedeutics of Internal Diseases and Faculty Therapy of the Institute of Medicine and Health Care named after G. R. Derzhavin.

Cite this paper as: Humbatova Leyla Ilgarovna, Shulcheva Anastasia Sergeevna, Anufrieva Alina Aleksandrovna, Yudichev Nikita Andreevich, Korshunova Arina Ivanovna, Bryksina Elena Sergeevna, Khuzhakulov Dzhonibek Khoshimzhonovich, Pavlov Bogdan Vladimirovich, (2025) The Impact Of Antiphospholipid Syndrome On Pregnancy Complications At Different Gestational Stages And The Influence Of Combined Therapeutic Approaches. *Journal of Neonatal Surgery*, 14 (8), 154-163.

ABSTRACT

The prevalence of antiphospholipid syndrome (APS) varies across different regions of the world, ranging from 1 to 50 cases per 100,000 individuals, with a higher incidence among women compared to men. Pregnancy in women with APS is associated with an increased risk of adverse outcomes, including a higher likelihood of placental insufficiency, preeclampsia, intrauterine growth restriction, miscarriage, stillbirth, and low birth weight relative to gestational age. Antiphospholipid antibodies (aPL) exert their pathogenic effects through multiple mechanisms, including an increase in circulating placental extracellular vesicles that induce endothelial dysfunction; disruption of trophoblast proliferation, differentiation, and apoptosis; mitochondrial DNA release into the cytoplasm, triggering Toll-like receptor activation and sterile inflammation in the placenta; among other pathways. These mechanisms contribute to the detrimental effects of aPL throughout pregnancy.

The aim of this review is to examine the impact of APS on all stages of pregnancy and to analyze recent trends in APS management during pregnancy. A review of the literature indicates that lupus anticoagulant (particularly in women with systemic lupus erythematosus) significantly increases the risk of adverse pregnancy outcomes. In other cases, unrelated to systemic lupus erythematosus, pathological effects have been demonstrated for antibodies targeting cardiolipin, β2-glycoprotein I, and phosphatidylserine/prothrombin, which elevate the likelihood of pregnancy complications. The cornerstone of APS treatment during pregnancy is the administration of low-dose aspirin and low-molecular-weight heparin, achieving favorable pregnancy outcomes in 70–80% of cases. The addition of pravastatin or hydroxychloroquine enhances the efficacy of this standard therapy.

Keywords: *pregnancy, antiphospholipid syndrome, preeclampsia, placental insufficiency, heparin therapy, aspirin.*

1. INTRODUCTION

Approximately 80% of pregnancy losses occur during the first trimester, whereas losses between 12 and 20 weeks are observed in only 1–5% of cases. About 15–25% of clinically recognized pregnancies result in miscarriage, and when unrecognized early losses are accounted for, the total miscarriage rate may reach 30–60% of all pregnancies. Recurrent pregnancy loss affects 1–5% of couples [1]. Among autoimmune conditions contributing to pregnancy loss, antiphospholipid syndrome (APS) plays a leading role, being diagnosed in 27–42% of women with recurrent pregnancy loss. In the absence of timely and adequate intervention, 90–95% of patients with antiphospholipid antibodies (aPL) experience embryo or fetal loss [2].

The estimated prevalence of APS varies across different countries and populations, ranging from 1 to 50 cases per 100,000 individuals. The prevalence of aPL among patients with obstetric complications is 6–9%, whereas in cases of arterial and venous thromboembolism, it reaches 9–10%. Mortality among APS patients is 50–80% higher than in the general population. APS appears to be more common in women, as it is strongly associated with systemic lupus erythematosus (SLE), which is diagnosed in women ten times more frequently than in men and predominantly affects those of reproductive age. However, after excluding cases of SLE and obstetric APS, the male-to-female ratio of APS patients approaches 1:1. In women, the peak incidence of APS occurs at 30–39 years and 70–79 years, whereas in men, it is observed between 55 and 79 years [3].

The presence of aPL in pregnant women significantly increases the risk of obstetric complications. Among patients with late pregnancy complications, the prevalence of aPL was found to be 31%, compared to 10% in women without complications. Up to 26% of women with late obstetric complications tested positive for at least one type of aPL [4]. Pregnancy complications associated with obstetric APS include early pregnancy loss, fetal demise, preterm birth due to severe preeclampsia, eclampsia, intrauterine growth restriction, and other consequences of placental insufficiency. Well-controlled obstetric care, including aspirin and heparin therapy, has improved pregnancy outcomes in women with obstetric APS. Currently, 70–80% of pregnancies in APS patients result in successful outcomes. However, despite the current standard of care, adverse outcomes still occur in 20–30% of cases [5].

Objective

The objective of this study is to analyze the impact of antiphospholipid syndrome (APS) on different stages of pregnancy and to examine current trends in APS therapy.

2. MATERIALS AND METHODS

A literature search was conducted using the PubMed and Google Scholar databases with the following key phrases: “antiphospholipid syndrome” (5,284 results over the past 10 years), “prevalence of pregnancy loss” (4,916 results over the past 10 years), and “antiphospholipid syndrome in pregnant women” (3,650 results over the past 10 years). Preference was given to reviews and recent original studies available in open-access, non-commercial sources.

3. RESULTS AND DISCUSSION

Antiphospholipid Syndrome: Definition, Classification, and Pathogenesis

Antiphospholipid syndrome (APS) is an autoimmune disorder and one of the most common causes of hypercoagulation. APS is characterized by thrombosis (arterial, venous, and microvascular) as well as pregnancy complications, including miscarriage, late intrauterine fetal demise, and severe preeclampsia.

The classification criteria for APS include the presence of antiphospholipid antibodies (aPL), specifically lupus anticoagulant, anticardiolipin antibodies, and anti-beta-2-glycoprotein I (anti-β2GPI) antibodies. Additionally, there are non-criteria antibodies that contribute to APS development (see Table 1) [6].

Table 1:Antiphospholipid antibodies

Criterion antiphospholipid antibodies (APA)	Non-criteria antiphospholipid antibodies
Lupus anticoagulant	Anti-phosphatidylserine/prothrombin antibodies
Anticardiolipin antibodies	Domain-specific anti-β2-glycoprotein I antibodies
Anti-β2-glycoprotein I antibodies	Annexin A5
	IgA isotypes

The presence of all three classification antiphospholipid antibodies (aPL) is rarely observed during pregnancy. The PROMISSE study demonstrated that only lupus anticoagulant (LA) was associated with an increased risk of adverse

pregnancy outcomes in pregnant women with aPL (n=44). In this study, LA was detected in 69% of women with adverse pregnancy outcomes (APOs) compared to 27% of patients without APOs (p=0.01).

The identified APOs included neonatal death, preterm birth before 36 weeks due to preeclampsia or placental insufficiency, and fetal growth restriction (FGR). APS-related features were found in 92% of women with APOs, whereas such features were present in only 45% of women in the control group. The authors concluded that LA, but not anticardiolipin (aCL) or anti-beta-2-glycoprotein I (anti-β2GPI) antibodies, is a predictor of APOs after 12 weeks of gestation [7].

However, other studies have reported different findings, which may be attributed to variations in the spectrum of aPL tested, differences in laboratory measurement methods, discrepancies in cohort characteristics, and other contributing factors.

There are numerous clinical classifications of APS. Currently, the Sydney classification, developed in 2006, remains the most widely used (see Table 2) [6].

Table 1: Sydney Classification Criteria for AFS

Clinical Criterion Clinical criteria must be present for 5 years from the date of positive antiphospholipid antibody tests. ● Vascular Thrombosis - Arterial - Venous - Microvascular - In elderly patients, other causes of thrombosis must be excluded. ● Pregnancy Morbidity - One or more pregnancy losses after the 10th week - One or more preterm births (less than 34 weeks) - Preeclampsia - Placental insufficiency - Three or more consecutive spontaneous abortions
Laboratory Criterion ● Lupus anticoagulant or medium-to-high levels of anticardiolipin IgG, IgM ● Anti-beta 2 glycoprotein I IgG and IgM ● Positive result for more than 3 months

The diagnosis of antiphospholipid syndrome (APS) requires a combination of at least one clinical criterion—thrombosis or obstetric morbidity—and the persistent presence of at least one type of antiphospholipid antibody (lupus anticoagulant (LA), IgG/IgM anti-β2-glycoprotein I (aβ2GPI), and/or IgG/IgM anticardiolipin (aCL)), detected on two separate occasions at least 12 weeks apart. Non-criteria manifestations of APS are observed in approximately 25% of patients, yet they are not included in the Sapporo classification criteria. These manifestations include autoimmune cytopenias, valvular heart disease, livedo reticularis, and neurological symptoms [8].

The pathogenesis of obstetric APS is linked to genes involved in cell adhesion, extracellular matrix regulation, and embryonic and skeletal development [9]. Complement activation and tumor necrosis factor-alpha (TNF-α) have been implicated in APS-related pregnancy complications, including preeclampsia. Both classical and alternativecomplement pathways play a role in APS pathogenesis. A study of 487 women with systemic lupus erythematosus (SLE) and/or APS found adverse pregnancy outcomes (APOs) in 20.5% of cases. As early as 12–15 weeks of gestation, Bb and sC5b-9 complement components were significantly elevated in women with APOs and remained elevated until 31 weeks, compared to those with normal pregnancy outcomes [10].

Animal models of obstetric APS have demonstrated the critical role of complement activation in pregnancy loss. Notably, APS-related pregnancy complications were prevented when complement activation was inhibited. This mechanism also explains the therapeutic effect of heparin, which blocks complement activation in APS [6].

Another pathogenic mechanism of aPL antibodies (aPLs) involves fibrinolysis and inhibition of protein C activity. Under

normal conditions, protein C, when activated by thrombin bound to thrombomodulin, degrades coagulation factors Va and VIIIa, thereby preventing excessive thrombosis [11].

The pathophysiology of recurrent pregnancy loss (RPL) in early vs. late gestation differs significantly. Early pregnancy loss is associated with the direct inhibitory effects of aPLs on trophoblast growth, placentation, and apoptosis. Trophoblast cells abundantly express antigens for aPLs, particularly β2GPI, making them highly susceptible to aPL-mediated damage.

aPLs impair trophoblast function by altering proliferation, differentiation, survival, migration, and invasion. Murine models have shown that aPLs disrupt placental morphogenesis, suppress trophoblast proliferation, and promote placental apoptosis. Furthermore, aPLs isolated from APS patients have been found to inhibit trophoblast invasion, including trophoblasts derived from both first- and third-trimester placentas.

Additionally, aPLs interfere with the trophoblast's ability to differentiate into an endothelial-like phenotype, contributing to aberrant spiral artery remodeling, a key event in preeclampsia and fetal growth restriction [12].

Late obstetric complications, including preeclampsia, intrauterine growth restriction (IUGR), and stillbirth, are associated with placental dysfunction due to thrombotic and inflammatory processes. Likely causes of such outcomes include inadequate development of extravillous spiral arteries, leading to reduced blood flow to the placenta and hypoxic damage, inadequate nutrient delivery to the fetus, and high-pressure blood flow that may damage the placenta. The complement system plays a crucial role in pregnancy complications associated with antiphospholipid antibodies (aPL). In mouse models, administration of aPL resulted in increased fetal loss and IUGR. In contrast, complement deficiency in mice exerted a protective effect against these complications [5]. Immunohistochemical analysis of 47 placentas from women with antiphospholipid syndrome (APS) and 23 placentas from healthy women revealed increased deposition of complement in the cytoplasm of trophoblasts (C4d and C3b), trophoblastic cells, basal membrane (C4d), and extravillous trophoblasts (C4d) in women with APS compared to the control group. A correlation was established between pathological placental features and complement deposition in the trophoblast cytoplasm, cell membrane, and basal membrane [13].

Knowledge of the pathogenesis of the most common late pregnancy complication, preeclampsia, is gradually expanding. Preeclampsia is a dangerous hypertensive condition affecting 3-7% of otherwise healthy pregnant women. APS increases the risk of preeclampsia by 10 times, partly due to mitochondrial damage in syncytiotrophoblasts. Thus, APS activates mechanisms that trigger the pathogenesis of preeclampsia, including the development of endothelial dysfunction via the action of mitochondrial DNA (mtDNA) and placental vesicles. Since mtDNA is a damage-associated molecular pattern (DAMP/alarmin) capable of activating endothelial cells, it is reasonable to assume that APS influences the number of placental vesicles released into the bloodstream, their mtDNA content, and endothelial cell activation [14]. Endothelial dysfunction can lead to a decrease in the concentration of endothelial vasodilators (NO, prostacyclin, hyperpolarizing factor) and an increase in the levels of vasoconstrictors (endothelin-1, thromboxane A2), resulting in vasoconstriction, hypertension, and other manifestations of preeclampsia [15]. Placental factors activate endothelial cells and inflammation during the early stages of pregnancy, leading to the emergence of preeclampsia symptoms. The placenta is represented by a multinucleated cell, the syncytiotrophoblast, which expels a large array of extracellular vesicles (EVs), or subcellular particles enclosed in a lipid membrane, into the maternal bloodstream. Small and nano-sized vesicles are present in the maternal circulation as early as 6 weeks of pregnancy and can interact with endothelial cells, monocytes, neutrophils, and platelets. In preeclampsia, the number of circulating placental EVs significantly increases, and they can be detrimental to maternal cells, contributing to the development of clinical preeclampsia symptoms. Antiphospholipid syndrome (APS) exhibits a strong tropism to the placenta and is rapidly internalized by the syncytiotrophoblast, where it causes mitochondrial swelling, internal leakage of the mitochondrial membrane, and release of cytochrome C into the cytoplasm. These processes may lead to cell death and the expulsion of dangerous macrovesicles, which then activate endothelial cells. When mitochondrial DNA (mtDNA) is released from the mitochondria, it can act as a danger-associated molecular pattern (DAMP) and activate intracellular toll-like receptors (TLRs) sensitive to danger, including TLR-9, triggering sterile inflammation. One study demonstrated that exposure to antiphospholipid antibodies (aPL) in human first-trimester placental explants did not affect the number or size of expelled micro- and nano-vesicles (n=5), however, the content of mtDNA in these vesicles was increased. These vesicles significantly activated endothelial cells, which was prevented by blocking TLR-9, the receptor for extracellular DNA. The authors concluded that aPL increase the risk of preeclampsia, in part by increasing the amount of mtDNA associated with placental vesicles. The fact that mtDNA is recognized as a DAMP by TLR-9, activating endothelial cells, may be leveraged for the development of pharmaceutical interventions aimed at reducing the effects of aPL during pregnancy [14].

4. OBSTETRIC ANTIPHOSPHOLIPID SYNDROME AT DIFFERENT STAGES OF PREGNANCY

The most widely accepted definition of early miscarriage is the loss of pregnancy within the first 12 complete weeks after conception. Up to 15% of clinically recognized pregnancies end in early miscarriage. Causes of early miscarriage and recurrent pregnancy loss include genetic abnormalities, anatomical features, endocrine or immune factors, infections (such as toxoplasmosis, rubella, cytomegalovirus, herpes simplex virus, etc.), and antiphospholipid antibodies. Antiphospholipid antibodies (aPL) are a frequent cause of early miscarriages [5]. A study involving 1155 women with three or more first-trimester pregnancy losses identified lupus anticoagulant in 0.5% and persistent anticardiolipin antibodies (≥40U/ml) in 0.5%

of the patients. The aPL tests were performed with an interval of at least 12 weeks, in accordance with the Sapporo criteria [16]. Another publication showed that aPL were found in 1% of women with early pregnancy losses. Women with aPL experienced early pregnancy losses in 44% of cases (compared to 21% in women without aPL). Embryonic loss was more frequent in women with anticardiolipin antibodies (50% vs. 16.5% in women with anti-β2GPI). However, the authors concluded that aPL do not have a clear association with an increased rate of subsequent losses [17]. A study involving 238 pregnant women with systemic lupus erythematosus (SLE) found that the presence of lupus anticoagulant was significantly associated with adverse pregnancy outcomes (odds ratio OR=4.2, 95% CI=1.8–9.7) [18].

Late pregnancy loss or fetal death is defined as pregnancy loss after 10–12 weeks, while stillbirth refers to the loss after 20 weeks (according to some specialists), although the World Health Organization (WHO) defines stillbirth as the birth of a child with no signs of life at 28 weeks or later [5]. Unexplained cases of late pregnancy loss should be investigated for antiphospholipid syndrome (APS). In a publication by R.M. Silver et al., elevated levels of IgG to cardiolipin and IgG to β2GPI were associated with more than a threefold increase in the chances of stillbirth. When comparing a subgroup of stillbirths unrelated to fetal anomalies or obstetric complications with term live births, it was found that stillbirth was associated with increased levels of IgG antibodies to cardiolipin (5.0% vs. 1.0%; OR=5.30, 95% CI=2.39–11.76); levels of IgG antibodies to β2GPI (1.9% vs. 0.6%; OR=3.00, 95% CI=1.01–8.90); and concentrations of IgM antibodies to cardiolipin (6.0% vs. 3.0%, OR=2.03, 95% CI=1.09–3.76) [19]. A year later, similar findings were reproduced by A.M. Peaceman, who noted that antiphospholipid antibodies were detected in 10% of patients with stillbirth and in 6% of patients with live births. The adjusted odds ratio for IgG antibodies to cardiolipin and antibodies to β2GPI was approximately 3. Abnormal antiphospholipid antibody test results were found in a significant proportion of patients with stillbirth, both with and without complications [20].

A 2018 French study reported a large cohort of women (n=65) with antiphospholipid syndrome (APS) and intrauterine fetal death (IUFD). The authors indicated that for the majority of these women (74%), IUFD was the first manifestation of antiphospholipid syndrome. Thirty-five percent of the women had a triple-positive antibody profile. IUFD occurred at a median gestational age of 24 weeks (interquartile range 18–27 weeks) and was associated with maternal and obstetric complications in a quarter of the women: half of them had preeclampsia, while the others had hemolysis, elevated liver enzymes, thrombocytopenia (HELLP syndrome), and/or placental abruption. In half of the women for whom data were available, fetal weight was below the expected gestational age. During a 4-year follow-up period, 28 (43%) women had at least one thrombosis, and 29% were diagnosed with systemic lupus erythematosus (SLE). Subsequently, 83% of the women had at least one live birth. One woman had three consecutive early miscarriages [21].

A study of 431 women with placental-mediated complications who delivered after 34 weeks of gestation found that the prevalence of antiphospholipid antibodies (anticardiolipin antibodies, β2GPI, and lupus anticoagulant) in the cohort was 4.9%. In the subgroup of women with small-for-gestational-age newborns, aPL were found in 3.9%, in preeclampsia in 3.3%, and in placental abruption in 13% of women (p=0.17) [22].

Placental insufficiency refers to the placenta's inability to deliver sufficient nutrients to the growing fetus. It may manifest as fetal growth restriction (FGR) and/or preeclampsia and/or placental abruption. FGR occurs in 2–8% of first pregnancies, while preeclampsia occurs in 0.5% of pregnancies in developed countries. Several studies have demonstrated an association between APS and placental insufficiency [5]. For example, Do Prado et al. found that the combined odds ratio (OR) for the association between anticardiolipin antibodies and preeclampsia was 2.86 (95% CI=1.37–5.98). The combined OR for anticardiolipin antibodies and severe preeclampsia was 11.15 (95% CI=2.66–46.75). Despite the established association between aPL and preeclampsia, the authors concluded that there is insufficient evidence to use anticardiolipin antibodies as predictors of preeclampsia in clinical practice [23]. A comparison of women who delivered before 34 weeks due to severe preeclampsia showed that women with antiphospholipid antibodies (aPL) (n=20) were hospitalized earlier (29 vs. 32 weeks, p=0.05), delivered at an earlier gestational age (30 weeks vs. 33 weeks, p=0.02), and had infants with lower average birth weight (1266.7 g vs. 1567.3 g, p=0.058) compared to the group (n=35) without aPL. Furthermore, women with aPL had lower platelet counts (97±49*10^3/μl vs. 141±61*10^3/μl, p<0.001) and higher maximum serum creatinine levels (1.0±0.3 mg/dl vs. 0.9±0.1 mg/dl, p=0.03). Neonatal complication rates were comparable, except for a higher incidence of retinopathy of prematurity (30% vs. 5.7%, p=0.02) and a trend toward higher perinatal mortality in the study group [24]. Thus, the presence of aPL in women with early preeclampsia was associated with more severe manifestations of the condition.

Previous studies did not use international classification criteria for APS. In the study by K.L. Gibbins et al., a positive test for aPL was defined as the presence of at least one of the following antibodies: lupus anticoagulant, anticardiolipin IgG or IgM ≥40 U, or anti-β2GPI IgG or IgM ≥40 U. A comparison of women with preterm delivery due to preeclampsia or placental insufficiency (n=148) with a control group (n=148) revealed that positive tests for aPL were more frequent in the study group (11.5% vs. 1.4%, OR=8.9, 95% CI=1.9-41.4). In women with aPL, the following antibodies were found: lupus anticoagulant (76%); anticardiolipin antibodies (41%); anti-β2GPI (24%) [25]. This study (from 2018) was claimed to be the first to use both obstetric and laboratory data in accordance with international APS criteria. However, as early as 2012, R. Ferrer-Oliveras studied the prevalence of aPL (including non-criteria antibodies) in Spanish women with preeclampsia (n=99) and in a healthy control group (n=83). Antibodies analyzed included IgG/IgM to cardiolipin, IgG/IgM to β2GPI, IgG/IgM to

phosphatidylserine, IgG/IgM to annexin-A5, and lupus anticoagulant. The prevalence of aPL in the study group was 14.14%, and in the control group, it was 7.23%. Excluding women who tested positive for anti-annexin-A5, the overall prevalence of phospholipid antibodies was 13.19% and 3.61%, respectively (p=0.034). When analyzing individual aPL types, it was found that only positivity for IgM-anticardiolipin showed significant differences between the preeclampsia group and the control group (8.1% vs. 1.2%, p=0.041). For two or more positive tests for aPL, the main and control groups had the following rates: IgG-anticardiolipin – 9.09% vs. 1.20% (p = 0.037); IgM-anticardiolipin – 10.91% vs. 1.20% (p = 0.016); IgG/IgM-anti-β2GPI – 10.91% vs. 1.90% (p = 0.016), IgM-anti-β2GPI – 9.09% vs. 1.20% (p = 0.037). In a comparison of women with early preeclampsia with the control group, IgM-anticardiolipin was present in 11.11% of women compared to 1.20% in the control group (p = 0.029). Therefore, the multipositive aPL test, IgM-anticardiolipins, and IgM-anti-β2GPI are associated with early and severe preeclampsia, and these tests may be useful for predicting this pathology [26].

Intrauterine growth restriction (IUGR) is a consequence of placental insufficiency and is associated with stillbirth. APS can contribute to IUGR [27]. A study of 55 women with APS, testing for antiphospholipid antibodies (aPL) including antibodies to cardiolipin, β2GPI, the phosphatidylserine/prothrombin complex, and lupus anticoagulant, found that only antibodies to the phosphatidylserine/prothrombin complex were more frequently present in women with late pregnancy complications. Late complications included intrauterine fetal death, preeclampsia, IUGR, and preterm birth. Titers of these antibodies (IgG class) were inversely correlated with the newborn's birth weight. Placentas with IUGR and the presence of IgG to phosphatidylserine/prothrombin showed vascular damage, thrombosis, fibrinoid necrosis, ischemic and hemorrhagic areas, and the presence of chorioangiomas [28]. Therefore, antibodies to phosphatidylserine/prothrombin may potentially be used to identify patients at high risk for fetal growth restriction and other manifestations of placental insufficiency. In another study (testing anticardiolipin, anti-β2GPI, and lupus anticoagulant), only positivity for anticardiolipin was significantly associated with IUGR, with a corrected odds ratio (OR) of 4.601 (95% CI=1.205-17.573) [29]. According to a meta-analysis by J. Xu et al., which combined 22 studies and 11,745 clinical cases, the combined OR for the association of antiphospholipid antibodies, anticardiolipin antibodies, β2GPI antibodies, and fetal growth restriction was 1.26 (95% CI=1.12-1.40), 2.25 (95% CI=1.55-2.94), and 1.31 (95% CI=1.12-1.49), respectively. Lupus anticoagulant did not increase the likelihood of IUGR (OR=0.82, 95% CI=0.54-1.10) [30].

In their publication, G. Saccone et al. assessed the risks of obstetric complications in women with primary antiphospholipid syndrome (APS), related to specific antibody profiles. The study cohort included 750 singleton pregnancies with primary APS: 54 (7.2%) were positive only for lupus anticoagulant; 458 (61.0%) were positive only for anticardiolipin antibodies; 128 (17.1%) were positive only for anti-β2GPI antibodies; 90 (12.0%) were positive for 2 types of antibodies and negative for lupus anticoagulant; and 20 (2.7%) were positive for all three types of antiphospholipid antibodies (aPL). The live birth rate in each of these categories was 79.6%, 56.3%, 47.7%, 43.3%, and 30.0%, respectively.

Compared to women with only one positive antibody test, women with multiple positive antibody tests had a significantly lower live birth rate (40.9% vs. 56.6%; adjusted OR=0.71; 95% CI=0.51-0.90). They also had an increased risk of preeclampsia without severe manifestations (54.5% vs. 34.8%; adjusted OR=1.56; 95% CI=1.22-1.95) and with severe manifestations (22.7% vs. 13.8%; adjusted OR=1.66; 95% CI=1.19-2.49), intrauterine growth restriction (53.6% vs. 40.8%; adjusted OR=2.31; 95% CI=1.17-2.61), and stillbirth (36.4% vs. 21.7%; adjusted OR=2.67; 95% CI=1.22-2.94). Women with only one positive anti-β2GPI test had a significantly lower live birth rate (47.7% vs. 56.3% and 79.6%; p<0.01) and significantly higher rates of preeclampsia without severe manifestations (47.7% vs. 34.1% and 11.1%; p<0.01) and with severe manifestations (17.2% vs. 14.4% and 0%; p=0.02), intrauterine growth restriction (48.4% vs. 40.1% and 25.9%; p<0.01), and stillbirth (29.7% vs. 21.2% vs. 7.4%; p<0.01) compared to women with anticardiolipin antibodies and women with only lupus anticoagulant.

In the group of women with positive results for more than one type of antibody, women with triple-positive results had a lower live birth rate (30% vs. 43.3%; adjusted OR=0.69; 95% CI=0.22-0.91) and a higher rate of intrauterine growth restriction (70.0% vs. 50.0%; adjusted OR=2.40; 95% CI=1.15-2.99) compared to women with dual-positive results and negative lupus anticoagulant results.

The authors concluded that anticardiolipin antibodies are the most common in APS, but anti-β2GPI is associated with the lowest live birth rates, the highest rates of preeclampsia, IUGR, and stillbirth compared to the presence of only anticardiolipin antibodies or lupus anticoagulant [31].

5. MANAGEMENT OF PREGNANT WOMEN WITH APS

The pregnancy outcomes in women with antiphospholipid syndrome (APS) are largely determined by previous thrombotic events, pregnancy-related pathology, adherence to medical recommendations, adequate prenatal care, and careful monitoring of pregnancy (Doppler velocimetry, ultrasound, etc.), as well as the spectrum of antiphospholipid antibodies (aPL). Ideally, a complete history and aPL profile should be established during the pre-pregnancy planning stage to properly stratify the risks in women with APS. Specifically, pregnant women with a history of obstetric and thrombotic APS face different risks of pregnancy complications. A comparison of three groups of pregnant women with APS—those with habitual miscarriage (group 1), those with late pregnancy loss or preterm birth due to placental dysfunction (group 2), and those with thrombotic

APS (group 3)—showed that group 3 had the highest rates of preterm birth (26.8% vs. 4.7%, p=0.05) compared to group 1, and more small-for-gestational-age infants compared to group 2 (39.5% vs. 4.8%, p=0.003). Group 2 had significantly longer gestational periods compared to their pregnancies before treatment (38.4 weeks [28.4–41.4] vs. 24.0 weeks [18–35], p<0.0001) and a 100% live birth rate after treatment with aspirin and low-molecular-weight heparin. It is important to note that all three groups received treatment with aspirin and low-molecular-weight heparin, which improved outcomes in women with obstetric APS (with a history of early and late pregnancy loss), but not in thrombotic APS. Thrombotic APS proved to be more resistant to treatment and caused more complications [32].

The standard treatment for pregnancy in APS is the administration of low-dose aspirin and low-molecular-weight heparin. The patient's medical history influences the choice of therapy. If the patient has had a normal pregnancy, no pregnancies, or only one early miscarriage, the use of low doses of aspirin is recommended, as it reduces the risk of preeclampsia. If the woman with APS has had one late fetal death, multiple early losses, severe preeclampsia, or HELLP syndrome in her history, low-dose aspirin and prophylactic doses of low-molecular-weight heparin are recommended [6, 33]. Since the pathogenesis caused by aPL antibodies begins early in pregnancy and during implantation, heparin prophylaxis is started immediately after pregnancy confirmation. Low-molecular-weight heparin is prescribed twice a day to ensure 24-hour coverage for the placenta. If the patient has had previous thrombotic events, full doses of heparin and low doses of aspirin are recommended. A meta-analysis showed that the use of antiplatelet agents reduced the risks of preeclampsia, preterm birth, delivery of small-for-gestational-age infants, and reduced the risk of fetal or neonatal death [34]. In women with intrauterine growth restriction and positive tests for antiphospholipids (including non-criteria), better pregnancy outcomes were observed when low-dose aspirin and low-molecular-weight heparin were administered [29].

The combination of aspirin and heparin demonstrates a cumulative effect, improving pregnancy outcomes in women with antiphospholipid syndrome (APS). A comparison of the effects of heparin (unfractionated or low-molecular-weight, 5000 IU subcutaneously per day) in combination with aspirin (75 mg/day) versus aspirin monotherapy (75 mg/day) on the frequency of live births in women with at least two previous miscarriages and a history of APS revealed that the combined regimen reduced first-trimester pregnancy losses (OR = 0.39, 95% CI = 0.24–0.65). Unfractionated heparin showed a more pronounced effect (OR = 0.26, 95% CI = 0.14–0.48) compared to low-molecular-weight heparin (OR = 0.70, 95% CI = 0.34–1.45). However, combined therapy did not show clear advantages in later stages of pregnancy [35]. In another study, isolated aspirin did not improve live birth rates in women with recurrent miscarriage and APS compared to placebo, but the combination of heparin with aspirin (either low-molecular-weight or unfractionated) increased the relative live birth rate by 1.27 times, particularly in the case of unfractionated heparin [36]. In contrast, a publication by M.D. Stephenson et al. showed that 69% of women receiving low-molecular-weight heparin (dalteparin) had successful pregnancies, while only 31% of women in the unfractionated heparin group experienced live births [37].

The American College of Obstetricians and Gynecologists provides recommendations for the management of obstetric APS in various clinical situations. Expert consensus suggests that clinical observation or prophylactic use of heparin until delivery and for the following 6 weeks postpartum may be justified for women with APS without a history of prior thrombotic events. For women with a history of sporadic pregnancy loss or any type of recurrent miscarriage, but without thrombotic events in their medical history, prophylactic doses of heparin and low-dose aspirin should be considered during pregnancy and for 6 weeks postpartum. Other treatment options for women with APS include corticosteroids and intravenous immunoglobulin. Reports suggest a 60–70% successful pregnancy rate in women with APS treated with prednisone and low-dose aspirin, though these results have not been consistently replicated by other authors. The effectiveness of prednisone during pregnancy remains controversial. Intravenous immunoglobulin is indicated in cases where women with APS are refractory to heparin or prednisone treatment. No advantages were observed for the combination of immunoglobulin + heparin + aspirin over heparin and aspirin alone. For this reason, the American College of Obstetricians and Gynecologists issued negative recommendations for the use of intravenous immunoglobulin in pregnant women with APS [38]. Other authors suggest intravenous immunoglobulin combined with plasmapheresis for pregnant women with very high APS risk, particularly in those with a high-risk antiphospholipid antibody profile and a history of thrombosis or refractory responses to previous treatments [39].

In recent years, research has focused on two drugs, pravastatin and hydroxychloroquine, which have shown promising results in the treatment of pregnant women with antiphospholipid syndrome (APS). The addition of pravastatin to low-molecular-weight heparin and low-dose aspirin may improve pregnancy outcomes in women with severe recurrent placental-mediated complications. Specifically, there is an increase in gestational age at delivery, a higher average birth weight, and a reduction in the risks of preeclampsia [40]. Another study showed that the combination of pravastatin with standard therapy, compared to standard therapy alone (low doses of aspirin and low-molecular-weight heparin), led to increased placental blood flow and improved preeclampsia characteristics. These beneficial effects were observed after just 10 days of treatment. Additionally, pravastatin therapy resulted in full-term live births for all women with APS. This effect is likely partly related to the protective effect of pravastatin on the endothelium [41].

Hydroxychloroquine is a traditional antimalarial drug frequently prescribed to patients with systemic lupus erythematosus (SLE). It has been shown that hydroxychloroquine counteracts some of the effects of antiphospholipid antibodies (APA),

such as the secretion of trophoblast IL-6 and inhibition of cell migration, as well as restoring trophoblast fusion, which is disrupted by APA. This led to the hypothesis that hydroxychloroquine might improve pregnancy outcomes in APS. In a retrospective single-center study, hydroxychloroquine treatment (Group A) was associated with a higher rate of live births (67% vs. 57%, p = 0.05) compared to women receiving similar therapy but without hydroxychloroquine (Group B). Additionally, Group A had lower rates of pregnancy complications associated with APS (47% vs. 63%, p = 0.04), and the odds of any pregnancy complications were reduced by 2.2 times. Pregnancy losses after 10 weeks (2% vs. 11%; p = 0.05) and placental complications (2% vs. 11%; p = 0.05) were less frequent in Group A than in Group B. The duration of pregnancy was longer in Group A compared to Group B (27.6 [6-40] vs. 21.5 [6-40] weeks; p = 0.03). Women receiving hydroxychloroquine also had a higher rate of spontaneous vaginal deliveries compared to Group B (37.3% vs. 14.3%; p = 0.01) [42]. Therefore, hydroxychloroquine improved pregnancy outcomes in women with APS according to several parameters. Furthermore, it was shown that adding hydroxychloroquine to standard therapy in APS patients (n = 102) significantly reduced the incidence of early severe preeclampsia (8.3% vs. 40.0%; p = 0.03) compared to the group receiving only standard treatment [43]. Thus, the overall effect of the therapy significantly reduced adverse pregnancy outcomes.

6. CONCLUSION

A review of the literature reveals that antiphospholipid syndrome (APS) remains a significant issue in obstetrics and gynecology, complicating pregnancy and increasing the frequency of adverse outcomes and losses. The pathogenesis mechanisms triggered by antiphospholipid antibodies (APA) persist throughout pregnancy, leading to trophoblast pathology, placental insufficiency, intrauterine growth restriction, miscarriages, preterm births, and stillbirths. The wide spectrum of APA contributes to significant variability in the data regarding pregnancy complication risks. Most authors have focused on the impact of criterion-based APA and often associated their pathological effects with pregnancy complications. However, antibodies against phosphatidylserine/prothrombin were found to be significantly more frequent in women with late pregnancy complications, showing multiple signs of placental damage. The primary pathological effects at different stages of pregnancy, as reported in the literature, are mainly linked to anticardiolipin and anti-β2GPI antibodies. Their presence increased the chances of stillbirth by at least three times.

Currently, the treatment of pregnant women with APS primarily involves the use of low doses of aspirin and low-molecular-weight heparin. Heparin enhances the effect of aspirin, reducing the frequency of pregnancy complications in obstetric APS. However, for women with thrombotic APS, this therapy is not sufficient. The efficacy of prednisone during pregnancy with APS appears to be debatable, and the addition of intravenous immunoglobulin to traditional therapy seems to offer no additional beneficial effect.

Recently, pravastatin and hydroxychloroquine have been proposed for the treatment of pregnant women with APS. These drugs, in several clinical trials, have enhanced the beneficial effects of standard therapy. They significantly improved pregnancy outcomes and reduced the frequency of preeclampsia when added to the "low-dose aspirin + low-molecular-weight heparin" regimen. Thus, there is now the potential to significantly improve the rate of live births and reduce the likelihood of pregnancy complications.

REFERENCES

[1] Genovese H.G., McQueen D.B. The prevalence of sporadic and recurrent pregnancy loss. Fertil Steril. 2023 Nov;120(5):934-936. doi: 10.1016/j.fertnstert.2023.08.954.

[2] Amrieva D.X., Ol`mesova A.R., Sklyarova S.A., Petrov Yu.A. Antiphospholipid syndrome as a cause of miscarriage. International journal of applied and fundamental research. 2019;9:100-103. (In Russian).

[3] Dabit J.Y., Valenzuela-Almada M.O., Vallejo-Ramos S., Duarte-García A. Epidemiology of Antiphospholipid Syndrome in the General Population. Curr Rheumatol Rep. 2022;23(12):85. doi: 10.1007/s11926-021-01038-2.

[4] Foddai S.G., Radin M., Cecchi I., et al. The prevalence of antiphospholipid antibodies in women with late pregnancy complications and low-risk for chromosomal abnormalities. J Thromb Haemost. 2020 Nov;18(11):2921-2928. doi: 10.1111/jth.15053.

[5] Schreiber K., Hunt B.J. Managing antiphospholipid syndrome in pregnancy. Thromb Res. 2019;181 Suppl 1:S41-S46. doi: 10.1016/S0049-3848(19)30366-4.

[6] Petri M. Antiphospholipid syndrome. Transl Res. 2020;225:70-81. doi: 10.1016/j.trsl.2020.04.006.

[7] Yelnik C.M., Laskin C.A., Porter T.F., et al. Lupus anticoagulant is the main predictor of adverse pregnancy outcomes in aPL-positive patients: validation of PROMISSE study results. Lupus Sci Med. 2016;3(1):e000131. doi: 10.1136/lupus-2015-000131.

[8] Manning J.E., Arachchillage D.J. Dilemmas in the diagnosis and management of antiphospholipid syndrome. J Thromb Haemost. 2024;22(8):2156-2170. doi: 10.1016/j.jtha.2024.03.027.

[9] Ripoll V.M., Pregnolato F., Mazza S., et al. Gene expression profiling identifies distinct molecular signatures in thrombotic and obstetric antiphospholipid syndrome. J Autoimmun. 2018;93:114–123. doi: 10.1016/j.jaut.2018.07.002.

[10] Kim M.Y., Guerra M.M., Kaplowitz E., et al. Complement activation predicts adverse pregnancy outcome in patients with systemic lupus erythematosus and/or antiphospholipid antibodies. Ann Rheum Dis. 2018;77(4):549–555. doi: 10.1136/annrheumdis-2017-212224.

[11] De Groot P.G., Derksen R.H. Pathophysiology of antiphospholipid antibodies, Neth. J. Med. 2004;62:267–272.

[12] Petronijević S.V., Vilotić A., Bojić-Trbojević Ž., et al. Trophoblast Cell Function in the Antiphospholipid Syndrome. Biomedicines. 2023;11(10):2681. https://doi.org/10.3390/biomedicines11192681.

[13] Shamonki J.M., Salmon J.E., Hyjed E., et al. Excessive complement activation is associated with placental injury in patients with antiphospholipid antibodies. American Journal of Obstetrics and Gynecology. 2007;196(2):167.e1-167.e5. https://doi.org/10.1016/j.ajog.2006.10.879.

[14] Tong M., Johansson C., Xiao F., et al. Antiphospholipid antibodies increase the levels of mitochondrial DNA in placental extracellular vesicles: Alarmin-g for preeclampsia. Sci Rep. 2017;7(1):16556. doi: 10.1038/s41598-017-16448-5.

[15] Possomato-Vieira J.S., Khalil R.A. Mechanisms of Endothelial Dysfunction in Hypertensive Pregnancy and Preeclampsia. Adv Pharmacol. 2016;77:361-431. doi: 10.1016/bs.apha.2016.04.008.

[16] Shehata H., Ali A., Silva-Edge M., et al. Thrombophilia screening in women with recurrent first trimester miscarriage: is it time to stop testing? - a cohort study and systematic review of the literature. BMJ Open. 2022;12(7):e059519. doi: 10.1136/bmjopen-2021-059519.

[17] Gibbins K.J., Mumford S.L., Sjaarda L.A., et al. Preconception antiphospholipid antibodies and risk of subsequent early pregnancy loss. Lupus. 2018;27(9):1437-1445. doi: 10.1177/0961203318776089.

[18] Larosa M., Le Guern V., Guettrot-Imbert G., et al. Evaluation of lupus anticoagulant, damage, and remission as predictors of pregnancy complications in systemic lupus erythematosus: the French GR2 study. Rheumatology (Oxford). 2022;61(9):3657-3666. doi: 10.1093/rheumatology/keab943.

[19] Silver R.M., Parker C.B., Reddy U.M., et al., Antiphospholipid antibodies in stillbirth, Obstet. Gynecol. 2013;122:641–657. doi: 10.1097/AOG.0b013e3182a1060e.

[20] Peaceman A.M. Antiphospholipid Antibodies in Stillbirth. Obstetrics & Gynecology. 2014;123(1):184. doi:10.1097/aog.0000000000000071.

[21] Belhocine M., Coutte L., Martin Silva N., et al. Intrauterine fetal deaths related to antiphospholipid syndrome: a descriptive study of 65 women. Arthritis Res Ther. 2018;20(1):249. doi: 10.1186/s13075-018-1745-2.

[22] Amikam U., Hochberg A., Shenhav M., et al. Anti-Phospholipid Antibodies in Women with Placenta-Mediated Complications Delivered at >34 Weeks of Gestation. J Clin Med. 2023;12(13):4516. doi: 10.3390/jcm12134516.

[23] Do Prado A.D., Piovesan D.M., Staub H.L., Horta B.L. Association of anticardiolipin antibodies with preeclampsia: a systematic review and meta- analysis, Obstet. Gynecol. 2010;116:1433-1443. doi: 10.1097/AOG.0b013e3181fe02ec.

[24] Zemet R., Dulitzki M., Baum M., et al. Early-onset preeclampsia - The impact of antiphospholipid antibodies on disease severity. Eur J Obstet Gynecol Reprod Biol. 2021;263:79-84. doi: 10.1016/j.ejogrb.2021.06.006.

[25] Gibbins K.J., Tebo A.E., Nielsen S.K., Branch D.W. Antiphospholipid antibodies in women with severe preeclampsia and placental insufficiency: a case-control study. Lupus. 2018;27(12):1903-1910. doi: 10.1177/0961203318787035.

[26] Ferrer-Oliveras R., Llurba E., Cabero-Roura L., Alijotas-Reig J. Prevalence and clinical usefulness of antiphospholipid and anticofactor antibodies in different Spanish preeclampsia subsets. Lupus. 2012;21(3):257-63. doi: 10.1177/0961203311425520.

[27] Page J.M., Blue N.R., Silver R.M. Fetal Growth and Stillbirth. Obstet Gynecol Clin North Am. 2021;48(2):297-310. doi: 10.1016/j.ogc.2021.03.001.

[28] Canti V., Del Rosso S., Tonello M., et al. Antiphosphatidylserine/prothrombin Antibodies in Antiphospholipid Syndrome with Intrauterine Growth Restriction and Preeclampsia. J Rheumatol. 2018;45(9):1263-1272. doi: 10.3899/jrheum.170751.

[29] Xi F., Cai Y., Lv M., et al. Anticardiolipin Positivity Is Highly Associated With Intrauterine Growth Restriction in Women With Antiphospholipid Syndrome. Clin Appl Thromb Hemost. 2020;26:1076029620974455. doi: 10.1177/1076029620974455.

[30] Xu J., Chen D., Tian Y., et al. Antiphospholipid Antibodies Increase the Risk of Fetal Growth Restriction: A Systematic Meta-Analysis. Int J Clin Pract. 2022;2022:4308470. doi: 10.1155/2022/4308470.

[31] Saccone G., Berghella V., Maruotti G.M., et al. Antiphospholipid antibody profile based obstetric outcomes of primary antiphospholipid syndrome: the PREGNANTS study. Am J Obstet Gynecol. 2017;216(5):525.e1-525.e12. doi: 10.1016/j.ajog.2017.01.026.

[32] Bramham K., Hunt B.J., Germain S., et al. Pregnancy outcome in different clinical phenotypes of antiphospholipid syndrome. Lupus. 2010;19(1):58-64. doi: 10.1177/0961203309347794.

[33] Liu X., Qiu Y., Yu E.D., et al. Comparison of therapeutic interventions for recurrent pregnancy loss in association with antiphospholipid syndrome: A systematic review and network meta-analysis. Am J Reprod Immunol. January 2020:e13219. doi: 10.1111/aji.13219.

[34] Duley L., Meher S., Hunter K.E., et al. Antiplatelet agents for preventing preeclampsia and its complications. Cochrane Database Syst Rev. 2019;2019(10). doi: 10.1002/14651858.CD004659.pub3.

[35] Ziakas P.D., Pavlou M., Voulgarelis M. Heparin treatment in antiphospholipid syndrome with recurrent pregnancy loss: a systematic review and meta-analysis. Obstet Gynecol. 2010 Jun;115(6):1256-1262. doi: 10.1097/AOG.0b013e3181deba40.

[36] Hamulyák E.N., Scheres L.J.J., Goddijn M., Middeldorp S. Antithrombotic therapy to prevent recurrent pregnancy loss in antiphospholipid syndrome – What is the evidence? J Thromb Haemost. 2021 May;19(5):1174-1185. doi: 10.1111/jth.15290.

[37] Stephenson M.D., Ballem P.J., Tsang P., et al. Treatment of antiphospholipid antibody syndrome (APS) in pregnancy: a randomized pilot trial comparing low molecular weight heparin to unfractionated heparin. J Obstet Gynaecol Can. 2004 Aug;26(8):729-34. doi: 10.1016/s1701-2163(16)30644-2.

[38] Committee on Practice Bulletins—Obstetrics, American College of Obstetricians and Gynecologists. Practice bulletin No. 132: antiphospholipid syndrome. Obstet Gynecol. 2012;120(6):1514–1521. doi: 10.1097/01.AOG.0000423816.39542.0f.

[39] Ruffatti A., Favaro M., Calligaro A., et al. Management of pregnant women with antiphospholipid antibodies. Expert Rev Clin Immunol. 2019;15(4):347-358. doi: 10.1080/1744666X.2019.1565995.

[40] Kupferminc M.J., Kliger C., Rimon E., et al. Pravastatin is useful for prevention of recurrent severe placenta-mediated complications - a pilot study. J Matern Fetal Neonatal Med. 2022;35(25):8055-8061. doi: 10.1080/14767058.2021.1940940.

[41] Lefkou E., Mamopoulos A., Dagklis T., et al. Pravastatin improves pregnancy outcomes in obstetric antiphospholipid syndrome refractory to antithrombotic therapy. J Clin Invest. 2016;126(8):2933-40. doi: 10.1172/JCI86957.

[42] Sciascia S., Hunt B.J., Talavera-Garcia E., et al. The impact of hydroxychloroquine treatment on pregnancy outcome in women with antiphospholipid antibodies. Am J Obstet Gynecol. 2016;214(2):273.e1-273.e8. doi: 10.1016/j.ajog.2015.09.078.

[43] Latino J.O., Udry S., Aranda F., et al. Risk factors for early severe preeclampsia in obstetric antiphospholipid syndrome with conventional treatment. The impact of hydroxychloroquine. Lupus. 2020;29(13):1736-1742. doi: 10.1177/0961203320952850.