Ref: Ro J Rheumatol. 2023;32(2)
DOI: 10.37897/RJR.2023.2.4

Consequences of antiphospholipid syndrome in pregnancy - A review

Astrit M. Gashi

Department of Obstetrics and Gynaecology, University Clinical Centre of Kosovo, Pristina, Kosovo
Faculty of Medicine, University of Pristine, Pristina, Kosovo

ABSTRACT

Background and objectives. Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the presence of antiphospholipid antibodies (aPL) in the blood. Antiphospholipid syndrome is defined by the presence of antiphospholipid antibodies, including lupus anticoagulant, anticardiolipin antibodies, and anti-beta-2 glycoprotein I antibodies. These antibodies target phospholipids-binding proteins and can leading to various clinical manifestations and complications of thromboembolic nature. Also, the antiphospholipid syndrome is strongly linked to adverse pregnancy outcomes, including recurrent miscarriages, fetal growth restriction, preeclampsia, and preterm birth. Placental dysfunction, impaired blood flow to the fetus, and thrombotic events within the placenta contribute to these complications. The purpose of this review was the research of consequences of antiphospholipid syndrome in pregnancy.

Materials and methods. This research involves systematically reviewing and analyzing existing literature on consequences of antiphospholipid syndrome in pregnancy. For relevant literature, academic databases like Pub Med, Scopus, Web of Science, and Google Scholar were used.

Search terms and keywords that were used to search for relevant literature in databases was: antiphospholipid syndrome; pregnancy; consequences, and Boolean operator (AND, OR). The criteria used to include literature in this review were; publication date, language, study objectives, study design, research methodology, key findings, and relevance to my research question. For citation and referencing were used the appropriate citation style (e.g., APA, MLA, Chicago, Harvard and Vancouver).

Results. The main findings in this review were that antiphospholipid syndrome (APS) of characterizing by dysregulation of the immune system and the production of autoantibodies. These autoantibodies can target various cells and proteins, leading to inflammation, tissue damage, and disrupted physiological processes. This syndrome is associated with a pro-thrombotic state, increasing the risk of blood clots in veins and arteries. Antiphospholipid syndrome (APS) can affect multiple organs and systems, including the skin, kidneys, heart, and central nervous system. Thrombotic events can occur in various organs, leading to deep vein thrombosis, pulmonary embolism, strokes, and other thromboembolic complications. Also, the antiphospholipid syndrome is strongly linked to adverse pregnancy outcomes, including recurrent miscarriages, fetal growth restriction, preeclampsia, and preterm birth. Placental dysfunction, impaired blood flow to the fetus, and thrombotic events within the placenta contribute to these complications. Manifestations may include skin rashes (livedo reticularis), kidney involvement (glomerulonephritis), heart valve abnormalities, and neurological symptoms etc.

Conclusions. We come to the conclusion that it is essential for the pregnant women with antiphospholipid syndrome to receive close monitoring and appropriate management to reduce the risk and severity of these pregnancy complications. This may include interventions such as anticoagulation therapy, regular prenatal care, monitoring of fetal growth and well-being, and prompt management of complications. A multidisciplinary approach involving obstetricians, rheumatologists, and other healthcare professionals is often necessary to optimize outcomes for both the mother and the baby.

Keywords: antiphospholipid syndrome, lupus anticoagulant, anticardiolipin antibodies, anti-beta-2 glycoprotein I antibodies

Corresponding author:
Astrit M. Gashi
E-mail: astritgashi772@gmail.com

Article History:
Received: 11 June 2023
Accepted: 19 June 2023

INTRODUCTION

Antiphospholipid syndrome (APS) is a multisystem rare autoimmune disorder that is characterized by the presence of antiphospholipid antibodies (aPL) in the blood, and that can manifest with a variety of clinical manifestations. These antibodies mistakenly target and bind to proteins associated with cell membranes, particularly phospholipids, leading to a hypercoagulable state (the increased tendency for blood clotting) and other clinical findings.

To meet the diagnostic criteria for antiphospholipid syndrome, a person must fulfil clinical and laboratory criteria defined by the Sydney classification criteria [1].

The clinical criteria include the following [2]:

- *Vascular thrombosis:* One or more episodes of blood clot formation in an artery or vein. It can manifest as deep vein thrombosis (DVT), pulmonary embolism, stroke, heart attack, or other arterial or venous thrombosis.
- *Pregnancy complications:* One or more unexplained fetal deaths at or beyond the 10th week of gestation, preterm birth before the 34th week due to severe pre-eclampsia or placental insufficiency, or three or more unexplained early pregnancy losses before the 10th week of gestation.
- *The laboratory criteria* for APS include the presence of at least one of the following antiphospholipid antibodies on two or more occasions, at least 12 weeks apart [3].
- *Lupus anticoagulant (LA):* Detected through coagulation tests such as activated partial thromboplastin time (aPTT), dilute Russell viper venom time (dRVVT), or other validated tests.
- *Anticardiolipin antibodies (aCL):* Measured using enzyme-linked immunosorbent assay (ELISA) or similar methods.
- *Anti-beta-2-glycoprotein I antibodies (anti-β2GPI):* Also measured through ELISA or similar methods.

It's important to note that aPL testing should be performed while the patient is not on anticoagulant therapy, as certain medications can affect the accuracy of the results. Diagnosing antiphospholipid syndrome requires the presence of both clinical and laboratory criteria. It is also crucial to rule out other potential causes of thrombosis or pregnancy complications before attributing them to APS.

Epidemiology

Antiphospholipid syndrome (APS) is considered a relatively rare autoimmune disorder, but its true prevalence may be underestimated due to misdiagnosis. The incidence of antiphospholipid syndrome (APS) was estimated to be around 5 new cases per 100,000 people per year, while the prevalence is around 40–50 cases per 100,000 persons [4-6]. The incidence rates can vary based on factors such as geographic location, population demographics, and changes in diagnostic criteria and awareness of the issue [6,7].

Antiphospholipid syndrome (APS) can affect individuals of any age, but it is most commonly diagnosed in young to middle-aged adults [8]. This disorder has a higher prevalence in women than in men, with a female-to-male ratio ranging from 3:1 to 9:1 [9]. Women of childbearing age are particularly susceptible to APS-related pregnancy complications [10].

Antiphospholipid syndrome (APS) can manifest as a primary condition or in association with other autoimmune diseases, most commonly systemic lupus erythematosus (SLE). Approximately 30% to 40% of patients with SLE also have antiphospholipid syndrome [11-13]. It can also be associated with other conditions such as rheumatoid arthritis, Sjögren's syndrome, and autoimmune thyroid disease [14- 16].

Although antiphospholipid syndrome (APS) has a global distribution, certain populations may have a higher prevalence. For example, populations with African, Hispanic, or Mediterranean ancestry have been found to have a higher incidence and severity of antiphospholipid syndrome [17,18]. The epidemiology of antiphospholipid syndrome may continue to evolve as awareness of the issue, diagnostic criteria, and screening practices constantly improve.

Pathophysiology

Antiphospholipid syndrome (APS) is an autoimmune disorder characterized by the presence of antiphospholipid antibodies (aPL) in the blood. These antibodies target phospholipid-binding proteins, including beta-2-glycoprotein I (β2GPI), prothrombin, and annexin A5, among others [19].

Antiphospholipid syndrome (APS) involves a complex interplay between aPL antibodies, endothelial cell dysfunction, pro-thrombotic factors, and impaired fibrinolysis. These processes contribute to the development of thrombosis, organ damage, and pregnancy complications commonly seen in antiphospholipid syndrome patients [20].

The pathophysiology of antiphospholipid syndrome (APS) involves several interconnected mechanisms:

- *Endothelial cell activation and damage:* aPL antibodies bind to endothelial cells, leading to their activation and dysfunction. This results in increased expression of adhesion molecules, such as selectins and integrins, promoting the attachment of immune cells and platelets to the endothelium. The activated endothelial cells also

release pro-inflammatory cytokines, further exacerbating the inflammatory response.

- *Thrombosis formation:* aPL antibodies promote a pro-thrombotic state by interfering with the normal balance of blood coagulation factors. They can bind to β2GPI, prothrombin, and other proteins involved in the coagulation cascade, leading to increased activation of platelets and clotting factors. This disruption of the coagulation system increases the risk of both arterial and venous thrombosis.
- *Impaired fibrinolysis:* aPL antibodies can also inhibit fibrinolysis, the process responsible for breaking down blood clots. This inhibition occurs by interfering with the function of plasmin, an enzyme involved in clot dissolution. As a result, clots are more likely to persist and contribute to the development of thrombotic events.
- *Pregnancy complications:* Antiphospholipid syndrome (APS) is strongly associated with adverse pregnancy outcomes, including recurrent miscarriages, fetal growth restriction, preeclampsia, and preterm birth. The exact mechanisms behind these complications are not fully understood but likely involve aPL-mediated placental dysfunction, impaired blood flow to the fetus, and increased thrombotic events within the placenta.

MATERIALS AND METHODS

This research involves systematically reviewing and analyzing existing literature on consequences of antiphospholipid syndrome in pregnancy. For relevant literature, academic databases like Pub Med, Scopus, Web of Science, and Google Scholar were used.

Search terms and keywords that were used to search for relevant literature in databases was: antiphospholipid syndrome; pregnancy; consequences, and Boolean operator (AND, OR). The criteria used to include literature in this review were; publication date, language, study objectives, study design, research methodology, key findings, and relevance to the research question. For citation and referencing were used the appropriate citation style (e.g., APA, MLA, Chicago, Harvard and Vancouver).

RESULTS

Clinical manifestations

Antiphospholipid syndrome (APS) is a multisystem autoimmune disorder that can manifest with a variety of clinical findings. The clinical presentation of antiphospholipid syndrome (APS) can vary widely among individuals, and some patients may have few or no symptoms. Here are some common clinical findings associated with antiphospholipid syndrome (APS):

Thrombotic events

Venous thrombosis: Deep vein thrombosis (DVT) is a common manifestation, often occurring in the legs. It can present with pain, swelling, and warmth in the affected limb.

Arterial thrombosis: Antiphospholipid syndrome (APS) can lead to strokes, transient ischemic attacks (TIAs), myocardial infarction (heart attack), and peripheral arterial occlusions. Symptoms depend on the affected organ or tissue.

Pregnancy complications

Recurrent miscarriages: Antiphospholipid syndrome (APS) is strongly associated with recurrent pregnancy loss, defined as three or more consecutive spontaneous miscarriages before the 10th weeks of gestation.

Fetal growth restriction: Poor fetal growth and reduced birth weight may occur due to impaired placental blood flow.

Preeclampsia: A condition characterized by high blood pressure and organ damage during pregnancy, leading to complications for both the mother and the fetus.

Preterm birth: Delivery before 37 weeks of gestation may occur in antiphospholipid syndrome pregnancies [21].

Skin manifestations

Livedo reticularis: A lace-like pattern of discoloration on the skin, typically seen on the limbs, caused by blood vessel abnormalities.

Cutaneous ulcerations: Non-healing ulcers may develop due to impaired blood flow to the skin.

Neurological manifestations

Stroke: antiphospholipid syndrome-related thrombosis can affect cerebral blood vessels, leading to a stroke. Symptoms depend on the location and extent of the brain injury.

Transient ischemic attacks (TIAs): Brief episodes of neurological dysfunction due to reduced blood flow to the brain.

Cognitive dysfunction: Some antiphospholipid syndrome patients may experience memory problems, difficulty concentrating, and other cognitive impairments.

Other manifestations

Heart valve abnormalities: Antiphospholipid syndrome (APS) can cause heart valve disease, particu-

larly a condition called Libman-Sacks endocarditis, which involves non-infectious inflammation and the formation of small vegetations on heart valves.

Kidney involvement: Antiphospholipid syndrome (APS) can lead to renal complications, such as renal artery thrombosis or glomerulonephritis.

It's essential to note that antiphospholipid syndrome (APS) is a complex disorder with a wide range of possible clinical manifestations. Not all individuals with antiphospholipid syndrome (APS) will experience all of these findings, and some may have additional symptoms specific to their individual case. If antiphospholipid syndrome (APS) is suspected, a comprehensive evaluation to confirm the diagnosis and guide appropriate management is need.

The pathophysiological mechanism of recurrent pregnancy loss from antiphospholipid syndrome

The association between antiphospholipid syndrome (APS) and recurrent pregnancy loss to includes several pathophysiological mechanisms. It's important to note that the exact mechanisms underlying antiphospholipid syndrome-related recurrent pregnancy loss are not fully understood and may involve a combination of factors.

Antiphospholipid syndrome (APS) can cause adverse pregnancy outcomes by affecting the placenta, impairing fetal development, and promoting thrombotic events.

The key mechanisms are:

1. Impaired placental function

APS-related antiphospholipid antibodies (aPL) can bind to phospholipid-binding proteins present in the placenta, leading to placental dysfunction. These antibodies may disrupt the normal development and function of trophoblast cells, which are responsible for establishing and maintaining proper blood flow between the mother and fetus. Impaired trophoblast function can result in inadequate nutrient and oxygen supply to the developing fetus, contributing to fetal growth restriction and compromised pregnancy outcomes.

2. Thrombosis and vascular complications

Antiphospholipid syndrome (APS) is characterized by a pro-thrombotic state, with aPL antibodies interfering with the coagulation system and promoting blood clot formation. Thrombotic events can occur within the placenta, leading to compromised blood flow and oxygenation to the fetus. These thrombi can also affect the uteroplacental circulation, reducing blood supply to the placenta and causing placental infarction or ischemia. Insufficient blood flow to the placenta increases the risk of miscarriage, fetal growth restriction, and other pregnancy complications.

3. Inflammatory response

aPL antibodies can induce an inflammatory response within the placenta. Inflammation can damage the placental tissue and disrupt the delicate balance of cytokines and growth factors necessary for proper fetal development. Chronic inflammation may lead to vascular abnormalities, such as endothelial dysfunction and increased permeability of blood vessels within the placenta.

4. Complement activation

Antiphospholipid syndrome (APS) can activate the complement system, a part of the immune system that helps eliminate foreign substances and damaged cells. Excessive or dysregulated complement activation within the placenta can contribute to tissue damage, inflammation, and impaired pregnancy outcomes.

Management of APS-related pregnancy complications typically involves a multidisciplinary approach, including close monitoring, anticoagulation therapy, and other interventions aimed at optimizing maternal and fetal outcomes [22].

The pathophysiological mechanism of fetal growth restriction from antiphospholipid syndrome

Fetal growth restriction (FGR) is a common complication of antiphospholipid syndrome (APS). The pathophysiological mechanisms contributing to fetal growth restriction from antiphospholipid syndrome involve impaired placental function and compromised fetal nutrient and oxygen supply.

Are some key mechanisms:

1. Placental insufficiency

APS-related antiphospholipid antibodies (aPL) can target and disrupt the function of placental cells, particularly trophoblasts. Trophoblasts play a crucial role in establishing and maintaining proper blood flow between the mother and fetus, facilitating the exchange of nutrients and oxygen. Impaired trophoblast function can lead to inadequate placental development, reduced placental surface area, and compromised nutrient and oxygen transfer to the fetus. The impaired placental function ultimately results in restricted fetal growth.

2. Abnormal placental blood flow

Thrombotic events promoted by aPL antibodies can occur within the placenta, affecting its vasculature. These thrombi can obstruct or narrow the blood vessels within the placenta, reducing blood flow to the developing fetus. Insufficient blood flow to the placenta hampers the delivery of vital nutrients and oxygen, negatively impacting fetal growth.

3. Vascular dysfunction and inflammation

APS-related inflammation and endothelial dysfunction within the placenta can contribute to fetal

growth restriction. Inflammatory processes and abnormal vasculature can disrupt the normal functioning of placental blood vessels. Impaired vascular function reduces the efficiency of nutrient and oxygen delivery to the fetus, affecting its growth and development.

4. Autoimmune-mediated damage

The autoimmune nature of antiphospholipid syndrome (APS) involves the production of autoantibodies targeting various phospholipid-binding proteins.

These autoantibodies may directly damage placental cells, impacting their ability to support optimal fetal growth. Autoantibodies targeting specific receptors or molecules on trophoblasts can interfere with their signaling pathways and functions, further contributing to fetal growth restriction.

Overall, the pathophysiology of fetal growth restriction from antiphospholipid syndrome is multifactorial, involving impaired placental function, abnormal placental blood flow, vascular dysfunction, inflammation, and autoimmune-mediated damage. The precise mechanisms can vary among individuals, and the severity of fetal growth restriction may also vary depending on the extent of placental involvement. Proper management of antiphospholipid syndrome-related fetal growth restriction involves close monitoring, interventions to optimize maternal and fetal well-being, and in some cases, anticoagulation therapy to mitigate thrombotic events and improve placental function [23].

The pathophysiological mechanism of preeclampsia from antiphospholipid syndrome

Preeclampsia is a serious complication of pregnancy characterized by high blood pressure and proteinuria, leading to organ damage. Antiphospholipid syndrome (APS) can contribute to the development of preeclampsia through various pathophysiological mechanisms.

The key mechanisms are:

1. Impaired placental function

APS-related antiphospholipid antibodies (aPL) can target the placenta and disrupt its normal function. These antibodies can interfere with the development and function of trophoblast cells, which are crucial for establishing proper blood flow between the mother and fetus. Impaired trophoblast function can lead to inadequate remodeling of uterine blood vessels, reducing the placental blood supply. The resulting placental dysfunction contributes to the development of preeclampsia.

2. Endothelial dysfunction

Antiphospholipid syndrome (APS) is associated with endothelial dysfunction, which is also a key feature of preeclampsia. aPL antibodies can directly affect endothelial cells, leading to their activation and dysfunction. Activated endothelial cells promote vasoconstriction, inflammation, and an imbalance in vasodilatory and vasoconstrictive factors. Endothelial dysfunction contributes to high blood pressure, reduced blood flow to organs, and the systemic manifestations of preeclampsia.

3. Thrombotic tendency

Antiphospholipid syndrome (APS) is characterized by a pro-thrombotic state, and this thrombotic tendency can contribute to the development of preeclampsia.

Thrombosis within the placental vasculature can compromise blood flow to the fetus and contribute to placental dysfunction.

Thrombi formation in maternal blood vessels can further impede blood flow and contribute to endothelial dysfunction and organ damage.

4. Inflammatory response

APS-related inflammation can promote an inflammatory state that contributes to the pathogenesis of preeclampsia. Inflammation disrupts the delicate balance of cytokines and growth factors necessary for normal pregnancy. Excessive inflammation can damage the endothelium, impair placental function, and contribute to the development of preeclampsia.

It's essential to note that while antiphospholipid syndrome (APS) can increase the risk of preeclampsia, not all women with antiphospholipid syndrome will develop preeclampsia, and preeclampsia can occur in the absence of antiphospholipid syndrome (APS) as well. The exact pathophysiological mechanisms underlying the development of preeclampsia in antiphospholipid syndrome are complex and likely involve the interaction of multiple factors. Close monitoring, early detection, and appropriate management are crucial in the care of pregnant women with antiphospholipid syndrome to reduce the risk and severity of preeclampsia [24].

The pathophysiological mechanism of preterm birth from antiphospholipid syndrome

Antiphospholipid syndrome (APS) has been associated with an increased risk of preterm birth, which refers to delivery before 37 weeks of gestation. The pathophysiological mechanisms underlying the relationship between antiphospholipid syndrome and preterm birth involve various factors:

1. Placental dysfunction

APS-related antiphospholipid antibodies (aPL) can target the placenta and disrupt its normal function. Impaired placental development and function can lead to reduced nutrient and oxygen supply to the developing fetus. Inadequate placental function increases the risk of complications, including preterm birth.

2. Inflammation and immune dysregulation

Antiphospholipid syndrome (APS) involves an abnormal immune response, including inflammation and immune dysregulation. Chronic inflammation within the placenta can contribute to premature rupture of membranes (PROM), which can lead to preterm birth. Immune dysregulation can lead to an overactive maternal immune response against the fetus or the placenta, resulting in placental dysfunction and preterm labor.

3. Thrombotic events

Antiphospholipid syndrome (APS) is characterized by a pro-thrombotic state, with an increased risk of thrombosis. Thrombotic events within the placenta can impair blood flow and nutrient supply to the fetus, increasing the risk of preterm birth. Thrombosis of uterine blood vessels can also disrupt placental function and contribute to preterm labor.

4. Vascular dysfunction and endothelial activation

APS-related antiphospholipid antibodies can activate endothelial cells and promote vascular dysfunction. Endothelial dysfunction and abnormal vascular responses can disrupt the delicate balance of factors involved in maintaining pregnancy and contribute to preterm labor.

5. Uterine contractility

Antiphospholipid syndrome-related factors may contribute to increased uterine contractility and irritability, leading to preterm contractions and labor. Inflammatory mediators and dysregulated immune responses can stimulate uterine contractions and contribute to the onset of preterm labor.

Management of pregnant women with antiphospholipid syndrome aims to identify and address these risk factors to reduce the incidence of preterm birth. Close monitoring, appropriate interventions, and timely administration of interventions such as anticoagulation therapy may be employed to improve maternal and fetal outcomes [25].

DISCUSSIONS

Antiphospholipid syndrome (APS) is a multisystem rare autoimmune disorder that is characterized by the presence of antiphospholipid antibodies (aPL) in the blood, and that can manifest with a variety of clinical manifestations.

Antiphospholipid syndrome is strongly associated with various pregnancy complications, including recurrent miscarriages, fetal growth restriction, preeclampsia, and preterm birth.

Antiphospholipid syndrome (APS) is a leading cause of recurrent pregnancy loss. Women with antiphospholipid syndrome may experience three or more consecutive spontaneous miscarriages before the 10th week of gestation. Impaired placental function, inadequate blood flow to the fetus, and thrombotic events within the placenta contribute to recurrent miscarriages [26].

Also, antiphospholipid syndrome increases the risk of fetal growth restriction (FGR), which refers to inadequate fetal growth and reduced birth weight. Placental dysfunction, compromised nutrient and oxygen transfer, and impaired blood flow to the fetus contribute to fetal growth restriction (FGR). It is confirmed that insufficient placental support affects the fetus's growth and development, resulting in fetal growth restriction (FGR) [27].

Antiphospholipid syndrome (APS) is associated with an increased risk of preeclampsia, a condition characterized by high blood pressure and proteinuria leading to organ damage during pregnancy. Impaired placental function, endothelial dysfunction, inflammation, and a pro-thrombotic state contribute to the development of preeclampsia. Preeclampsia can lead to complications for both the mother and the fetus if not appropriately managed [28].

Antiphospholipid syndrome (APS) increases the risk of preterm birth, defined as delivery before 37 weeks of gestation. Placental dysfunction, inflammation, immune dysregulation, thrombotic events, vascular dysfunction, and increased uterine contractility contribute to preterm labor. Preterm birth carries risks for the health and development of the baby [29,30].

CONCLUSIONS

We come to the conclusion that it is essential for the pregnant women with antiphospholipid syndrome to receive close monitoring and appropriate management to reduce the risk and severity of these pregnancy complications. This may include interventions such as anticoagulation therapy, regular prenatal care, monitoring of fetal growth and well-being, and prompt management of complications. A multidisciplinary approach involving obstetricians, rheumatologists, and other healthcare professionals is often necessary to optimize outcomes for both the mother and the baby.

Ethics approval and consent to participate

This study is a literature review. It was conducted using only aggregated data in literature. Institutional review board approval was not required.

Conflict of interest and financial support:
The author declares that there is no financial interest or conflict of interest.

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