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Antiphospholipid syndrome and pregnancy: A review article

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Abstract

Introduction: Antiphospholipid syndrome has been associated with numerous health complications in patients. However, a significant number of pregnant women or women planning to conceive have an increased risk of developing complications leading to adverse pregnancy outcomes.

Objective: The aim of this study is to investigate and analyze the adverse pregnancy outcomes in women with antiphospholipid syndrome or antiphospholipid antibodies.

Material and methods: In this study, the methodology used was a systematic literature review with a search of English articles, conducted in electronic databases, such as Pubmed, Google Scholar, Cochrane and scientific journals. The time frames for the search of the articles were from 2014 to 2024.

Results: Antiphospholipid syndrome can have adverse effects on both the pregnant woman and the fetus. However, the risk varies from woman to woman and depends on which antiphospholipid antibodies she is positive to, her medical history, i.e. whether she has a history of thrombosis, complications in a previous pregnancy such as miscarriage, intrauterine deaths, placental insufficiency, whether there is another co-morbid condition - usually autoimmune disease, and the treatment she has received. The analysis of the studies in this paper emphasize the importance of categorizing women according to the characteristics of the antiphospholipid syndrome, as well as early diagnosis of the syndrome in order to receive appropriate treatment to prevent or minimize possible adverse outcomes.

Conclusion: Understanding the pathophysiology and complications of antiphospholipid syndrome that may occur during pregnancy is of major importance for planning perinatal care.

Keywords: Antiphospholipid syndrome; Antiphospholipid antibodies; Pregnancy; Obstetric outcomes

1. Introduction

Antiphospholipid syndrome (APS), or Hughes syndrome, is an autoimmune, non-inflammatory hypercoagulable disorder characterized by the presence of autoantibodies to various phospholipids, or phospholipid-binding proteins. It is the most common acquired thrombophilia. Autoantibodies include cardiolipin antibodies, lupus anticoagulant and antibodies to B2 glycoprotein. These autoantibodies have thrombophilic (prothrombotic) and anticoagulant activity. However, thrombophilic (procoagulant) activity predominates, resulting in venous/arterial thrombosis, and miscarriages [1]. They are also responsible during pregnancy for intrauterine death, intrauterine growth restriction (IUGR), premature delivery due to severe pre-eclampsia and placental insufficiency [2].

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In the absence of other underlying disease, antiphospholipid syndrome is classified as primary [3]. When another autoimmune disease is present, usually systemic lupus erythematosus or other connective tissue disease is called secondary antiphospholipid syndrome [4, 5].

2. Methodology

This study complied with the guidelines of the PRISMA statement. The Pubmed, Google Scholar and Cochrane scientific databases were searched for original studies published from 2014 to 2024 to identify cohort studies, randomized cotrolled trials of pregnant women with antiphospholipid syndrome that included information on fetal or maternal pregnancy outcome. In the databases, the search was performed in a simple and complex combined manner. Keywords were used: antiphospholipid syndrome and pregnancy, antiphospholipid antibodies and pregnancy, antiphospholipid syndrome and pregnancy outcome, preeclampsia, placental insufficiency, lupus anticoagulant, anticoagulant treatment. The search resulted in 1110 studies. After removing 937 duplicates, the potentially relevant studies through initial title review were 173. 110 studies were rejected after reading the title and 63 were potentially relevant studies after reading the abstract. 30 articles were excluded and potentially relevant articles after reading the full text were 33. 18 studies excluded as not relevant to the topic, with a language other than English and were published before 2014. The final studies included in the systematic review were 15. The inclusion criteria were a) these studies analyzed adverse pregnancy outcomes in patients with antiphospholipid syndrome, b) they were written in English language. The rejection criteria are (a) that the full text was not provided and (b) they referred to antiphospholipid syndrome in general and not to pregnancy. The search timeframes for the articles were from 2014 to 2024 and the search language was English (Figure 1, Table 1).

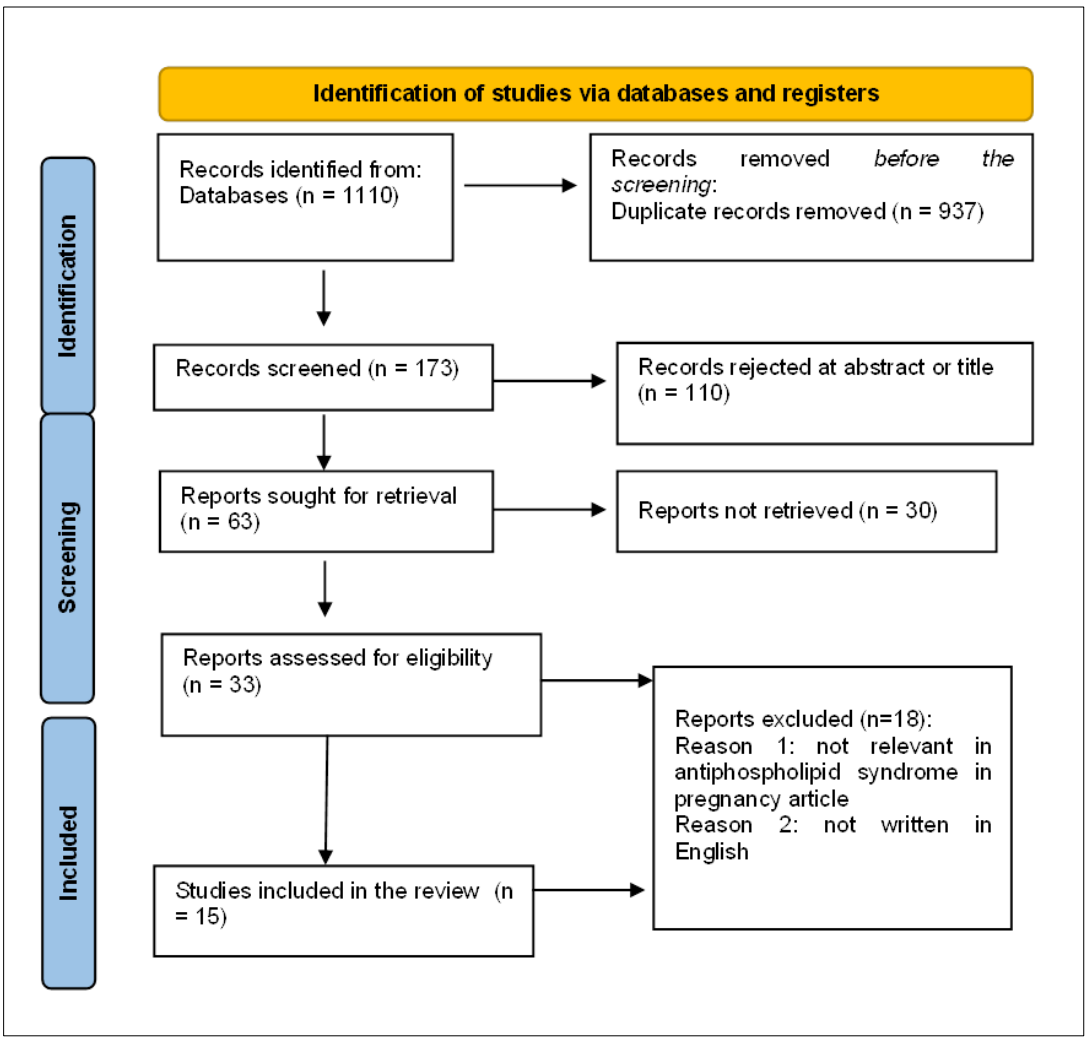

Figure 1 Results of studies based on the PRISMA method

Table 1 Summary of the 15 included studies in the systematic revie

	Author, year (country)	**Purpose**	**Type of study**	**Sample**	**Main results/ conclusions**
1.	Ruffatti et al., 2014 (Italy, Spain, France and Sweden)	Evaluation of the effect of different treatment regimens in pregnant women with antiphospholipid syndrome; investigation of factors associated with miscarriage.	Multicentre Retrospective Cohort Study	156 pregnant women with antiphospholipid syndrome with 196 pregnancies, receiving conventional and/or additional anticoagulation	The triple-positive thrombosis subgroup receiving additional therapy had significantly higher live birth rates than those who receiving conventional therapy alone.
2.	Bouvier et al., 2014 (France and Switzerland)	Investigation of obstetric outcomes in pregnant women with obstetric antiphospholipid syndrome treated with low molecular weight heparin and low dose aspirin	Prospective cohort study	513 pregnancies of patients with antiphospholipid syndrome with a history of obstetric complications , 791 pregnancies of women without the syndrome but with a history of obstetric complications.	In women with antiphospholipid syndrome, a history of intrauterine death is a risk factor for intrauterine death, pre-eclampsia, prematurity and any placental complications. Receiving conventional treatment reduced miscarriage rates, but not pre-eclampsia rates. Cardiolipin IgM antibody is a risk factor for placental complication. In women with antiphospholipid syndrome, a history of spontaneous abortion has higher rates for preeclampsia, placental complications and neonatal mortality.
3.	Sciascia et al., 2015 (United Kingdom and Italy)	Evaluation of pregnancy outcomes in women with antiphospholipid antibodies treated with hydroxychloroquine along with conventional therapy	Retrospective cohort study	96 women with antiphospholipid antibodies with 170 pregnancies, divided into 2 groups: A group 31 women receiving hydroxychloroquine and B group 65 women not receiving hydroxychloroquine	Hydroxychloroquine treatment is associated with increased rates of live birth, spontaneous vaginal delivery and longer gestation. It is also associated with reduced rates of miscarriage and pregnancy complications.
4.	Mekinian et al., 2017 (France, Spain and Italy)	Description of obstetric outcomes and treatment of obstetric antiphospholipid syndrome.	Multicenter retrospective cohort study	49 women with obstetric antiphospholipid syndrome with a history of complications during pregnancy	Laboratory findings associated with adverse obstetric outcomes are triple positivity and lupus anticoagulant at high titers. The addition of hydroxychloroquine and steroids to conventional

					therapy increased live births.
5.	Deguchi et al., 2017 (Japan)	To investigate the clinical features of pregnancies with antiphospholipid syndrome and to evaluate risk factors.	Retrospective cohort study	69 women with antiphospholipid syndrome with 81 pregnancies	Risk factor for miscarriage is a history of miscarriage, for preterm delivery <34 weeks in women on conventional treatment is positivity to ≥ 2 antibodies. Factor for hypertensive events in pregnancy is low complement levels and for thrombocytopenia is ≥ 2 antibodies and secondary antiphospholipid syndrome.
6.	Saccone et al., 2017 (Italy and USA)	To evaluate the risk of obstetric complications in women with primary antiphospholipid syndrome associated with a specific antibody profile	Multicentre Retrospective Cohort Study	750 singleton pregnancies with primary antiphospholipid syndrome receiving conventional anticoagulation from the 1st trimester of pregnancy	The most common antibody is cardiolipin, while β2 glycoprotein1 is associated with adverse outcomes. Positive ≥1 antibodies are associated with poor perinatal outcomes. Triple positivity despite conventional treatment has a 30% live birth rate despite conventional treatment.
7.	Gabbay-Benziv et al., 2018 (Israel)	Investigation of clinical characteristics, antibody and antibody titers associated with severe adverse outcomes in pregnancies beyond 20 weeks in patients with antiphospholipid syndrome.	Retrospective cohort study	99 pregnant women with antiphospholipid syndrome, divided into subgroups based on , antibodies, titres and history of thrombosis or pregnancy complications	No difference in moderate and severe outcomes was found between women with obstetric or thrombotic antiphospholipid syndrome. Positive lupus anticoagulant was associated with prematurity <37 weeks. Elevated antibody titer is associated with severe prematurity <32 weeks.
8.	Fredi et al., 2018 (Italy and France)	Investigation of risk factors for adverse pregnancy outcomes in pregnant women with confirmed positive antibodies or primary antiphospholipid syndrome.	Multicentre Retrospective Cohort Study	200 women with antiphospholipid syndrome with 283 pregnancies	Pregnant women with a history of thrombosis and those with low levels of complement and/or autoimmunity, such as autoimmune thyroiditis, had an increased risk of complications
9.	Gibbins et al., 2018 (USA)	To evaluate the relationship between preconception	Prospective cohort study	786 chorionic positive women with a history of 1 or 2 previous	Positive antiphospholipid antibodies are rare in women with 1 or 2

		antiphospholipid antibodies and miscarriages.		miscarriages and no more than 2 live births.	miscarriages and are not clearly associated with the miscarriages studied in the study
10.	Lazzaroni et al., 2019 (Italy and Russia)	Evaluation of pregnancy outcomes and factors associated with adverse pregnancy outcomes in antibody carriers	Multicenter Retrospective Cohort Study	62 pregnant women with positive antiphospholipid antibodies without clinical features	Pregnant women with triple positivity have an increased risk of obstetric complications despite prophylactic anticoagulation with aspirin and heparin
11.	Hogden et al., 2019 (Sweden)	Investigation of obstetric outcomes in patients with primary thrombotic or primary obstetric antiphospholipid syndrome compared with controls.	Retrospective cohort study	Group 1: 30 pregnant women with antiphospholipid syndrome.Group 2: pregnant women who gave birth in the same period without antiphospholipid syndrome	Group 1: 30 pregnant women with antiphospholipid syndrome.Group 2: pregnant women who gave birth in the same period without antiphospholipid syndrome.
12.	Alijotas-Reig et al., 2019 (Spain, Greece, France, Italy, Argentina, Austria, Russia and Finland)	To review the clinical features, laboratory data and obstetric outcomes in women with obstetric antiphospholipid syndrome.	Multicentre Retrospective and Synchronous Study	1000 women with antiphospholipid syndrome, where they had 2553 previous pregnancies and 1000 pregnancies during the study.	Recurrent miscarriages, prematurity and intrauterine deaths were the most common adverse outcomes in the survey. Perinatal outcomes were excellent when aspirin and heparin were administered
13.	Yang and Liang, 2021 (China)	To investigate the risk factors for adverse pregnancy outcomes in women with antiphospholipid syndrome.	Retrospective cohort study	Group A: 59 women with antiphospholipid syndrome with 64 pregnancies, Group B: 256 women and pregnancies without syndrome.	Compared with the control group, pregnant women with antiphospholipid syndrome had increased rates of preeclampsia, premature rupture of hymen, bleeding in labour, intrauterine death and prematurity ≤ 34 weeks. ≥3 miscarriages and double positivity are risk factors for adverse outcomes.
14.	Liu et al., 2022 (China)	To evaluate hydroxychloroquine as a new treatment in pregnant women with antiphospholipid syndrome	Retrospective cohort study	96 cases of obstetric antiphospholipid syndrome, divided into 2 groups. One group (n=59) received hydroxychloroquine while the other (n=37) did not.	Patients who received hydroxychloroquine had increased rates of preterm delivery while patients who did not had increased rates of spontaneous abortion, fetal distress and muddy amniotic fluid
15.	Long et al., 2023 (China)	To determine perinatal outcomes in women with antiphospholipid	Randomized controlled trial	81 women with positive antiphospholipid antibodies, divided	Aspirin and/or heparin reduced rates of severe pre-eclampsia and increased rates of live

		syndrome and chronic hypertension receiving conventional anticoagulant treatment		into 3 groups based on whether they were treated or not	birth. However, aspirin plus heparin can lead to a full-term pregnancy with better perinatal outcomes

3. Results

The study by Bouvier et al, (2013) included 513 pregnancies of patients with antiphospholipid syndrome with a history of obstetric complications who received aspirin plus heparin and 791 pregnancies of women without the syndrome but with a history of obstetric complications [6]. In women with antiphospholipid syndrome, history of intrauterine death is a risk factor for intrauterine death, pre-eclampsia, prematurity and any placenta- mediated complications. Receiving conventional treatment reduced miscarriage rates but not pre-eclampsia rates. Cardiolipin IgM antibody is a risk factor for placenta- mediated complications. In women with antiphospholipid syndrome, a history of spontaneous abortion has higher rates for preeclampsia, placenta- mediated complications and neonatal mortality. The study by Lazzaroni et al, (2019) [7], included 62 pregnant women who were carriers of antiphospholipid antibodies without a history of thrombosis or obstetric complications. Pregnant women with triple positivity have an increased risk of obstetric complications despite prophylactic anticoagulant therapy with aspirin plus heparin. Similar results were obtained by Ruffatti et al, (2014) [8] who included 156 pregnant women with antiphospholipid syndrome with 196 pregnancies receiving conventional and/or additional anticoagulant therapy. They concluded that women with triple positivity when receiving additional treatment beyond conventional (aspirin & heparin) had significantly higher live birth rates. The same conclusion was reached by Hogden et al, (2019) [9], who included 30 pregnant women with antiphospholipid syndrome and compared obstetric outcomes with pregnant women who gave birth at the same time without antiphospholipid syndrome. They concluded that pregnant women with a history of obstetric morbidity and triple positivity had adverse outcomes despite anticoagulants. The study by Fredi et al, (2018) [10], included 200 women with antiphospholipid syndrome with 283 pregnancies and found that pregnant women with a history of thrombosis had a higher risk of pregnancy complications. In contrast, the study by Gabbay-Benziv et al, (2018) [11], included 99 pregnant women with antiphospholipid syndrome, divided into subgroups based on antibody profile, antibody titer and history of thrombosis or pregnancy complications. No differences in mild or severe outcomes were found between women with obstetric or thrombotic antiphospholipid syndrome; positive lupus anticoagulant was associated with preterm <37 weeks. Elevated antibody titer is associated with severe prematurity <32 weeks. The study by Sciascia et al., (2015) [12], evaluated pregnancy outcomes in 31 women with antiphospholipid antibodies who received hydroxychloroquine treatment along with conventional therapy and 65 women who did not.

Hydroxychloroquine treatment was associated with increased rates of live births, spontaneous vaginal deliveries and longer pregnancy duration. It is also associated with reduced rates of miscarriage and pregnancy complications. Mekinian et al, (2017) [13], described the obstetric outcomes and treatment of obstetric antiphospholipid syndrome in 49 women with obstetric antiphospholipid syndrome with a history of pregnancy complications. Laboratory findings associated with adverse obstetric outcomes are triple positivity and lupus anticoagulant at high titers. The addition of hydroxychloroquine and steroids to conventional therapy increased live births. In the study by Deguchi et al, (2017) [14], 69 women with antiphospholipid syndrome with 81 pregnancies were included. They conclude that risk factor for miscarriage is history of miscarriage, risk factor for preterm delivery <34 weeks in women on conventional treatment is positivity to ≥ 2 antibodies. Risk factor for hypertensive events in pregnancy are low complement levels and risk factors for thrombocytopenia are ≥ 2 antibodies and secondary antiphospholipid syndrome. Saccone et al, (2017) [15], included 750 singleton pregnancies with primary antiphospholipid syndrome receiving conventional anticoagulation from the 1st trimester of pregnancy. They concluded that the most common antiphospholipid antibody was anti-cardiolipin, while anti-β2 glycoprotein1 was associated with adverse outcomes. More than one antibody positivity was associated with poor perinatal outcomes. Triple positivity despite conventional treatment, has a 30% live birth rate. The study by Gibbins et al, (2018) [16], included 786 women with positive human chorionic gonadotropin with a history of 1 or 2 previous miscarriages and no more than 2 live births, and concluded that positive antiphospholipid antibodies are rare in women with 1 or 2 miscarriages and are not clearly associated with the miscarriages occurred in the study. Alijotas-Reig et al, (2018) [17], included 1000 women with antiphospholipid syndrome, who they had 2553 previous pregnancies and 1000 pregnancies during the study. Recurrent miscarriages, prematurity and intrauterine deaths were the most common adverse outcomes in the study. Perinatal outcomes were excellent when aspirin plus heparin were administered. The study by Yang and Liang, (2021) [18], included 59 women with antiphospholipid syndrome with 64 pregnancies and 256 women and pregnancies without the syndrome. Compared to the control group, pregnant women with antiphospholipid syndrome had increased rates of preeclampsia, premature rupture of membranes, bleeding in labor, intrauterine death, and prematurity ≤ 34 weeks. ≥3 miscarriages and double positivity are risk factors for adverse

outcomes. Liu et al, (2022) [19], studied 96 cases of obstetric antiphospholipid syndrome where 59 were receiving hydroxychloroquine while the rest were not. Patients who received hydroxychloroquine had increased rates of preterm delivery while patients who did not had increased rates of spontaneous abortions, fetal distress and amniotic fluid muddy. The study by Long et al, (2023) [20], included 81 women with positive antiphospholipid antibodies, divided into 3 groups based on whether or not they received treatment. Aspirin and/or heparin reduced rates of severe preeclampsia and increased rates of live birth. However, aspirin along with heparin may lead to a full-term pregnancy with better perinatal outcomes.

4. Discussion

In the study by Hodgen et al, (2019) [9], patients with obstetric antiphospholipid syndrome had worse neonatal outcomes, such as intrauterine growth restriction (IUGR) and low birth weight, compared to patients with a history of thrombotic antiphospholipid syndrome. The study by Yang and Liang (2021) [18], reached the same conclusion, where patients with a history of 3 or more miscarriages, without a history of thrombosis, are at increased risk for adverse outcomes. In the study by Ruffatti et al, (2014) [8], and Saccone et al, (2017) [15], a history of thrombosis is a risk factor for adverse pregnancy outcomes. In contrast, in the study by Gabbay-Benziv et al., (2018) [11], neither obstetric nor thrombotic antiphospholipid syndrome had statistically significant differences for mild or severe adverse outcomes.

Triple positivity appears to be a risk factor for adverse pregnancy outcomes in the studies by Saccone et al., (2017), Lazzaroni et al., (2019), Ruffatti et al, (2014), Hogden et al., (2019), Sciascia et al., (2015), Deguchi et al., (2017), [15,7,8,9,12,14]. In contrast, in the study by Fredi et al., (2018), Bouvier et al., (2014) and Yang and Liang, (2021), [10,6,18] triple positivity was not a risk factor.

In the study by Saccone et al., (2017) [15], the antiphospholipid antibody associated with adverse pregnancy outcomes is anti-β2 glycoprotein. In the study of Ruffatti et al., (2014), Alijotas-Reig et al., (2018), Bouvier et al., (2014), [8,17,6], the most frequent antibody is lupus anticoagulant, as in the study of Gabbay-Benziv et al., (2018) [11], where it is associated with prematurity. Lupus anticoagulant is also associated with adverse pregnancy outcomes in the study by Mekinian et al., (2017) [13]. Researchers Fredi et al., (2018) [10], found cardiolipin antibody more common, as did researchers Bouvier et al., (2014) [6], where it is associated with placenta-mediated complications. In contrast, in the study by Mekinian et al., (2017) [13], cardiolipin antibody was associated with favorable pregnancy outcomes.

Conventional treatment with low-dose aspirin and/or low molecular weight heparin appeared to be effective in the studies of Lazzaroni et al., (2019), Gabbay-Benziv et al., (2018), Fredi et al., (2018), Deguchi et al., (2017), Alijotas-Reig et al., (2018) [7,11,10, 14,17]. In contrast, in the studies by Liu et al., (2022), Yang and Liang (2021), Sciascia et al., (2015) [19,18,12], additional treatment beyond conventional treatment such as hydroxychloroquine therapy appeared to be effective in limiting adverse outcomes. Furthermore, in the study by Mekinian et al., (2017) [13], it was found that additional therapy beyond conventional antithrombotic treatment, specifically the use of steroids, is effective. In the study by Long et al., (2023) and Bouvier et al., (2014) [20, 6], it was found that conventional anticoagulants can limit adverse outcomes to some extent, and additional therapies are necessary. This is also agreed by Saccone et al., (2017) [15], as aspirin and heparin treatment had no effect on reducing adverse outcomes in triple positivity and in history of thrombosis.

5. Conclusion

According to the analysis of the research in this study, we find that antiphospholipid syndrome is a rare autoimmune disease but if it remains undiagnosed and left untreated, it can have devastating consequences on the health of the pregnant woman as well as the fetus.

It may coexist with another autoimmune condition, most commonly systemic lupus erythematosus or other connective tissue disease, and for this reason these patients should be closely monitored by various health professionals.

The type of antiphospholipid syndrome should be taken into account, i.e. whether it is obstetric or thrombotic antiphospholipid syndrome, primary or secondary, as well as the profile of antiphospholipid antibodies, because this will determine the treatment.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest

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