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The association of antiphospholipid syndrome under medical treatment with adverse pregnancy outcomes

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Abstract

Objectives: We aim to clarify the association and strength of association between antiphospholipid syndrome (APS) and adverse pregnancy outcomes.

Methods: Our study included an analysis of 191 hospitalized singleton pregnant women with APS and 984 healthy singleton pregnant women at Obstetrics and Gynecology Hospital Affiliated to Fudan University from July 2017 to September 2023. The exposure factor was diagnosed as antiphospholipid syndrome, and the main outcomes were adverse pregnancy outcomes, including miscarriage, preterm birth, low birth weight, gestational hypertension, and eclampsia.

Results: Our analysis indicated that the odds ratio (OR) for miscarriage in APS patients was 2.50 (95 % CI, 1.025 ± 15.794; $p=0.046$), for preterm birth was 2.8 (95 % CI, 1.025 ± 15.794; $p=0.046$), for low birth weight was 2.28 (95 % CI, 1.025 ± 15.794; $p=0.046$), and for fetal growth restriction was $OR=2.48$ (1.45, 4.23) $p<0.05$. The OR for preeclampsia was 1.00, and for gestational hypertension was 0.96, $p>0.05$. After adjustment for confounders of age and BMI confounders, the odds ratio (OR) for miscarriage was 2.50 (95 % CI: 1.52–4.11) $p<0.05$. Preterm birth was 2.89 (95 % CI: 1.79–4.65) $p<0.05$, low birth weight was 2.28 (95 % CI: 1.52–3.55) $p<0.05$, intrauterine growth restriction was 2.48 (95 % CI: 1.45–4.23) $p<0.05$. The OR of preeclampsia was 1.00 (95 % CI: 0.59–1.71) $p>0.05$, and that of pregnancy-induced hypertension was 0.96 (95 % CI: 0.53–1.75) $p>0.05$. After adjustment for confounders of age, BMI, eclampsia and diabetes, the OR for preterm infants were 3.06 (95 % CI: 1.87–5.00) $p<0.05$, and those of low birth weight infants were 2.55 (95 % CI: 1.49–4.37) $p<0.05$. After adjustment for confounders of age, BMI, diabetes, eclampsia,

and gestational week, the OR for low birth weight infants was 2.02 (95 % CI: 1.26–3.26) $p<0.05$.

Conclusions: Antiphospholipid syndrome was significantly associated with the risk of miscarriage, preterm birth, low birth weight, and intrauterine growth restriction as adverse pregnancy outcomes.

Keywords: antiphospholipid syndrome; adverse pregnancy outcomes; OR

Introduction

Antiphospholipid syndrome (APS) emerges as a prevalent autoimmune affliction, distinguished by the presence of antiphospholipid antibodies coursing through the bloodstream. Epidemiological investigations reveal that its incidence within the general populace hovers around 4 to 5 cases per 100,000 individuals; however, this figure escalates notably among expectant mothers, where the positivity rate of antiphospholipid antibodies ascends to a concerning 6–9 % [1]. Patients may endure recurrent adverse pregnancy outcomes, including miscarriage, preterm birth, and fetal growth restriction, phenomena that have captured significant attention [2]. These adverse outcomes not only inflict profound repercussions on the physical and mental well-being of the affected individuals but also impose considerable economic strains upon families and society at large.

While numerous investigations have delved into the pregnancy complications associated with antiphospholipid syndrome (APS), these inquiries predominantly concentrate on the association between APS and specific adverse outcomes, seldom undertaking a comprehensive examination of all potential adverse pregnancy outcomes within a singular study. For instance, one investigation revealed that thrombocytopenia during the early stages of pregnancy heightened the risk of preterm delivery among patients afflicted with phospholipid antibody syndrome [3]. In another notable study, the presence of triple positivity for antiphospholipid antibodies emerged as a significant risk factor for the onset of severe early preeclampsia [4]. A meta-review encompassing 1,124 articles meticulously included eight studies – comprising five randomized controlled trials and three prospective

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cohort studies – to elucidate the intricate relationship between APS and fetal growth restriction [5].

In pursuit of clarity regarding the risks of adverse pregnancy outcomes in women afflicted with APS, this study adopted a retrospective cohort design, systematically collecting pregnancy outcomes and clinical data from female patients diagnosed with antiphospholipid syndrome at our institution within a specified time period. The investigation encompassed 191 pregnant women grappling with antiphospholipid syndrome alongside 984 healthy pregnant counterparts, utilizing a logistic regression model to examine the odds ratios (OR) of adverse pregnancy outcomes in individuals with antiphospholipid syndrome (APS).

Patients and methods

Study design and participants

We meticulously selected case groups, specifically the APS group, alongside healthy control groups from the cohort of mothers registered at our esteemed institution between July 2017 and September 2023. This retrospective analysis aimed to elucidate the impact of APS on pregnancy outcomes among women of childbearing age. The criteria for inclusion in the APS group were as follows: 1) pregnant women with a singleton pregnancy; 2) mothers diagnosed with APS prior to conception, as per the clinical information derived from the Hospital Information System; 3) an age not exceeding 40 years; 4) registration within the obstetrics department of our hospital, possessing comprehensive prenatal check-up records and documented pregnancy outcomes, alongside the provision of informed consent for case analysis.

Conversely, the exclusion criteria encompassed: 1) individuals necessitating artificial termination of pregnancy in the early stages; 2) absence of requisite data for analysis, including a complete medical history and pregnancy outcomes; 3) those with pre-existing hypertension or diabetes; 4) mothers afflicted with mental illness or chromosomal abnormalities; 5) individuals uncooperative with prenatal check-ups for various reasons; 6) patients diagnosed with malignant tumors.

Furthermore, we identified women of childbearing age with singleton pregnancies, who were free from underlying diseases and had no history of blood or immune system disorders. These women underwent prenatal evaluations at our institution during the same period. These individuals, having tested negative for phospholipid antibodies prior to pregnancy and aged ≤ 40 years, constituted the control group, thereby enhancing the accuracy of our study. The diagnosis of APS was established by experienced physicians in accordance

with the 2006 Sydney criteria, which require the presence of at least one clinical criterion (vascular thrombosis or pregnancy morbidity) and one laboratory criterion (detection of lupus anticoagulant, anticardiolipin antibodies, β_2 -glycoprotein I antibodies, or Anti-phosphatidylserine/prothrombin complex antibodies (aPS/PTantibodies) in plasma/serum on two occasions at least 12 weeks apart). Pertinent clinical data and outcomes for both mothers and neonates were systematically retrieved from the Hospital Information System and the Laboratory Information System [6]. This study adhered to the principles set forth in the Declaration of Helsinki and was approved by the Research Ethics Committee of Fudan University Affiliated Obstetrics and Gynecology Hospital.

Clinical care and pharmacologic therapies

All patients in this study received medical care supervised by senior obstetricians at our hospital. Treatment regimens for managing APS were selected based on the 2011 guidelines established by the Chinese Medical Association Rheumatology Branch [7]. Pregnant women with positive antiphospholipid antibodies received low-dose aspirin (LDA, 75–100 mg/d) or low molecular weight heparin (LMWH, 1 mg/kg, subcutaneously once or twice daily). For patients diagnosed with gestational thrombocytopenia, low-dose corticosteroids (prednisone 5–15 mg/d) were prescribed, additionally, those with previous pregnancy morbidity and thrombosis, elevated ANA, or placental insufficiency during pregnancy received hydroxychloroquine (200–400 mg/day) along with LDA and/or LMWH anticoagulation therapy.

Data collection

APS was considered the exposure factor in this study. The levels of antiphospholipid antibodies were quantified using a fully automated chemiluminescence instrument (YHLO iFlash 3000) and commercial kits (YHLO Company). Confounding factors, including age, body mass index (BMI), preeclampsia, diabetes, and gestational age at delivery, were adjusted for in the analysis. Laboratory measurements were performed prior to the current pregnancy of the patients. The inter-batch coefficient of variation for all tests was less than 10 %. Diagnostic information regarding APS was retrieved from hospital information system (HIS) records.

The primary outcome measures included adverse pregnancy outcomes such as miscarriage, preterm birth, low birth weight infants, intrauterine growth restriction (IUGR), gestational hypertension, preeclampsia, and eclampsia. Miscarriage was defined as unexplained fetal demise

occurring after 10 weeks of gestation with morphologically normal findings. Preterm birth was characterized by delivery before 34 weeks of gestation. Low birth weight infants were identified based on birth weights below the 10th percentile for gestational age and sex, according to the Intergrowth-21st criteria [8]. IUGR was diagnosed when fetal abdominal circumference growth fell below the 10th percentile over two-week intervals as assessed by ultrasound. Gestational hypertension was defined as the first appearance of systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg after 20 weeks of gestation. All data were sourced from HIS records.

Statistical analysis

Preeclampsia was diagnosed gestation hypertension consists with proteinuria defined as either a urine dipstick showing $\geq 2+$ protein or 24-h urine collection with ≥ 300 mg protein. This diagnostic criterion following the guidelines of the American College of Obstetricians and Gynecologists [9]. In this study, continuous variables are expressed as mean $\pm$ standard deviation, and differences between the two groups are compared using the Student's *t*-test. Group differences in age, height, weight, and blood pressure values were compared using independent Student's *t*-tests. The differences in adverse pregnancy outcomes between the two groups. Univariate logistic regression analysis revealed an association between APS and adverse pregnancy outcomes. Multivariable logistic regression models further quantified the adjusted odds ratios (aOR) and 95 % confidence intervals (95 % CI) after controlling for confounding variables (e.g., maternal age, parity, and comorbidities). Statistical significance was defined as $p < 0.05$.

Statistical analysis of the software was conducted using IBM SPSS (Version 21.0, IBM Corporation, Armonk, NY, USA) and the R statistical software package (R Foundation for Statistical Computing; <https://www.rproject.org>; Version 3.4.3).

Results

Clinical characteristics of the study participants

The current study included a cohort of 191 women of child-bearing age diagnosed with APS, with a mean age of 32.3 ± 4.3 years, and a control group of 984 pregnant women without APS, with a mean age of 30.4 ± 3.3 years. The body mass index for both groups was noted to be 22.0 ± 1.8 kg/m² for the APS

cohort and 22.0 ± 2.0 kg/m² for the control group. A comprehensive overview of the baseline characteristics and relevant clinical features of the subjects, including but not limited to age, body mass index (BMI), and gestational weeks, which may be associated with the manifestation of APS, is presented in Table 1. A notable incidence of adverse pregnancy outcomes, including preterm birth, miscarriage, and low birth weight, was observed within the APS cohort.

Adverse pregnancy outcomes encompassed low birth weight, preterm delivery, miscarriage, preeclampsia, gestational hypertension, and gestational diabetes. Clinical characteristics of the study participants were presented in Table 1.

Odds ratio of adverse pregnancy outcomes between APS group and the control group

Univariate regression analysis (Table 2, non-adjusted model) revealed that the odds ratio (OR) for miscarriage in APS patients was 2.52 (95 % CI: 1.54–4.11, $p < 0.01$), for preterm birth was 2.94 (95 % CI: 1.84–4.71, $p < 0.01$), for low birth weight infants was 2.29 (95 % CI: 1.48–3.56, $p < 0.01$), and for intrauterine growth restriction was 2.53 (95 % CI: 1.45–4.23, $p = 0.0006$). The OR for preeclampsia was 1.05 (95 % CI: 0.62–1.77, $p = 0.8505$), and for gestational hypertension was 1.00 (95 % CI: 0.56–1.78, $p = 0.9968$).

In Table 2, Model 1, multivariable logistic regression analysis adjusted for age and BMI demonstrated that the risk ratios. The risk ratios for adverse pregnancy outcomes in APS patients were as follows: miscarriage (RR=2.50, 95 % CI: 1.52–4.11, $p = 0.002$), preterm birth (RR=2.89, 95 % CI: 1.79–4.65, $p < 0.0001$), low birth weight infants (RR=2.28, 95 % CI: 1.52–3.55, $p = 0.03$), and intrauterine growth restriction (OR=2.48, 95 % CI: 1.45–4.23, $p = 0.009$). For preeclampsia, the OR value was

Table 1: Clinical characteristics of the APS group and control group.

Characteristics	APS group (n=191)	Control group (n=984)	p-Value
Age, years	32.3 ± 4.3	30.4 ± 3.3	0.804
Body mass index, kg/m ²	22.0 ± 1.8	22.0 ± 2.0	0.015
Miscarriage rate	13.61 %	5.89 %	<0.001
Preterm birth rate	18.18 %	7.02 %	<0.001
Low-birth weight infants	20.0 %	9.83 %	<0.001
Gestational hypertension	9.08 %	9.09 %	0.997
Preeclampsia and eclampsia	11.02 %	13.61 %	0.851
Gestational diabetes mellitus	33 (20.00 %)	180 (19.44 %)	0.867

Results are given as mean (SD) or median (Q1-Q3)/n (%).

Table 2: Risk of adverse outcomes adjusted OR (95 % CI).

Adverse pregnancy outcome	Non-adjusted model OR 95 % CI	p-Value	Model 1 OR 95 % CI	p-Value	Model 2 OR 95 % CI	p-Value	Model 3 OR 95 % CI	p-Value
Fetal loss	2.52 (1.54, 4.11)	0.0002	2.52 (1.54, 4.11)	0.0002				
Hypertension during pregnancy	1.0 (0.56, 1.78)	0.9968	0.96 (0.53, 1.75)	0.9041				
Preeclampsia	1.05 (0.62, 1.77)	0.8505	1.0 (0.59, 1.71)	0.9992				
Gestational diabetes	1.04 (0.68, 1.57)	0.8869	1.04 (0.68, 1.59)	0.8685				
Premature birth (delivery at ≤ 34 weeks)	2.94 (1.84, 4.71)	<0.0001	2.89 (1.79, 4.65)	<0.0001	3.06 (1.87, 5.00)	<0.0001		
FGR	2.53 (1.50, 4.29)	0.0006	2.48 (1.45, 4.23)	0.0009	2.55 (1.49, 4.37)	0.0007		
Low birth weight infant	2.29 (1.48, 3.56)	0.0002	2.28 (1.46, 3.55)	0.0003			2.02 (1.26, 3.26)	0.0037

Adjusted Model 1: The OR, values of preterm birth and fetal growth restriction after adjusting for confounding factors of age and BMI. Adjusted Model 2: The OR, values of preterm birth and fetal growth restriction after adjusting for confounding factors of age, BMI, eclampsia and diabetes. Adjusted Model 3: The OR, values of preterm birth and fetal growth restriction after adjusting for confounding factors of age, BMI, eclampsia, diabetes and gestational age at delivery. The confounders adjusted in Model 2 (age, BMI, eclampsia, and diabetes) are factors that influence preterm birth outcomes. In contrast, Model 3 further adjusts for gestational week to account for factors specifically affecting fetal growth restriction (FGR).

1.00 (95 % CI: 0.59–1.71, $p > 0.05$), and for gestational hypertension, the OR value was 0.96 (95 % CI: 0.53–1.75, $p > 0.05$).

In Model 2, which incorporated age, BMI, preeclampsia, and diabetes as confounding factors, the OR for preterm infants increased to 3.06 (95 % CI: 1.87–5.00), $p < 0.001$ while the OR for Intrauterine growth restriction to 2.55 (95 % CI: 1.49–4.37), $p = 0.037$.

Finally, in Model 3, which considered age, BMI, diabetes, preeclampsia, and gestational week as confounding factors, the OR for low birth weight infants was recalculated to 2.02 (95 % CI: 1.26–3.26), $p = 0.037$.

Discussion

Main results

Table 1 demonstrates significant differences between the two groups in terms of abortion, premature birth, low birth weight infants, and fetal growth restriction. Among the adverse pregnancy outcomes observed in the APS group, the incidence of low birth weight (20.0 %) was the highest, indicating a substantial negative impact of the disease on fetal development. Furthermore, the incidence of low birth weight exceeded that of premature birth (18.18 %), suggesting that APS may influence fetal growth by affecting maternal hemorheology and placental function, rather than solely attributing low birth weight to premature birth.

Univariate logistic regression analysis further revealed that antiphospholipid antibody syndrome (APS) was significantly associated with increased risks of miscarriage, preterm birth, low birth weight infants, and intrauterine growth restriction (FGR) (Table 2, non-adjusted model). APS

emerged as an independent risk factor for these outcomes. However, no significant differences were observed in the odds ratios (ORs) for preeclampsia and gestational hypertension.

Multivariate logistic regression analysis revealed that, after adjusting for confounding factors of age and BMI (Model 1), the OR values for preterm birth and intrauterine growth restriction decreased, indicating that the effects of APS were independent of age and BMI. However, after further adjustment for additional confounding factors including eclampsia and diabetes (Model 2), the OR values for preterm birth and intrauterine growth restriction increased, suggesting that preeclampsia and diabetes are significant risk factors influencing preterm birth in pregnant women and fetal intrauterine growth restriction. Although our study did not demonstrate an increased risk of preeclampsia associated with APS, the occurrence of preeclampsia may further impact fetal development.

However, after incorporating the confounding factor of gestational age at birth in Model 3, the OR value for low birth weight further decreased. This indicates that both preterm birth and APS are significant influencing factors for low birth weight, which aligns with the proportion of adverse pregnancy outcomes presented in Table 1. Despite its influence being attenuated by other factors, APS remains an independent risk factor for low-birth weight infants.

Comparison with findings of previous studies

Our research aligned closely with the conclusions of prior literature. One study highlighted that patients with APS were at a higher risk of pregnancy complications, particularly a

markedly increased risk of fetal loss and preterm birth [5], further substantiating the potential adverse effect of APS during pregnancy. A retrospective and prospective analysis of 1,000 APS patients in Europe revealed that recurrent miscarriage, fetal loss, and stillbirth are the most prevalent adverse pregnancy outcomes [10]. Another study demonstrated that phospholipid antibodies served as independent risk factors for premature rupture of membranes, with an odds ratio (OR) of 2.11 [11]. Additionally, a meta-analysis indicated that the risk of fetal growth restriction (FGR) was elevated in APS patients. The pooled odds ratios associated with antiphospholipid antibodies (aPL), anticardiolipin antibodies (ACA), anti- β_2 glycoprotein I antibodies (β_2 GPI), and FGR were 1.26, 2.25, and 1.31, respectively [5], which corroborated our findings.

However, notable differences also existed. Some studies have documented an association between APS and gestational hypertension or preeclampsia [12]. In contrast, our findings differed significantly, as no difference was observed between the disease group and the control group regarding gestational hypertension and preeclampsia. This discrepancy might be attributable to various factors, including sample size, regional population characteristics, hospital-specific practices, and variations in clinical treatment efficacy. Our hospital, recognized as the largest academic center for obstetrics and gynecology in our country, served a higher proportion of high-risk patients, which potentially elevated the incidence of adverse pregnancy outcomes in the control population. Nevertheless, standardized preconception counseling and optimized management strategies for high-risk patients have effectively mitigated certain adverse outcomes. Additionally, several studies have demonstrated that the combined use of aspirin and hydroxychloroquine (HCQ) can significantly reduce the incidence of preeclampsia in pregnant women with autoimmune diseases [13, 14]. This therapeutic approach aligned with the protocol used for APS patients in our hospital, leading to a marked reduction in the incidence of gestational hypertension and preeclampsia within the disease group.

Our findings further elucidated the lack of a significant association between antiphospholipid syndrome and gestational diabetes, a relationship that has not been adequately investigated in the existing literature.

Interpretation

The pathophysiology of APS primarily involves inflammatory responses and thrombotic events at the maternal-fetal interface, which can compromise the health of both the mother and the fetus [15]. A hallmark of APS is the

production of antiphospholipid antibodies (aPLs). Prior research has demonstrated that aPLs recognized a variety of phospholipids, phospholipid-binding proteins, and phospholipoprotein complexes, exerting their pathogenic effect predominantly through binding to phospholipids on the cell surface [13].

aPLs bind to phospholipids on the surface of trophoblast cells, thereby inducing dysfunction and inflammation in placental trophoblasts at the maternal-fetal interface. The correct invasion of trophoblast cells into the maternal decidua was critical for a successful pregnancy. During early pregnancy, insufficient trophoblast implantation can lead to excessively strong blood flow in the vessels, causing physical or oxidative damage to the placenta and potentially resulting in early miscarriage. The adjusted OR value (Model 1 and Model 2) for miscarriage presented in Table 2 was relatively high, consistent with findings from prior studies.

When aPLs bind to endothelial cells, the activation of the complement system induced endothelial cell injury and exposed procoagulant substances beneath the endothelium, thereby promoting thrombosis [16]. Thrombi formed within the placental vasculature were critical factors contributing to complications such as fetal growth restriction and preterm birth [17–19]. In our study, we observed that the odds ratios (OR) for fetal growth restriction and preterm birth were relatively high, confirming that APS serves as an independent risk factor for these conditions.

Furthermore, thrombosis in the placental blood vessels exacerbated the ischemic and hypoxic conditions of the placenta. The resultant ischemia and hypoxia induced oxidative stress responses, leading to the production of substantial reactive oxygen species (ROS). ROS not only directly impaired placental cell viability but also compromised the structural integrity and functional capacity of the placenta, thereby disrupting substance exchange and contributing to the development of gestational hypertension and preeclampsia [20].

Perspective

The diverse adverse outcomes associated with APS highlight significant variability among individuals in clinical settings, underscoring the urgent need for personalized and customized programs to enhance clinical management and optimize patient outcomes. Future research should explore the complex biological pathways involved in APS-related complications while identifying innovative therapeutic strategies to mitigate other adverse pregnancy outcomes that may be affected.

We propose intensified prenatal surveillance in high-risk pregnancies, comprising: serial Doppler studies (uterine/umbilical arteries, venous flow), coagulation parameter monitoring, and cytokine profiling (IL-6, IL-8). These measures enable early detection of placental insufficiency and fetal growth restriction.

Limitations

As the leading academic institution in obstetrics and gynecology within the country, our study relies on relatively recent data (2017–2023) from a single establishment, which may limit the generalizability of our findings. Additionally, the retrospective nature of this investigation introduces further limitations. The accuracy and completeness of clinical records are critical to the integrity of our data analysis, upon which our conclusions are based.

Conclusions

Our investigation elucidates the significant association between APS and adverse pregnancy outcomes, aiming to unravel the complex factors that influence these outcomes. Testing for antiphospholipid antibodies serves as a reliable and accessible laboratory indicator. Screening for these antibodies can be strategically implemented in high-risk populations. Through comprehensive pre-pregnancy assessments, timely communication of potential risks, and personalized interventions, we can strive to improve the prognosis of pregnancies affected by APS.

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Research ethics: This study was approved by the Institutional Review Board of Obstetrics & Gynecology Hospital of Fudan University (Approval No. 2025.05) and conducted in accordance with the Declaration of Helsinki. All procedures involving human participants followed ethical standards for medical research.

Informed consent: Written informed consent was obtained from all participants prior to their inclusion in the study.

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Xiang. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

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Data availability: The raw data supporting this study were sourced from the Laboratory Information System (LIS) of Obstetrics & Gynecology Hospital of Fudan University. Due to patient privacy protections mandated by the hospital's ethical regulations and China's Personal Information Protection Law (PIPL), these original datasets are not publicly available. De-identified data can be made available upon reasonable request to the corresponding author, subject to approval by the hospital's Ethics Committee and execution of a data confidentiality agreement.

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