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Original Research

Risk Factors for Adverse Pregnancy Outcomes in Patients with Antiphospholipid Syndrome

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Abstract

Background: Pregnancy complications of antiphospholipid syndrome (APS) are up to 20–30%. It is of great value to identify well-recognized predictors of adverse pregnancy outcomes (APOs) in APS. This study aims to explore the risk factors for APOs in patients with obstetric APS. **Methods**: This study included 142 women with APS delivered at Peking University People's Hospital from February 2014 to August 2022. APOs included fetal death, neonatal death due to complications related to prematurity, preterm delivery <37 weeks due to placental insufficiency, hypertension, or preeclampsia, and small for gestational age (SGA) <10%. The association between pregnancy outcomes and clinical variables was assessed and the risk factors for APOs were analyzed. **Results**: APO occurred in 42.7% of pregnancies, including preterm delivery (23.4%), SGA (18.5%), and fetal death (6.5%). Patients in the APO group showed a significantly higher prevalence of underlying autoimmune disease (17% *vs.* 4.2%, $p = 0.017$) and lupus anticoagulant (LA) positivity (41.5% *vs.* 23.9%, $p = 0.037$) than those without APO. A significantly lower proportion of patients in the APO group were treated with low molecular weight heparin (LMWH) (58.5% *vs.* 76.1%, $p = 0.037$) and LMWH + low dose aspirin (LDA) (34.0% *vs.* 54.9%, $p = 0.020$) than in the non-APO group. Underlying autoimmune disease (odds ratio (OR): 5.147, 95% confidence interval (95% CI): 1.049–25.254, $p = 0.043$) was a risk factor for APOs and regular outpatient follow-up at the Department of Rheumatology and Immunology (OR: 0.429, 95% CI: 0.190–0.967, $p = 0.041$) was a protective factor for APOs. **Conclusions**: Underlying autoimmune disease is a risk factor for APOs and regular outpatient follow-up at the Department of Rheumatology and Immunology could be a protective factor for APOs.

Keywords: adverse pregnancy outcomes; APS; underlying autoimmune disease; regular outpatient follow-up at the Department of Rheumatology and Immunology

1. Introduction

Obstetric antiphospholipid syndrome (OAPS) manifests as an autoimmune disorder marked by pregnancy complications and the enduring existence of antiphospholipid antibodies (aPLs) [1]. Among aPLs, lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti-β2-glycoprotein I antibodies (aβ2GPI) are widely detected and included in antiphospholipid syndrome (APS) classification criteria [2]. APS predominantly affects women, with a female-to-male ratio of 3.5:1 in primary APS and 7:1 in secondary APS. The overall frequency of antiphospholipid antibodies (aPLs) associated with pregnancy morbidity was approximately 6% [3].

The reproductive challenges associated with OAPS encompass recurrent miscarriage, fetal demise, and premature birth resulting from conditions such as preeclampsia, eclampsia, or intrauterine growth restriction [2]. Treatment with low-dose aspirin (LDA) and/or low molecular weight heparin (LMWH) has improved the pregnancy outcomes of OAPS [2,4,5]. However, this treatment still fails in approximately 20% of OAPS patients [6,7]. The incidence of adverse pregnancy outcomes (APOs) in OAPS is significantly higher than in healthy pregnant women [8]. Additional treatments to improve pregnancy outcomes include hydroxychloroquine (HCQ), low-dose prednisolone, and intravenous immunoglobulins (IVIG) [9], pravastatin [10], eculizumab [11], and certolizumab [12].

Identifying the risk factors related to APOs before or at the start of gestation could be a vital step for managing APS to prevent obstetric complications and establish optimal therapies. A systematic review and meta-analysis revealed that prior thrombosis, aPL profiles with double or triple positivity, and the presence of lupus anticoagulant are the foremost predictors of adverse pregnancy outcomes (APOs) [13]. However, the differences in the diagnostic criteria of APS and definition of APOs make the predictors

vary from study to study. In order to predict pregnancy outcome and to provide obstetric management references, we investigated the risk factors for APOs in OAPS patients in a tertiary center.

2. Methods

2.1 Study Population

Female patients diagnosed with OAPS [1] who participated in follow-ups throughout their pregnancies at Peking University People's Hospital (PKUPH) from February 2014 to August 2022 were included in this study. We performed the sample size calculation according to the rule of "10 events per variable", which is also known as 10 EPV [14]. The exclusion criteria included patients with APOs due to metabolic or endocrine alterations, anatomic abnormalities of the uterus, and carriage of parental chromosomal abnormalities [15].

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of PKUPH (2019PHB252). All patients signed written informed consents before participation in this study.

2.2 Definition of APOs

APOs were characterized by: (1) fetal demise occurring after 12 weeks of gestation; (2) neonatal death resulting from complications related to prematurity; (3) preterm delivery before 37 weeks of gestation due to gestational hypertension, preeclampsia, or placental insufficiency; and (4) the birth of small-for-gestational-age (SGA) neonates (birth weight $<$10th percentile) [16,17].

2.3 Screening and Follow-up

Data included age, medical history, physical examination, previous pregnancies, laboratory data, and treatments, regular follow-up. Laboratory data included aPLs profile, antinuclear antibodies (ANA), complete blood count (CBC), and complement levels. Laboratory tests were performed during each trimester (early, middle and late trimester) and at three months postpartum. Regular follow-up is defined as more than 3 times rheumatology outpatient visits throughout pregnancy and three months postpartum.

2.4 Statistical Analysis

Quantitative data were compared using nonparametric tests (Mann–Whitney U), while proportions were compared using either the chi-squared test or Fisher's exact test. The identification of risk factors for adverse pregnancy outcomes (APOs) was conducted through binary logistic regression analysis. The logistic regression analysis included factors with $p < 0.05$ in the univariate analysis and factors related to pregnancy outcomes that had been reported in previous studies, including double aPLs positivity, triple aPLs positivity, and high titers of aβ2GPI and/or aCL [6,15,18–22]. Calculation of odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) was performed. Statistical analysis was conducted using SPSS 27.0 (IBM Corp, Armonk, NY, USA). A significance level of $p < 0.05$ was employed to determine statistical significance.

3. Results

3.1 Baseline Demographic Data and Clinical Characteristics

One hundred and twenty-four APS patients were enrolled in this study. Of the 124 patients, 119 patients were classified as obstetric APS, 4 as thrombotic APS, and 1 had both manifestations. The mean maternal age at conception was 32.5 $\pm$ 3.9 years. Of the 124 patients, 12 (9.7%) patients had among 124 patients, 12 (9.7%) had concurrent autoimmune diseases. In the APO group, 9 (17%) had a combination of other autoimmune diseases, including 6 (11.3%) with systemic lupus erythematosus (SLE), 2 (3.8%) with Sjogren's syndrome (SS) and 1 (1.9%) with immune thrombocytopenia (ITP). In the non-APO group, 3 (4.2%) had underlying autoimmune disease, including 1 (1.4%) with SLE, 1 (3.8%) with rheumatoid arthritis (RA), and 1 (1.9%) with ITP. 82 (66.1%) patients were single aPL positive, 27 (21.8%) patients were double-positive, and 15 (12.1%) patients were triple positive. 25 (20.2%) patients had hypocomplementemia, and 26 (21.0%) had thrombocytopenia. Regarding the treatments of these patients, 77 (62.1%) patients used LDA, 85 (68.5%) used LMWH, 57 (46.0%) took a combination of LDA and LMWH, and 39 (31.5%) used glucocorticoid (GC) (Table 1). The median number of spontaneous abortions prior to this pregnancy was 1 in both groups, and the difference was not statistically significant.

There were 116 (93.5%) live births with 124 babies (8 twin pregnancies) at a mean gestational age of 36.6 $\pm$ 5.1 weeks. APOs occurred in 53 (42.7%) of pregnancies, including 8 (6.5%) fetal death, 29 (23.4%) preterm delivery, and 23 (18.5%) SGA. The prevalence of premature rupture of membranes, oligohydramnios, gestational diabetes, preeclampsia, HELLP (hemolysis, elevated liver enzymes, low platelet count) syndrome, and gestational hypertension were 21.8%, 19.4%, 18.5%, 10.5%, 1.6%, and 0.8%, respectively (Table 2).

3.2 Comparison between Patients with or without APO

There were nine patients in the APO group with underlying autoimmune disease, which was significantly higher than in the non-APO group (17% *vs.* 4.2%, $p = 0.017$). The proportion of caesarean sections was higher in the APO group than in the non-APO group (64.2% *vs.* 43.7%, $p = 0.024$). There was no difference in aPLs except LA (41.5% *vs.* 23.9%, $p = 0.037$) between the two groups. Regarding treatments during pregnancy, there were significant differences in LMWH (58.5% *vs.* 76.1%, $p = 0.037$) and a combination of LMWH and LDA (34.0% *vs.* 54.9%, $p = 0.020$) of patients in the two groups. Patients in the APO group

Table 1. Characteristics of APS patients with or without APO.

Characteristics	Total (n = 124)	APO patients (n = 53)	Non-APO patients (n = 71)	*p*
Age (years)	32.5 ± 3.9	32.2 ± 4.2	32.7 ± 3.7	0.475
Underlying autoimmune disease (n; %)	12 (9.7)	9 (17.0)	3 (4.2)	0.017*
Cesarean section (n; %)	65 (52.4)	34 (64.2)	31 (43.7)	0.024*
Thrombosis (n; %)	5 (4.03)	4 (7.5)	1 (1.4)	0.163
ANA positive (n; %)	30 (24.2)	16 (35.6)	14 (24.6)	0.226
aPLs† positive at screening				
Single aPL positive	82 (66.1)	34 (64.2)	48 (67.6)	0.688
Double aPLs positive (n; %)	27 (21.8)	10 (18.9)	17 (23.9)	0.498
Triple aPLs positive (n; %)	15 (12.1)	9 (17.0)	6 (8.6)	0.150
aCL positive (n; %)	57 (46.0)	24 (45.3)	33 (46.5)	0.895
aβ2GPI positive (n; %)	88 (71.0)	36 (67.9)	52 (73.2)	0.519
LA positive (n; %)	39 (31.5)	22 (41.5)	17 (23.9)	0.037*
High titers of aβ2GPI and/or aCL (n; %)	56 (45.2)	25 (47.2)	31 (43.7)	0.698
Hypocomplementemia (n; %)	25 (20.2)	13 (24.5)	12 (16.9)	0.295
Thrombocytopenia (n; %)	26 (21.0)	10 (18.9)	12 (16.9)	0.777
Treatment during pregnancy				
GC (n; %)	39 (31.5)	21 (39.6)	18 (25.4)	0.090
LDA (n; %)	77 (62.1)	28 (52.8)	49 (69.0)	0.066
LMWH (n; %)	85 (68.5)	31 (58.5)	54 (76.1)	0.037*
LMWH + LDA (n; %)	57 (46.0)	18 (34.0)	39 (54.9)	0.020*
Regular outpatient follow-up at Department of Rheumatology and Immunology (n; %)	70 (56.5)	24 (45.3)	46 (64.8)	0.030*

APS, antiphospholipid syndrome; APO, adverse pregnancy outcome; ANA, antinuclear antibodies; aPLs, antiphospholipid antibodies; LA, lupus anticoagulant; aCL, anticardiolipin antibodies; aβ2GPI, anti-β2-glycoprotein I antibodies; GC, glucocorticoid; LDA, low-dose aspirin; LMWH, low molecular weight heparin; *$p < 0.05$.

†Including LA, aCL, and aβ2GPI. Both Immunoglobulin G (IgG) and Immunoglobulin M (IgM) positivity or single positivity were recorded as one antibody positivity.

were less likely to visit the Department of Rheumatology and Immunology than those in the non-APO group (45.3% *vs.* 64.8%, $p = 0.030$) (Table 1).

3.3 Risk Factors for APO in Patients

Logistic regression analysis demonstrated that underlying autoimmune disease (odds ratio (OR): 5.147, 95% confidence interval (95% CI): 1.049–25.254, $p = 0.043$) was a risk factor for APOs. Regular outpatient follow-up at the Department of Rheumatology and Immunology (OR: 0.429, 95% CI: 0.190–0.967, $p = 0.041$) was a protective factor for APOs (Fig. 1).

4. Discussion

In this study, we demonstrated that underlying autoimmune disease are positively associated with APOs. The use of LMWH and LMWH + LDA are negatively associated with APOs. Underlying autoimmune disease is a risk factor for APOs. Regular outpatient follow-up at the Department of Rheumatology and Immunology could be a protective factor for APOs.

Several studies have substantiated that expectant women with APS face a heightened risk of pregnancy complications [2,23,24]. These APS patients required careful risk assessment and medical management [9]. The first step in evaluating pregnant women with APS is to accurately determine their aPLs antibody status using standardized laboratory methods and threshold levels. Individuals with aPLs should be risk-stratified based on the presence of a high-risk aPLs profile, thrombosis and/or an adverse maternal history, and the coexistence of other autoimmune disease, such as systemic lupus erythematosus (SLE) [5,9,25]. Moreover, the evaluation of maternal-fetal risk should consider factors such as maternal age, obstetric history, the standard of medical care, and relevant associated risk factors [26].

Numerous previous studies have demonstrated that the presence of SLE and/or other autoimmune disease are risk factors for APOs [6,7,15,20,22,27,28]. Consistent with prior studies, our study found that underlying autoimmune disease was a risk factor for APOs in APS patients [7,28]. The underlying autoimmune disease also has potential maternal and fetal complications. Controlling underlying autoimmune disease with certain medications is also an im-

Table 2. Pregnancy outcomes and obstetrical complications of the study cohort.

Pregnancy outcomes and obstetrical complications	Data (n = 124)
Live birth, n (%)	116 (93.5)
Fetal death, n (%)	8 (6.5)
Neonatal death, n (%)	0 (0.0)
Preterm delivery (<37 gestational weeks), n (%)	29 (23.4)
SGA, n (%)	23 (18.5)
Preeclampsia, n (%)	13 (10.5)
Eclampsia, n (%)	0 (0.0)
Premature rupture of membranes, n (%)	27 (21.8)
Oligohydramnios, n (%)	24 (19.4)
HELLP syndrome, n (%)	2 (1.6)
Gestational diabetes, n (%)	23 (18.5)
Gestational hypertension, n (%)	1 (0.8)

SGA, small for gestational age; HELLP syndrome, hemolysis, elevated liver enzymes, low platelet count.

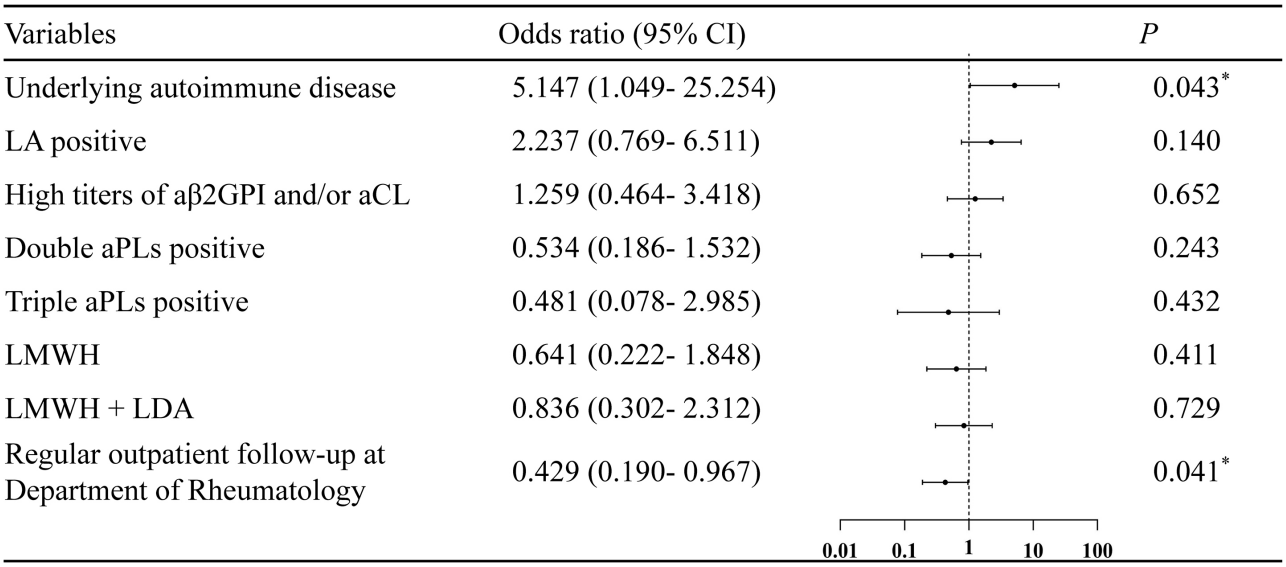

Fig. 1. Binary logistic regression analysis between APO and non-APO groups. 95% CI, 95% confidence interval; LA, lupus anticoagulant; aCL, anticardiolipin antibodies; aβ2GPI, anti-β2-glycoprotein I antibodies; aPLs, anti-phospholipid antibodies; LMWH, low molecular weight heparin; LDA, low-dose aspirin; $^{*}p < 0.05$.

portant part of treatment. Therefore, a detailed patient history, physical examination, and laboratory tests of autoantibodies should be performed before pregnancy.

APLs positivity was strongly associated with APOs in APS patients. In our study, the proportion of LA positivity was significantly higher in APO patients. In the PROMISSE (predictors of pregnancy outcome: biomarker in antiphospholipid antibody syndrome and systemic lupus erythematosus) study, 39% of LA-positive women had APOs, and the study also demonstrated that LA positive women were at the highest risk for APOs, and in the absence of LA, aCL, and aβ2GPI did not predict APO [29]. LA positivity on its own is a high-risk factor in OAPS. Triple positivity for aPL is one of the described risk factors for an adverse obstetric outcome. Nevertheless, we did not observe a similar outcome, possibly due to the limited number of patients exhibiting triple positivity for aPL. We intend to enhance our research by increasing the sample size for future investigations.

Medical intervention for pregnant women with APS must be highlighted. Standardized treatment is important for pregnancy outcomes of APS patients and significantly impacts neonatal outcomes. In our study, APS patients taking LMWH alone or in combination with LDA were more likely to be APO-free. Early combined therapy with aspirin and LMWH could improve pregnancy outcomes and increase live birth rates [30]. As such, they are recommended as a standardized treatment for OAPS [9,31–34]. However, some people believe that the combination of aspirin and LMWH is not suitable for all pregnant women

with antiphospholipid syndrome. Van Hoorn's [35] study of preeclampsia and/or fetal growth restriction in pregnant women with APS who delivered before 34 weeks of gestation found that there was no significant difference in the effects of restricting aspirin alone or aspirin combined with LMWH, which was associated with gestational hypertensive disorders and/or fetal growth. There is currently no unified conclusion on how to treat pregnancies with antiphospholipid syndrome, which could be related to population characteristics and the specificity of the pathogenesis.

This study found an encouraging result: a significantly higher proportion of regular visits to the Departments of Rheumatology and Immunology in APS patients without APOs than in the control group. This was consistent with another Chinese APS cohort, and regular outpatient follow-up at the Department of Rheumatology was a protective factor for APOs [36]. It is recommended to check before pregnancy and during the first labor examination in the first trimester [37]. In the second trimester of pregnancy, abnormal uterine artery Doppler evaluation is highly predictive of adverse perinatal outcomes [38]. For mothers suffering from APS, regular visits allow rheumatologists to quickly identify potential complications, conduct appropriate treatments, and improve pregnancy outcomes.

This study also had certain limitations. First, it was a single-center retrospective cohort study, which had an admission bias. Second, only Chinese patients are included, which does not allow the results to be generalized. Third, the sample size may influence the results because few patients present some variables. However, we included a relatively large number of OAPS patients, which could also reflect the pregnancy outcomes and influencing factors of Chinese APS patients and provide a reference for further in-depth research.

5. Conclusions

Underlying autoimmune disease are associated with APOs. The use of LMWH and LMWH + LDA are negatively associated with APOs. Underlying autoimmune disease is a risk factor for APOs. Regular outpatient follow-up at the Department of Rheumatology and Immunology could be a protective factor for APOs.

Availability of Data and Materials

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author Contributions

YKH, LH, JYJ, ZYS, LL, XWZ and CL conceived and designed the project. YKH and LH collected and input the clinical and laboratory data. YKH completed the statistical analyses. YKH and CL conducted table and figure predations. YKH and CL wrote the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript. All authors discussed the results and contributed to the final manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Peking University People's Hospital (PKUPH; 2019PHB252). All patients signed written informed consents before participation in this study.

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Conflict of Interest

The authors declare no conflict of interest.

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