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Clinical Features and Outcomes of Twin Pregnancies with Antiphospholipid Antibodies Positivity: A Retrospective Study

Pengzhu Huang[1,2,*], Rongrong Wu[1,2,*], Xin Guo[1,2,*], Xiaoli Gao[1,2], Ye Yan[1,2], Cha Han[1,2], Fengxia Xue[1,2]

[1]Department of Gynecology and Obstetrics, Tianjin Medical University General Hospital, Tianjin, People's Republic of China; [2]Tianjin Key Laboratory of Female Reproductive Health and Eugenics, Tianjin Medical University General Hospital, Tianjin, People's Republic of China

*These authors contributed equally to this work

Correspondence: Fengxia Xue; Cha Han, Department of Gynecology and Obstetrics, Tianjin Key Laboratory of Female Reproductive Health and Eugenics, Tianjin Medical University General Hospital, Tianjin, People's Republic of China, Tel +86-22-60363769, Fax +86-22-27813550, Email xuefengxia@tmu.edu.cn; tjhancha@tmu.edu.cn

Objective: This study aimed to evaluate the impact of twin pregnancies with antiphospholipid antibody (aPL) positivity, a rare and complex clinical condition that remains a huge challenge for management.

Methods: This study enrolled twin-pregnant women at our hospital between January 2018 and August 2023. Women with and without aPL positivity were selected using propensity score matching (PSM). Clinical features and pregnancy outcomes were compared between the two groups in the PSM cohort. To analyze the effect of aPL positivity on pregnancy outcomes, multivariate logistic models were used to obtain adjusted odds ratios (aOR) with 95% confidence intervals (CI).

Results: Among the 773 women with twin pregnancies, aPL positivity was found in 26 women (3.36%). In the PSM cohort, there were 24 twin-pregnant women with positive aPL, and 48 women without aPL were selected as controls. Twin-pregnant women with aPL positivity had a higher proportion of abortion (8.33% vs 0, $P = 0.043$), preterm birth < 34 weeks (33.33% vs 8.33%, $P = 0.007$) and very low birthweight (<1500 g) (20.83% vs 4.17%, $P = 0.016$) than the control group. In addition, stillbirth of one fetus was observed in one twin-pregnant woman with positive aPL. Multivariate logistic regression analysis revealed that twin pregnancy with aPL positivity was associated with preterm birth < 34 weeks (aOR = 2.76, 95% CI: 0.83–4.70, $P = 0.005$), very low birthweight (<1500 g) (OR = 2.40, 95% CI: 0.18–4.67, $P = 0.034$) and small for gestational age (SGA) (aOR = 1.66, 95% CI: 0.22–3.10, $P = 0.024$).

Conclusion: Twin pregnancies with aPL positivity were correlated with obstetric complications, including abortion, preterm birth < 34 weeks and very low birthweight (<1500 g). The detection of aPL may be of clinical significance for women with twin pregnancies and should be considered in future studies.

Keywords: twin pregnancy, antiphospholipid antibody, pregnancy outcomes, propensity score matching

Introduction

Antiphospholipid syndrome (APS) is a thromboinflammatory disorder caused by circulating antiphospholipid antibodies (aPL) and mainly characterized by thrombotic events, pregnancy morbidity and multiple autoimmune and inflammatory complications.[1] The incidence of APS was 1 to 2 cases per 100,000 population, and the estimated prevalence of APS was 40 to 50 cases per 100,000 population.[2–4] According to the classification criteria proposed in 2006, APS is defined as the presence of at least one clinical criterion (vascular thrombosis and/or pregnancy morbidity) along with one laboratory criterion (persistently positive aPL including the presence of lupus anticoagulant (LA), anticardiolipin antibody (aCL), or anti-β2 glycoprotein-I (aβ2GPI) on two or more occasions, at least 12 weeks apart).[5] Clinically, there are two main types of APS: patients with primary APS have no clinical or laboratory evidence of another disease, and secondary APS might

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be correlated with systemic autoimmune diseases such as systemic lupus erythematosus (SLE), infections, malignancies, non-malignant hematologic conditions, drugs and other disorders.[6] Patients with primary APS have a poor prognosis, particularly those with a high risk of new thrombotic events and organ damage.[7] Pregnant women with primary APS have adverse obstetric outcomes, including an increased risk of preeclampsia, low birthweight at delivery, Apgar score less than 7 at 5th minute and small infants.[8]

In addition to "classical" APS, aPL is also correlated with various conditions, such as aPL carriers without clinical symptoms and aPL positivity with non-criteria manifestations.[5,6] aPL can be found not only in a small percentage of the healthy population but also in clinical conditions such as rheumatic diseases, infections, malignancies and pregnancy complications.[9] In addition, aPL is associated with poor pregnancy outcomes and is found in 6% of women with pregnancy morbidity, including pregnancy loss, intrauterine growth restriction, preeclampsia/eclampsia and HELLP syndrome[10] One study including 283 pregnancies with aPL positivity reported adverse pregnancy outcomes in 50 cases, which were associated with concomitant organ-specific autoimmune disease and low complement levels at conception or during the first trimester[11] According to the 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases, pregnant women positive for the aPL test but not diagnosed with APS are recommended to receive prophylactic low-dose aspirin (81 or 100 mg daily) throughout pregnancy, whereas pregnant women with APS should be treated with low-dose aspirin and prophylactic/therapeutic low-dose low-molecular-weight heparin.[12] Besides, European League Against Rheumatism (EULAR) recommended low-dose aspirin (75–100mg daily) for people with a high-risk aPL profile including LA or double (any combination of LA, aCL or aβ2GPI) or triple aPL positivity.[13]

Despite substantial advances in the understanding of APS and aPL during pregnancy, their related obstetric complications are still inevitable and sometimes life-threatening, and risk stratification of this complex condition may be important to improve pregnancy outcomes.Twin pregnancy is a common clinical phenomenon. With the increased use of assisted reproductive technology (ART), the twinning rate worldwide has increased by a third, from 9.1 to 12.0 twin deliveries per 1000 deliveries between 1980 to 1985 and 2010 to 2015, and more than 1.6 million twin pairs were born each year.[14] 80% of all twin deliveries worldwide were currently occurred in Asia and Africa, and the twinning rate has also increased substantially in many countries in Europe, North America and Asia.[14] In China, the twinning rate increased from 2.84% in 2012 to 3.22% in 2020.[15] Twin pregnancy is correlated with a higher rate of maternal complications and maternal death as well as poor perinatal outcomes, including preterm delivery, low birthweight, Apgar scores less than 7 at 5th minute, fetal death and neonatal intensive care unit admission.[16] Compared to singleton pregnancies, women with twin pregnancies are at a fourfold higher risk of severe acute morbidity.[17] However, high-quality evidence for the management of twin pregnancies is still lacking.[18] Several studies have explored the clinical characteristics and prognosis of twin pregnancy along with its comorbidities such as preeclampsia and gestational diabetes mellitus.[19–21] But twin pregnancies with APS or aPL positivity are rarely reported and remain a significant challenge for treatment. Here, we retrospectively evaluated the clinical characteristics and pregnancy outcomes of twin pregnancies with aPL positivity, which could broaden our insights into this rare but complex condition and optimize its management.

Materials and Methods

Study Design and Population

This study retrospectively enrolled women with twin pregnancies who were hospitalized in the Obstetrics Department of Tianjin Medical University General Hospital between January 2018 and August 2023. The inclusion criteria for this study were as follows: (1) twin pregnancy; and (2) complete information regarding clinical characteristics, laboratory tests and pregnancy outcomes. And patients who were positive for at least one kind of aPL including LA, IgG/IgM aCL and IgG/IgM aβ2GPI were considered as aPL positivity. The exclusion criteria were as follows: (1) congenital anomalies of the fetus; (2) chromosomal abnormalities in parents that may affect pregnancy outcomes; (3) twin-to-twin transfusion syndrome (TTTS); and (4) missing data for maternal or neonatal outcomes. According to the 2019 UK National Institute for Health and Care Excellence (NICE) guideline, TTTS was diagnosed when the amniotic sac of one baby had the deepest vertical pocket (DVP) depth less than 2 cm and the amniotic sac of another baby had a DVP depth of over 8 cm before 20th gestational week or over

10 cm from 20th gestational week.[22] The results of aPL tests performed before conception or during pregnancy were retrospectively collected.

This study had two main aspects. First, the included patients were divided into two groups based on whether they were positive for aPL, and propensity score matching (PSM) was performed to balance differences in potential confounders in baseline characteristics between these two groups, including age, weight gain, parity, chorionicity, mode of conception, platelet count and selected comorbidities such as diabetes mellitus and polycystic ovarian syndrome (PCOS). The clinical characteristics and pregnancy outcomes were compared between the twin pregnancy with aPL positivity group and twin pregnancy without aPL positivity in both the entire cohort and PSM cohort. Second, twin-pregnant women with aPL positivity were divided into two subgroups based on adverse pregnancy outcomes to investigate the impact of aPL on pregnancy outcomes in twin pregnancies.

Data Collection

Clinical data and laboratory values were reviewed and collected by a well-trained obstetrician from electronic medical records. Demographic characteristics and obstetric information of the patients enrolled in this study included maternal age, BMI, weight gain during pregnancy, parity, blood pressure, chorionicity, mode of conception, mode of delivery, antiphospholipid profile and pregnancy complications, such as PCOS, preeclampsia, diabetes mellitus and thyroid diseases. Coagulation functions, including activated thromboplastin time (APTT), D-dimer, fibrinogen (FIB), prothrombin time (PT) and thrombin time (TT), were evaluated at admission. Therapies, such as low-dose aspirin (LDA), low-molecular-weight heparin (LMWH), a combination of LDA and LMWH, hydroxychloroquine and corticosteroids, have been reported. Maternal outcomes included spontaneous abortion, gestational week of delivery, preterm birth, premature rupture of membranes (PROM), preterm premature rupture of membranes (PPROM), thrombocytopenia and intensive care unit (ICU) admission. Neonatal outcomes included live birth, stillbirth, low birthweight, very low birthweight and small for gestational age (SGA).

Definition of Outcomes

The primary endpoint of this study was the composite adverse pregnancy outcomes that may affect the maternal and/or neonatal prognosis of pregnant women. Adverse pregnancy outcomes included spontaneous abortion, stillbirth, preterm birth, preeclampsia, PROM and SGA.[23,24] Spontaneous abortion was defined as pregnancy loss before 28 weeks of gestation with the fetal weight less than 1000 g. Stillbirth was defined as fetal death at or after 28 weeks of gestation. Preterm birth was defined as delivery before 37 weeks of gestation and was further divided into two types based on the gestational weeks of delivery: preterm birth before 37 weeks and preterm birth before 34 weeks. Preeclampsia was defined as sudden-onset hypertension after the 20th gestational week and at least one correlated complication such as proteinuria, organ dysfunction and uteroplacental dysfunction. PROM was defined as the rupture of membranes before the onset of labor. PPROM was defined as PROM occurring before 37 weeks of gestation. Low birthweight was defined as birthweight less than 2500 g. Very low birthweight was defined as birthweight less than 1500 g. SGA was defined as birthweight less than 10th percentile for the corresponding gestational age.

Statistical Analysis

Continuous variables are presented as central tendency (mean) and dispersion (standard deviation and range), denoted as mean ± SD or medians with interquartile range. Categorical variables were described as frequencies and percentages. When comparing the differences between groups, we first used the Shapiro–Wilk test to evaluate the normality of the quantitative variables, a *t*-test or non-parametric Mann–Whitney test to compute descriptive statistics and χ^2 or Fisher's exact test to analyze the differences in categorical variables between groups. To balance the impact of confounding factors on the analysis results, PSM was performed at a ratio of 1:2 to reduce differences in baseline characteristics between the aPL positivity and control groups in twin pregnancies. The width of the caliper was adjusted to make the absolute standardized mean difference (SMD) for each covariate less than 0.1, which indicated a balance in the baseline characteristics between the study groups. Univariable logistic regression was performed to evaluate the impact of aPL positivity on adverse pregnancy outcomes between twin pregnancies with and without aPL positivity in the PSM cohort.

Furthermore, we conducted multivariate logistic regression adjusted for maternal age, parity, weight at admission, BMI, thyroid diseases and diabetes mellitus in the PSM cohort. The results were reported as adjusted odds ratios (aOR) and 95% confidence intervals (95% CI). A 2-tailed $P < 0.05$ was considered statistically significant. All statistical analyses were performed using Stata Statistical Software Release 15 (Stata Corp LP, College Station, TX, USA) and graphs were plotted using Microsoft Excel and GraphPad Prism 9.1.

Results

Demographics and Baseline Characteristics of Study Population

This study reviewed 806 women with twin pregnancies in our hospital between January 2018 and August 2023. Of these, 33 were excluded and 773 women who met the inclusion criteria were included. A total of 26 women were tested with aPL positivity, indicating that the rate of aPL positivity in twin pregnancies was 3.36%. The remaining 747 twin-pregnant women were tested negative for aPL (Figure 1).

Comparisons of the demographics and baseline characteristics of twin-pregnant women with negative and positive aPL were presented in Table 1. In the entire cohort, ART was more frequent in twin pregnancy with positive aPL than those without (92.31% vs 59.44%, $P = 0.001$). The proportions of other characteristics, including age, BMI, weight gain during pregnancy, parity, blood pressure, chorionicity, mode of delivery, comorbidities such as PCOS, preeclampsia, diabetes mellitus and thyroid diseases and platelet counts were not significantly different between the two groups. Then, 24 women with positive aPL and 48 without aPL were selected after PSM. In the PSM cohort, demographic and baseline characteristics were balanced between twin pregnancies with aPL positivity and twin pregnancies without aPL positivity (SMD < 0.1).

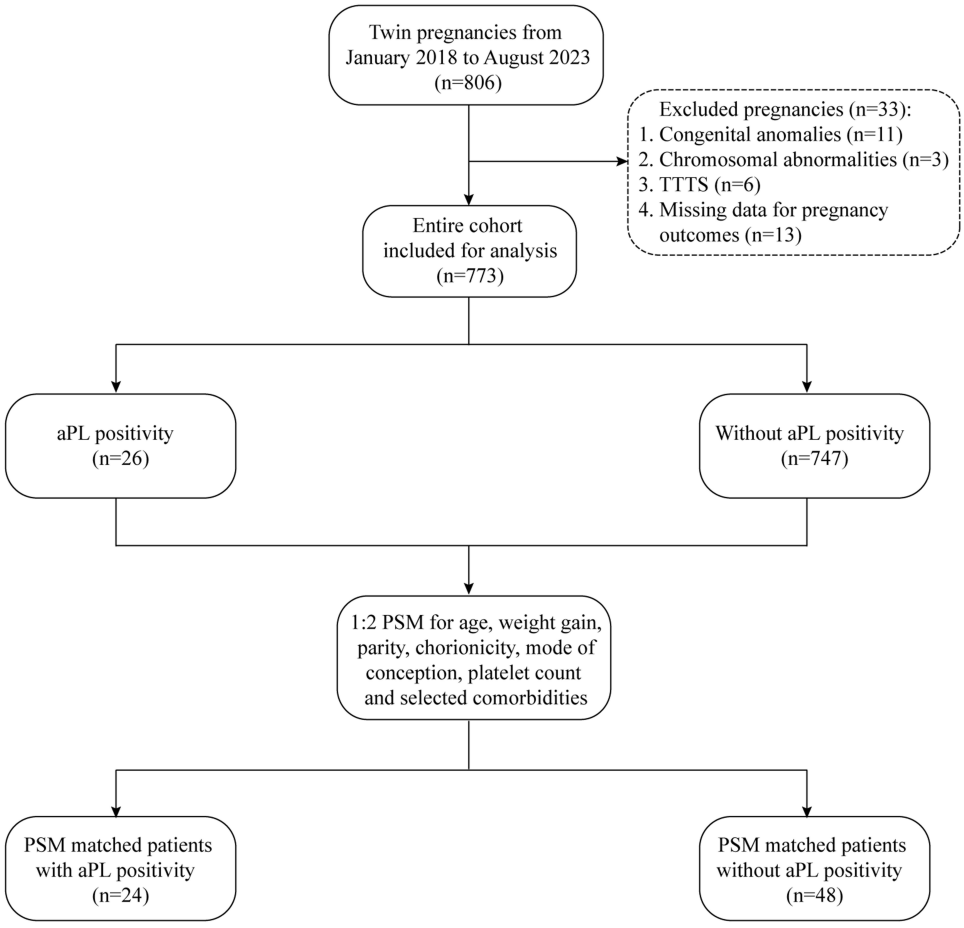

Figure 1 The flow diagram for patient selection.

Table 1 Demographics and Baseline Characteristics of twin-pregnant women with negative and positive aPL

Characteristics	Entire Cohort of Twin Pregnancies				PSM Cohort of Twin Pregnancies			
	aPL Negative (n=747)	aPL Positive (n=26)	*P* value	SMD	aPL Negative (n=48)	aPL Positive (n=24)	*P* value	SMD
Maternal age, years	32.66 ± 4.16	33.69 ± 2.71	0.07	0.29	33.92 ± 3.68	33.63 ± 2.72	0.71	0.09
Maternal age ≥35, n (%)	234 (31.33)	10 (38.46)	0.44	—	15 (31.25)	9 (37.50)	0.73	—
BMI, kg/m^2	29.44 ± 4.68	29.12 ± 3.40	0.65	—	28.24 ± 4.28	29.10 ± 3.50	0.37	—
Weight gain, kg	16.33 ± 6.29	15.79 ± 6.37	0.69	0.08	15.44 ± 6.16	15.79 ± 6.37	0.83	0.056
Parity	0 (0,1)	0 (0,1)	0.31	0.43	1 (1,2)	2 (1,3)	0.03*	0.09
Primiparity, n (%)	624 (83.53)	25 (96.15)	0.09	—	45 (93.75)	23 (95.83)	0.72	—
Multiparity, n (%)	123 (16.47)	1 (3.85)	0.09	—	3 (6.25)	1 (4.17)	0.72	—
SBP, mm Hg	126.12 ± 14.62	127.23 ± 15.54	0.72	—	124.42 ± 11.75	127.33 ± 14.57	0.40	—
DBP, mm Hg	75.84 ± 10.77	77.46 ± 12.76	0.53	—	76.92 ± 8.39	76.58 ± 12.56	0.91	—
Chorionicity								
Monochorionic, n (%)	157 (21.02)	2 (7.69)	0.08	0.42	5 (10.42)	2 (8.33)	0.78	0.07
Dichorionic, n (%)	545 (72.96)	24 (92.31)	0.08	—	43 (89.58)	22 (91.67)	0.78	0.07
Mode of conception								
Spontaneous, n (%)	303 (40.56)	2 (7.69)	0.001*	—	4 (8.33)	2 (8.33)	1.00	—
ART, n (%)	444 (59.44)	24 (92.31)	0.001*	0.83	44 (91.67)	22 (91.67)	1.00	0.00
Mode of delivery								
Vaginal, n (%)	42 (5.62)	0 (0)	0.81	—	1 (2.08)	0 (0)	0.50	—
Caesarean, n (%)	679 (90.90)	24 (92.31)	0.81	—	47 (97.92)	22 (91.67)	0.50	—
Comorbidities								
PCOS, n (%)	50 (6.69)	3 (12.50)	0.34	0.17	5 (10.42)	2 (8.33)	0.78	0.07
Preeclampsia, n (%)	131 (17.54)	6 (25.00)	0.47	—	8 (16.67)	5 (20.83)	0.67	—
Diabetes mellitus, n (%)	203 (27.18)	8 (33.33)	0.69	0.08	14 (29.17)	7 (29.17)	1.00	0.00
Thyroid diseases, n (%)	135 (18.07)	6 (25.00)	0.52	0.12	10 (20.83)	6 (25.00)	0.69	0.09
Platelet count, ×10^9/L	192.52 ± 58.26	191.08 ± 47.84	0.88	0.03	185.63 ± 52.81	190.04 ± 43.20	0.71	0.09

Notes: All data are presented as mean ± standard deviation, median, interquartile range, or n (%). *$P < 0.05$.
Abbreviations: aPL, antiphospholipid antibodies; ART, Assisted reproductive technology; BMI, body mass index; DBP, diastolic blood pressure; PCOS, polycystic ovary syndrome; SBP, systolic blood pressure.

Pregnancy Outcomes of Twin Pregnancy with and without Positive aPL

The pregnancy outcomes of the 26 twin-pregnant women with aPL positivity were shown in Figure 2. We found that 34.62% (9/26) of patients had term pregnancies. Preterm birth was observed in 57.69% (15/26) of the patients, and one patient at 33th gestational week delivered one dead fetus and another alive. Two patients had spontaneous abortion (7.69%), and they had fetal loss at 15^{+4} and 21^{+4} weeks of gestation, respectively.

A comparison of maternal and neonatal outcomes between the aPL positivity and control groups in twin pregnant women was shown in Table 2. In the PSM cohort, there was no significant difference in the proportion of composite adverse pregnancy outcomes between the two groups (79.17% vs 75.00%, $P = 0.70$). However, when we analyzed the percentage of each maternal or neonatal outcome, we found that twin-pregnant women with aPL positivity had a higher proportion of abortion (8.33% vs 0, $P = 0.043$), preterm birth at < 34 weeks (33.33% vs 8.33%, $P = 0.007$) and very low birthweight (<1500 g) (20.83% vs 4.17%, $P = 0.016$) than the control group. In addition, using univariate logistic analysis, we found that aPL positivity was associated with preterm birth < 34 weeks of gestation (OR = 1.70, 95% CI: 0.38–3.03, $P = 0.012$) and very low birthweight (<1500 g) (OR = 1.91, 95% CI: 0.18–3.64, $P = 0.03$). After adjusting for confounding factors including aPL positivity, age, gravidity, body weight, BMI, thyroid diseases and diabetes mellitus, we found that twin pregnancy with positive aPL was associated with preterm birth < 34 weeks (aOR = 2.76, 95% CI: 0.83–4.70, $P = 0.005$), very low birthweight (<1500 g) (aOR = 2.40, 95% CI: 0.18–4.67, $P = 0.034$) and SGA (aOR = 1.66, 95% CI: 0.22–3.10, $P = 0.024$).

Risk factors for preterm birth < 34 weeks, very low birthweight (<1500 g) and SGA were described in Figure 3, which showed the correlation between aPL positivity and these three outcomes. However, the proportion of other pregnancy outcomes, such as preterm birth < 37 weeks, PROM, PPROM, low birthweight (<2500 g), preeclampsia, thrombocytopenia and ICU admission, were not significantly different between twin pregnancies with positive aPL and those without.

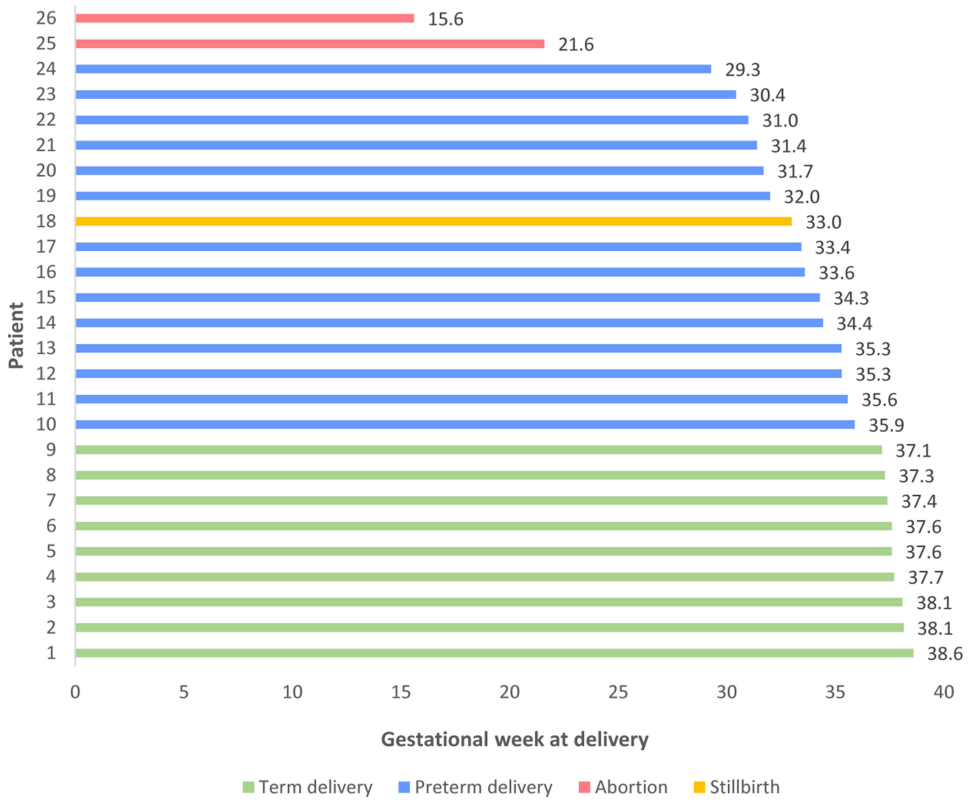

Figure 2 Distribution of pregnancy outcomes of twin pregnancy with aPL positivity.

Clinical Characteristics and Treatments of Twin Pregnancy with Positive aPL

Among the 24 twin-pregnant women with aPL in the PSM cohort, 79.17% (19/24) had adverse pregnancy outcomes. As shown in Table 3, among twin-pregnant women with aPL positivity, primiparity was observed more frequently in those

Table 2 Maternal and Fetal Outcomes of Control and Twin Pregnancy with aPL Positivity in PSM Cohort

	Control in Twin Pregnancies (n=48)	Twin Pregnancy with aPL Positivity (n=24)	*P* value[a]	aOR	*P* value[b]
Adverse pregnancy outcomes, n (%)	36 (75.00)	19 (79.17)	0.70	0.51 (−0.89, 1.91)	0.48
Abortion, n (%)	0 (0)	2 (8.33)	0.043*	—	—
Stillbirth[#], n (%)	0 (0)	1 (4.17)	0.15	—	—
Preterm birth < 37 weeks, n (%)	25 (52.08)	14 (58.33)	0.61	0.37 (−0.79, 1.53)	0.54
Preterm birth < 34 weeks, n (%)	4 (8.33)	8 (33.33)	0.007*[c]	2.76 (0.83, 4.70)	0.005*
PROM, n (%)	9 (18.75)	5 (20.83)	0.83	0.37 (−0.97, 1.71)	0.58
PPROM, n (%)	6 (12.50)	5 (20.83)	0.35	0.82 (−0.59, 2.23)	0.26
Low birthweight (<2500 g)[#], n (%)	27 (56.25)	15 (62.50)	0.34	0.97 (−0.36, 2.30)	0.15
Very low birthweight (<1500 g)[#], n (%)	2 (4.17)	5 (20.83)	0.016*[d]	2.40 (0.18, 4.67)	0.034*
SGA[#], n (%)	16 (33.33)	12 (50.00)	0.09	1.66 (0.22, 3.10)	0.024*
Preeclampsia, n (%)	8 (16.67)	5 (20.83)	0.66	0.13 (−1.30, 1.55)	0.86
Thrombocytopenia, n (%)	5 (10.42)	3 (12.50)	0.79	0.22 (−1.49, 1.93)	0.80
ICU admission, n (%)	1 (2.08)	3 (12.50)	0.06	2.03 (−0.56, 4.61)	0.13

Notes: All data are presented as the mean ± standard deviation or n (%). [#]The number of pregnancies in which at least one fetus in the twin pregnancy had this outcome. [a]*P* value was calculated for the difference in the percentage of pregnancy outcomes between control and twin pregnancies with aPL positivity. [b]*P* value was calculated for the aOR of pregnancy outcomes. Multivariate analysis was adjusted for maternal age, gravidity, weight at admission, BMI, thyroid diseases and diabetes mellitus. [c]Significant in the univariate analysis, $P = 0.012$ (OR = 1.70, 95% CI 0.38–3.03). [d]Significant in the univariate analysis, $P = 0.03$ (OR = 1.91, 95% CI 0.18–3.64). *$P < 0.05$.

Abbreviations: aPL, antiphospholipid antibodies; ICU, intensive care unit; PROM, premature rupture of membrane; PPROM, preterm premature rupture of membranes; SGA, small for gestational age.

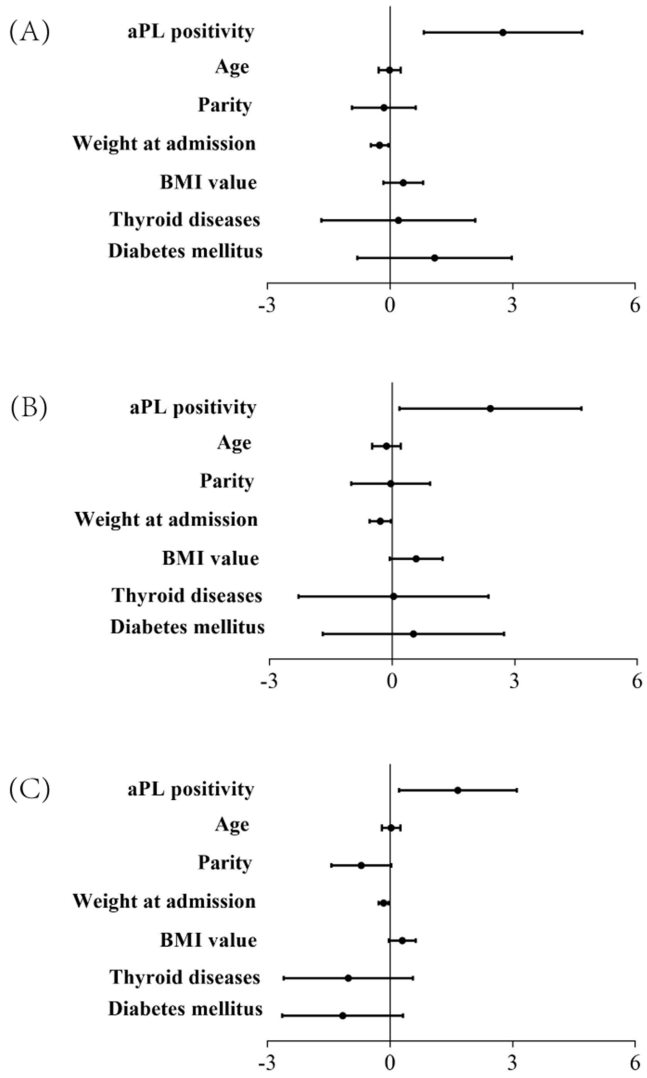

Figure 3 Forest plot of risk factors for preterm birth < 34 weeks (**A**), very low birthweight (<1500 g) (**B**) and SGA (**C**).

with adverse pregnancy outcomes than in those without (100.00% vs 80.00%, $P = 0.046$), whereas thrombocytopenia was less common (5.26% vs 40%, $P = 0.037$). Women with adverse pregnancy outcomes were more likely to have comorbidities, including PCOS, preeclampsia, diabetes mellitus and thyroid diseases; however, the difference was not statistically significant. Besides, the prevalence of APS-related treatments such as LDA, LMWH, hydroxychloroquine and corticosteroids were not different between women with adverse pregnancy outcomes and those without among twin-pregnant women with positive aPL.

aPL Profile in Twin Pregnancy with or Without Adverse Pregnancy Outcomes

The aPL profiles of the 24 twin-pregnant women with positive aPL in the PSM cohort were shown in Table 4. There was no significant difference in the aPL profiles between women with and without adverse pregnancy outcomes. LA was the most common aPL in both groups (73.68% vs 80.00%, $P = 0.88$), followed by aCL (36.84% vs 20.00%, $P = 0.36$). In addition, triple aPL positivity for LA, aCL and anti-β2GPI was only observed in the twin pregnant group with adverse pregnancy outcomes and not in the non-adverse pregnancy outcomes group.

Table 3 Clinical Characteristics and Treatments of Twin-Pregnant Women with aPL Positivity

Characteristics	Non-Adverse Pregnancy Outcomes (n=5)	Adverse Pregnancy Outcomes (n=19)	*P* value
Maternal age, years	33.20 ± 1.48	33.73 ± 2.98	0.58
Maternal age ≥ 35, n (%)	1 (20.00)	8 (42.11)	0.36
BMI, kg/m^2	29.55 ± 3.63	28.98 ± 3.57	0.76
Weight gain, kg	18.00 ± 5.87	15.21 ± 6.52	0.39
Parity	0 (0,1)	0 (0,1)	0.21
Primiparity, n (%)	4 (80.00)	19 (100.00)	0.046*
Multiparity, n (%)	1 (20.00)	0 (0)	0.046*
Chorionicity			
Monochorionic, n (%)	1 (20.00)	1 (5.26)	0.29
Dichorionic, n (%)	4 (80.00)	18 (94.74)	0.29
Mode of conception			
Spontaneous, n (%)	0 (0)	2 (10.53)	0.45
ART, n (%)	5 (100.00)	17 (89.47)	0.45
Mode of delivery			
Vaginal, n (%)	0 (0)	0 (0)	—
Caesarean, n (%)	5 (100.00)	17 (89.47)	0.57
Comorbidities			
PCOS, n (%)	0 (0)	2 (10.53)	0.45
Preeclampsia, n (%)	0 (0)	5 (26.32)	0.20
Diabetes mellitus, n (%)	1 (20.00)	6 (31.58)	0.61
Thyroid diseases, n (%)	0 (0)	6 (31.58)	0.15
Thrombocytopenia, n (%)	2 (40.00)	1 (5.26)	0.037*
Treatment			
No treatment, n (%)	0 (0)	2 (10.53)	0.45
LDA, n (%)	1 (20.00)	12 (63.16)	0.08
LMWH, n (%)	5 (100.00)	14 (73.68)	0.20
LDA+LMWH, n (%)	1 (20.00)	6 (31.58)	0.61
Hydroxychloroquine, n (%)	0 (0)	4 (21.05)	0.26
Corticosteroids, n (%)	1 (20.00)	5 (26.32)	0.77

Note: *$P < 0.05$.

Abbreviations: aPL, antiphospholipid antibodies; ART, Assisted reproductive technology; BMI, body mass index; PCOS, polycystic ovary syndrome; LDA, low-dose aspirin; LMWH, low-molecular-weight heparin.

Table 4 aPL Profile in Twin-Pregnant Women with or Without Adverse Pregnancy Outcomes

Serological Profile	Non-Adverse Pregnancy Outcomes (n=5)	Adverse Pregnancy Outcomes (n=19)	*P* value
LA positivity, n (%)	4 (80.00)	14 (73.68)	0.88
aCL positivity, n (%)	1 (20.00)	7 (36.84)	0.36
Anti-β2GPI positivity, n (%)	0 (0)	2 (10.53)	0.16
Single aPL positivity, n (%)	4 (100.00)	17 (89.47)	0.91
Single LA positivity, n (%)	4 (80.00)	12 (63.16)	0.89
Single aCL positivity, n (%)	1 (20.00)	5 (26.32)	0.65
Triple aPL positivity, n (%)	0 (0)	2 (10.53)	0.16

Abbreviations: aCL, anticardiolipin; aPL, antiphospholipid antibody; anti-β2GPI, anti-β2 glycoprotein I; LA, lupus anticoagulant.

Coagulation Functions in Twin Pregnancy with and without Positive aPL

The coagulation functions of the twin pregnant women were analyzed based on aPL positivity and pregnancy outcomes (Table 5). Among twin-pregnant women without aPL positivity, parameters for coagulation function, including PT, APTT,

Table 5 Coagulation Function of Control and Twin Pregnancy with aPL Positivity in PSM Cohort

	Control Group in Twin Pregnancies				Twin Pregnancies with aPL Positivity			
	Non-Adverse Pregnancy Outcomes (n=12)	Adverse Pregnancy Outcomes (n=36)	t	*P* value	Non-Adverse Pregnancy Outcomes (n=5)	Adverse Pregnancy Outcomes (n=19)	t	*P* value
PT	10.26 ± 0.56	10.26 ± 0.67	<0.01	1.00	10.26 ± 0.93	10.20 ± 0.80	0.13	0.90
APTT	27.23 ± 2.04	27.4 ± 2.14	−0.27	0.79	28.30 ± 1.55	27.50 ± 2.98	0.82	0.43
TT	17.48 ± 1.32	18.35 ± 1.74	−1.82	0.08	17.26 ± 1.04	18.77 ± 1.77	−2.44	0.03*
FIB	4.61 ± 0.71	4.40 ± 0.83	0.83	0.41	4.05 ± 3.43	5.02 ± 1.41	−2.49	0.02*
D-dimer	4520.58 ± 1810.40	3436.97 ± 1660.12	1.83	0.08	3501.20 ± 1375.82	2916.05 ± 1912.47	0.77	0.46

Note: *$P < 0.05$.
Abbreviations: aPL, antiphospholipid antibodies; APTT, activated thromboplastin time; FIB, fibrinogen; PT, prothrombin time; TT, thrombin time.

TT, FIB and D-dimer, were not significantly different between those with adverse pregnancy outcomes and those without. However, in twin-pregnant women with positive aPL, those with adverse pregnancy outcomes had increased levels of TT (18.77 ± 1.77 vs 17.26 ± 1.04 sec, $P = 0.03$) and FIB (5.02 ± 1.41 vs 4.05 ± 3.43 g/L, $P = 0.02$) than those without.

Discussion

This retrospective study reported the clinical characteristics and obstetric outcomes of twin-pregnant women with aPL. The prevalence of aPL positivity before conception and during pregnancy in twin pregnant women was 3.36%. The proportion of composite adverse pregnancy outcomes was comparable between the aPL-positive and control groups in twin pregnant women. However, after analyzing each outcome, we found that abortion, preterm birth < 34 weeks and very low birthweight (<1500 g) were more frequent in twin pregnant women with positive aPL. Moreover, aPL positivity was associated with several maternal and neonatal outcomes, such as preterm birth < 34 weeks, very low birthweight (<1500 g) and SGA.

APS is associated with an increased risk of obstetric complications such as preeclampsia, PROM, postpartum hemorrhage, fetal loss and premature delivery at ≤ 34 weeks.[24] In addition to the influence of APS on pregnancy outcomes, the factors leading to APS-related pregnancy morbidity have been widely explored. One meta-analysis of 27 studies found that predictors of poor pregnancy outcomes in women with APS included a history of thrombosis, APS laboratory category I (double or triple aPL positivity), triple aPL positivity, and lupus anticoagulant positivity.[25]

In addition to APS during pregnancy, aPL-positive pregnant women may have adverse obstetric outcomes. One prospective study enrolling 55 pregnant women who were persistently positive for the aPL test found that 15 (27%) women had early pregnancy loss < 10 weeks of gestation, only 26 (47%) of them had term live delivery, and nearly one-fourth of women at or beyond 10 weeks of gestation experienced aPL-related pregnancy morbidity.[26] Furthermore, since aPL positivity has been found to affect pregnancy outcomes, there may be a large number of cases of positive aPL and poor pregnancy outcomes in clinic, and the subsequent pregnancy and treatment of these women is a serious problem that needs to be addressed. Among women with positive aPL and prior adverse pregnancy outcomes, 38.3% (49/128) had adverse pregnancy outcomes in subsequent pregnancies, including fetal losses (65.3%), preterm deliveries (26.5%) and delivery after 37th week of gestation with preeclampsia/eclampsia, fetal growth restriction or intrauterine distress (8.2%), and antinuclear antibody (ANA) titer ≥ 1:160, age, previous three or more adverse pregnancy outcomes and glucocorticoid use were associated with obstetric complications.[27] In addition, 29.52% of women with a combination of aPL positivity and previous pregnancy losses would have pregnancy failure, including pregnancy losses, stillbirths and neonatal deaths;[28] prior pregnancy losses ≥ 3, maternal age at pregnancy ≥ 35 years, and no treatment during pregnancy were independent risk factors for subsequent pregnancy failure in women with positive aPL and a history of pregnancy losses.[28]

Regardless of the aPL entity, pregnant women who were positive for aPL had a higher incidence of adverse pregnancy outcomes than healthy controls, even asymptomatic carriers of aPL.[29] One study enrolling 163 pregnancies with aPL antibodies and 785 controls reported that adverse pregnancy outcomes occurred in 41.9% of APS, 25% of non-criteria APS and 28.3% of aPL carriers, which was higher than 5.6% in controls.[29] The aPL category is another important factor affecting obstetric outcomes in patients with APS. One study that enrolled 750 singleton pregnancies with primary APS found that among sole aPL in APS, aCL antibody was the most common, and anti-β2GPI had a stronger association with poor pregnancy outcomes, including low live birth rate, preeclampsia, intrauterine growth restriction and stillbirth.[30] Patients positive for multiple aPL were correlated with a higher incidence of poor pregnancy outcomes than those with only one positive aPL.[30] One meta-analysis including 19 studies explored the relationship between aPL and fetal loss and found that lupus anticoagulant, rather than aCL antibodies or β2GP1, was significantly correlated with late fetal loss in patients with positive aPL.[31] One prospective study that enrolled women with persistent positivity for LA found that 70% of pregnancies were associated with pregnancy complications, including spontaneous abortions and deliveries < 34th week of gestation.[32] In addition to the specific aPL, the dynamic changes of the aPL profile and time of aPL detection may be important factors in evaluating pregnancy outcomes. One study that included 97 pregnancies in women with obstetric APS (OAPS) compared the effect of serological detection of aPL before pregnancy and during the first trimester in the prediction of response to conventional treatment and found that compared with high baseline serological risk (triple positivity for aPL and/or high titers of aCL and/or anti-β2GPI before pregnancy), high serological risk during pregnancy (triple positivity for aPL and/or high titers of aCL and/or anti-β2GPI in the first trimester) was associated with a higher value for predicting pregnancy outcomes with conventional treatment (91.8% vs 82.5%).[33] Therefore, aPL should be detected in the first trimester of pregnancy to better identify serological risk factors of APS-related obstetric outcomes.[33]

Normal pregnancy is associated with changes in the hemostatic system, and a hypercoagulable state could protect pregnant women from hemorrhage during delivery.[34] This procoagulant state is enhanced in twin pregnancies. Compared to singleton pregnant women, twin pregnant women had significantly increased levels of FIB throughout pregnancy, and their levels of PT and TT were reduced.[35,36] In this study, we found that among pregnant women with positive aPL, the levels of FIB and TT were higher in those with composite adverse pregnancy outcomes than in those without, indicating that the potential role of imbalance between coagulation and fibrinolysis may affect pregnancy outcomes in twin-pregnant women with aPL positivity.

Although aPL positivity is associated with a higher risk of obstetric complications, its impact on twin pregnancies remains unclear. In this study, we explored the clinical characteristics and pregnancy outcomes of twin-pregnant women with aPL, which may broaden our insight and guide the clinical management of similar conditions. Another strength of this study was the use of the PSM method to compare the differences between the groups, which may have minimized the bias of selection for confounding factors. However, there are still some limitations in this study. Firstly, since twin-pregnant women with aPL positivity was a rare condition in clinic, the sample size was relatively small. We retrospectively collected the information and summarized the available data without exploring the features of this disease in more patients. We would incorporate a broader population and expand the scope of geographical coverage in our future work. Secondly, this study focused on the clinical characteristics and pregnancy outcomes of twin pregnant women with positive aPL. There has been no comparison between these patients and singleton pregnant women with positive aPL. Whether twin pregnancies increase the risk of poor obstetric outcomes in pregnancies with aPL positivity remains unclear.

Conclusion

This study summarizes the clinical features, laboratory test results and pregnancy outcomes of twin pregnant women with positive aPL. Although aPL positivity was rarely observed in women with twin pregnancies, it may be associated with obstetric complications, including abortion, preterm birth < 34 weeks and very low birthweight (<1500 g). Moreover, aPL tests may be important in the clinical management of twin pregnancies. The detection of aPL in twin pregnancies could be used for risk stratification and guidance for subsequent treatment, which may be important to minimize adverse maternal and/or neonatal outcomes and optimize the prognosis of this population.

Ethics Approval

This study was performed in accordance with the principles of the Declaration of Helsinki and approved by the Ethics Committee of Tianjin Medical University General Hospital (number: IRB2020-KY-102). Written informed consent about the access to the patients' medical record was not required, because this study was retrospective and the data were retrieved from electronic medical records. And patients' identities were anonymous and all information was maintained with strict confidentiality.

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Disclosure

The authors declare no conflicts of interest in this work.

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