

# Impact of Subchorionic Hematoma on Pregnancy Outcomes in Obstetric Antiphospholipid Syndrome

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**Objective:** This study aimed to investigate the effects of subchorionic hematoma (SCH) in patients with obstetric antiphospholipid syndrome (OAPS) on pregnancy outcomes, as well as the clinical value of anticoagulant therapy.

**Methods:** This retrospective study included 109 OAPS patients treated at the Fourth Hospital of Shijiazhuang from December 2019 to December 2021. Patients were divided into two groups: SCH group (n=40) and non-SCH group (n=69). Baseline data, laboratory indicators (anti- $\beta$ 2GP I, lupus anticoagulant, ACL, D-D, AA, ADP, ATIII, PS, and PC), complications, and pregnancy outcomes were compared between the groups.

**Results:** There were no significant differences between the two groups concerning the abortion rate, live birth rate (all  $P > 0.05$ ). However, we reported a significantly higher rate of preterm delivery occurring between 34–37 in the SCH group (13.7% vs 1.7%,  $P = 0.027$ ). The proportion of patients with triple-positive antiphospholipid antibodies (aPLs) was significantly higher in the SCH group compared to the non-SCH group (7.5% vs 0.0%,  $P = 0.047$ ). During pregnancy but before routine first-trimester therapy was initiated, the levels of  $\beta$ 2GP I, LA, ACL, D-D, AA, and ADP in the SCH group were higher than those in the non-SCH group, while ATIII, PS, and PC levels were lower (all  $P < 0.05$ ). After treatment, the levels of  $\beta$ 2GP I, LA, ACL, D-D, AA, and ADP decreased in both groups compared to their pre-treatment levels (all  $P < 0.05$ ); however, the levels of D-D and PS in the SCH group remained higher than those in the non-SCH group (all  $P < 0.05$ ).

**Conclusion:** In patients with OAPS who present with SCH during pregnancy, laboratory indicators suggest more severe immune disorders and coagulopathy, as well as an increased risk of preterm delivery.

**Keywords:** obstetric antiphospholipid syndrome, subchorionic hematoma, anticoagulant therapy, preterm delivery

## Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder primarily characterized by thrombotic events and/or obstetric complications during pregnancy. The diagnosis is confirmed by the persistent presence of antiphospholipid antibodies (aPLs) including lupus anticoagulant (LA), anticardiolipin antibodies (aCL), and anti- $\beta$ 2 glycoprotein I antibodies (anti- $\beta$ 2GPI Ab) at titers exceeding the 99th percentile.<sup>1</sup> APS can be categorized into two types: typical APS and atypical APS. Typical APS refers to patients who meet both the clinical and laboratory criteria as established by the APS diagnostic guidelines. In contrast, atypical APS, also known as non-criteria APS (NOAPS), refers to patients who meet only one of the clinical or laboratory criteria, but not both, according to the APS diagnostic guidelines.<sup>2</sup> Cases fulfilling Sydney criteria for obstetric morbidity with no previous thrombosis were defined as obstetric antiphospholipid syndrome (OAPS), which is a significant causative factor of recurrent spontaneous abortion (RSA), with the probability

of pathological pregnancy estimated at 51.0% to 68.4%.<sup>3</sup> However, the impact of APS on pregnancy outcome varied due to environment induced by gut microbiome.<sup>4</sup>

Subchorionic hematoma (SCH) refers to the accumulation of blood between the chorion and the uterine wall during pregnancy. This condition typically occurs in the first trimester but can persist into the second trimester. SCH is reported to occur in 1.7% to 28.3% of the general obstetric population and up to 39.5% of women with symptoms of threatened miscarriage.<sup>5</sup> Patients with RSA who exhibit symptoms of SCH face an elevated risk of miscarriage, preterm birth, intrauterine growth restriction, and other adverse pregnancy outcomes.<sup>6</sup> Previous studies have indicated that the occurrence of SCH may be associated with autoimmune abnormalities, such as positive antiphospholipid antibodies or coagulation disorders.<sup>7</sup> An observational study found that the incidence of SCH in patients using low-dose aspirin (LDA) was nearly four times higher than that in patients not using LDA.<sup>8</sup>

Anticoagulation is the first-line treatment for OAPS and is effective in both the prevention and management of thrombotic complications.<sup>9</sup> It is recommended that anticoagulant therapy is intended for the duration of the whole gestation.<sup>10</sup> Some patients refused continuing anticoagulant therapy for concerns about increased bleeding. However, the impact of this choice has not been investigated. Based on this background, the present study aims to investigate the effects of SCH on pregnancy outcomes in patients with OAPS, as well as the clinical value and safety of anticoagulation therapy for these patients. This research will provide foundational data and identify new directions for further studies in this field.

## Materials and Methods

### Patient Selection

This retrospective study included 109 patients diagnosed with OAPS who received treatment at the Department of Gynecological Endocrinology, Fourth Hospital of Shijiazhuang, from December 2019 to December 2021. Based on the detection of intrauterine pregnancy via color Doppler ultrasound, 40 patients exhibiting symptoms of subchorionic hemorrhage (SCH) were assigned to the study group (SCH group), while the remaining 69 patients without SCH symptoms were assigned to the control group (non-SCH group).

### Inclusion Criteria

1. Meeting the diagnostic criteria for OAPS (including atypical APS):<sup>1</sup>
2. Diagnosed as having a singleton pregnancy by ultrasound, with or without SCH.
3. Normal chromosomes for both husband and wife.
4. Normal mental and cognitive functions.
5. Normal thyroid function.
6. Absence of genital tract infections in all patients.

### Exclusion Criteria

1. Recurrent pregnancy loss (RSA) because of other medical conditions rather than APS.
2. Patients with cervical lesions, ovarian tumors, or any combined malignant tumors.
3. One or both partners with chromosomal abnormalities or familial genetic diseases.
4. Presence of serious diseases such as endocrine disorders, cardiovascular and cerebrovascular diseases, liver and kidney diseases, or coagulation system diseases.
5. Those with any uterine anomalies.

The study was approved by the Ethics Committee of The Fourth Hospital of Shijiazhuang (No. 20200059). All patients and their families participated voluntarily and signed informed consent forms.

### Preconception and Early Pregnancy Interventions

All patients were administered LDA for three months prior to conception (dosage adjusted based on body weight and bleeding status during pregnancy) and low molecular weight heparin in early pregnancy. All patients were evaluated for

folate metabolism before pregnancy. It is suggested that the patients with CC type received 0.4 mg active folic acid until at least three months of pregnancy. The patients with TT and CT types should receive 0.4–0.8mg active folic acid until at least three months of pregnancy. Hydroxychloroquine (Shanghai Zhongxi Pharmaceutical Co., Ltd.; 0.1–0.2 g/dose, administered twice daily) should be administered two months before pregnancy for patients who failed previous conventional treatment or high-risk aPLs spectrum. The dosage should be adjusted at any time according to the severity of pregnancy history and the antibody titer of high-risk aPLs spectrum. Discontinuation should be considered if the antibody titer becomes negative or close to normal. Low-dose prednisone (Prednisone Acetate; Suicheng Pharmaceutical Co., Ltd.; 5–10 mg/day) was administered in early pregnancy. The dosage was adjusted at any time according to the severity of pregnancy history and the level of antibody titer of high-risk aPLs spectrum, and the medication was stopped when the antibody titer turned negative or decreased close to normal. During early pregnancy, both groups were treated with standard pregnancy maintenance measures, which included dydrogesterone tablets (10 mg, three times a day, discontinued until 12 weeks of gestation) and Zishen Yutai pills mainly containing dodder seed, sand kernel, ripe rehmannia, ginseng (one packet, three times a day, discontinued until 12 weeks of gestation), in addition to low molecular weight heparin for anticoagulation. The treatment cycle was limited to three months, with evaluations conducted before and after the treatment period.

## Management of the SCH Group

Patients diagnosed with SCH were further divided into two subgroups based on whether they continued anticoagulant therapy: the anticoagulation group and the non-anticoagulation group. The anticoagulation subgroup received low molecular weight heparin (Qilu Pharmaceutical Co., Ltd.; 5000 IU/day) until two weeks before delivery and/or LDA (Aspirin; Linfen Baozhu Pharmaceutical Co., Ltd.; 50–100 mg/day) was discontinued two weeks before delivery. During treatment, complete blood count, liver and kidney function, coagulation profiles, and hypersensitivity reactions were monitored regularly.

## Clinical Indicators

The primary outcome measures were the early miscarriage rate and live birth rate. Secondary indicators included laboratory indicators such as  $\beta$ 2-glycoprotein I ( $\beta$ 2GPI), lupus anticoagulant (LA), anticardiolipin antibodies (ACL), D-dimer (D-D), arachidonic acid (AA), adenosine diphosphate (ADP), antithrombin III (ATIII), protein S (PS), and protein C (PC), as well as rates of late miscarriage, preterm birth, gestational diabetes mellitus (GDM), preeclampsia, placental abruption, fetal growth restriction (FGR), amniotic fluid issues, cervical insufficiency, and the occurrence, disappearance, and duration of SCH.

## Operational Definitions

Pregnancy outcomes were defined as follows: spontaneous abortion or fetal loss within 12 weeks of gestation was classified as early abortion; pregnancies extending beyond 12 weeks were classified as persistent pregnancies.<sup>11</sup> Abortions and intrauterine stillbirths occurring after 12 weeks but before 28 weeks were classified as late abortions.

## Statistical Analysis

All data collected in this study were analyzed using SPSS version 26.0 software. Continuous variables of normal distribution were presented as mean  $\pm$  standard deviation ( $\bar{x} \pm s$ ) and those of skewed distribution were presented as median and interquartiles. To assess differences between two groups, independent sample *t*-tests were utilized for normally distributed independent variables, while paired sample *t*-tests were employed for normally distributed paired variables. For non-normally distributed variables, the Mann–Whitney *U*-test was applied to independent samples, and the Wilcoxon signed-rank test was used for paired samples. Categorical data are expressed as frequency (n) and percentage (%), with differences between groups analyzed using the Chi-square test or Fisher's exact test, as appropriate. A *p*-value of less than 0.05 was deemed statistically significant.

## Results

### Comparison of Baseline Data Between the Two Groups

Among 109 OAPS patients, there were 34 cases (12 cases in the study group and 22 cases in the control group) diagnosed with typical APS, and none exhibited arterial thrombosis. Additionally, 75 cases (28 cases in the study group and 47 cases in the control group) were identified as atypical APS, all of which met the laboratory criteria. Within this group, 60 cases experienced fewer than 2 consecutive miscarriages within 10 weeks of pregnancy, while 15 cases had intermittent miscarriages occurring more than 3 times within the same period. In the study group, there were 3 cases of undifferentiated connective tissue disease (UCTD) and 1 case of rheumatoid arthritis (RA); in the control group, there were also 3 cases of UCTD and 1 case of connective tissue disease (CTD). The proportion of triple-positive aPLs in the study group was higher than that in the control group ( $P = 0.047$ , Table 1).

### Comparison of Pregnancy Outcomes Between the Two Groups

The incidence of preeclampsia, placental abruption, and preterm birth was slightly higher in the study group compared to the control group. Notably, the rate of preterm birth between 34 to 37 weeks was significantly higher in the study group than in the control group ( $P = 0.027$ , Table 2). Prior to treatment, levels of  $\beta 2$ GPI, LA, ACL, D-D, AA, and ADP were elevated in the study group compared to the control group (all  $P < 0.05$ ). Conversely, levels of ATIII, PS, and PC were lower in the study group (all  $P < 0.05$ ). Post-treatment, levels of D-D and PS remained higher in the study group compared to the control group (both  $P < 0.05$ , Table 3).

### Influence of Anticoagulant Therapy in the SCH Group on Pregnancy Outcomes

Among the 40 patients in the SCH group, 31 were categorized in the anticoagulation group, and 9 were in the non-anticoagulation group. The results indicated no differences between the two groups regarding the onset time of SCH, the

**Table 1** Comparison of Baseline Data Between the Two Groups

Characteristic	Study Group (n = 40)	Control Group (n = 69)	P value
Maternal age (y)	30(22–40)	31(22–41)	0.720
>35 year (n, %)	5(12.50)	14(20.29)	0.301
BMI (kg/m <sup>2</sup> )	23(16–28)	22(16–28)	0.441
Prior pregnancy (n, %)	4(2–7)	3(2–8)	0.398
Prior delivery (n, %)	1(0–2)	0(0–3)	0.388
Prior pregnancy losses (n, %)	3(1–7)	2(1–6)	0.320
2<Prior pregnancy losses<3	23(57.50)	37(53.62)	0.695
Prior pregnancy losses≥3	17(42.50)	32(46.38)	0.695
History of fetal abortion<10 week	3(7.50)	8(11.59)	0.723
History of fetal abortion≥10 week	1(2.50)	1(1.45)	1.000
Atypical OAPS (n, %)	12(30.00)	22(31.88)	0.838
Non-atypical OAPS (n, %)	28(70.00)	47(68.12)	0.838
Appearance of SCH (day)	52(30–98)	0	
Autoimmune diseases (n, %)	4(10.0)	4(5.8)	0.642
Laboratory indicators (n, %)			
APLs single positive	28(70.00)	46(66.67)	0.719
APLs double positive	9(22.50)	14(20.29)	0.785
APLs triple positive	3(7.50)	0	0.047

**Notes:** The continuous data were presented as medians and interquartiles and the count data were presented as number/percentage.

**Abbreviations:** BMI, body mass index; SCH, subchorionic hematoma; OAPS, obstetric antiphospholipid syndrome; APLs, anti-phospholipid antibodies; aPLs single positive, referring to one of the three indicators of aPLs positive; aPLs double positive, referring to two of three indicators of aPLs positive; aPLs triple positive, referring to all three indicators of aPL positive.

**Table 2** Comparison of Pregnancy Outcomes Between the Two Groups

Outcomes	Study Group (n = 40)	Control Group (n = 69)	P value
Early abortion (n, %)	3 (7.50)	5 (7.58)	1.000
Persistent pregnancy (n, %)	37 (92.50)	61 (88.41)	0.723
Late abortion (n, %)	1 (2.70)	1 (1.64)	1.000
Live birth (n, %)	36 (90.00)	60 (86.90)	0.868
Preterm delivery (n, %)	6 (16.67)	3 (5.00)	0.076
GW<34 (n, %)	1 (2.78)	2 (3.33)	1.000
34 ≤ GW <37 (n, %)	5 (13.89)	1 (1.67)	0.027
Delivery gestational age (week)	38 (32–40)	38 (26–40)	0.307
Method of delivery (n, %)			
Natural Delivery	13 (36.11)	28 (46.67)	0.311
Cesarean Delivery	23 (63.89)	32 (53.33)	0.311
Pregnancy complications (n, %)	8 (22.22)	9 (15.00)	0.369
GDM	2 (5.56)	2 (3.33)	0.227
Pre-eclampsia	4 (11.11)	3 (5.00)	0.419
Placental abruption	2 (5.56)	1 (1.67)	0.554
Low amniotic fluid	0	2 (3.33)	1.000
Cervical insufficiency	0	1 (1.67)	1.000

**Notes:** Indications for caesarean include many medical conditions, which consist of factors concerning fetus, birth canal, mater, placenta, and umbilical cord. In clinical practice, we make a decision for caesarean section based on international guidelines and comprehensive discussion.

**Abbreviations:** GW, gestational weeks; GDM, gestational diabetes mellitus.

**Table 3** Comparison of Laboratory Indicators in the Two Groups

Indicators	Study Group (n = 40)	Control Group (n = 69)	P value
β2GPI (IU/mL)			
Before treatment	45.64±32.99	37.02±29.78	< 0.001
After treatment	28.53±24.51*	25.70±23.13 <sup>#</sup>	0.360
LA			
Before treatment	1.27±0.53	1.12±0.35	0.008
After treatment	1.12±0.33*	1.07±0.31 <sup>#</sup>	0.270
ACL (IU/mL)			
Before treatment	9.16±12.00	9.28±9.14	< 0.001
After treatment	7.41±9.66*	6.92±6.23 <sup>#</sup>	0.465
DD (mg/mL)			
Before treatment	222.22±484.44	82.18±80.60	0.001
After treatment	200.40±152.40*	148.50±128.40 <sup>#</sup>	0.012
AA (%)			
Before treatment	46.62±8.76	38.52±9.53	0.001
After treatment	32.83±20.69*	29.04±12.56 <sup>#</sup>	0.812
ADP (%)			
Before treatment	75.50±9.61	76.57±8.56	< 0.001
After treatment	62.71±11.64*	62.67±12.04 <sup>#</sup>	0.989
ATIII (%)			
Before treatment	99.88±17.31	109.00±11.69	0.004
After treatment	107.27±18.33*	106.90±14.84	0.178
PS (%)			
Before treatment	60.28±17.57	71.59±21.66	< 0.001
After treatment	88.57±22.74*	74.99±20.69	0.001

(Continued)

**Table 3** (Continued).

Indicators	Study Group (n = 40)	Control Group (n = 69)	P value
PC (%)			
Before treatment	103.26±15.11	108.43±16.62	0.024
After treatment	109.30±13.08*	112.00±17.04	0.386

**Notes:** \*the differences of the parameters between after treatment and before treatment in the study group, P<0.05; #the differences of the parameters between after treatment and before treatment in the control group, P<0.05.

**Abbreviations:** β2GPI, anti-β2-glycoprotein-I; LA, lupus anticoagulant; ACL, anticardiolipin; DD, D dimer; AA, arachidonic acid; ADP, adenosine diphosphate; ATIII, antithrombin III; PS, Protein S; PC, Protein C.

**Table 4** Effect of Anticoagulant Therapy on Pregnancy Outcomes

Variables	Anticoagulation Group (n=31)	Non-Anticoagulation Group (n=9)	P value
Duration of SCH (day)	25.9 ± 19.1	31.7 ± 16.1	0.408
Appearance of SCH (day)	54.2 ± 14.4	55.1 ± 11.4	0.535
Disappearance of SCH (week)	11.1 ± 3.1	11.9 ± 3.3	0.819
Early abortion (n, %)	3 (9.7)	1 (11.1)	1.000
Preterm delivery (n, %)	6 (19.4)	1 (11.1)	1.000
Live birth (n, %)	28 (90.3)	8 (88.9)	0.536

**Abbreviation:** SCH, subchorionic hematoma.

duration of SCH, the time until SCH resolution, the early miscarriage rate, the preterm birth rate, and the live birth rate (all P > 0.05). However, the duration of SCH was longer in the non-anticoagulation group (Table 4).

## Discussion

Research has demonstrated that SCH occurs with a certain frequency in patients with OAPS.<sup>12</sup> The etiology of SCH remains to be fully elucidated; it is generally believed that SCH primarily results from the separation of the chorionic plate from the underlying decidua, leading to hemorrhage and the subsequent accumulation of a substantial volume of blood between the chorion and decidua.<sup>13</sup> The impact of SCH on pregnancy outcomes remains controversial. A meta-analysis conducted in 2011 suggested that SCH is associated with an increased risk of early and late pregnancy loss, placental abruption, and premature rupture of membranes.<sup>14</sup> Another report indicated that the rate of spontaneous miscarriage diagnosed with SCH at or before 7 weeks (19.6%) is significantly higher than that diagnosed after 8 weeks.<sup>15</sup> However, a recent retrospective study suggested that SCH occurring before 14 weeks of gestation is not independently associated with pregnancy loss before 20 weeks, nor is the size of the hematoma related to miscarriage.<sup>16</sup> In addition, Elmas et al<sup>17</sup> found that the presence of SCH increased abortion rates in abortus imminens cases and the presence of SCH in cases with ongoing pregnancy did not increase the complications of delivery. In this study, no statistically significant differences were observed between the two groups regarding early and late miscarriage rates, ongoing pregnancy rates, live birth rates, adverse pregnancy outcomes, and pregnancy complications. However, there was a trend towards increased rates of preeclampsia, placental abruption, and preterm delivery among OAPS patients with SCH without statistical differences, which is consistent with findings from an international study.<sup>18</sup> This information can provide reassurance to patients and offer clinical guidance for healthcare providers managing such cases.

In this study, it was found that prior to treatment, levels of β2GP I, LA, ACL, D-D, AA, and ADP in the SCH group were significantly higher than those in the control group, while ATIII, PS, and PC were significantly lower. Among the many possible causes of SCH, immune factors and a hypercoagulable state have received considerable attention.<sup>11</sup> Baxi et al<sup>9</sup> reported that antiphospholipid antibodies may increase the tendency for platelet aggregation, thus leading to thrombosis and/or vasculitis, and heightening the possibility of SCH. Alijotas et al<sup>10</sup> suggested that in women with

a history of adverse obstetrical outcomes, positive antiphospholipid antibodies—especially when accompanied by low C4 and/or high gammaglobulinemia—are more likely to result in intrauterine hematoma. These findings suggest that the immune disorder and hypercoagulable state were more severe in OAPS patients with SCH. The spectrum of high-risk aPLs or aPLs with persistently medium-high titers is associated with a greater likelihood of adverse pregnancy outcomes.<sup>3</sup> PC, PS, and AT-III are three types of anticoagulant proteins in the human body that play essential roles in maintaining the dynamic homeostasis of coagulation and the balance between anticoagulation and fibrinolytic systems. Deficiencies in these anticoagulant proteins can weaken the body's anticoagulant function, leading to a prethrombotic state, which may ultimately result in adverse pregnancy outcomes such as embryonic or fetal failure and stillbirth.<sup>19</sup> Therefore, it is crucial to regularly test these laboratory parameters during treatment to facilitate real-time adjustments of the drug regimen and to prevent adverse pregnancy outcomes.

Furthermore, the study observed that levels of  $\beta$ 2GP I, LA, ACL, D-D, AA, and ADP decreased in both groups after treatment compared with before treatment, with no significant differences between the groups. This indicates that SCH did not influence the reduction of aPLs titers. However, it is important to note that the aim of drug therapy for OAPS patients is not to reduce aPLs titers, but rather to mitigate the risk of thrombosis associated with high aPLs titers and to prevent or manage excessive immune disorders caused by these elevated levels. Consequently, changes in aPLs antibody titers during pregnancy should not dictate drug dose adjustments or discontinuation.<sup>1</sup>

Without proactive intervention, patients with atypical OAPS are at risk of experiencing adverse pregnancy outcomes similar to those associated with typical OAPS, warranting significant attention from healthcare providers. The latest consensus indicates that the risk of arteriovenous thrombosis increases with the detected titer of aPLs, with “triple positive patients” exhibiting the highest risk of thrombosis.<sup>3</sup> The proportion of triple positive aPLs in the study group was higher than that in the control group, suggesting that coagulation dysfunction in OAPS patients with hematoma is more severe, necessitating more standardized anticoagulant therapy.

Among the laboratory diagnostic indicators of OAPS, the relationship between ACL and/or  $\beta$ 2GP I and autoimmune recurrent miscarriage has been established as an important indicator reflecting changes in immune status in patients with OAPS, serving as a significant factor for thrombosis and pathological pregnancy.  $\beta$ 2GP I-dependent aPLs are considered the main pathogenic autoantibody in OAPS, noted for their specificity and sensitivity in diagnosing OAPS and their close clinical association.<sup>20</sup> This study revealed that the positive rate of simple anti- $\beta$ 2GP I was as high as 81.6% (89 cases), significantly exceeding that of LA (20.1%) and ACL (13.7%), further corroborating this perspective.

Anticoagulation is currently recognized as the most effective treatment for OAPS.<sup>1</sup> There is no consensus on the treatment of SCH, and the primary goal of clinical management is to reduce symptoms and promote the absorption of hematomas. The use of anticoagulant therapy remains controversial. Some scholars have reported significant success in treating RSA with SCH using a combination of low-molecular-weight heparin and immunoglobulin, with no adverse reactions noted.<sup>21</sup> Previous studies have indicated that the use of LDA may increase the incidence of SCH in early pregnancy.<sup>10,12</sup> Moreover, the incidence of SCH among patients attending fertility clinics (those experiencing infertility and recurrent pregnancy loss) was found to be highly correlated with LDA use compared to general obstetric patients. However, these studies did not connect pregnancy outcomes to SCH, nor did they assess the impact of maternal age on statistical differences between the two groups.

There were no significant differences between the anticoagulant group and the non-anticoagulant subgroup regarding the appearance of SCH, resolution of SCH, early miscarriage rate, preterm delivery rate, or live birth rate. However, the duration of SCH in the non-anticoagulant group was prolonged, suggesting that anticoagulant therapy may facilitate the resorption of SCH. Furthermore, the live birth rates were comparable between the two subgroups, indicating that discontinuing anticoagulant therapy after the onset of SCH may not be beneficial in preventing miscarriage in patients with OAPS.

Based on the design of this study, it is not possible to definitively conclude whether anticoagulant therapy increases the incidence of SCH in patients with OAPS. However, a previous study which involved a retrospective cohort analysis of 274 cases of recurrent pregnancy loss, revealed that the incidence of thrombophilia was significantly higher in the SCH group compared to the non-SCH group.<sup>15</sup> This finding suggests that a hypercoagulable state in the maternal

circulation may contribute to the formation of SCH, which might be a precursor of abortion. However, the influence of hypercoagulable state in the maternal circulation on abortion need further study.

It is crucial to acknowledge and address several limitations of this study. Firstly, while this study is conducted at a single center and follows a retrospective design, it has a relatively small sample size. The characteristics and treatment of patients with SCH may vary across different demographics and medical settings, which may limit the generalizability of the findings. Additionally, this study focused exclusively on a specific set of laboratory indications and pregnancy outcomes. It did not thoroughly investigate other potential factors that could influence the relationship between SCH and OAPS, such as genetic factors, environmental exposures, or underlying comorbidities. Further prospective study enrolling a large sample of subjects and investigating potential factors including genetic factors, environmental exposures, or underlying comorbidities were needed.

## Conclusion

The presence of SCH does not appear to reduce the live birth rate in patients with OAPS, nor does it increase the incidence of early or late miscarriage, pregnancy complications, or adverse pregnancy outcomes. However, in patients with OAPS and SCH, coagulopathy and immune dysregulation are more pronounced, highlighting the need for standardized anticoagulation therapy.

## Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of The Fourth Hospital of Shijiazhuang (No. 20200059). All patients and their families participated voluntarily and signed informed consent forms., and the study was performed in accordance with the Helsinki II declaration. Informed consent was obtained from all the study subjects before enrollment.

## Data Sharing Statement

Data is provided within the manuscript files.

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## Disclosure

The authors declare that they have no competing interests.

## References

1. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost.* 2006;4(2):295–306. doi:10.1111/j.1538-7836.2006.01753.x
2. Alijotas-Reig J, Esteve-Valverde E, Ferrer-Oliveras R, et al. Group, Comparative study of obstetric antiphospholipid syndrome (OAPS) and non-criteria obstetric APS (NC-OAPS): report of 1640 cases from the EUROAPS registry. *Rheumatology.* 2020;59(6):1306–1314. doi:10.1093/rheumatology/kez419
3. Sammaritano LR. Antiphospholipid syndrome. *Best Pract Res Clin Rheumatol.* 2020;34(1):101463. doi:10.1016/j.berh.2019.101463
4. Jansen VL, Davids M, van Mourik DJ, et al. Gut microbiome composition and intestinal immunity in antiphospholipid syndrome patients versus healthy controls. *Lupus.* 2024;33(12):1373–1378. doi:10.1177/09612033241274515
5. Al-Memar M, Vaulet T, Fourie H, et al. First-trimester intrauterine hematoma and pregnancy complications. *Ultrasound Obstet Gynecol.* 2020;55(4):536–545. doi:10.1002/uog.20861
6. Norman SM, Odibo AO, Macones GA, Dicke JM, Crane JP, Cahill AG. Ultrasound-detected subchorionic hemorrhage and the obstetric implications. *Obstet Gynecol.* 2010;116(2 Pt 1):311–315. doi:10.1097/AOG.0b013e3181e90170
7. Johns J, Hyett J, Jauniaux E. Obstetric outcome after threatened miscarriage with and without a hematoma on ultrasound. *Obstet Gynecol.* 2003;102(3):483–487. doi:10.1016/s0029-7844(03)00580-5
8. McIntyre JA, Coulam CB, Faulk WP. Recurrent spontaneous abortion. *Am J Reprod Immunol.* 1989;21(3–4):100–104. doi:10.1111/j.1600-0897.1989.tb01011.x
9. Baxi LV, Pearlstone MM. Subchorionic hematomas and the presence of autoantibodies. *Am J Obstet Gynecol.* 1991;165(5 Pt 1):1423–1424. doi:10.1016/0002-9378(91)90383-3
10. Alijotas J, Izquierdo M, Serra B, Cusido MT, Ribera M, Carrera JM. Antinuclear autoantibodies, complement level, hypergammaglobulinemia and spontaneous intrauterine hematoma in pregnant women. *Am J Reprod Immunol.* 2003;50(1):1–6. doi:10.1034/j.1600-0897.2003.00054.x

11. Tuuli MG, Norman SM, Odibo AO, Macones GA, Cahill AG. Perinatal outcomes in women with subchorionic hematoma: a systematic review and meta-analysis. *Obstet Gynecol.* 2011;117(5):1205–1212. doi:10.1097/AOG.0b013e31821568de
12. Truong A, Sayago MM, Kutteh WH, Ke RW. Subchorionic hematomas are increased in early pregnancy in women taking low-dose aspirin. *Fertil Steril.* 2016;105(5):1241–1246. doi:10.1016/j.fertnstert.2016.01.009
13. Lopez-Pedraza C, Aguirre MA, Ruiz-Limon P, et al. Immunotherapy in antiphospholipid syndrome. *Int Immunopharmacol.* 2015;27(2):200–208. doi:10.1016/j.intimp.2015.06.006
14. Knight JS, Branch DW, Ortel TL. Antiphospholipid syndrome: advances in diagnosis, pathogenesis, and management. *BMJ.* 2023;380:e069717. doi:10.1136/bmj-2021-069717
15. Naert MN, Muniz Rodriguez A, Khadraoui H, Naqvi M, Fox NS. Association between first-trimester subchorionic hematomas and adverse pregnancy outcomes after 20 weeks of gestation in singleton pregnancies. *Obstet Gynecol.* 2019;134(4):863–868. doi:10.1097/AOG.0000000000003487
16. Fu Z, Ding X, Wei D, Li J, Cang R, Li X. Impact of subchorionic hematoma on pregnancy outcomes in women with recurrent pregnancy loss. *Biomol Biomed.* 2023;23(1):170–175. doi:10.17305/bjms.2022.7705
17. Elmas B, Ozgu BS, Zorlu U, et al. Do first-trimester subchorionic hematomas affect pregnancy outcomes? *Z Geburtshilfe Neonatol.* 2023;227(1):31–35. doi:10.1055/a-1929-9500
18. Alimohamadi S, Javadian P, Gharedaghi MH, et al. Progesterone and threatened abortion: a randomized clinical trial on endocervical cytokine concentrations. *J Reprod Immunol.* 2013;98(1–2):52–60. doi:10.1016/j.jri.2013.01.004
19. Buchholz T, Lohse P, Kosian E, Thaler CJ. Vasoconstrictively acting AT1R A1166C and NOS3 4/5 polymorphisms in recurrent spontaneous abortions (RSA). *Am J Reprod Immunol.* 2004;51(5):323–328. doi:10.1111/j.1600-0897.2004.00163.x
20. Pierangeli SS, Favaloro EJ, Lakos G, et al. Standards and reference materials for the anticardiolipin and anti-beta2glycoprotein I assays: a report of recommendations from the APL Task Force at the 13th International Congress on Antiphospholipid Antibodies. *Clin Chim Acta.* 2012;413(1–2):358–360. doi:10.1016/j.cca.2011.09.048
21. Hamulyak EN, Scheres LJ, Marijnen MC, Goddijn M, Middeldorp S. Aspirin or heparin or both for improving pregnancy outcomes in women with persistent antiphospholipid antibodies and recurrent pregnancy loss. *Cochrane Database Syst Rev.* 2020;5(5):CD012852. doi:10.1002/14651858.CD012852.pub2

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