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Anticardiolipin Positivity Is Highly Associated With Intrauterine Growth Restriction in Women With Antiphospholipid Syndrome

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Abstract

The purpose of our study was to evaluate pregnancy outcomes of women with antiphospholipid antibodies (aPL) positivity and assess risk factors associated with adverse pregnancy outcomes. Pregnant women with aPL positivity were enrolled prospectively in China from January 2017 to March 2020. Treatment of low-dose aspirin and low molecular weight heparin were given. Pregnancy outcomes and coagulation function were recorded and compared with normal pregnancies. Multivariable logistic regression was performed to identify risk factors associated to intrauterine growth restriction (IUGR). 270 pregnant women, including 44 diagnosed as Antiphospholipid syndrome (APS), 91 as non-criteria APS (NCAPS) and 135 normal cases as control, were enrolled in the study. The live birth rate in aPL carriers and APS group was 97% and 95.5%, respectively. Adverse pregnancy outcomes did not show significant difference between aPL carriers and normal pregnancies, and between APS and NCAPS, except for IUGR. The incidence of IUGR was significantly higher in aPL carriers than normal pregnancies, and in APS patients than NCAPS ($P < 0.05$). After controlling for age, in vitro fertilization (IVF), pregnancy losses related to APS and treatment, anticardiolipin (aCL) positivity was the only variable significantly associated with IUGR, with an adjusted odds ratio of 4.601 (95% CI, 1.205-17.573). Better pregnant outcomes of aPL positive women, include APS and NCAPS, were achieved in our study with treatment based on low-dose aspirin (LDA) plus low molecular weight heparin (LMWH). The incidence of IUGR was still higher in them, and aCL positivity was the only one risk factor associated with IUGR.

Keywords

antiphospholipid syndrome, anticardiolipin, intrauterine growth restriction, low molecular weight heparin, low-dose aspirin

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Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by venous or arterial thrombosis and/or adverse pregnancy outcomes in the presence of persistent laboratory evidence of antiphospholipid antibodies (aPL).[1] The diagnosis of APS is according to the 2006 Sydney (revised Sapporo) criteria,[1] requiring at least 1 clinical manifestation and 1 laboratory criteria which are as follows: 1). clinical manifestation: arterial/venous thrombosis or pregnancy morbidity (unexplained fetal death at $\geq$10 gestational weeks, or preterm births beyond 34 weeks because of preeclampsia or intrauterine growth restriction (IUGR), or more than 3 times consecutive early pregnancy loss beyond 10 weeks); 2). laboratory criteria: aPL positivity on more than 2 times tests apart from at least 12 weeks, including lupus anticoagulant (LA), anticardiolipin (aCL) and anti-beta 2 glycoprotein 1 antibodies (anti-β2GP1) at medium or high titer.

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APS has great probabilities leading to adverse pregnancy outcomes, which may bring pregnant women and their family with huge psychologic and economic burden. With the development of diagnosis and treatment of recurrent miscarriages and infertility before assisted reproduction procedures, aPL is taken as one of important immunologic indexes in the diagnostic protocols.[2] Therefore, a huge number of pregnant women are treated as non-criteria APS (NCAPS), with asymptomatic clinical manifestations, such as 2 unexplained miscarriages, 3 non-consecutive miscarriages, late preeclampsia, or 2 or more unexplained in vitro fertilization (IVF) failure; or with low positive aCL or anti-β2GP1. In women with recurrent miscarriages, only 10% of women could reach the diagnostic criteria of APS, while 15% of women reported to have persistent positivity of aPL, not fulfilling clinical criteria of APS or with low titer of aPL (95-99th centile).[3,4] The EUROAPS study in 2012 reported the women with non-criteria APS had similar pregnancy outcomes compared with women with APS and could also benefit from standard treatment for APS.[5] In a recent study, it has been reported that adverse pregnant outcomes related to aPL were identified in 17.7%.[6] Namely, despite being asymptomatic, those women are at increased risk of obstetric morbidity because of persistent presence of aPL. It has been demonstrated that aPL itself may be pathogenic and was associated with elevated possibilities of further pregnancy complications and mobidity.[7,8]

With respect to adverse pregnancy outcomes, thrombosis is not only happened in large vessels, but also referred to placental vascular which would result in placental insufficiency and associated with preeclampsia, IUGR, stillbirth and preterm delivery. aPL induced a direct pathogenic role such as a procoagulant and proinflammatory response in vascular and obstetric events,[1] especially triple aPL positivity, confirmed as the most significant risk factor by a large body of evidence.[9] Among them, either LA or anti-β2GP1, or both have been suggested as the highest risk factor associated with adverse events through different studies.[10-12]

The prognosis of pregnancies had improved greatly for APS, but 20-30% of APS women were still struggled in the way of having a healthy neonate even with conventional treatment of prophylactic heparin plus low-dose aspirin (LDA) in Europe.[4] And many researches had discussed the risk factors associated with adverse pregnancy outcomes, most of them were only restricted in APS, or merely involved NCAPS.[13]

Our prospective study is aimed to observe the pregnant outcomes of APS and NCAPS women in Hangzhou China and to investigate the risk factors associated with adverse pregnancy outcomes according to the aPL profile.

Method

The study was performed prospectively from January 2017 to March 2020 at women's hospital, Zhejiang university, School of medicine in Hangzhou, China. The study was approved by the ethical committee of Zhejiang university and written informed consent was obtained from all patients. Pregnant women with aPL positivity were included in our study, and would be treated and monitored through the whole duration of pregnancy and eventually gave birth in our hospital. Only singleton pregnancy would be included, multiple pregnancy would be excluded.

At the preconception visit or during the first trimester of pregnancy, aPL and other immunological tests were performed, such as antinuclear antibodies (ANA), antibodies to extractable nuclear antigens(anti-ENA), anti–double-stranded DNA antibodies(anti-dsDNA) and thyroid peroxidase antibody (TPOAb), and therapy was begun. Pregnancy history, the reason of miscarriage and prethrombotic state were evaluated. Patients were divided into APS group and NCAPS group according to the APS diagnostic criteria.[1] Patients in APS group would receive LDA (75 mg per day) plus low molecular weight heparin (LMWH) subcutaneously 1 or 2 dose per day. Patients in NCAPS group would receive LDA alone, or LDA combined with LMWH subcutaneously per day according to their uterine artery Doppler velocimetry before 20 weeks and umbilical artery Doppler velocimetry after 20 weeks. If pregnancy complications such as IUGR, oligohydramnios were shown, we would give 2 doses of LMWH to patients. If patients had other positive immunological index, they might receive other therapies, such as corticosteroids or hydroxychloroquine (HCQ).

The primary outcome was live birth. The second outcomes were pregnancy complications, including preeclampsia/eclampsia, placental abruption, oligohydramnios, preterm delivery before 37 gestational weeks, IUGR and maternal thrombotic events (venous and/or arterial) during pregnancy. Gestational week at delivery, mode of delivery, bleeding at partum and fetal outcomes such as weight, APGAR scores were recorded. Coagulation function of patients before and after delivery were also recorded.

There were 135 pregnant women with aPL positivity enrolled in the study. Among them, 44 were diagnosed as APS, and 91 as NCAPS. We also prospectively selected normal pregnant women who gave birth in our hospital without history of recurrent miscarriages and immunological problems as control group, with individual matching by gestational weeks, age and BMI of aPL positivity patients. Multiple pregnancies were also excluded. Their pregnancy outcomes and demographic data were also recorded.

Laboratory Assays

aCL and anti-β2GP1 were tested using an enzyme-linked immunosorbent assay kit from EUROIMMUN (Germany). The detection limit for aCL is 12 PLU/ml, and for anti-β2GP1 is 20 RU/ml. LA was detected with the use of a panel of 3 tests that included the dilute Russell's viper venom time, a lupus anticoagulant-sensitive partial thromboplastin time, and the dilute prothrombin time.

Statistical Analysis

Statistically analysis was performed using the Statistical Packages of Social Sciences for Windows, version 22.0 (SPSS,

Table 1. Demographic Characteristics and Pregnancy Outcomes Between aPL Carriers and Control Group.

Characteristics	aPL carriers (n = 135)	Control(n = 135)	P-value
Age, y	31.4 ± 3.7	31.0 ± 4.7	NS
Pregestational BMI, kg/m^2	21.1 ± 2.9	21.1 ± 2.8	NS
Increased BMI, kg/m^2	5.2 ± 1.6	5.2 ± 1.5	NS
Gravidity	3 (1-8)	2 (1-6)	<0.001
Parity	0 (0-2)	0 (0-3)	<0.001
IVF, n (%)	28 (20.7%)	10 (7.4%)	<0.001
Diabetes mellitus (including GDM), n (%)	23 (17.0%)	18 (13.3%)	NS
Preeclampsia, n (%)	12 (8.9%)	6 (4.4%)	NS
IUGR, n (%)	12 (8.9%)	2 (1.5%)	<0.05
Oligohydramnios, n (%)	5 (3.7%)	5 (3.7%)	NS
Placenta abruption	7 (5.2%)	1 (0.74%)	NS
Premature delivery < 37 weeks	10 (7.4%)	11 (8.1%)	NS
Still birth, n (%)	4 (3.0%)	0	0.055
Gestational weeks of delivery	37.8 ± 2.3	38.5 ± 2.3	<0.05
Delivery mode			
Vaginal delivery, n	75 (55.6%)	87 (64.4%)	NS
Caesarean section, n	60 (44.4%)	48 (35.6%)	NS
Bleeding at delivery, ml	243.3 ± 109.1	260 ± 125.2	NS
Weight at birth, g	3047.5 ± 661.6	3231.1 ± 531.7	<0.05
Apgar score < 7 at 5 minutes, n	5 (3.7%)	2 (1.5%)	NS
D-Dimer before delivery, mg/L	1.3 ± 0.6	3.1 ± 11.4	NS
Fibrinogen before delivery, g/L	4.9 ± 0.8	4.7 ± 0.7	<0.001
Platelets before delivery, *10^9/L	200.8 ± 66.7	194.1 ± 58.3	NS
D-Dimer after delivery, mg/L	3.8 ± 3.5	4.3 ± 3.9	NS
Fibrinogen after delivery, g/L	4.7 ± 0.8	4.3 ± 0.75	<0.001
Platelets after delivery, *10^9/L	183.4 ± 62.7	171.8 ± 49.7	NS

NS, not significance.

Chicago, IL, USA). A P value of <0.05 was considered statistically significance. Continuous variables were presented as mean ± standard deviation or median (range). Categorical variables were presented as numbers and percentages. Fisher's exact test of chi-squared test for categorical variables and Student's t-test or Wilcoxon-Mann-Whitney test for continuous variables were applied when appropriate. Multivariable logistic regression, presented as adjusted odds ratio (OR) with the 95% of confidence interval (CI), was performed to identify risk factors associated to IUGR.

Results

Description of the Cohort

There were 135 pregnant women with aPL positivity and 44 were diagnosed as APS, and 91 as NCAPS. The mean age of women with aPL positivity was 31.4 ± 3.7 years old and mean pregestational BMI was 21.1 ± 2.9 kg/m^2. 28 (20.7%) patients were assisted by in vitro fertilization: 4 in APS group and 24 in NCAPS group. 87 cases were with single aPL positivity, 42 cases with double aPL positivity and 6 cases with triple aPL positivity. There were 14 patients in APS group and 25 patients in NCAPS group receiving 2 doses of LMWH per day. The median value of aCL IgG/IgM, anti-β2GP1 IgG/IgM and LA was 3 (0.70, 93.30), 18.8 (2.0, 155.80) and 1.06 (0.75. 8.90), respectively.

Pregnancy Outcomes in Women With aPL Positivity and Comparison With Control Population

In aPL carriers group, the mean gestational weeks of delivery was 37.8 ± 2.3 weeks and amount of bleeding at birth was 243.3 ± 109.1 ml. As for adverse pregnancy outcomes, 23 (17.0%) women had developed GDM. 12 (8.9%) developed preeclampsia, 12 (8.9%) newborns were SGA, 5 (3.7%) had oligohydramnios and 10 (7.4%) gave birth before 37 weeks. Five infants (3.7%) had an APGAR score <7 after 5 minutes and 4 (3.0%) were still birth. Therefore, the live birth rate was 97%. Details were shown in Table 1.

135 normal pregnancies were selected as control group. Table 1 shows the comparison of demographic characteristics and pregnancy outcomes in these 2 groups. There was a clear difference in gravidity and parity, where women with aPL positivity had more times of miscarriages and less times of parity (P < 0.001). In aPL group, more were assisted by IVF than control group (20.7% vs. 7.4%, P < 0.001). aPL group had a higher incidence of IUGR (8.9% vs. 1.5%, P < 0.05) and lower birth weight than control group (3047.5 ± 661.6 g vs. 3231.1 ± 531.7, P < 0.05). The incidence rate of still birth in aPL carriers group was higher than in control group (3.0% vs. 0, P = 0.055). Other pregnancy outcomes, such as preeclampsia/eclampsia, placental abruption, oligohydramnios, preterm delivery before 37 gestational weeks and gestational weeks of delivery, delivery mode and bleeding amount at delivery,

Table 2. Clinical Characteristics and Pregnancy Outcomes Between APS and NCAPS Group.

Demographic characteristics	APS (n = 44)	NCAPS (n = 91)	P-value
Age, y	31.3 ± 4.0	31.4 ± 3.6	NS
Pregestational BMI, kg/m^2	20.9 ± 2.7	21.2 ± 3.0	NS
Increased BMI during pregnancy, kg/m^2	5.1 ± 1.8	5.3 ± 1.5	NS
Unexplained pregnancy loss <10 weeks	1 (0-4)	1 (0-4)	NS
≥3 times, n (%)	12 (27.3%)	1 (1.1%)	<0.01
Unexplained fetal death >10 weeks	1 (0-4)	0 (0-3)	<0.01
N (%)	35 (79.5%)	17 (18.7%)	<0.01
Premature births before 34 weeks because of preeclampsia or IUGR, n (%)	3 (6.8%)	1 (1.1%)	NS
Previous thrombosis, n (%)	2 (4.5%)	0	NS
With other immunologic diseases, n (%)	4 (9.1%)	2 (2.2%)	NS
Gestational outcome and obstetrical complications*			
IVF, n (%)	4 (9.1%)	24 (26.4%)	<0.05
Diabetes mellitus (including GDM), n (%)	7 (15.9%)	16 (17.6%)	NS
Preeclampsia, n (%)	3 (6.8%)	9 (9.9%)	NS
IUGR/SGA, n (%)	7 (15.9%)	5 (5.5%)	<0.05
Oligohydramnios, n (%)	4 (9.1%)	1 (1.1%)	NS
Placenta abruption, n (%)	3 (6.8%)	4 (4.4%)	NS
Premature delivery<37 weeks, n (%)	6 (13.6%)	6 (6.6%)	NS
Still birth, n (%)	2 (4.5%)	2 (2.2%)	NS
Gestational weeks of delivery, wk	37.3 ± 3.3	38.0 ± 1.5	NS
Delivery mode			
Vaginal delivery, n (%)	26 (59.1%)	49 (53.8%)	NS
Caesarean section, n (%)	18 (40.9%)	42 (46.2%)	NS
Bleeding at delivery, ml	227.7 ± 114.8	250.9 ± 106.1	NS
Weight at birth, g	2864.1 ± 864.0	3139.2 ± 514.3	<0.05
Apgar score < 7 at 5 minutes, n	1 (2.3%)	2 (2.2%)	NS
D-Dimer before delivery, mg/L	1.2 ± 0.5	1.4 ± 0.6	<0.05
Fibrinogen before delivery, g/L	4.8 ± 0.8	5.0 ± 0.8	NS
Platelets before delivery, *10^9/L	189.0 ± 53.8	206.6 ± 71.7	NS
D-Dimer after delivery, mg/L	3.2 ± 3.4	4.1 ± 3.6	NS
Fibrinogen after delivery, g/L,	4.6 ± 0.8	4.8 ± 0.9	NS
Platelets after delivery, *10^9/L	175.9 ± 49.0	187.0 ± 68.4	NS
During of LDA use, wk	30.0 ± 8.5	27.5 ± 12.2	NS
Total use of LMWH	50.0 ± 19.4	39.3 ± 19.0	<0.01
Use of steroids, n	21 (47.7%)	55 (60.4%)	NS
Use of HCQ, n	3 (6.8%)	31 (34.1%)	<0.01

NS, not significance.

the rate of neonatal asphyxia (APGAR score < 7 at 5 minutes) showed no significance in 2 groups. Fibrinogen before and after delivery in aPL carriers were significantly higher than in control group, while D-Dimer and platelets showed no difference before and after delivery.

Pregnancy Outcomes in Women With APS Compared to NCAPS

The details about clinical characteristics and pregnancy outcomes of these patients are reported in Table 2. In APS group, 4 patients had other immunologic diseases: 2 had Sjogren syndrome, 1 had systemic lupus erythematosus (SLE) and 1 had autoimmune thyroiditis. While in NCAPS group, 2 patients had autoimmune thyroiditis. In APS group, one patient was diagnosed as secondary APS and combined with systemic lupus erythematosus (SLE) and found fetal death at 21th weeks of gestation. Another still birth in APS group was happened at 20th weeks because of placental abruption. In NCAPS group, 2 patients found fetal death at 29th and 34th weeks of gestation, respectively. The live birth rate in APS and NCAPS group was 95.5% and 97.8%, respectively.

The times of pregnancy losses related to APS was significantly lower in NCAPS group than in APS group, including miscarriages beyond 10 weeks and fetal deaths over 10 weeks. In NCAPS group, more patients were assisted by IVF than in APS group (26.4% vs. 9.1%, $P < 0.05$). After treatment, the number of preeclampsia, oligohydramnios, placenta abruption, premature delivery and still birth between APS and NCAPS group showed no significant difference. However, the cases of IUGR in APS group were significantly more than in NCAPS group (15.9% vs. 5.5%, $P < 0.05$). And birth weight were significantly lighter in APS group than in NCAPS group (2864.1 ± 864.0 g vs. 3139.2 ± 514.3 g, $P < 0.05$). There were no maternal thrombotic events observed during pregnancy. The gestational weeks of delivery, delivery mode,

Table 3. Comparison of IUGR in aPL Carriers.

Clinical/ serological features	IUGR (12)	Non-IUGR (123)	P-value
Age, y	31.9 ± 3.5	31.3 ± 3.8	NS
Unexplained pregnancy loss<10 weeks	1 (0-3)	1 (0-4)	NS
Unexplained fetal death >10 weeks	0 (0-1)	0 (0-4)	NS
IVF, n (%)	1 (8.3%)	27 (22.0%)	NS
Preeclampsia, n (%)	0	12 (9.8%)	NS
aCL positivity, n (%)	7 (58.3%)	33 (26.8%)	<0.05
Anti-β2GP1 positivity, n (%)	10 (83.3%)	102 (82.9%)	NS
LA positivity, n (%)	2 (16.7%)	34 (27.6%)	NS
Single aPL positivity, n (%)	6 (50%)	81 (65.9%)	NS
Double aPL positivity, n (%)	6 (50%)	36 (29.3%)	NS
Triple aPL positivity, n (%)	0	6 (4.9%)	NS
During of LDA use, wk	23.3 ± 15.7	28.8 ± 10.6	NS
Total use of LMWH	48.3 ± 25.0	42.2 ± 19.2	NS
Use of steroids, n (%)	7 (58.3%)	69 (56.1%)	NS
Use of HCQ, n (%)	2 (16.7%)	32 (26.0%)	NS

NS, not significance.

Table 4. Multivariate Analysis of Serological Features in IUGR in aPL Carriers.

Laboratory features	P-Value	Adjusted odds ratio*	95% Confidence interval
aPL positivity			
aCL positivity	0.026	4.601	1.205-17.573
Anti-β2GP1 positivity	0.808	1.244	0.214-7.234
LA positivity	0.408	2.119	0.358-12.546
The max value of aPL before or during pregnancy			
aCL IgM/IgG	0.017	1.032	1.006-1.060
Anti-β2GP1 IgM/IgG	0.960	0.999	0.977-1.022
LA	0.746	0.783	0.178-3.441
aPL positivity			
Single	NA	Reference	
Double or triple	0.314	1.870	0.553-6.322

*adjusted for age, IVF, unexplained pregnancy loss<10 weeks, unexplained fetal death >10 weeks and the use of LMWH.

bleeding amount at delivery and number of neonatal APGAR score < 7 at 5 minutes showed no significance. As shown in Table 2, D-Dimer before delivery was significantly lower in APS group than in NCAPS group (1.2 ± 0.5 vs. 1.4 ± 0.6, $P < 0.05$). While D-Dimer after delivery, fibrinogen and platelets before and after delivery showed no significance between 2 groups. In treatment, total use of LMWH in APS group was significantly more than in NCAPS and the number of patients who took HCQ in APS group was significantly lower than in NCAPS. The use of LDA and steroids showed no significance in 2 groups.

Factors Associated With IUGR

The comparison of clinical and laboratory features between patients with and without IUGR is illustrated in Table 3. aCL positivity was significantly more frequent in patients with IUGR (58.3% vs. 26.8%, $P < 0.05$). Other factors, such as age, miscarriage history, if IVF, if preeclampsia, single, double or triple positive aPL profile, and type of treatment showed no significance compared between patients with and without IUGR.

In multivariate logistic analysis, after controlling for age, if IVF, pregnancy losses related to APS and the use of LMWH, aCL positivity was the only variable significantly associated with IUGR, with an adjusted OR of 4.601 (95%CI, 1.205-17.573). The value of aCL IgM/IgG also showed significance associated with IUGR, with an adjusted OR of 1.032 (95%CI, 1.006-1.060). Details are shown in Table 4.

Discussion

As the treatments of recurrent miscarriages and infertility continue to advance, more and more aPL carriers including APS and NCAPS have been diagnosed and treated. Therefore, in our study, more women were assisted by IVF in NCAPS group than in control and APS group, respectively. Though some patients diagnosed as NCAPS, not fulfilling the clinical manifestation of APS, they might be APS actually as doctors and patients

were reluctant to start treatment until 3 times of consecutive early pregnancy loss.

Antiphospholipid antibodies play an important role in placental inflammation and are associated with vascular/thrombotic problems and obstetrical complications.[14] Many studies have identified triple aPL positivity as a major risk factor for both thrombosis and adverse pregnancy outcomes both in APS and NCAPS patients.[13,15] In the multicenter PREGNANTS cohort, anti-β2GP1 was the one associated with the lowest live birth rate and highest incidence of preeclampsia, IUGR, and stillbirth, compared with the presence of aCL or LA alone.[10] Conversely, in the prospective PROMISSE study, LA was the main predictor of adverse pregnancy outcomes in aPL carriers.[12] In our study, we identified aCL as the mainly independent risk factor for IUGR in aPL carriers, compared with anti-β2GP1 and LA. We did not find triple aPL positivity associated with adverse pregnancy outcomes mainly because of the small size of patients with triple aPL positivity (only 6 cases). Furthermore, we found that with the elevated value of aCL IgM/IgG, the incident rate of IUGR increased (OR: 1.032, 95%CI: 1.006-1.060). Among the 135 aPL positive women, 12 (8.9%) were diagnosed IUGR. In the 12 IUGR women, 58.3% were ACL positive, while 26.8% patients were ACL positive in the 123 non-IUGR pregnant women.

In our study, we found that after treatment, pregnancies of women with aPL positivity had generally satisfactory fetal and maternal outcomes. Adverse pregnancy outcomes such as preeclampsia/eclampsia, placental abruption, oligohydramnios and preterm delivery in aPL carriers showed no significant difference compared to normal pregnancies. However, the incidence of IUGR and stillbirth in aPL carriers was still higher than control group, especially IUGR ($P < 0.05$). Also, after treatment, the incidence of IUGR was higher in APS group than in NCAPS group. This suggests that multiple pathological events occur during pregnancy and there may be some other factors not yet identified, such as unconventional aPL, where further research is needed.

The live birth rate in aPL carriers (97%) and APS group (95.5%) in our study was really high compared with other studies, namely, 54.3% in the multicenter PREGNANTS cohort,[10] 77.7% in a collaborative European study (EURO-APS),[5] and 87.9% in a multicenter study in Italy.[6] As we did not observe thrombosis in our study, the APS patients included in the cohort were supposed to be obstetric APS. Mechanisms underlying aPL-mediated damage could differ in obstetric APS and thrombotic APS.[5] Obstetric APS may have generally satisfactory pregnancy outcomes when treated.

With respect to treatment, current opinions of the first-line therapy is LDA plus LMWH.[16] Other additional therapies, such as hydroxychloroquine (HCQ), steroids, intravenous-immunoglobulins (IVIG), plasma exchange, may be applied to pregnant women with high risks.[9] Till date, therapeutic options to NCAPS patients include no therapy, LDA alone, or LDA combined with prophylactic-dose heparin.[17] However, there are no generalized recommendations on how to treat women not fulfilling the APS criteria and the results of different studies are controversial. A 2015 systematic review, including 3 trials of primary prophylaxis to prevent adverse pregnancy outcomes in asymptomatic women with aCL positivity (154 pregnancies in total), did not find a benefit from LDA therapy.[8] In the EUROAPS cohort, 75.82% of the non-criteria APS patients received therapies and when treated both APS and non-criteria APS patients had similar good fetal-maternal outcomes.[18] Generally speaking, the treatment assigned to NCAPS patients was globally less intensive than APS patients. In our study, we could also tell that LMWH was used more in APS group than in NCAPS group. However, we actually found the use of HCQ was more frequently in NCAPS group, which indicated that patients with non-criteria APS might have some atypical immunological problems. As our study pointed out aCL as the unique risk factor of IUGR compared with other aPL, treatment could be given due to this risk stratification.

We also assessed the coagulative state in aPL carriers and had 2 findings consistent with previous views.[19] First, even with anticoagulant therapy, patients with aPL positivity were still in a hypercoagulable state with higher fibrinogen before and after delivery compared with control group. Second, D-Dimer in APS group was lower than NCAPS group due to the more use of LMWH. These suggested that though LMWH and LDA would affect coagulation function, the effect was not beyond a safe range, as postpartum bleeding did not increase.[20]

There were some limitations of this study. First, the relatively small size of the patient cohort. Since APS has a low incidence, a collaborative study including several pregnancy clinics should be considered in the future research. Second, the study only tested limited antibodies. More immunological factors such as complement C3 and C4, antiphosphatidylserine/prothrombin antibodies (aPS/PT), should be added in further study, which might be associated with adverse pregnancy outcomes.[21,22]

Conclusion

Better pregnant outcomes of aPL positive women, include APS and NCAPS, were achieved in our study with treatment based on LDA plus LMWH. The incidence of IUGR was still higher in them, and aCL positivity was the only one risk factor associated with IUGR. The value of aCL IgM/IgG was positively correlated with IUGR.

Authors' Note

Fangfang Xi and Yuliang Cai contributed equally to this study.

Declaration of Conflicting Interests

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