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ORIGINAL ARTICLE

Characteristics of pregnancy complications and treatment in obstetric antiphospholipid syndrome in China

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Abstract

Objectives Antiphospholipid syndrome (APS) is an autoimmune disease characterized by obstetric complications and thrombotic events associated with antiphospholipid antibodies (aPL). We aimed to compare the clinical characteristics and treatment of primary APS (PAPS) and secondary APS (systemic lupus erythematosus-APS, SAPS) patients and investigate risk factors associated with obstetric complications in Shanghai, China.

Methods We retrospectively collected and analyzed the data of obstetric APS (OAPS) patients from 2000 to 2017 in the APS-Shanghai (APS-SH) database.

Results One hundred eighty OAPS patients with a total of 450 pregnancies were included in this study. Two hundred twenty-one (49.11%) pregnancies resulted in miscarriage, and 161 (35.77%) pregnancies resulted in intrauterine death. In our cohort, when women were treated, 57 out of 66 pregnancies resulted in live births (86%). Of the 9 treated patients who failed to have live births, 3 had intrauterine deaths, 3 had fetal growth restriction, 2 had pneumorrhagia of the newborn, and 1 had a miscarriage. OAPS patients were divided into two groups: PAPS and SAPS. More SAPS patients than PAPS patients used glucocorticoids (GCs) and hydroxychloroquine (both $p < 0.001$). However, there was no significant difference in the GC dosage between SAPS and PAPS patients ($p = 0.188$). Lupus anticoagulant (LAC) and IgG aβ2GPI were risk factors for miscarriage (odds ratio (OR) = 2.398, 95% confidence interval (CI) = 1.276–4.505, $p = 0.002$; OR = 2.907, 95% CI = 1.558–5.405, $p = 0.001$, respectively) and intrauterine death (OR = 2.439, 95% CI = 1.299–4.580, $p = 0.006$; OR = 2.060, 95% CI = 1.089–3.897, $p = 0.026$, respectively).

Conclusions The live birth rate of OAPS patients in Shanghai was 86%. Even if OAPS patients were treated, pregnancy complications could occur, and these patients might need further second-line treatment.

Key Points
- *This is the first study to report data on Chinese OAPS patients. The live birth rate was 86%.*
- *Lupus anticoagulant and IgG aβ2GPI were risk factors for miscarriage and intrauterine death in our cohort.*
- *Despite active treatment, 9 patients had obstetric complications. Therefore, further second-line treatment is still needed.*

Keywords Antiphospholipid antibodies · Obstetric antiphospholipid syndrome · Pregnancy · Treatment.

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease that is related to antiphospholipid (aPL) antibodies. These antibodies mainly include antibodies to cardiolipin (ACL), β2-glycoprotein I (aβ2GPI), and lupus anticoagulant (LAC) [1]. In 1983, the connection between obstetric complications and the presence of aPL antibodies was first confirmed by Graham Hughes [2]. He described an increased risk of obstetric complications, such as preeclampsia or eclampsia, preterm birth, and fetal growth restriction [3]. APS is considered to be the cause of 15% of recurrent early miscarriages [4].

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Preconception counseling is necessary to reduce the risk of obstetric complications [5].

In an observational study of 1000 APS patients from 13 European countries, in which patients were followed up for 10 years, 127 (15.5%) women became pregnant (188 pregnancies), and 72.9% of pregnancies resulted in one or more live births [6]. In another European study, which included only OAPS patients, 338 women with 1253 pregnancies were recorded [7]. Of these, 192 (77.7%) had live births, and 55 (22.3%) did not. De Jesús GR et al. reported that the live birth rate was 22.2% before treatment, but after treatment, it increased to 83.8% [8]. However, the live birth rate in Chinese OAPS patients is currently unknown.

The majority of clinical manifestations are similar between primary APS (PAPS) and secondary APS (SAPS), but these two types of APS are still two distinct entities with specific features [9]. Romain Paule et al. reported that 28% of PAPS patients could have been mistakenly classified as SLE. Thus, their treatment might be deleterious [10]. Therefore, it is important to compare the clinical characteristics and treatment of PAPS and SAPS patients.

Furthermore, with respect to treatment, the accepted first-line therapy consists of low-dose aspirin (acetylsalicylic acid, ASA) plus low-molecular-weight heparin (LMWH) [11]. New emerging treatments, such as hydroxychloroquine (HCQ), statins, rituximab, eculizumab, and intravenous immunoglobulin (IVIG), have also been used [12]. It has been advocated that OAPS patients should be treated according to their risks of obstetric complications. LAC and IgG ACL have been reported to be risk factors for adverse pregnancy outcomes [13]. T. Marchetti et al. indicated that IgG aβ2GPI was a risk factor for severe preeclampsia compared with the control group [14]. The risk factors for obstetric complications in Chinese patients were not clear.

Therefore, we conducted this retrospective study to compare the clinical characteristics and treatment of primary and secondary OAPS patients and investigate risk factors associated with obstetric complications using the previously described APS-Shanghai (APS-SH) database [15].

Methods

Patients

This study included 180 women who had been identified as having pregnancy morbidity from the APS-SH database between January 2000 and December 2017. The APS-SH database was established in 2000 by qualified rheumatologists in Shanghai, as previously described [15]. The diagnosis was ultimately confirmed by two rheumatologists (Chengde Yang and Jialin Teng) according to lab findings and clinical manifestations. All patients met the 1999 diagnostic criteria for APS [16]. Patients included before 2006 were checked in accordance with the revised Sydney criteria [17]. PAPS was considered for those who did not fulfill the classification criteria for any other autoimmune diseases. SAPS was considered when the patient met the specific criteria of systemic lupus erythematosus (SLE), classified according to the American College of Rheumatology (ACR) revised criteria [18].

In this study, we included patients with obstetric complications. That is, 210 patients in the APS-SH database who had only thrombosis and male patients were excluded from this study. All OAPS patients were evaluated for infections, such as tuberculosis, syphilis, HCV, HBV, and HIV, before pregnancy to rule out infection-related obstetric complications. OAPS patients in our cohort had cesarean sections because the anticoagulant had to be ceased before delivery. The multidisciplinary treatment (MDT) group consisted of neonatologists, and doctors from the department of obstetrics and gynecology were organized to control high-risk pregnancies.

Data collection

Patients who were serologically positive for IgG and IgM ACL, IgG and IgM aβ2GPI, or LAC were defined as patients with positive aPL antibodies. Patients with IgG and IgM ACL, IgG and IgM aβ2GPI, or LAC positivity were defined as single-antibody positive. Positivity for any two of the aPL antibody categories, namely, IgG and IgM ACL, IgG and IgM aβ2GPI, and LAC, was defined as double-antibody positive, and positivity for IgG and IgM ACL, IgG and IgM aβ2GPI, and LAC was defined as triple-antibody positive. Patients were considered to have catastrophic APS (CAPS) if they presented with an acutely devastating APS featuring multiorgan involvement [19]. Obstetric complications included miscarriage, intrauterine death, preeclampsia or eclampsia, preterm birth, and fetal growth restriction (FGR). Patients with unexplained miscarriage (excluding maternal and paternal factors) at < 10 weeks were categorized as miscarriage, while patients with an unexplained death of a morphologically normal fetus at > 10 weeks were categorized as intrauterine death, excluding fetuses associated with hormonal or anatomical alternations inherited from either parent [20]. Eclampsia or preeclampsia was defined as arterial pressure ≥ 160/110 mmHg and proteinuria ≥ 5 g in a 24-h urine sample. Intrauterine growth restriction was defined as birth weight < the 10th percentile, and preterm birth was defined as delivery at < 34 weeks of gestation. Hypocomplementemia was defined as a low complement 3 (C3) level and/or complement 4 (C4) level.

Thrombosis was confirmed according to the established criteria for each manifestation, using laboratory, imaging/Doppler, or histopathologic studies. All patients in our cohort had regular ultrasound examinations of the fetal heart. The patients were monitored (blood test, urine test, physical examination, and ultrasound) throughout the entire duration of pregnancy. The following clinical and demographic data were

recorded: age, duration, APGAR score, newborn weight, adjusted Global Antiphospholipid Syndrome Score (aGAPSS) [21], and obstetric complications. The following laboratory data were recorded: the erythrocyte sedimentation rate (ESR); IgG and IgM ACL, IgG and IgM aβ2GPI, and LAC; and C3 and C4 levels.

According to the Sydney criteria, ACL antibody of the IgG and IgM isotypes in the serum or plasma present at a medium or high titer (i.e., > 40 GPL or MPL or greater than the 99th percentile) and aβ2GPI antibody of the IgG and IgM isotypes present in the serum or plasma at a titer greater than the 99th percentile. In our study, these antibodies were measured by standardized ELISA on at least two occasions that were at least 12 weeks apart. We only included patients who had medium and high titers of antibody, as required by the Sydney criteria.

The levels of the LAC, IgG and IgM ACL, and IgG and IgM aβ2GPI antibodies in our cohort were all measured since 2000. IgG and IgM ACL and IgG and IgM aβ2GPI antibodies were measured with ELISA kits (Euroimmun, Germany). According to the Sydney criteria, medium/high titers of ACL were over 40 GPL or MPL. Positive aβ2GPI was defined as the 99th percentile of the healthy controls. The LAC levels for all patients were measured according to the criteria from the ISTH Subcommittee [22], using the Automated Coagulation Laboratory (ACL) 300R (Milan, Italy). All patients were screened using the dilute Russell's viper venom time (dRVVT) testing as well as the activated partial thromboplastin time (APTT). If the ratio of the dRVVT screening time/dRVVT confirming time was > 1.20, LAC was regarded as positive.

The study followed the ethical standards for human experimentation established in the Declaration of Helsinki and was approved by the Institutional Research Ethics Committee of Ruijin Hospital, Shanghai, China. All patients provided written informed consent for their inclusion in the study.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (version 23.0; SPSS, IBM, Chicago, IL, USA). The Shapiro-Wilk method was used to test the normality of continuous data. Continuous variables are expressed as the mean ±SD or median (range) per distribution type, and categorical data are expressed as frequencies and percentages. Statistical analysis was performed using Student's *t* test or ANOVA for normal data and the Mann-Whitney *U* test or Kruskal-Wallis H test for nonnormal data. Categorical data were analyzed by $\chi 2$ test or Fisher's exact test. Potential risk factors for miscarriage, intrauterine death, and preeclampsia or eclampsia were identified by univariate logistic regression. A multivariate logistic regression model was used to determine the independent risk factors by means of backward stepwise regression (the entry and removal probability were 0.05 and 0.10, respectively). Age and type of APS (PAPS or SAPS) were considered confounders and were adjusted in the multivariate model. A p value of less than 0.05 was considered statistically significant.

Results

General characteristics

In this study, we included 180 APS patients with obstetric complications. The mean age was 35 ± 9 years. In total, 450 pregnancies were recorded. A total of 221 (49.11%) pregnancies resulted in miscarriage, and 161 (35.77%) patients experienced intrauterine death. In addition, 28 (6.22%) pregnancies were associated with preeclampsia or eclampsia. Eleven (2.44%) pregnancies were associated with preterm labor, and 30 (6.67%) pregnancies were associated with FGR. A total of 66 pregnancies were treated regularly and followed-up in our center. OAPS patients with LAC accounted for 57.77% (104/180). The numbers of patients with positive IgM ACL, IgG ACL, IgM aβ2GPI, and IgG aβ2GPI were 32/180 (17.77%), 111/180 (61.66%), 53/180 (29.44%), and 83/180 (46.11%), respectively. The number of patients with aPL double positivity was 59/180 (32.77%), and the number of patients with aPL triple positivity was 56/180 (31.11%). Sixty-one patients had hypocomplementemia (33.89%), and 49 patients had autoimmune thrombocytopenia (27.22%). In addition, two (1.11%) patients developed CAPS during pregnancy. Sixty-five patients (36.11%) had a history of thrombosis: 24 (36.92%) had arterial thrombosis, and 41 (63.07%) had venous thrombosis (Table 1). Only 3 patients developed incident thrombosis during pregnancy.

Treatment of OAPS patients

Of 66 treated patients, 45 (68.18%) used ASA and LMWH. In addition, 40 (60.60%) patients took HCQ, and 46 (69.69%) used GC. Fourteen (21.21%) patients used IVIG, 1 (1.51%) patient used AZA, and 1 (1.51%) used CsA (Table 2). Furthermore, 38 of the 45 patients who used ASA had a live birth, with a live birth rate of 84.44%. The effectiveness of LMWH, GC, and IVIG was 39/45 (86.66%), 41/46 (89.13%), and 13/14 (92.85%), respectively. With treatment, there were 57 live births (86%) out of 66 pregnancies. Nine patients had obstetric complications: 3 had intrauterine death; 3 had fetal growth restriction; 2 had pneumorrhagia of the newborn; and 1 had a miscarriage (Table 3).

Comparison of PAPS and SAPS

The SAPS patients had a higher ESR than the PAPS patients ($p < 0.001$). More patients used glucocorticoids (GCs) ($p =$

Table 1 Clinical characteristics of OAPS patients

Item	*N* (%)
Number	180
Age (years)	32 (20–71)
Pregnancy	450
Miscarriage, < 10 weeks	221/450 (49.11)
Intrauterine death, > 10 weeks	161/450 (35.77)
Live birth	57/450 (12.66)
FGR	30/450 (6.67)
Preeclampsia or eclampsia	28/450 (6.22)
Preterm, < 34 weeks	11/450 (2.44)
Neonatal death	3/68 (4.41)
Newborn weight (kg)	2.80 ± 0.67
APGAR score	8.75 ± 1.91
CAPS	2/180 (1.11)
Thrombotic history	65/180 (36.11)
LAC positive	104/180 (57.77)
IgM ACL positive	32/180 (17.77)
IgG ACL positive	111/180 (61.66)
IgM aβ2GPI positive	53/180 (29.44)
IgG aβ2GPI positive	83/180 (46.11)
Normal pregnancy	68/450 (15.11)
Hypertension	28/450 (6.22)
Gestational diabetes	3/450 (0.67)
Thrombosis during pregnancy	3/450 (0.67)
aPL double positivity	59/180 (32.77)
aPL triple positivity	56/180 (31.11)
Autoimmune thrombocytopenia	49/180 (27.22)
Hypocomplementemia	61/180 (33.89)

FGR, fetal growth restriction; *CAPS*, catastrophic antiphospholipid syndrome; *kg*, kilogram; *LAC*, lupus anticoagulant; *ACL*, anti-cardiolipin antibody; *aβ2GPI*, anti-β2 glycoprotein I antibody

0.002) and HCQ (both $p < 0.001$) in the SAPS group than in the PAPS group. However, the GC dosages in the two groups were not significantly different ($p = 0.188$). IVIG was applied to 20.83% of PAPS cases and 24.24% of SAPS cases ($p = 0.762$) (Table 4).

Table 2 The treatment of OAPS patients

Treatment	*N* (%)
ASA	45/63 (71.43)
LMWH	45/63 (71.43)
HCQ	40/63 (63.49)
GC	46/63 (73.01)
IVIG	14/63 (22.22)
AZA	1/63 (1.58)
CsA	1/63 (1.58)

ASA, aspirin; *LMWH*, low-molecular-weight heparin; *GC*, glucocorticoid; *HCQ*, hydroxychloroquine; *IVIG*, intravenous immune globulin; *AZA*, azathioprine; *CSA*, cyclosporin

Risk factors for miscarriage, intrauterine death, and preeclampsia or eclampsia

The univariate and multivariate logistic regression analyses of miscarriage are shown in Table 5. In the univariate analysis, aGAPSS, LAC, and IgG aβ2GPI were related to miscarriage ($p = 0.007$, 0.010, and 0.001, respectively). Then, age and type of APS were considered confounders and adjusted in the multivariate analysis. LAC and IgG aβ2GPI were risk factors for miscarriage (odds ratio (OR) = 2.398, 95% confidence interval (CI) = 1.276–4.505, $p = 0.007$; OR = 2.907, 95% CI = 1.558–5.405, $p = 0.001$, respectively) (Table 5). In the univariate analysis, aGAPSS, LAC, and IgG aβ2GPI were related to intrauterine death ($p = 0.027$, 0.007, and 0.034, respectively). In the multivariate analysis, LAC and IgG aβ2GPI were risk factors for intrauterine death (OR = 2.439, 95% CI = 1.299–4.580, $p = 0.006$; OR = 2.060, 95% CI = 1.089–3.897, $p = 0.026$, respectively) (Table 6). The univariate and multivariate analyses showed no significant risk factors for preeclampsia or eclampsia in our cohort (Supplementary Table 1). However, in the multivariate logistic regression analysis of preeclampsia or eclampsia, the OR of LAC was over 1, and the p value was 0.082, which was close to 0.05 (OR = 2.359, 95% CI = 0.896–6.398, $p = 0.082$).

Discussion

This is the first study to report the clinical characteristics of PAPS and SAPS patients and investigate risk factors associated with obstetric complications of OAPS in China. In our study, we found that the live birth rate for OAPS with treatment was 86%, which is consistent with the live birth rates reported in other studies, namely, 72.9% for 13 European countries in 2014, 85% in the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS) in 2018, and 83.8% in the study by De Jesús GR et al. [6–8]. It has also been reported that the frequency of adverse pregnancy outcomes in four subgroups (thrombotic APS, obstetric APS, non-criteria-APS, and aPL carriers) is 24.2%, 18.7%, 9.2%, and 17.9%, respectively [13]. However, the live birth rates of the PAPS and SAPS groups in our cohort were similar ($p = 0.303$). LAC was demonstrated to predict pregnancy complications after 3 months of pregnancy [23]. In other studies, aβ2GPI was reported to be associated with a lower live birth rate and an increase in pregnancy complications [24, 25]. Our study confirmed that LAC and IgG aβ2GPI are risk factors for miscarriage and intrauterine death, an observation that is similar to previously reported results.

Table 3 Characteristics of 9 patients who failed to have live births after treatment of OAPS

Item	PAPS or SAPS	Complications	Treatment	Obstetric outcomes
P1	PAPS	Protein urine	ASA+LMWH+GC+HCQ	Intrauterine death
P2	PAPS	/	LMWH	FGR
P3	PAPS	Eclampsia	ASA+LMWH+GC+IVIG	Pneumorrhagia of the newborn
P4	PAPS	/	ASA+LMWH+HCQ	FGR
P5	PAPS	/	ASA	Miscarriage
P6	PAPS	HBP	ASA+LMWH+GC+HCQ	Intrauterine death
P7	SAPS	/	HCQ+ASA	FGR
P8	SAPS	HBP	ASA+GC	Pneumorrhagia of the newborn
P9	SAPS	Venous thrombosis of lower extremities	LMWH+GC+HCQ	Intrauterine death

P, patient; *PAPS*, primary antiphospholipid syndrome; *SAPS*, secondary antiphospholipid syndrome; *HBP*, high blood pressure; *FGR*, fetal growth restriction; *ASA*, aspirin; *LMWH*, low-molecular-weight heparin; *GC*, glucocorticoid; *HCQ*, hydroxychloroquine; *IVIG*, intravenous immune globulin

The correlation between other aPL antibodies such as anti-phosphatidylserine/prothrombin antibodies (aPS/PT) and morbidity is unclear [26, 27]. Moreover, no correlations were identified between IgG/IgM anti-annexin A5 antibodies, IgG/

Table 4 General characteristics and laboratory features of the primary and secondary OAPS patients

Item	Primary (*n*%)	Secondary (*n*%)	*p* value
N	66	114	/
Duration (years)	5 (0.04–30.00)	5 (0.02–25.00)	0.079
Age (years)	33 (20–60)	32 (22–71)	0.284
miscarriage, < 10 weeks	33 (50.00)	56 (49.12)	0.910
Intrauterine death, > 10 weeks	40 (60.60)	67 (58.77)	0.809
Preeclampsia or eclampsia	13 (19.69)	12 (10.52)	0.086
FGR	9 (13.63)	12 (10.52)	0.531
Preterm	4 (6.06)	5 (4.38)	0.619
aGAPSS	9.39 ± 3.68	8.58 ± 3.85	0.709
ESR (mm/h)	27.21 ± 24.16	49.66 ± 37.52	< 0.001***
LAC positive	42 (63.63)	62 (54.38)	0.226
IgM ACL positive	10 (15.15)	22 (19.29)	0.483
IgG ACL positive	44 (66.66)	67 (58.77)	0.294
IgM aβ2GPI positive	20 (30.30)	33 (28.94)	0.848
IgG aβ2GPI positive	35 (53.03)	48 (42.10)	0.156
Thrombotic history	21 (31.81)	45 (39.47)	0.304
Live birth	24 (36.36)	33 (28.94)	0.303
Treatment of live birth			
ASA	16/24 (66.66)	22/33 (66.66)	1.000
LMWH	16/24 (66.66)	21/33 (63.63)	0.362
GC	8/24 (33.33)	33/33 (100)	< 0.001***
GC dosage (mg)	10.00 ± 4.80	13.89 ± 6.93	0.188
HCQ	8/24 (33.33)	27/33 (81.81)	< 0.001***
IVIG	5/24 (20.83)	8/33 (24.24)	0.762
AZA	0/24 (0)	1/33 (3.03)	1.000
CsA	0/24 (0)	1/33 (3.03)	1.000

FGR, fetal growth restriction; *aGAPSS*, adjusted Global Antiphospholipid Syndrome Score; *ESR*, erythrocyte sedimentation rate; *LAC*, lupus anticoagulant; *ACL*, anti-cardiolipin antibody; *aβ2GPI*, anti-β2 glycoprotein I antibody; *ASA*, aspirin; *LMWH*, low-molecular-weight heparin; *HCQ*, hydroxychloroquine; *GC*, glucocorticoid; *IVIG*, intravenous immune globulin; *AZA*, azathioprine; *CSA*, cyclosporin. *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Table 5 Univariate and multivariate logistic regression for miscarriage

Item	Level	Univariate analysis			Multivariate analysis		
		OR	95% CI	*p* value	OR	95% CI	*p* value
Duration		0.985	0.930–1.044	0.608	NI		
Age		1.017	0.982–1.053	0.347	1.011	0.973–1.050	0.579
Type of APS	Primary	Reference					
	Secondary	1.036	0.565–1.899	0.910	0.826	0.430–1.584	0.564
Thrombotic history	Absent	Reference					
	Present	0.920	0.501–1.691	0.789	NI		
aGAPSS		0.895	0.827–0.970	0.007	0.949	0.862–1.044	0.282
ESR		0.997	0.987–1.006	0.486	NI		
LAC	Negative	Reference					
	Positive	2.212	1.208–4.049	0.010	2.398	1.276–4.505	0.007
IgM ACL	Negative	Reference					
	Positive	0.717	0.332–1.548	0.397	NI		
IgG ACL	Negative	Reference					
	Positive	0.678	0.370–1.241	0.208	NI		
IgM aβ2GPI	Negative	Reference					
	Positive	0.665	0.349–1.268	0.216	NI		
IgG aβ2GPI	Negative	Reference					
	Positive	2.717	1.486–4.975	0.001	2.907	1.558–5.405	0.001

NI, not included

IgM/IgA anti-prothrombin, or IgG aβ2GPI-D1 and obstetric complications [28–30]. These antibodies were not included in our cohort. More studies are needed to discuss the function of these "noncriteria" antibodies.

A recent paper of the EUROAPS reported that miscarriages were the most prevalent clinical manifestation in 386 cases (38.6%). In our cohort, miscarriages were also the most common manifestation, accounting for 221 (49.11%) of cases. In the European study, preeclampsia and FGR occurred in 181 (18.1%) and 161 (16.1%) cases, respectively. However, in our cohort, preeclampsia and FGR occurred in 28 (6.22%) and 30 (6.67%), respectively, and these frequencies were much lower than those in the European study [31]. ASA plus LMWH improved the results of pregnancy and was associated with reduced complications [32]. Therefore, this paper also advocated that clinicians consider a standardized treatment for all OAPS patients. In our cohort, the PAPS patients were treated with ASA and LMWH. However, in severe and complicated cases, such as cases of thrombocytopenia, IVIG and glucocorticoids were also used. For the SAPS patients, HCQ, ASA, and LMWH were used throughout pregnancy. Other medications, such as IVIG, glucocorticoids, azathioprine, and cyclosporin, were used in accordance with the patients' conditions.

When the pregnancy outcomes of patients treated by the addition of HCQ were compared with the outcomes of previous pregnancies under conventional treatment, pregnancy losses decreased from 81 to 19% [33]. HCQ has also been recommended for use before pregnancy to patients who have a history of uncomplicated fetal death but who are refractory to conventional treatment [34]. In our cohort, HCQ was given to a mother who had anti-SSA and anti-SSB antibodies to avoid a conduction block of the newborn. Furthermore, IVIG has been shown to be useful in more complicated and severe situations, such as in patients who are not responsive to conventional treatment [35]. This regimen was the same treatment regimen used in our cohort. In this study, IVIG was applied to 20.83% of PAPS patients and 24.24% of SAPS patients ($p = 0.762$). IVIG, plasmapheresis, or low-dose prednisone (10 mg/day) could be a second-line therapy [36]. SAPS patients usually took low-dose prednisone and HCQ as a background treatment. However, PAPS patients with thrombosis and triple aPL positivity or a history of poor pregnancy outcomes could be considered for these second-line therapies. Obstetric complications still occurred in 9 patients with treatment who failed to have a live birth. For these patients, a more advanced strategy was needed to tackle these problems, such as a combination of several second-line treatments or the development of new treatments.

There are several limitations in this paper. First, the study covered a period of 17 years. Thus, the 1999 diagnostic criteria and 2006 Sydney criteria were used. However, in our cohort, we checked all patients to ensure that they met the Sydney criteria. Second, some patients were lost follow-up. Since this is a retrospective study, some data were missing. In

Table 6 Univariate and multivariate logistic regression for intrauterine death

Item	Level	Univariate analysis			Multivariate analysis		
		OR	95% CI	*p* value	OR	95% CI	*p* value
Duration		1.043	0.977–1.113	0.206	NI		
Age		0.972	0.938–1.007	0.120	0.980	0.945–1.017	0.290
Type of APS	Primary	Reference					
	Secondary	0.944	0.503–1.769	0.856	1.122	0.578–2.178	0.733
Thrombotic history	Absent	Reference					
	Present	0.921	0.491–1.724	0.796	NI		
aGAPSS		1.096	1.010–1.190	0.027	1.044	0.945–1.153	0.397
ESR		1.003	0.993–1.013	0.588	NI		
LAC	Negative	Reference					
	Positive	2.340	1.261–4.343	0.007	2.439	1.299–4.580	0.006
IgM ACL	Negative	Reference					
	Positive	1.378	0.608–3.121	0.442	NI		
IgG ACL	Negative	Reference					
	Positive	1.141	0.614–2.120	0.676	NI		
IgM aβ2GPI	Negative	Reference					
	Positive	1.756	0.877–3.518	0.112	NI		
IgG aβ2GPI	Negative	Reference					
	Positive	1.958	1.052–3.643	0.034	2.060	1.089–3.897	0.026

NI, not included

the statistical analysis, for occasional cases in which data were missing in the continuous dataset, the data were replaced with mean or median interpolation. There was no missing value for categorical data in our database. Third, the sample size was relatively small, and this study lacked the statistical power for a multiple regression analysis. Fourth, histopathological examinations were not performed in the placentae.

Conclusion

In conclusion, the live birth rate of OAPS patients was 86% in our cohort. Even if the OAPS patients were treated, pregnancy complications could still occur, and these patients might require further second-line treatment.

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Compliance with ethical standards

Disclosures None.

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