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Pregnancy outcomes in antiphospholipid antibody positive patients: prospective results from the AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Clinical Database and Repository ('Registry')

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ABSTRACT

Objectives To describe the outcomes of pregnancies in antiphospholipid antibody (aPL)-positive patients since the inception of the AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking Registry.

Methods We identified persistently aPL-positive patients recorded as 'pregnant' during prospective follow-up, and defined *'aPL-related outcome'* as a composite of: (1) Preterm live delivery (PTLD) at or before 37th week due to pre-eclampsia (PEC), eclampsia, small-for-gestational age (SGA) and/or placental insufficiency (PI); or (2) Otherwise unexplained fetal death after the 10th week of gestation. The primary objective was to describe the characteristics of patients with and without aPL-related composite outcomes based on their first observed pregnancies following registry recruitment.

Results Of the 55 first pregnancies observed after registry recruitment among nulliparous and multiparous participants, 15 (27%) resulted in early pregnancy loss <10 weeks gestation. Of the remaining 40 pregnancies: (1) 26 (65%) resulted in term live delivery (TLD), 4 (10%) in PTLD between 34.0 weeks and 36.6 weeks, 5 (12.5%) in PTLD before 34th week, and 5 (12.5%) in fetal death (two associated with genetic anomalies); and (2) The aPL-related composite outcome occurred in 9 (23%). One of 26 (4%) pregnancies with TLD, 3/4 (75%) with PTLD between 34.0 weeks and 36.6 weeks, and 3/5 (60%) with PTLD before 34th week were complicated with PEC, SGA and/or PI. Fifty of 55 (91%) pregnancies were in lupus anticoagulant positive subjects, as well as all pregnancies with aPL-related composite outcome.

Conclusion In our multicentre, international, aPL-positive cohort, of 55 first pregnancies observed prospectively, 15 (27%) were complicated by early pregnancy loss. Of the

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Although pregnancy morbidity is commonly associated with antiphospholipid antibodies (aPL), there are few prospective studies evaluating pregnancy outcomes in persistently aPL-positive patients with or without antiphospholipid syndrome (APS) classification.

WHAT THIS STUDY ADDS

⇒ This study used a large-scale, international aPL registry to prospectively analyse pregnancy outcomes based on patients' aPL-related histories, coexisting systemic lupus erythematosus (SLE), and treatment characteristics.

⇒ Of 55 first pregnancies observed prospectively after registry recruitment, 15 (27%) were complicated by early pregnancy loss; of the remaining 40 pregnancies, composite pregnancy morbidity (preterm live delivery at or before 37th week due to pre-eclampsia, small-for-gestational age, and/or placental insufficiency, or otherwise unexplained fetal death after the 10th week of gestation) was observed in 9 (23%) pregnancies, despite prophylactic treatment.

⇒ The composite aPL-related pregnancy morbidity was observed only in lupus anticoagulant (LA)-positive patients.

⇒ The frequencies of different aPL-related pregnancy morbidities were similar in patients with history of obstetric APS versus thrombotic APS, and with history of APS classification versus no APS classification.

⇒ Although term live deliveries were significantly more common in patients without SLE, fetal death and composite pregnancy morbidity were not different between patients with or without SLE.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE AND/OR POLICY

⇒ Clinicians should be aware that: (1) approximately one- fourth of pregnancies reaching 10 weeks of gestation in persistently aPL-positive patients may result in pregnancy morbidity independent of aPL-related history or treatment strategy; and (2) our findings support previous studies that LA- positivity is the primary predictor of poor pregnancy outcomes in aPL-positive patients.

remaining 40 pregnancies, composite pregnancy morbidity was observed in 9 (23%) pregnancies.

BACKGROUND

Antiphospholipid syndrome (APS) is characterised by thrombosis and/or obstetric complications in association with antiphospholipid antibodies (aPL); namely lupus anticoagulant (LA), anticardiolipin antibodies, and anti-β_2 glycoprotein-I antibodies (aβ_2GPI).[1] APS may exist in its primary form when it occurs in otherwise healthy persons, or may be associated with other autoimmune diseases, particularly SLE.[2]

Adverse pregnancy outcomes (APO) attributed to APS include pregnancy losses before and after 10 weeks of gestation, and complications associated with poor placentation, including intrauterine growth restriction and indicated premature delivery due gestational hypertensive disease or placental insufficiency (PI).[3 4] However, few prospective studies have evaluated pregnancy outcomes in patients with persistent aPL positivity with or without meeting classification criteria for APS.

The Antiphospholipid Syndrome Alliance for Clinical Trials and International Networking (APS ACTION) was created in 2010 specifically to conduct large-scale multicentre clinical studies and trials in persistently aPL-positive patients. The goal of the APS ACTION Clinical Database and Repository ('Registry") is to study the natural course of disease over at least 10 years in persistently aPL-positive patients with or without other systemic autoimmune diseases.[5] In this study, our objective was to describe the outcomes of the new pregnancies of aPL-positive patients since the inception of the registry.

METHODS

The inclusion criteria for the APS ACTION Registry are positive aPL based on the updated Sapporo classification criteria at least twice within 1 year prior to enrolment. Retrospective and cross-sectional aPL-specific data, and blood samples (for aPL positivity confirmation) are collected at registry entry.[1] Patients are followed once a year and/or at the time of new aPL-related thrombosis or pregnancy morbidity. Data are managed using REDCap electronic data capture tool, a secure, web-based system designed to support research studies.[6]

In this study, we identified all patients who were recorded as pregnant during the prospective follow-up. 'Obstetric APS' (OAPS) and 'Thrombotic APS' (TAPS) were defined based on the updated Sapporo classification criteria.[1] Our "nulliparous" definition was based on no history of prior pregnancy. An *'aPL-related composite pregnancy morbidity'* was defined as: (1) Preterm live delivery (PTLD) at or before 37th week due to pre-eclampsia (PEC), eclampsia, small-for-gestational age (SGA) and/or PI; or (2) Otherwise unexplained fetal death after the 10th week. Pregnancy-related data collected during the registry are listed in the online supplemental section.

Our primary objective was to describe the demographic and clinical characteristics of patients with and without composite pregnancy morbidities based on their first observed pregnancies following the registry recruitment (independent of their pregnancy history). Secondly, we described: (1) The outcomes of subsequent pregnancies after the first one observed following the registry recruitment; and (2) All pregnancy outcomes based on APS-related history and treatments.

Data were summarised in a descriptive fashion; mean+SD was used for continuous variables. Selected categorical variables were compared using χ^2 test or Fisher's exact test, where appropriate. The level of statistical significance was set at $p<0.05$.

Patient and public involvement statement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

As of March 2021, 55 patients with 77 pregnancies were included in the analysis. Seventeen of 55 (31%) patients were nulliparous women; and of these 17 first pregnancies, 5 were term live delivery (TLD) (29%), 4 PTLD (24%), 4 fetal death (24%) and 4 early pregnancy loss (24%). Overall, 5 of 17 (29%) first pregnancies in nulliparous women resulted in composite pregnancy morbidity, compared with 4/38 (11%) (p: 0.1) in multiparous women (21 were TLD, 5 PTLD, 1 fetal death, and 11 early pregnancy loss). Of 55 first pregnancies observed after registry recruitment, 9 (16%) fulfilled the criteria of the composite outcome (table 1).

Table 2 demonstrates the clinical and laboratory characteristics of 55 patients with first observed pregnancies after they were recruited in the registry, based on different pregnancy outcomes. Fifteen (27%) pregnancies resulted in early pregnancy loss <10 weeks gestation. Of the remaining 40 pregnancies, 26 (65%) resulted in TLD, 4 (10%) in PTLD between 34.0 weeks and 36.6 weeks, 5 (12.5%) in PTLD before 34th week, and 5 (12.5%) in fetal death (2 fetal deaths associated with congenital anomalies). PEC, SGA and/or PI developed in 1/26 (4%), 3/4 (75%) and 3/5 (60%) of pregnancies with TLD, PTLD between 34.0 weeks and 36.6 weeks, and PTLD before 34 weeks, respectively. Thus, the composite pregnancy morbidity occurred in 9/40

Table 1 Demographics and clinical features of 55 aPL-positive patients with first observed pregnancies after the registry recruitment, by composite pregnancy morbidity (preterm live delivery at or before 37th week due to pre-eclampsia, small-for-gestational age, and/or placental insufficiency, or otherwise unexplained fetal death after the 10th week of gestation)

N (%)	Composite pregnancy morbidity (N: 9)	No composite pregnancy morbidity (N: 46)
Demographics*		
Race		
White (n:33)	4 (12%)	29 (88%)
Latin American (n:9)	0	9 (100%)
Asian (n:8)	3 (38%)	5 (63%)
Black (n:1)	1 (100%)	0
Mean age at registry entry (years, mean±SD): 31.5±5.4	30±5.9	31.9±5.2
Mean maternal age (years, mean±SD): 33.4±5.2	32.2±5.7	33.7±5.1
Systemic autoimmune disease diagnosis		
Primary APS† (n:31)	5 (16%)	26 (84%)
APS† with SLE (n:9)	1 (11%)	8 (89%)
Primary aPL-positivity (no APS) (n:10)	1 (10%)	9 (90%)
aPL-positivity (no APS) with SLE (n:5)	2 (40%)	3 (60%)
aPL/APS† Classification		
Thrombotic and obstetrical APS† (n:14)	1 (7%)	13 (93%)
Thrombotic APS† (n:18)	4 (22%)	14 (78%)
Obstetrical APS† (n:8)	1 (13%)	7 (88%)
aPL without APS† (n:15)	3 (20%)	12 (80%)
Clinical characteristics		
History of arterial thrombosis, venous thrombosis or microthrombosis (n:32)	5 (16%)	27 (84%)
1 Event (n:18)	2 (11%)	16 (89%)
2 Events (n:10)	3 (30%)	7 (70%)
3 Events and more (n:4)	0	4 (100%)
History of pregnancy (n:38)	4 (11%)	34 (89%)
Pregnancy morbidity (n:30)	4 (13%)	26 (87%)
No pregnancy morbidity (n:8)	0	8 (100%)
Non-criteria manifestations		
Thrombocytopenia (n:14)	4 (29%)	10 (71%)
Livedo reticularis (n:6)	1 (17%)	5 (83%)
White matter lesions (n:3)	1 (33%)	2 (67%)
Autoimmune haemolytic anaemia (n:2)	1 (50%)	1 (50%)
Cardiac valve disease (n:3)	1 (33%)	2 (67%)
aPL-nephropathy (n:1)	1 (100%)	0
Laboratory characteristics		
Triple aPL-positive (n:18)	3 (17%)	15 (83%)
LA-positive alone‡ (n:17):	4 (24%)	13 (76%)
Double aPL-positive (n:17)	2 (12%)	15 (88%)
LA+aCL (n:13)	2 (15%)	11 (85%)
aCL+aβ2GPI (n:2)	0	2 (100%)
LA+aβ2GPI (n:2)	0	2 (100%)

*Eighteen of 55 were recruited from North America, 11 South America, 19 Europe and 7 Asia.
†APS based on the updated Sapporo classification criteria[1]
‡aCL and $a\beta_2$GPI not tested in two pregnancies; $a\beta_2$GPI not tested in three pregnancies.
aCL, anticardiolipin antibody; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; $a\beta_2$GPI, anti-β_2 glycoprotein-I antibody; LA, lupus anticoagulant.;

(23%) pregnancies progressing beyond 10 weeks. Forty-eight of 55 (87%) pregnancies were treated with low-dose aspirin (LDA) (81–160 mg) and/or low-molecular-weight heparin (LMWH); 50 of 55 (91%) pregnancies were recorded in LA-positive subjects, as well as all pregnancies with composite pregnancy morbidity.

When we analysed the outcomes of the subsequent 22 pregnancies, 5 (23%) pregnancies resulted in early

Table 2 Clinical and laboratory characteristics of patients with 55 first pregnancies observed following registry recruitment, by pregnancy outcomes

	TLD	PTLD*	PTLD†	FD‡	FD§	EPL
	≥37.0 weeks	34.0–36.6 weeks	<34.0 weeks	>20.0 weeks	10.0–19.6 weeks	<10.0 weeks
	n: 26	n:4	n:5	n:2	n:3	n:15
N=55 pregnancies	**47%**	**7%**	**9%**	**4%**	**5%**	**27%**
Additional pregnancy morbidity						
SGA and PEC	NR	1**	NR	NR	NR	NR
SGA	1	NR	1‡‡	NR	NR	NR
PEC	NR	2††	2§§	NR	NR	NR
PI	NR	NR	NR	NR	NR	NR
History of SLE¶¶	6 (23%)	2 (50%)	1 (20%)	1 (50%)	1 (33%)	3 (20%)
History of thrombosis	13 (50%)	2 (50%)	5 (100%)	1 (50%)	1 (33%)	10 (67%)
Arterial	5 (19%)	–	1 (20%)	–	–	1 (7%)
Venous	10 (38%)	2	4 (80%)	1 (50%)	1 (33%)	10 (67%)
Arterial and venous	2 (8%)	–	–	–	–	1 (7%)
History of pregnancy	21 (81%)	1 (25%)	4 (80%)	–	1 (33%)	11 (73%)
History of pregnancy morbidity	15 (58%)	1 (25%)	4 (80%)	–	1 (33%)	9 (60%)
≥1 fetal death ≥10 weeks	10 (38%)	–	2 (40%)	–	–	6 (40%)
≥1 preterm delivery ≤34 weeks	4 (15%)	–	–	–	–	4 (27%)
≥1 (pre)-embryonic loss <10 weeks	7 (27%)	–	2 (40%)	–	–	5 (33%)
Laboratory category						
LA (+) only¶	9 (35%)	2 (50%)	2 (40%)	1 (50%)	1 (33%)	2 (13%)
Double aPL (+)	6 (23%)	–	1 (20%)	1 (50%)	2 (67%)	7 (47%)
Triple aPL (+)	9 (35%)	2 (50%)	2 (40%)	–	–	5 (33%)
Treatment during pregnancy						
No LDA/LMWH	–	–	–	–	1 (33%)	6 (40%)
LDA alone	2 (8%)	–	–	–	1 (33%)	2 (13%)
LMWH alone	5 (19%)	–	–	–	1 (33%)	–
LDA+LMWH	19 (73%)	4 (100%)	5 (100%)	2 (100%)	–	7 (47%)
Hydroxychloroquine	17 (65%)	2 (50%)	2 (40%)	–	1 (33%)	5 (33%)
Hypertension	1 (4%)	–	–	–	–	1 (7%)
Obesity	4 (15%)	–	3 (60%)	–	–	3 (20%)

*One spontaneous PTLD, GA 34 weeks.
†Two spontaneous PTLD, GA 32 weeks and 33 weeks respectively.
‡Two fetal deaths associated with anomalies: 1 triple X syndrome (47 XXX) at 21 weeks, 1 cystic fibrosis at 20 weeks.
§1/3 morphologically normal, 2/3 fetal loss of unknown fetal status.
¶aCL and aβ_2GPI not tested in two pregnancies; aβ_2GPI not tested in three pregnancies.
**GA at 36 weeks.
††GA 35 weeks and 36.4 weeks.
‡‡GA 24 weeks.
§§GA 33.6 weeks and 26 weeks.
¶¶pregnancy outcomes in 14 patients with SLE were 6 for TLD (1 SGA), 3 PTLD ((2 PEC at GA 36.4 weeks and 26 weeks), 2 FD (GA 20 weeks and 12 weeks), and 3 EPL.
aCL, anticardiolipin antibody; aβ_2GPI, anti-β2 glycoprotein-I; EPL, early pregnancy loss; FD, fetal death; GA, gestational age; LA, lupus anticoagulant; LDA, low-dose aspirin; LMWH, low-molecular-weight heparin; NR, not reported; PEC, pre-eclampsia; PI, placental insufficiency; PTLD, preterm live delivery; SGA, small-for-gestational age; TLD, term live delivery.

pregnancy loss <10 weeks gestation. Of the remaining 17 pregnancies, 10 (59%) resulted in TLD, 2 (12%) in PTLD between 34.0 weeks and 36.6 weeks, 1 (6%) in PTLD before 34th week, and 4 (24%) in fetal death. PEC, SGA and/or PI developed in 2/10 (20%) and 1/2 (50%) of patients with TLD and PTLD between 34.0 weeks and 36.6 weeks, respectively. Thus, the composite pregnancy morbidity occurred in 5/17 (29%) pregnancies progressing beyond 10 weeks. Nineteen of 22 (86%) pregnancies were treated with LDA and/or LMWH; 20

of 22 (91%) pregnancies were recorded in LA-positive subjects, as well as all pregnancies with composite pregnancy morbidity (online supplemental table 1).

Table 3 describes medications and outcomes of 77 pregnancies during follow-up, stratified according to a prior APS history. Sixty-seven of 77 pregnancies (87%) were treated with LDA (81-100 mg) and/or LMWH, (84% and 88% of pregnancies with and without APS classification, respectively). Seven patients were treated with LDA only, 6 with LMWH only, and 54 with LDA and LMWH. Of 14 pregnancies with composite pregnancy morbidity, 9 (64%) received LDA and LMWH, whereas 2 (14%) were treated with LDA only, 1 (7%) was treated with LMWH only, and 2 (14%) did not receive any treatment (online supplemental table 3). In a subgroup analysis comparing nulliparous and multiparous women, of 17 nulliparous women with first pregnancies, 12% received no treatment, 12% LDA only, 12% LMWH only and 65% both. Similarly, of 38 multiparous women, 13% received no treatment, 8% LDA only, 11% LMWH only, 68% both. Additionally, in a different subgroup analysis of pregnancies progressing beyond 10 weeks (56/77), 3/56 (5%) did not receive any treatment. Despite treatment, 12 (23%) of 53 pregnancies (9 with and 3 without APS classification) resulted in composite pregnancy morbidity.

Table 4 demonstrates the comparison of patients with different APS-related histories based on different 77 pregnancy outcomes. TLD, PTLD, fetal death, and early pregnancy loss rates were not different between patients with/without TAPS, with/without OAPS, with/without APS, with OAPS vs with TAPS, and with history of positive LA vs negative. Furthermore, the analysis of the composite pregnancy morbidity showed no significant differences between the groups (table 4).

Table 5 shows pregnancy outcomes based on different aPL profiles. Seventy of 77 (91%) pregnancies were in LA-positive patients. PTLD and fetal death were seen only in LA-positive patients; and among patients with aPL-related composite pregnancy morbidity, 100% were LA-positive (as part of single, double or triple aPL-positivity). Obstetric outcomes were similar between LA-positive patients with single, double or triple aPL positivity.

In a subgroup analysis of 23 pregnancies in 14 patients with SLE, pregnancy outcomes were 6 TLD (26%) (with 1 SGA), 6 PTLD (26%) (2 PEC and 1 PEC + neonatal death), 5 fetal death (22%), and 6 early pregnancy loss (26%). The composite pregnancy morbidity occurred in 7/17 (41%) pregnancies progressing beyond 10 weeks. Seventeen of 23 (74%) were treated with LDA and LMWH (2/17 with prophylactic dose LMWH and 15/17 with therapeutic dose) (online supplemental table 2). Of 14 pregnancies progressing beyond 10 weeks and composite pregnancy outcome, 7 were present in patients with SLE (3 during the first observed pregnancy after the registry recruitment and 4 during the subsequent pregnancy).

In a different subgroup analysis comparing pregnancy outcomes based on pregnancy histories prior to APS ACTION Registry recruitment, there were no significant differences between patients with first pregnancies ever versus those with previous pregnancy histories, except PTLD, which was significantly more common in patients with first pregnancies when compared to those with any previous pregnancy history (29% vs 9%) (online supplemental table 4).

DISCUSSION

Our prospective follow-up of international cohort of aPL-positive pregnant patients with or without other systemic autoimmune diseases identified 55 first pregnancies observed after APS ACTION Registry recruitment. Of these, 15 (27%) ended in early pregnancy loss. Of the remaining 40 pregnancies, aPL-related composite pregnancy morbidity was observed in 9 (23%) pregnancies, including six PTLD and three fetal death. Pregnancy outcomes may differ in APS patients with history of thrombosis or pregnancy morbidity. A retrospective analysis of 73 women with 89 pregnancies showed that PTLD (not attributable to PEC and/or PI) and SGA rates are significantly higher in patients with TAPS than those with pure OAPS.[7] Another retrospective study of 69 women with 81 pregnancies showed that, despite LDA and unfractionated heparin, a history of any pregnancy morbidity, but not of thrombosis, was a predictor of future pregnancy complications.[8] However, the Vienna LA and Thrombosis Study, including 23 aPL-positive women with 40 pregnancies, showed that a history of pregnancy complications or thrombosis, or prepregnancy aPL levels, was not associated with APOs.[9] In our study, aPL-related pregnancy events were not statistically different in patients with OAPS versus TAPS. Most interestingly, there was no difference in pregnancy outcomes when we compared patients with and without APS clinical classification criteria.

The positive LA test is the primary predictor of poor pregnancy outcomes in patients with or without SLE.[10] More than one positive aPL test, especially the triple aPL-positivity, also contributes to the risk of pregnancy morbidity.[11–13] Based on our univariate analysis, aPL-related obstetric outcomes were similar between LA-positive patients with triple, double, or single aPL positivity. However, our composite aPL-related pregnancy morbidity was observed only in LA-positive patients (100%).

Patients with aPL and/or SLE have a higher frequency of pregnancy-related complications, including fetal death and PEC.[14–16] A previous APS ACTION Registry analysis demonstrated that pregnancy morbidity in patients with aPL and concomitant SLE, compared with those without SLE, had a similar frequency of pregnancy morbidity.[17] In our current analysis, term live deliveries were significantly more frequent in patients without SLE; however, fetal death and composite pregnancy morbidity were not statistically different between two groups.

Table 3 Medications and outcomes of patients during 77 pregnancies, stratified based on APS history (outcomes were TLD with no pregnancy morbidity unless indicated otherwise)

	History of OAPS (N:9)		History of TAPS (N:25)		History of OAPS+TAPS (N:24)		No TAPS/OAPS (N:19)	
Treatment	**# of patients**	**Pregnancy morbidity**	**# of patients**	**Pregnancy morbidity**	**# of patients**	**Pregnancy morbidity**	**# of patients**	**Pregnancy morbidity**
LDA	2	FD:1 EPL:1	1	–	–	–	4	PTLD:1 FD:1 EPL:1
Prophylactic dose LMWH	–	–	–	–	1	–	1	–
Therapeutic dose LMWH	–	–	2	FD:1	1	–	1	–
LDA+prophylactic dose LMWH	4	PTLD+SGA:1 EPL:1	2	–	3	TLD+PEC:1 EPL:1	5	TLD+SGA:1
LDA+therapeutic dose LWMH	3	–	16	PTLD:1 PTLD+SGA:1 PTLD+PEC:2 EPL:5 FD:2*	16	TLD+SGA+PEC:1 PTLD:2 PTLD+PEC:1 EPL:4 FD:1	4	PTLD:1 PTLD+PEC:2 FD:1*
LDA+prophylactic dose UFH	–	–	–	–	–	–	1	EPL:1
No treatment	–	–	4	EPL:3	3	FD:1 EPL:2	3	FD:1 EPL:1

In 22/67 pregnancies, LDA and/or LMWH started preconceptionally, in 45/67 pregnancies LDA and/or LMWH started after the conception (mean and median gestational weeks of treatment initiation are 4.6 weeks and 5 weeks, respectively).
*Fetal death associated with anomalies (triple X syndrome and cystic fibrosis, respectively).
APS, antiphospholipid syndrome; EPL, early pregnancy loss; FD, fetal death; LDA, low-dose aspirin; LMWH, low-molecular-weight heparin; OAPS, obstetric APS; PEC, pre-eclampsia; PTLD, preterm live delivery; SGA, small-for-gestational age; TAPS, thrombotic APS; TLD, term live delivery; UFH, unfractionated heparin.

Table 4 Comparative outcomes of 77 pregnancies, stratified based on antiphospholipid antibody related history

	History of OAPS with/without TAPS			History of TAPS with/without OAPS			History of OAPS and TAPS			History of OAPS versus TAPS (excluding those with both)			History of APS		
	Yes (n=33)	No (n=44)	P value	Yes (n=49)	No (n=28)	P value	Yes (n=24)	No (n=53)	P value	OAPS only (n=9)	TAPS only (n=25)	P value	Yes (n=58)	No (n=19)	P value
TLD (n=36)	17 (52%)	19 (43%)	0.4	22 (45%)	14 (50%)	0.8	12 (50%)	24 (45%)	1.0	5 (56%)	10 (40%)	0.4	27 (47%)	9 (47%)	1.0
PTLD (n=12)	4 (12%)	8 (18%)	0.5	7 (14%)	5 (18%)	0.7	3 (13%)	9 (17%)	0.4	1 (11%)	4 (16%)	1.0	8 (14%)	4 (21%)	0.4
FD* (n=9)	3 (9%)	6 (14%)	0.7	5 (10%)	4 (14%)	0.7	2 (8%)	7 (13%)	0.6	1 (11%)	3 (12%)	1.0	6 (10%)	3 (16%)	0.6
EPL (n=20)	9 (27%)	11 (25%)	1.0	15 (31%)	5 (18%)	0.2	7 (29%)	13 (25%)	0.3	2 (22%)	8 (32%)	0.6	17 (29%)	3 (16%)	0.3
Composite pregnancy morbidity (n=14)	5 (15%)	9 (20%)	0.7	8 (16%)	6 (21%)	0.7	3 (13%)	11 (21%)	0.5	2 (22%)	5 (20%)	1.0	10 (17%)	4 (21%)	0.7

*two fetal deaths associated with anomalies: 1 triple X syndrome (47 XXX) at 21 weeks, 1 cystic fibrosis at 20 weeks.
APS, antiphospholipid syndrome; APS, antiphospholipid syndrome; EPL, early pregnancy loss; FD, fetal death; LDA, low-dose aspirin; LMWH, low-molecular-weight heparin; OAPS, obstetric APS; PTLD, preterm live delivery; TAPS, thrombotic APS; TLD, term live delivery.

Table 5 Outcomes of patients during 77 pregnancies, stratified based on antiphospholipid antibody profile

	LA (+) only* (n=27)	LA (+) with aCL or aβ$_2$GPI (+) (n=21)	aCL and/or aβ$_2$GPI (+) (n=7)	Triple aPL (+) (n=22)
TLD (N: 36)	11 (41%)	9 (43%)	4 (57%)	12 (55%)
PTLD (n=12)	6 (22%)	2 (10%)	–	4 (18%)
FD† (n=9)	4 (15%)	3 (14%)	1 (14%)	1 (5%)
EPL (n=20)	6 (22%)	7 (33%)	2 (29%)	5 (23%)
Composite pregnancy morbidity (n=14)	7 (26%)	3 (14%)	–	4 (18%)

*aCL and aB2GPI not tested in five pregnancies, aB2GPI not tested in four additional pregnancies.
†Two fetal deaths associated with anomalies: 1 triple X syndrome (47 XXX) at 21 weeks, 1 cystic fibrosis at 20 weeks.
aCL, anticardiolipin antibody; aPL, antiphospholipid antibodies; aβ$_2$GPI, anti-β2 glycoprotein-I antibody; EPL, early pregnancy loss; FD, fetal death; LA, lupus anticoagulant; PTLD, preterm live delivery; TLD, term live delivery.

Treatment with LDA and heparin combination improves the obstetrical outcomes in APS, and 70%–90% of so-treated pregnancies are reported to result in live deliveries.[18 19] A meta-analysis of five randomised controlled trials suggested the superiority of heparin and LDA combination over LDA alone in terms of higher live delivery rates in patients with OAPS diagnosed primarily because of recurrent early pregnancy loss.[20] One randomised controlled trial by Alalaf *et al* reported that the live delivery rates (TLD or PTLD) in APS pregnancies treated with LDA alone and LMWH alone were 72% and 86%, respectively, both rates higher than in our study (43% and 83%, respectively).[21] Scientifically credible proof from properly designed, prospective trials that treatment (LDA and/or heparin) significantly improves pregnancy outcomes, including rates of fetal death, PEC or PI, in patients with LA is lacking.[22] Though the great majority of our patients received LDA and/or LMWH treatment, of the 40 pregnancies progressing beyond 10 weeks, 65% resulted in TLD and 23% developed the composite pregnancy morbidity (PEC, SGA and/or PI, or otherwise unexplained fetal death). Based on a subgroup analysis of 14 patients with SLE with 11 pregnancies progressing beyond 10 weeks, 55% resulted in TLD, and 36% developed composite pregnancy morbidity (compared with 29 non-SLE pregnancies progressing beyond 10 weeks with 69% TLD and 21% composite pregnancy morbidity). Our sample size and study design did not allow us to perform a multivariate analysis adjusting for potential confounders such as lupus or medications.

A large multicentre study, PROMISSE (Predictors of pRegnancy Outcome: bioMarkerIn APS and SLE), was designed to prospectively assess the frequency of APO in women with SLE. APOs included one or more of the following: (1) Unexplained fetal death after 12 weeks' gestation; (2) Neonatal death prior to hospital discharge due to complications of prematurity and/or PI; (3) Preterm delivery or termination of pregnancy <36 weeks due to gestational hypertension, PEC or PI; (4) SGA neonate, defined as birth weight <5th percentile, absent anatomical or chromosomal abnormalities. In our study, when we used the PROMISSE APO definition in 55 first pregnancies observed after registry recruitment, APO was 6/55 (11%), compared with 9/55 (16%) (our composite outcome). Our findings were similar with the PROMISSE Study, and the reason for the numerical difference was: (1) PROMISSE patients were enrolled at or beyond 12 weeks, thus, fetal death between 10–12 weeks was not studied; (2) Definition of preterm delivery was earlier than 36 weeks (vs 37 weeks); and (3) The definition of SGA was <5th percentile (vs 10th percentile).

We are uncertain as to whether or not the early pregnancy loss rate of 27% in our patients is higher than in the general population. First, we speculate that the patients in our registry were more observant than the general population regarding the detection of pregnancy, for example, were more likely to be using home pregnancy tests for the early detection of pregnancy (in the general population, the detection of early pregnancy using sensitive urine pregnancy tests shows that over 30% of pregnancies are lost after implantation).[23] Second, though the mean maternal age of our patients was 33 years, 36% of our patients were older than age 35 years (the rate of early pregnancy loss increases sharply from 20% at age 35 years to 40% at age 40 years, and 80% at age 45 years).[24]

We recognise that there is a correlation between adverse outcomes across pregnancies. The multiparous patients represented in our study may have had less morbid prior pregnancy outcomes, thus may have been more likely to choose to undertake another pregnancy, and thus may have more likely had better pregnancy outcomes. The difference in the composite outcome between the nulliparous patients (29%) and multiparous patients (11%) is suggestive of this bias, though the difference was not significant. This important issue notwithstanding, we limited our primary analysis to all first pregnancies observed after the registry recruitment (independent of pregnancy history prior to registry entry) to reduce the

information bias, that is, no systematic data collection prior to registry entry. We also believe that this approach can partially reduce the selection bias, that is, eliminating autocorrelation from subsequent pregnancies. For the sake of completeness and for interested readers, outcomes of subsequent pregnancies were included in the secondary analysis.

Our study has several limitations including relatively small number of pregnancies and the lack of a control group. Furthermore, the registry has a heterogeneous group of aPL-positive patients representing a real-world experience; however, given that multiple factors contribute to obstetric outcomes, a future multivariate analysis with higher number of pregnancies may provide additional information. Our composite pregnancy outcome measure is different than the pregnancy morbidity definitions included in the Updated Sapporo Classification Criteria, which was intentional to capture all the morbidities that patients may experience in the real world. Despite these limitations, our descriptive prospective cohort study is important comparing pregnancy outcomes in aPL-positive patients based on their APS history. Moreover, inclusion of patients from multiple international centres enhances our registry and minimises the bias that may be observed more frequently in the single-centre studies.[25]

In conclusion, based on the prospective follow-up of our international cohort of aPL-positive pregnant patients with or without systemic autoimmune diseases, excluding patients with early pregnancy losses, close to a fourth of the patients develop pregnancy morbidity (PTLD with PEC, SGA and/or PI, and otherwise unexplained fetal death) despite prophylactic treatment.

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Pregnancy Outcomes of Antiphospholipid Antibody Positive Patients: Prospective Results from AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) Clinical Database and Repository ("Registry")

SUPPLEMENT

Index:

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1.Methods

Data Collection Points:

During the baseline visit, only historical pregnancy outcomes are collected (history of pregnancy ever, number of pregnancies, number of live deliveries, history of any pregnancy morbidity, unexplained death at or beyond 10th week, number of unexplained deaths at or beyond 10th week, premature delivery before 34th week due to eclampsia, preeclampsia or placental insufficiency, any unexplained spontaneous abortions before 10th week , three consecutive unexplained spontaneous abortions before 10th week).(Of note, we do not collect data on historical pregnancy-related medications.

For the new pregnancies occurring during the follow-up, we collect: the gestational week and type of delivery; pregnancy outcomes (liveborn/stillborn at or beyond 20 weeks, fetal death [FD] at or beyond 20 weeks, FD between 10.0 - 19.6 weeks, early pregnancy loss [EPL] before 10 weeks, term live delivery [TLD], and preterm live delivery [PTLD]); antepartum complications (PEC, eclampsia, suspected fetal growth restriction, placental insufficiency [PI], chronic and gestational hypertension, chronic renal disease, and premature rupture of the membranes), neonatal outcomes (early neonatal death, hypoxic ischemic encephalopathy, small for gestational age [SGA], neonatal intensive care unit admission, and fetal anomalies). During the follow-up visit, for any new pregnancy, we collect all the pregnancy-related medications including dose and frequency. These medications include prophylactic dose unfractionated heparin, anticoagulant dose unfractionated heparin, prophylactic dose low molecular weight heparin, anticoagulant dose low molecular weight heparin, low dose aspirin, hydroxychloroquine, prednisone, antihypertensive agent, prenatal vitamins, and progesterone. Details on medication start date (preconceptionally or gestational week of start date) are also collected.

2.Results

Erton ZB, *et al. Lupus Sci Med* 2022; 9:e000633. doi: 10.1136/lupus-2021-000633

Supplement Table 1: Clinical and Laboratory Characteristics of 22 Subsequent Pregnancies Occurring after First Pregnancies Observed

Following APS ACTION Registry Recruitment, by Pregnancy Outcomes

N= 22 pregnancies	**TLD ≥ 37.0 w n: 10 (45%)**	**PTLD* 34.0 – 36.6w n:2 (9%)**	**PTLD** < 34.0 w n:1 (5%)**	**FD*** >20.0w n:3 (14%)**	**FD**** 10.0-19.6w n:1 (5%)**	**EPL <10.0w n:5 (23%)**
Additional Pregnancy Morbidity						
• SGA and PEC	1	NR	NR	NR	NR	NR
• SGA	NR	NR	NR	NR	NR	NR
• PEC	1	1[a]	NR	NR	NR	NR
History of Systemic Lupus Erythematosus	-	2 (100%)	1 (100%)	2 (67%)	1 (100%)	3 (60%)
History of Thrombosis	9 (90%)	-	-	2 (67%)	1 (100%)	5 (100%)
• Arterial	2 (20%)	-	-	1 (33%)	-	2 (40%)
• Venous	8 (80%)	-	-	2(67%)	1 (100%)	4 (80%)
• Arterial and venous	1 (10%)	-	-	1 (33%)	-	1 (20%)
History of Pregnancy	7 (70%)	-	-	3(100%)	1 (100%)	4 (80%)
History of Pregnancy Morbidity	6 (60%)	-	-	3(100%)	1 (100%)	4 (80%)
• ≥1 Fetal death ≥ 10w	5 (50%)	-	-	2 (67%)	1 (100%)	2 (40%)
• ≥1 Preterm delivery ≤ 34w	2 (20%)	-	-	-	1 (100%)	-
• ≥1 (Pre)-embryonic loss < 10w	4 (40%)	-	-	2 (67%)	1 (100%)	3 (60%)
Laboratory Category						
• LA (+) Only	2 (20%)	1 (50%)	1 (100%)	2 (67%)	-	4 (80%)
• Double aPL (+)	4 (40%)	1 (50%)	-	1 (33%)	-	-
• Triple aPL (+)	3 (30%)	-	-	-	1 (100%)	-

Treatment During Pregnancy						
• No LDA / LMWH	2 (20%)	-	-	-	1 (100%)	-
• LDA alone	-	1 (50%)	-	1 (33%)	-	-
• LMWH alone	-	-	-	-	-	-
• LDA + LMWH	8 (80%)	1 (50%)	1 (100%)	2 (67%)	-	5 (100%)
• Hydroxychloroquine	4 (40%)	-	1 (100%)	2 (67%)	1 (100%)	3 (60%)
Hypertension	-	-	-	-	1 (100%)	-
Obesity	1 (10%)	-	-	-	1 (100%)	-

TLD: term live delivery; **PTLD**: preterm live delivery; **FD**: fetal death; **EPL:** early pregnancy loss; **SGA**: small-for-gestational age; **PEC**: preeclampsia; **PI**: placental insufficiency; **LDA:** low-dose aspirin; **LMWH**: low-molecular-weight-heparin; **LA**: lupus anticoagulant; **NR:** not reported. [a]: gestational age (GA) at 34 weeks. *: one spontaneous PTLD, GA 36 w. **: one spontaneous PTLD, GA 27 w.***: all fetal deaths are morphologically normal. ****: fetal loss of unknown fetal status. *****: aCL and aβ2GPI not tested in 3 pregnancies, aCL tested but aβ2GPI not tested in 1.

Supplement Table 2: Pregnancy Outcomes Based on History of Systemic Lupus Erythematosus (SLE)

	N=77 All Pregnancies			N= 55 1st Pregnancies after Recruitment		
	SLE-Yes (N=23)	**SLE-No (N=54)**	**P**	**SLE-Yes (N=14)**	**SLE-No (N=41)**	**P**
TLD	6 (26%)	30 (56%)	<0.0001	6 (43%)	20 (49%)	0.7
PTLD	6 (26%)	6 (11%)	0.1	3 (21%)	6 (15%)	0.6
FD *	5 (22%)	4 (7%)	0.1	2 (14%)	3 (7%)	0.5
EPL	6 (26%)	14 (26%)	1.0	3 (21%)	12 (29%)	0.7
Composite Pregnancy Morbidity	7 (30%)	7 (13%)	0.1	3 (21%)	6 (15%)	0.6

TLD: term live delivery; **PTLD**: preterm live delivery; **FD**: fetal death; **EPL:** early pregnancy loss; **SLE:** systemic lupus erythematosus. *: two fetal deaths associated with anomalies: 1 triple X syndrome (47 XXX) at 21 weeks, 1 cystic fibrosis at 20 weeks.

Supplement Table 3: Clinical and Laboratory Characteristics of Patients with Composite Pregnancy Outcome

Patients	History of Pregnancy	APS History	SLE	aPL Profile	Treatment	Pregnancy Outcome*
1	+	aPL Only	+	Double aPL LA (+) aβ_2GPI IgM 20-40U	LDA+LMWH (T)	PTLD+ PEC-34 W
2	+	TAPS	-	Triple aPL (+) LA (+) aCL IgG 40-79U aβ_2GPI IgG> 80U	LDA+LMWH (T)	PTLD+SGA-24 W
3	-	TAPS	-	Triple aPL LA (+) aCL IgG 40-79U aβ_2GPI IgG>80U	LDA+LMWH (T)	PTLD+PEC-33.6 W
4	-	TAPS	-	Double aPL LA (+) aCL IgG> 80U	LMWH ONLY(T)	FD-14 W
5	+	TAPS	-	Triple aPL LA(+) aCL IgG 40-79U aβ_2GPI IgG 20-40U	LDA+LMWH (T)	PTLD+PEC-35 W
6	-	TAPS + OAPS(b&c)	+	Single aPL LA (+)	LDA+LMWH (T)	FD- 24 W

7	+	aPL Only	+	Single aPL LA (+)	LDA+LMWH (T)	PTLD+PEC-36.4 W
8	-	TAPS+ OAPS (a&b)	+	Triple aPL LA(+) aCL IgG 40-79U aβ_2GPI IgG 20-40U	NO Treatment	FD-15 W
9	-	aPL Only	-	Single aPL LA (+) aβ_2GPI not tested	LDA+LMWH (P)	PTLD+ SGA+PEC-36 W
10	-	TAPS+ OAPS (a)	+	Double aPL LA (+) aβ_2GPI IgM 20-40U	LDA+LMWH (T)	PTLD+PEC-26 W
11	-	OAPS (a)	-	Double aPL LA (+) aCL IgG 20-40U aβ_2GPI IgG 40-80U	LDA ONLY	FD- 26 W
12	-	TAPS	+	Single aPL LA (+) aCL and aβ_2GPI not tested	LDA+LMWH (T)	FD-23 W
13	+	aPL Only	-	Triple aPL LA (+) aCL IgG 40-79U aβ_2GPI IgG 40-79U	NO Treatment	FD-10 W
14	+	aPL Only	+	Single aPL	LDA ONLY	FD-12 W

				LA (+) aCL and aβ$_2$GPI not tested		

TLD: term live delivery; **PTLD**: preterm live delivery; **FD**: fetal death; **SGA**: small-for-gestational age; **PEC**: preeclampsia; **LDA:** low-dose aspirin; **LMWH**: low-molecular-weight-heparin; **P:** prophylactic dose; **T:** therapeutic dose; **aPL:** antiphospholipid antibodies; **LA:** lupus anticoagulant; **aCL:** anticardiolipin antibody; **aβ$_2$GPI:** anti-β$_2$ glycoprotein-I antibody; **OAPS:** obstetric APS.

Supplement Table 4: Pregnancy Outcomes (N=77) During the Registry Follow-up, by Pregnancy History Prior to Registry Recruitment

	History of Previous Pregnancies			History of Any* Pregnancy Morbidity in Patients with Previous Pregnancies (n: 53)		
	Yes (N=53)	No (N=24)	P	Yes (N=44)	No (N=9)	P
TLD (N=36)	28 (53%)	8 (33%)	0.1	21 (48%)	7 (78%)	0.1
PTLD (N=12)	5 (9%)	7 (29%)	0.04	5 (11%)	-	
FD**(N=9)	5 (9%)	4 (17%)	0.4	5 (11%)	-	
EPL (N=20)	15 (28%)	5 (21%)	0.5	13 (30%)	2 (22%)	1.0
Composite Pregnancy Morbidity (N=14)	8 (15%)	6 (25%)	0.3	8 (18%)	-	

TLD: term live delivery; PTLB: preterm live delivery; FD: fetal death; EPL: early pregnancy loss. *: any pregnancy morbidity includes (pre) embryonic or embryonic loss (<10 weeks gestation), fetal death (>10 weeks gestation), (pre)eclampsia, or placental insufficiency. **: two fetal deaths associated with anomalies: 1 triple X syndrome (47 XXX) at 21 weeks, 1 cystic fibrosis at 20 weeks.

Perinatal Observations:

Of 48 pregnancies resulting in term live delivery (TLD) and preterm live delivery (PTLD), 24 (50%) were delivered vaginally and 24 (50%) by cesarean section. Delivery methods showed no relationship with clinical APS history and were similar in pregnancies with TLD and PTLD outcomes (data not shown). Following observations were noted during and/or after delivery: a) one triple aPL-positive patient with history of TAPS developed severe preeclampsia and HELLP syndrome; she received corticosteroids and intravenous immunoglobulin (IVIG) and had a PTLD at 33.6 gestational week resulting in neonatal intensive care unit admission; b) another triple aPL-positive patient with history of TAPS developed pulmonary emboli at 24th week of gestation, while on LDA and LMWH; she had had suspected fetal growth restriction as an antepartum complication and had a PTLD of a SGA infant at 24 gestational weeks; c) one preterm delivery resulted in neonatal death; d) one preterm-born neonate (complicated with PEC) required neonatal intensive care unit care; e) another premature delivery (complicated with preterm premature rupture of membranes) required neonatal intensive care unit care; and f) one term delivery (related to chronic non-pregnancy hypertension) required neonatal intensive care unit care.