









# 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')

Zeynep Belce Erton <sup>1</sup>, Ecem Sevim,<sup>2,3</sup> Guilherme Ramires de Jesús <sup>4,5</sup>, Ricard Cervera,<sup>6</sup> Lanlan Ji,<sup>7</sup> Vittorio Pengo <sup>8</sup>, Amaia Ugarte,<sup>9</sup> Danieli Andrade <sup>10</sup>, Laura Andreoli <sup>11,12</sup>, Tatsuya Atsumi,<sup>13</sup> Paul R Fortin <sup>14</sup>, Maria Gerosa,<sup>15</sup> Yu Zuo,<sup>16</sup> Michelle Petri <sup>17</sup>, Savino Sciascia,<sup>18</sup> Maria G Tektonidou <sup>19</sup>, Maria Angeles Aguirre- Zamorano,<sup>20</sup> D Ware Branch,<sup>21,22</sup> Doruk Erkan,<sup>23</sup> on behalf of APS ACTION

**To cite:** Erton ZB, Sevim E, de Jesús GR, *et al.* 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'). *Lupus Science & Medicine* 2022;9:e000633. doi:10.1136/lupus-2021-000633

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/lupus-2021-000633>).

ZBE and ES contributed equally.

For 'Presented at statement' see end of article.

Received 1 December 2021  
Accepted 14 May 2022



© Author(s) (or their employer(s)) 2022. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Dr Doruk Erkan; [erkand@hss.edu](mailto:erkand@hss.edu)

## 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- $\beta_2$  glycoprotein-I antibodies (a $\beta_2$ GPI).<sup>1</sup> APS may exist in its primary form when it occurs in otherwise healthy persons, or may be associated with other autoimmune diseases, particularly SLE.<sup>2</sup>

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).<sup>3,4</sup> 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 multi-centre 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.<sup>5</sup> 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.<sup>1</sup> 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.<sup>6</sup>

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.<sup>1</sup> 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  $\chi^2$  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+aβ <sub>2</sub> GPI (n:2)	0	2 (100%)
LA+aβ <sub>2</sub> GPI (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<sup>1</sup>

‡aCL and aβ<sub>2</sub>GPI not tested in two pregnancies; aβ<sub>2</sub>GPI not tested in three pregnancies.

aCL, anticardiolipin antibody; aPL, antiphospholipid antibodies; APS, antiphospholipid syndrome; aβ<sub>2</sub>GPI, anti-β<sub>2</sub> 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
<b>N=55 pregnancies</b>	<b>47%</b>	<b>7%</b>	<b>9%</b>	<b>4%</b>	<b>5%</b>	<b>27%</b>
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 <sub>2</sub> GPI not tested in two pregnancies; aβ <sub>2</sub> GPI 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 <sub>2</sub> GPI, anti-β <sub>2</sub> 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.<sup>7</sup> 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.<sup>8</sup> 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.<sup>9</sup> 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.<sup>10</sup> More than one positive aPL test, especially the triple aPL-positivity, also contributes to the risk of pregnancy morbidity.<sup>11-13</sup> 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.<sup>14-16</sup> 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.<sup>17</sup> 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)

Treatment	History of OAPS (N:9)		History of TAPS (N:25)		History of OAPS+TAPS (N:24)		No TAPS/OAPS (N:19)	
	# 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 LMWH	3	-	16	PTLD:1 PTLD+SGA:1 PTLD+PEC:2 EPL:5 FD:2*	16	PTLD:1 PTLD+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)			
	Yes		No		Yes		No		Yes		No		OAPS only		TAPS only	
	(n=33)	(n=44)	(n=49)	(n=28)	(n=24)	(n=53)	(n=25)	(n=19)	(n=58)	(n=19)	(n=25)	(n=19)	(n=58)	(n=19)	(n=25)	(n=19)
TLD (n=36)	17 (52%)	19 (43%)	22 (45%)	14 (50%)	12 (50%)	24 (45%)	5 (56%)	10 (40%)	27 (47%)	9 (47%)	10 (40%)	9 (47%)	27 (47%)	10 (40%)	9 (47%)	1.0
PTLD (n=12)	4 (12%)	8 (18%)	7 (14%)	5 (18%)	3 (13%)	9 (17%)	1 (11%)	4 (16%)	8 (14%)	4 (21%)	4 (16%)	4 (21%)	8 (14%)	4 (16%)	4 (21%)	0.4
FD* (n=9)	3 (9%)	6 (14%)	5 (10%)	4 (14%)	2 (8%)	7 (13%)	1 (11%)	3 (12%)	6 (10%)	3 (16%)	3 (12%)	3 (16%)	6 (10%)	3 (12%)	3 (16%)	0.6
EPL (n=20)	9 (27%)	11 (25%)	15 (31%)	5 (18%)	7 (29%)	13 (25%)	2 (22%)	8 (32%)	17 (29%)	3 (16%)	8 (32%)	3 (16%)	17 (29%)	8 (32%)	3 (16%)	0.3
Composite pregnancy morbidity (n=14)	5 (15%)	9 (20%)	8 (16%)	6 (21%)	3 (13%)	11 (21%)	2 (22%)	5 (20%)	10 (17%)	4 (21%)	5 (20%)	4 (21%)	10 (17%)	5 (20%)	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; OAPS, 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 <sub>2</sub> GPI (+) (n=21)	aCL and/or aβ <sub>2</sub> 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<sub>2</sub>GPI, anti-β<sub>2</sub> 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.<sup>18–19</sup> 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.<sup>20</sup> 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).<sup>21</sup> 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.<sup>22</sup> 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).<sup>23</sup> 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).<sup>24</sup>

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.<sup>25</sup>

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.

#### Author affiliations

- <sup>1</sup>Division of Rheumatology, Hospital for Special Surgery, New York, New York, USA
- <sup>2</sup>Medicine, Yeshiva University Albert Einstein College of Medicine, Bronx, New York, USA
- <sup>3</sup>Internal Medicine, Montefiore Medical Center, Bronx, New York, USA
- <sup>4</sup>Department of Obstetrics, Universidade do Estado do Rio de Janeiro, Rio de Janeiro, Rio de Janeiro, Brazil
- <sup>5</sup>Department of Obstetrics, Instituto Fernandes Figueira - FIOCRUZ, Rio de Janeiro, Rio de Janeiro, Brazil
- <sup>6</sup>Autoimmune Diseases, Hospital Clínic de Barcelona Institut Clínic de Medicina i Dermatologia, Barcelona, Spain
- <sup>7</sup>Department of Rheumatology and Clinical Immunology, Peking University First Hospital, Beijing, Beijing, China
- <sup>8</sup>Cardiac Thoracic and Vascular Sciences, University of Padova, padua, Italy
- <sup>9</sup>Internal Medicine, Hospital de Cruces, Barakaldo, Spain
- <sup>10</sup>Rheumatology, University of Sao Paulo, Sao Paulo, Sao Paulo, Brazil
- <sup>11</sup>Department of Clinical and Experimental Sciences, University of Brescia, Brescia, Italy
- <sup>12</sup>Unit of Rheumatology and Clinical Immunology, ASST Spedali Civili di Brescia, Brescia, Italy
- <sup>13</sup>Medicine II, Hokkaido University School of Medicine, Sapporo, Japan
- <sup>14</sup>Medicine - Rheumatology, Centre Hospitalier de l'Université Laval, Quebec City, Quebec, Canada
- <sup>15</sup>Dept. of Clinical & Community Science University of Milano, Division of Rheumatology, Milano, Italy
- <sup>16</sup>Internal Medicine/Division of Rheumatology, University of Michigan, Ann Arbor, Michigan, USA
- <sup>17</sup>Rheumatology, Johns Hopkins University, Baltimore, Maryland, USA

<sup>18</sup>Dipartimento di Malattie Rare, Immunologiche, Ematologiche ed Immunoematologiche. Centro di Ricerche di Immunopatologia e Documentazione su Malattie Rare (CMID). Struttura Complessa a Direzione Universitaria di Immunologia Clinica, Ospedale Torino Nord Emergenza San G. Bosco ed Università di Torino, Torino, Italy

<sup>19</sup>First Department of Propaedeutic Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece

<sup>20</sup>Rheumatology, University Hospital "Reina Sofia", Cordoba, Spain

<sup>21</sup>Maternal-Fetal Medicine, University of Utah Health Sciences Center, Salt Lake City, Utah, USA

<sup>22</sup>Maternal- Fetal Medicine, Intermountain Healthcare, Salt Lake City, Utah, USA

<sup>23</sup>Rheumatology, Barbara Volcker Center for Women and Rheumatic Diseases, Hospital for Special Surgery, Weill Cornell Medicine, New York, New York, USA

#### Presented at

This study was previously presented as a poster at the American College of Rheumatology Convergence 2021. The APS ACTION Registry was created using REDCAP provided by the Clinical and Translational Science Center at Weill Cornell Medical College (CTSC grant UL1 TR000457).

**Acknowledgements** The authors thank Deanna Jannat-Khan (Biostatistician, Hospital for Special Surgery, New York, NY, USA) for her guidance during data analysis.

**Collaborators** We want to thank JoAnn Vega, CCRC, for her administrative support as the APS ACTION Global Lead Coordinator. We also want to thank all our APS ACTION Members: Guillermo Pons-Estel (Santa Fe, Argentina); Bill Giannakopoulos, Steve Kriilis (Sydney, Australia); Guilherme de Jesus, Roger Levy, Flavio Signorelli (Rio de Janeiro, Brazil), Danieli Andrade, Gustavo Balbi (Sao Paulo, Brazil); Ann E. Clarke, Leslie Skeith (Calgary, Canada), Paul R. Fortin (Quebec City, Canada); Lanlan Ji, Zhouli Zhang (Beijing, China), Chengde Yang, Hui Shi (Shanghai, China); Stephane Zuily, Denis Wahl (Nancy, France); Maria G. Tektonidou (Athens, Greece); Cecilia Nalil, Laura Andreoli, Angela Tincani (Brescia, Italy), Cecilia B. Chighizola, Maria Gerosa, Pierluigi Meroni (Milan, Italy), Vittorio Pengo, Chunyan Cheng (Padova, Italy), Giulia Pazzola (Reggio Emilia, Italy), Savino Sciascia, Silvia Foddai, Massimo Radin (Turin, Italy); Stacy Davis (Kingston, Jamaica); Olga Amengual, Tatsuya Asumi (Sapporo, Japan); Imad Uthman (Beirut, Lebanon); Maarten Limper, Philip de Groot (Utrecht, The Netherlands); Guillermo Ruiz - Irastorza, Amaia Ugarte (Barakaldo, Spain), Ignasi Rodriguez-Pinto, Ricard Cervera, Jose Pardos-Gea (Barcelona, Spain), Esther Rodriguez Almaraz, Maria Jose Cuadrado (Madrid, Spain), Maria Angeles Aguirre Zamorano, Chary Lopez-Pedraza (Cordoba, Spain); Bahar Artim-Esen, Murat Inanc (Istanbul, Turkey); Maria Laura Bertolaccini, Hannah Cohen, Maria Efthymiou, Munther Khamashta, Ian Mackie, Giovanni Sanna (London, UK); Jason Knight, Yu Zuo (Ann Arbor, Michigan, US), Michelle Petri (Baltimore, Maryland, US), Rebecca K. Leaf (Boston, Massachusetts, US), Robert Roubey (Chapel Hill, North Carolina, US), Thomas Ortel (Durham, North Carolina, US), Emilio Gonzalez, Rohan Willis (Galveston, Texas, US), Nina Kello (New Hyde Park, New York, US), Michael Belmont, Steven Levine, Jacob Rand, Medha Barbhuiya, Doruk Erkan, Jane Salmon, Michael Lockshin (New York City, New York, US), Ali A. Duarte Garcia (Rochester, Minnesota, US), and D. Ware Branch (Salt Lake City, Utah, US).

**Contributors** ZBE and ES contributed equally to this manuscript. DE is the author acting as guarantor.

**Funding** The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

**Competing interests** MAP is the chair for the Belimumab Pregnancy Registry, supported by GSK. DWB is the co-principal investigator of The TNF-alpha Blockade with Certolizumab to Prevent Pregnancy Complications in High-Risk Patients with APS, supported by a grant from the NIH/NIAMS R21AR21069189-03S1. DWB is the principal investigator of The Certolizumab to Prevent Pregnancy Complications in High-Risk Patients with APS or SLE, supported by UCB Pharma Inc.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** This study involves human participants and was approved by HSS APS ACTION IRB # 2014-252. Participants gave informed consent to participate in the study before taking part.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** No data are available. Not applicable. No data are available.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

#### ORCID iDs

Zeynep Belce Erton <http://orcid.org/0000-0002-9099-8649>

Guilherme Ramires de Jesús <http://orcid.org/0000-0002-6715-0180>

Vittorio Pengo <http://orcid.org/0000-0003-2064-6071>

Danieli Andrade <http://orcid.org/0000-0002-0381-1808>

Laura Andreoli <http://orcid.org/0000-0002-9107-3218>

Paul R Fortin <http://orcid.org/0000-0002-7278-2596>

Michelle Petri <http://orcid.org/0000-0003-1441-5373>

Maria G Tektonidou <http://orcid.org/0000-0003-2238-0975>

#### REFERENCES

- Miyakis S, Lockshin MD, Atsumi T, *et al*. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006;4:295–306.
- Cervera R, Piette J-C, Font J, *et al*. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. *Arthritis Rheum* 2002;46:1019–27.
- Branch DW, Khamashta MA. Antiphospholipid syndrome: obstetric diagnosis, management, and controversies. *Obstet Gynecol* 2003;101:1333–44.
- George D, Erkan D. Antiphospholipid syndrome. *Prog Cardiovasc Dis* 2009;52:115–25.
- Erkan D, Lockshin MD. Aps action – antiphospholipid syndrome alliance for clinical trials and international networking. *Lupus* 2012;21:695–8.
- Harris PA, Taylor R, Thielke R, *et al*. Research electronic data capture (REDCap)--a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
- Bramham K, Hunt BJ, Germain S, *et al*. Pregnancy outcome in different clinical phenotypes of antiphospholipid syndrome. *Lupus* 2010;19:58–64.
- Deguchi M, Yamada H, Sugiura-Ogasawara M, *et al*. Factors associated with adverse pregnancy outcomes in women with antiphospholipid syndrome: a multicenter study. *J Reprod Immunol* 2017;122:21–7.
- Gebhart J, Posch F, Koder S, *et al*. Increased mortality in patients with the lupus anticoagulant: the Vienna lupus anticoagulant and thrombosis study (LATS). *Blood* 2015;125:3477–83.
- Lockshin MD, Kim M, Laskin CA, Ca L, *et al*. Prediction of adverse pregnancy outcome by the presence of lupus anticoagulant, but not anticardiolipin antibody, in patients with antiphospholipid antibodies. *Arthritis Rheum* 2012;64:2311–8.
- Ruffatti A, Tonello M, Cavazzana A, *et al*. Laboratory classification categories and pregnancy outcome in patients with primary antiphospholipid syndrome prescribed antithrombotic therapy. *Thromb Res* 2009;123:482–7.
- Mankee A, Petri M, Magder LS. Lupus anticoagulant, disease activity and low complement in the first trimester are predictive of pregnancy loss. *Lupus Sci Med* 2015;2:e000095.
- Kaneko K, Mishima S, Goto M, *et al*. Clinical feature and antiphospholipid antibody profiles of pregnancy failure in young women with antiphospholipid antibody syndrome treated with conventional therapy. *Mod Rheumatol* 2018;28:670–5.
- Danowski A, de Azevedo MNL, de Souza Papi JA, *et al*. Determinants of risk for venous and arterial thrombosis in primary antiphospholipid syndrome and in antiphospholipid syndrome with systemic lupus erythematosus. *J Rheumatol* 2009;36:1195–9.
- De Carolis S, Tabacco S, Rizzo F, *et al*. Antiphospholipid syndrome: an update on risk factors for pregnancy outcome. *Autoimmun Rev* 2018;17:956–66.
- Ünlü O, Zuilü S, Erkan D. The clinical significance of antiphospholipid antibodies in systemic lupus erythematosus. *Eur J Rheumatol* 2016;3:75–84.
- Unlu O, Erkan D, Barbhayya M, *et al*. The impact of systemic lupus erythematosus on the clinical phenotype of antiphospholipid antibody-positive patients: results from the antiphospholipid syndrome alliance for clinical trials and international clinical database and Repository. *Arthritis Care Res* 2019;71:134–41.
- Alijotas-Reig J, Ferrer-Oliveras R, Ruffatti A, *et al*. The European registry on obstetric antiphospholipid syndrome (EUROAPS): a survey of 247 consecutive cases. *Autoimmun Rev* 2015;14:387–95.
- Bouvier S, Cochery-Nouvellon E, Lavigne-Lissalde G, *et al*. Comparative incidence of pregnancy outcomes in treated obstetric antiphospholipid syndrome: the NOH-APS observational study. *Blood* 2014;123:404–13.
- Mak A, Cheung MW-L, Cheak AA-cia, *et al*. Combination of heparin and aspirin is superior to aspirin alone in enhancing live births in patients with recurrent pregnancy loss and positive anti-phospholipid antibodies: a meta-analysis of randomized controlled trials and meta-regression. *Rheumatology* 2010;49:281–8.
- Alalaf S. Bemiparin versus low dose aspirin for management of recurrent early pregnancy losses due to antiphospholipid antibody syndrome. *Arch Gynecol Obstet* 2012;285:641–7.
- de Jesús GR, Benson AE, Chighizola CB, *et al*. 16Th international Congress on antiphospholipid antibodies Task force report on obstetric antiphospholipid syndrome. *Lupus* 2020;29:1601–15.
- Wilcox AJ, Weinberg CR, O'Connor JF, *et al*. Incidence of early loss of pregnancy. *N Engl J Med* 1988;319:189–94.
- Practice Committee of the American Society for Reproductive Medicine. Evaluation and treatment of recurrent pregnancy loss: a Committee opinion. *Fertil Steril* 2012;98:1103–11.
- Unverzagt S, Prondzinsky R, Peinemann F. Single-Center trials tend to provide larger treatment effects than multicenter trials: a systematic review. *J Clin Epidemiol* 2013;66:1271–80.