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

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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.