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Preconception Antiphospholipid Antibodies and Risk of Subsequent Early Pregnancy Loss

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Abstract

Objectives—To prospectively estimate the association of preconception aPL with subsequent pregnancy loss using a cohort design. Antiphospholipid antibodies (aPL) have been associated with recurrent early pregnancy loss (EPL) prior to 10 weeks in previous case-control studies. Prospective ascertainment of pregnancy loss is challenging, as most women do not seek care prior to EPL.

Methods—Secondary analysis of the Effects of Aspirin in Gestation and Reproduction trial of preconception low dose aspirin. Preconception anti-cardiolipin (aCL) and anti- β 2-glycoprotein-I (a- β 2-I) were assessed in 1208 women with one or two prior pregnancy losses and no more than two prior live births. Comparison cohorts were defined by positive aPL or negative aPL status. All women were followed for six menstrual cycles while trying to conceive; if successful, they underwent an ultrasound at 6–7 week's gestation. EPL was defined as loss prior to 10 weeks gestation; embryonic loss was loss after visualization of an embryo but prior to 10 weeks; clinical loss was any loss after visualization of an embryo (with or without fetal cardiac activity detected).

Results—14/1208 (1%) tested positive for aPL (+aPL). 786/1208 (65%) women had a positive hCG during the study period; 9/786 (1%) had +aPL. 589/786 (75%) of pregnant women had live births; 24% had pregnancy losses. Women with +aPL experienced EPL at similar rates as women with –aPL, 44% vs 21% (aRR 2.4, 95% CI 0.5–10.9). Embryonic loss was more common in women with +aCL IgM (aRR 4.8, 95% CI 1.0–23.0) and in women with two positive aPLs. Clinical pregnancy loss was more common in women with positive a- β 2-I IgM (50% vs 16.5%, aRR 3.7, 95% CI 1.3–10.8).

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Conclusion—Positive levels of aPL are rare in women with one or two prior pregnancy losses and not clearly associated with increased rate of subsequent loss.

Clinical Trial Registration—The original source study was registered at [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00467363) #NCT00467363.

Introduction

Antiphospholipid antibodies (aPL) are linked to recurrent early pregnancy loss (EPL). Rates of aPL in women with recurrent EPL are 5–15%, compared to 2–6% in women without recurrent losses (1–3). Furthermore, three consecutive, otherwise unexplained pregnancy losses prior to 10 weeks is one of the obstetric diagnostic criteria for antiphospholipid syndrome (APS) (4). The diagnosis of APS is made by the presence of both aPL and either obstetric criteria or thrombosis. Other clinical criteria include thrombosis, one or more unexplained fetal deaths >10 weeks, and one or more pregnancies delivered prior to 34 weeks gestation for severe preeclampsia or placental insufficiency (4).

Although aPL have a well-established association with late pregnancy loss (5), the relationship between early pregnancy loss and aPL remains controversial (6–8). The paucity of data regarding aPL and early pregnancy loss is due largely to difficulty in ascertainment. EPL consists of pre-implantation, pre-embryonic, and embryonic losses, which many women experience prior to obtaining obstetric care. Accordingly, prospective cohort studies of women enrolled during pregnancy using clinic or provider-based recruitment strategies fail to capture early pregnancy losses. Further, many studies evaluating the association of aPL and pregnancy loss combine early pregnancy loss (<10 weeks) and later fetal losses. The majority of previous studies used a case-control design and are at high risk for selection biases due to truncation (9). Only one prospective cohort study assessed early pregnancy loss in association with aPL in women with previous pregnancy loss. They found aPL were associated with a relatively higher embryonic loss rate (28 vs 13%) (10), but they did not assess the precise timing of loss or further subdivide losses into pre-implantation, pre-embryonic, or embryonic losses.

Given these knowledge gaps, our objective was to assess 1) the frequency of aPL and 2) the association between aPL and subsequent early pregnancy loss, in a large, prospective cohort of women with one or two prior pregnancy losses enrolled prior to conception and followed closely through the preconception and early pregnancy time period.

Materials and Methods

Study Population

This secondary analysis is a prospective cohort study from the Effects of Aspirin in Gestation and Reproduction (EAGeR) randomized-controlled trial of preconception low dose aspirin. The EAGeR trial (June 2007 through August 2012) included 1228 women ages 18 to 40 years who were attempting conception and had experienced one or two prior pregnancy losses, no more than two prior live births and no more than one elective termination or ectopic pregnancy, and had regular menstrual cycles (21–42 days in length) (11, 12). For this analysis, cohorts were defined by whether women tested positive (+aPL) or

negative (–aPL). All participating centers obtained Institutional Board approval for the primary study, and informed consent was obtained from all participants. University of Utah Institutional Review Board application “Effects of Aspirin in Gestation and Reproduction (EAGeR)” (#00021732) was approved February 7, 2008. Exclusion criteria included, but were not limited to: clinical indication for use of anticoagulant therapy (including diagnosis of APS); chronic use of non-steroidal anti-inflammatory drugs (NSAIDs); major medical disorders; current use of contraception; and history of infertility or subfertility. Major medical disorders included diabetes, hypertension, systemic lupus erythematosus, untreated or active cancer, any history of prior cancer, liver disease, renal disease, rheumatoid arthritis, cardiac disease, pulmonary disease other than mild asthma, neurologic disease requiring medical treatment, hyperthyroidism, hypothyroidism, seizure disorder requiring the use of anticonvulsant medications, untreated vitamin B12 deficiency, severe anemia (hematocrit <30%), hemophilia, gout, and nasal polyps. Women were excluded if they lacked both intact Fallopian tubes, both ovaries, or a uterus; if they did not have regular menstrual cycles; or if they had more than one missed menses in the previous 12 months. Women were randomized to receive 81 mg aspirin (LDA) daily or placebo starting after biospecimen collection at the enrollment visit, through up to six menstrual cycles of attempting pregnancy and until 36 weeks of pregnancy if pregnancy was achieved within six menstrual cycles. All participants received folic acid. For this analysis, all enrolled women with data on aPL measured at the enrollment visit were included (n=1208).

aPL Assessment and Classification

Antiphospholipid antibodies were assessed using samples obtained at the baseline visit, prior to conception or randomization to aspirin or placebo. Antibody levels were determined using DIASTAT® assays by Euro Diagnostica, specific for each aPL antibody, including anti-cardiolipin (aCL) IgM, aCL IgG, anti- β 2-glycoprotein-I (a- β 2-GP1) IgM, and a- β 2-GP1 IgG. Inter-assay coefficients of variance for positive controls were 7.8% for aCL IgM, 12.1% for aCL IgG, 7.9% for a- β 2-GP1 IgM, and 15% for a- β 2-GP1 IgG. Lower limits of detection were 0.6 U/mL for aCL IgG, 0.9 U/mL for aCL IgM, 0.1 U/mL for a- β 2-GP1 IgG, and 0.1 U/mL for a- β 2-GP1 IgM.

Antibody levels ≥ 40 U/mL were considered “positive” for aCL IgG and IgM and anti- β 2-GP1 IgG and IgM. Various definitions of positive aPL (+aPL) status were also defined: 1) any positive single antibody test, 2) two positive in any combination, 3) aCL IgG positive 4) aCL IgM positive, 5) a- β 2-GP1-IgG positive, or 6) a- β 2-GP1-IgM positive. Outcomes were compared between +aPL and negative aPL (–aPL) status using the various definitions. We also repeated analyses using a titer value of ≥ 20 U/mL as a cutoff for determining antibody positivity.

Outcome Assessment

Pregnancies were identified using spot urine pregnancy tests at the clinical sites (Quidel Quickvue, Quidel Corporation, sensitive to 25 mIU/mL hCG), as well as urine hCG testing that was performed later in the laboratory on the last 10 days of each woman’s first and second cycle of study participation (using daily first-morning urine collected at home) and on spot urine samples collected at all visits scheduled to occur at a woman’s next expected

menses (day 2–4 of cycle). Free beta hCG was measured in these urine samples to enable more sensitive detection of very early pregnancy than possible with conventional urine pregnancy testing. Two laboratory assays for free beta hCG (Catalogue No. 4221-16, Diagnostic Automation Inc; Catalogue No. RIS0011R, BioVendor) were sequentially employed to determine first “potentially positive” values (n=164), of which 21 were verified as positive tests for early hCG detected pregnancy (13).

The primary outcome was early pregnancy loss (EPL), defined as a loss prior to 10 weeks’ gestation, and included pre-implantation losses, pre-embryonic losses, and embryonic losses. Secondary outcomes were live birth, hCG pregnancy (all pregnancies detected by positive urine hCG), clinically confirmed pregnancy (via visualization of an embryo with ultrasound at approximately 6–7 weeks of gestation), clinical loss (defined as loss after ultrasound confirmation of pregnancy), embryonic loss, preterm birth prior to 37 weeks, and preeclampsia (based on a diagnosis in the medical record using standard clinical and laboratory criteria), and small for gestational age at birth (SGA) (defined as birth weight at or below the 10th %ile for gestational age using the reference developed by Kramer, et al) (14). We included preeclampsia, SGA, and preterm birth as outcomes because preterm birth due to preeclampsia or placental insufficiency is also part of APS. Embryonic losses were defined as losses occurring before 10 weeks’ gestation with ultrasound visualization of an embryo at or prior to the loss. Preclinical loss was loss prior to clinically confirmed pregnancy via ultrasound visualization of an embryo. We acknowledge that these categories overlap, but because they have different diagnostic strategies, we found it useful to analyze all of them.

Statistical Analysis

Demographic variables were compared between +aPL and –aPL groups using Chi-square tests and t-tests, where appropriate. Pregnancy outcomes were reported by +aPL and –aPL status as frequencies and compared using Fishers exact test. Women who withdrew prior to pregnancy outcome ascertainment were not included in this analysis. Outcomes were compared using the varying definitions for +aPL status. Risk ratios were estimated where possible using log binomial models with robust variance and were adjusted for the known confounders of number of previous losses, number of previous live births, maternal age, maternal body mass index (BMI), and allocation of aspirin/placebo per treatment group. Odds ratios were calculated in some cases when the number of cases was too small; in some scenarios no models could be estimated due to insufficient cases. Outcomes of live birth, hCG pregnancy, and clinical pregnancy were calculated among all women who completed follow-up, whereas pregnancy outcomes including loss, preterm, preeclampsia, and SGA are restricted to women who became pregnant during the study period. In order to correctly estimate the association between aPL and pregnancy loss, preterm, and preeclampsia, inverse probability weights were used to control for potential bias introduced by restricting the analysis to pregnant women(15, 16). Analyses were conducted in SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Of the 1228 women enrolled in the EAGeR trial, 1208 (98.4%) had available data on aPL. Of these women, 14 of 1208 (1.2%) tested positive for any aPL using a threshold of 40 U/mL; 786 (65.1%) of the 1208 women had a positive hCG test during the study period. Among those with a positive hCG test, nine of 786 (1.1%) tested positive for any aPL (Figure 1). Demographic characteristics of women who tested positive for any aPL versus no aPL positivity are represented in Table 1. There were no differences in characteristics between the +aPL and -aPL groups. The study population was predominantly white nonsmokers. Mean age was 28.7 years and mean BMI was 26.3 kg/m². There were no individuals with previously diagnosed APS.

Overall, 589 out of 786 (75%) women with positive hCG tests had live births and 186 (24%) had documented pregnancy losses. Four out of nine (44.4%) women with any +aPL experienced EPL, compared to 159 out of 777 (20.5%) women with -aPL ($p=0.09$) (Table 2). After adjustment, there remained no difference in rate of EPL between +aPL and -aPL groups, though the estimate was imprecise due to few cases of aPL positivity (aRR 2.41, 95% CI 0.53–10.89) (Table 3).

Two out of 9 (22.2%) women with any +aPL experienced embryonic pregnancy loss, compared to 70 out of 777 (9%) in -aPL ($p=0.20$). Embryonic loss was more common in women with +aCL IgM (aRR 4.82, 95% CI 1.01–22.98) compared with -aPL and in women with any 2 +aPL antibodies compared with -aPL. Clinical pregnancy loss was more common in women with +a β 2-GP1 IgM 40 U/mL (50% vs 16.5%, aRR 3.67, 95% CI 1.25–10.77).

SGA was more common in women with positive +a β 2-GP1 a- β 2-GP1-IgM than with negative -a β 2-GP1 a- β 2-GP1-IgM (aRR 5.4, 95% CI 1.16–25.16). None of the other secondary outcomes differed between aPL groups. Specifically, the rate of hCG pregnancy was similar between +aPL and -aPL groups (64.3% vs 65.1%, aRR 1.14, 95% CI 0.81–1.62) (Table 3). The overall live birth rate (including women both with and without hCG pregnancy) was also similar between +aPL and -aPL women (35.7% vs 48.9%, aRR 0.84 [95% CI 0.42–1.66]).

When analysis was repeated using 20 U/mL as cutoff for +aPL, there were 36 women out of 1208 (3.0%) who tested +aPL. There was no difference in EPL or any other pregnancy loss rates among groups. Women with +aPL were less likely to have a positive hCG test than women with -aPL (47.2% vs 65.7%, $p=0.03$) but this difference did not persist after adjustment for maternal age and BMI (aRR 0.78, 95% CI 0.56–1.1). aCL IgG>20 was associated with increased risk of preterm birth (50% vs 6.5%; aRR 5.58, 95% CI 1.25–24.83) and a diagnosis of preeclampsia (33% vs 7.6%; RR 6.32, 95% CI 1.56–25.6) relative to -aPL, although the RR for preeclampsia could not be adjusted as it only included one case.

Pregnancy outcomes for the nine women with +aPL who became pregnant during the study period are outlined in Table 4. The four women with +aPL who experienced pregnancy loss

had aPL titers as follows: 1) aCL IgM=44.42 U/mL, 2) a β 2-GP1 IgM=122.52 U/mL, 3) a β 2-GP1 IgM=79.42 U/mL, and 4) a β 2-GP1 IgG=82.07 U/mL, all well over the 40 U/mL cutoff.

Discussion

Using a prospectively observed cohort of 1208 women with one or two prior pregnancy losses, we found that the presence of any +aPL test in women was very uncommon, affecting only 14 women in total. We also found that the presence of a +aPL result was not associated with an increased risk of subsequent EPL. We acknowledge, however, that this conclusion regarding the risk of subsequent loss is limited by small numbers.

Our findings are consistent with the observational study of Chauler et al. in which women with an early pregnancy loss in their first pregnancy were assessed for aPL, and their subsequent conceived pregnancy was evaluated (10). The authors evaluated over 5,700 women with a single prior miscarriage <10 weeks gestation for aPL. For aCL and a- β 2-GP1 immunoassays, positive results were those that exceeded the threshold of >99th percentile value of controls in their laboratory. Of 5742 women tested, 3.5% were positive at least once for any aPL. After excluding those with traditional risk factors for early miscarriage, 2.9% were repeatedly positive. Although we used a different immunoassay product and a cutoff of 40 U/mL in both the aCL and a- β 2-GP1 assays, we believe our findings to be largely similar, though we found a lower rate of +aPL (1.2%), even with the inclusion of women with two prior pregnancy losses and later losses. Moreover, 3% of our patients were positive using a cutoff of 20 U/mL. Chauleur et al. also studied subsequent pregnancy outcomes in 142 +aPL cases (all available) compared to 142 -aPL controls. A second pregnancy loss occurred in 18 women without aPL-Abs (13%) and 44 women (31%) with aPL-Abs (OR = 3.09, 95% CI [1.68–5.7]), rates of loss that were comparable to the 20.5% and 44.4% with subsequent EPL observed here in women without and with antibodies, respectively. Though we did not find as large an increase in odds of pregnancy loss with +aPL, despite our inclusion of women with two prior pregnancy losses and later losses, our findings are similar to those of Chauler et al. Also, we would note that the confidence intervals in both studies are fairly wide.

Previous case-control studies comparing aPL in women with and without recurrent pregnancy loss report associations between EPL and aPL inconsistently (7). A meta-analysis demonstrated an association between aCL and EPL, but EPL was defined as less than 13 instead of 10 weeks' gestation, and only two studies were included (17). One case-control study compared 273 women with EPL, 74 women with recurrent IVF failure, and 200 control women. In this study, EPL was defined as 2 or more losses prior to 10 weeks gestation, excluding any ectopic pregnancies. Women with pregnancy losses beyond 10 weeks were excluded. This is important because their case phenotype was truly an EPL only phenotype. In that study, women with recurrent EPL did not have an increased rate of aPL. Moreover, when the recurrent EPL group was narrowed to women with 3 or more EPLs (n=108), there was still no association with aPL (18). It may be that any association between aPL and EPL is minimal and difficult to detect when EPL is strictly defined. Additionally, it is exceedingly difficult to assess EPL, as most women do not seek care during early gestation. Our findings overcome this common shortfall in study designs because we

enrolled women prior to conception with thorough prospective ascertainment (and timing) of pregnancy and loss, permitting accurate ascertainment and assessment of the timing of all pregnancy losses.

We found a very low frequency of baseline aPL in this population (1.2%); much lower than the 5% reported in previous low-risk populations and the 15% reported in women with recurrent pregnancy loss (7). In turn, this limited our power to detect small associations between aPL and early pregnancy loss.

It is not clear why the rate of +aPL was so low in our cohort. We believe this is most likely due to using robust thresholds to define positive results for aPL and stringent criteria for EPL. Our findings may reflect a more accurate assessment of incidence in this population because of our rigorous definitions of positive results. Many older case-control studies used lower titers, multiples of the mean or multiples-of-the-median to define positive results (7). Other studies include early fetal losses as well, as it can be difficult to assess whether loss was embryonic or fetal retrospectively. In addition, our cohort included women with one or two prior losses, as opposed to recurrent pregnancy loss. Many definitions of recurrent early pregnancy loss require three consecutive losses, as do current criteria for APS. However, in practice many practitioners are currently testing for aPL after only two losses, making our study cohort clinically relevant.

Generalizability of these results is limited by our population characteristics. Participants were generally healthy, non-Hispanic white, educated, affluent and thin compared to the general population. It is possible that aPL would be more common in a higher risk population.

Another limitation was lack of assessment of lupus anticoagulant (LAC). There are limited data regarding the association between LAC and EPL perhaps because positive tests for LAC are even less common than for aCL and a β 2-GPI in an early pregnancy loss population (8, 19). Chauler et al found that less than 10% of women with a prior pregnancy loss and +aPL results were positive for LAC alone, suggesting we would miss very few +aPL cases in the population we studied due to not performing a test for LAC. Also, while we acknowledge the association between LAC and both thrombosis and second- and third trimester obstetric complications in APS (10, 20), a meta-analysis of 25 studies found no data available for association between LAC and pregnancy loss prior to 13 weeks(17). Additionally, one study evaluating women with recurrent pregnancy loss (RPL) found no cases of LAC presence in women who had recurrent EPL alone and did not meet other clinical criteria for APS(19). Similarly, a study grouping women with all obstetric criteria for APS found no association between LAC and recurrent EPL or between aCL and recurrent aPL(21). Thus, assessment of LAC is unlikely to alter our results or increase power.

We also were limited by a single time point of assessment for aPL. Diagnostic confirmation of APS requires repeat confirmatory testing for aPL at least 12 weeks later. We were not, however, attempting to make a diagnosis of APS, as no women in this group met clinical criteria for APS.

We did not assess aneuploidy as a cause of pregnancy loss in this study. However, as previously reported, karyotype or chromosomal microarray was performed on 82 of the clinical losses. Of these, 29/82 (35.4%) were abnormal(13). Low dose aspirin use was not associated with aneuploidy. For this analysis, we did not evaluate the association of +aPL and aneuploidy, as these results were only available for a small proportion of pregnancy losses.

A significant strength of this study is its prospective nature, with participants enrolled and evaluated prior to attempting conception. There was also very close follow up to allow thorough detection of early conception and thus all early losses. This study design makes our rate of EPL very reliable for this population. Additionally, we collected full demographic variables on participants at baseline, prior to knowledge of aPL status. This allows for unbiased adjustment of our associations and better control for possible confounders.

In sum, we conclude that positive levels of aPL are quite rare in women with one or two early pregnancy losses. Thus, our data do not support testing such women for aPL. Moreover, it is not clear that a positive test is associated with overall rate of subsequent pregnancy loss. Our study had insufficient sample size to make definitive conclusions regarding the relationship between aPL and early pregnancy loss. When deciding whether or not to utilize a clinical test, it is important to evaluate the test's utility. Wald et al. have published critical questions to consider when choosing to recommend a test(22). These questions include costs, benefits, and what therapy would follow a positive result. Currently, aPL testing for women with one or two previous losses do not meet these predefined criteria.

Similarly, we cannot make determinations about early pregnancy loss as a criterion for APS. The issue deserves further study. Meanwhile, it is reasonable to consider women with aPL and late pregnancy loss and early pregnancy loss as two different populations until these relationships are clarified.

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Figure 1.
Participant flow through cohort development.

Table 1

Demographic characteristics of participants with and without aPL

	+aPL*	−aPL	P-value
N	14	1194	
Maternal Age (mean ± SD)	29.2 ± 5.8	28.7 ± 4.8	0.736
BMI (mean ± SD)	27 ± 5.9	26.3 ± 6.5	0.679
White Race	12 (85.7)	1132 (94.8)	0.167
>HS Education	13 (92.9)	1031 (86.4)	0.707
Previous losses			
1	9 (64.3)	799 (66.9)	0.783
2	5 (35.7)	395 (33.1)	
Previous live births			
0	7 (50)	552 (46.2)	0.188
1	7 (50)	431 (36.1)	
2	0 (0)	211 (17.7)	
Treatment Assignment (Aspirin)	6 (42.9)	601 (50.3)	0.603
Smoking in past year			
Never	13 (100)	1037 (87.5)	0.81
<6 times/week			
Daily			
Alcohol consumption in past year			
Often	9 (69.2)	784 (66.4)	1
Sometimes	4 (30.8)	370 (31.4)	
Never	0 (0)	26 (2.2)	
Exercise			
Low	6 (42.9)	307 (25.7)	0.219
Moderate	3 (21.4)	494 (41.4)	
High	5 (35.7)	393 (32.9)	
Vitamin use			
Yes	10 (71.4)	948 (80.5)	0.444
Yes, but no folic acid	3 (21.4)	141 (12)	
No vitamins, no folic acid	1 (7.1)	89 (7.6)	

* +aPL is presence of any antiphospholipid antibody ≥ 40 U/mL

Table 2

Outcomes of pregnancies comparing positive aPL to negative aPL status using varying criteria, n (row %).

	Any +aPL			Two positive			aCL IgM			aCL IgG			aβ2G1 IgM			aβ2G1 IgG		
	+	-	p-value	+	-	p-value	+	-	p-value	+	-	p-value	+	-	p-value	+	-	p-value
	N=9	N=777		N=2	N=784		N=2	N=784		N=1	N=785		N=4	N=782		N=4	N=782	
Live birth	5 (56)	584 (75)	0.42	1 (50)	588 (75)	>0.99	1 (50)	588 (75)	>0.99	1 (100)	588 (75)	>0.99	2 (50)	587 (75)	>0.99	3 (75)	586 (71)	>0.99
EPL (loss < 10 weeks' gestation)	4 (44)	159 (21)	0.09	1 (50)	162 (21)	0.37	1 (50)	162 (21)	0.37	0 (0)	163 (21)	>0.99	2 (50)	161 (21)	0.19	1 (25)	162 (21)	>0.99
Embryonic Loss	2 (22)	70 (9)	0.20	1 (50)	71 (9)	0.18	1 (50)	71 (9)	0.18	0 (0)	72 (9)	>0.99	1 (25)	71 (9)	0.32	0 (0)	72 (9)	>0.99
Clinical Loss	3 (33)	128 (17)	0.19	1 (50)	130 (17)	0.21	1 (50)	130 (17)	0.21	0 (0)	131 (17)	>0.99	2 (50)	129 (17)	0.09	0 (0)	131 (17)	>0.99
Preterm Delivery	1 (11)	51 (7)	0.37	0 (0)	52 (7)	>0.99	0 (0)	52 (7)	>0.99	1 (100)	51 (7)	0.09	0 (0)	52 (7)	>0.99	1 (25)	51 (7)	0.24
Preeclampsia	1 (11)	58 (8)	0.55	0 (0)	59 (8)	>0.99	0 (0)	59 (8)	>0.99	1 (100)	58 (7)	0.08	0 (0)	59 (8)	>0.99	1 (25)	58 (7)	0.27
SGA	1 (20)	40 (7)	0.31	1 (100)	40 (7)	0.07	1 (100)	40 (7)	0.07	0 (0)	41 (7)	>0.99	1 (50)	40 (7)	0.14	0 (0)	41 (7)	>0.99

Table 3

Associations between +aPL status and pregnancy outcomes using various definitions for +aPL, RR (95% CI). Positive aPL status was defined by titer 40.

		Any pos	2 pos*	aCL IgM	aCL IgG	aB2G1 IgM	aB2G1 IgG
		Positive versus Negative	Yes versus No	Positive versus Negative	Positive versus Negative	Positive versus Negative	Positive versus Negative
Overall							
Live birth	RR	0.9 (0.48, 1.67)	0.9 (0.22, 3.6)	0.9 (0.22, 3.6)	--	0.9 (0.34, 2.4)	1.08 (0.53, 2.21)
	aRR	0.88 (0.47, 1.65)	0.89 (0.22, 3.62)	0.89 (0.22, 3.62)	--	0.88 (0.33, 2.34)	1.07 (0.52, 2.2)
hCG pregnancy	RR	1.25 (1.01, 1.54)*	--	--	--	--	1.11 (0.71, 1.72)
	aRR	1.26 (1, 1.58)*	--	--	--	--	1.11 (0.71, 1.73)
Clinically confirmed pregnancy	RR	1.2 (0.88, 1.64)	--	--	--	--	0.9 (0.44, 1.84)
	aRR	1.14 (0.83, 1.56)	--	--	--	--	0.85 (0.41, 1.74)
Among pregnancies							
EPL (loss < 10 weeks' gestation)	RR	2.26 (0.52, 9.89)	2.26 (0.52, 9.89)	2.26 (0.52, 9.89)	--	2.26 (0.81, 6.31)	1.05 (0.17, 6.65)
	aRR	2.41 (0.53, 10.89)	2.41 (0.53, 10.89)	2.41 (0.53, 10.89)	--	2.54 (0.88, 7.31)	0.95 (0.15, 6.05)
Embryonic loss	RR	2.34 (0.65, 8.37)	5.18 (1.17, 22.93)*	5.18 (1.17, 22.93)*	--	2.66 (0.47, 14.87)	--
	aRR	2.33 (0.64, 8.45)	4.82 (1.01, 22.98)*	4.82 (1.01, 22.98)*	--	2.75 (0.48, 15.63)	--
Clinical loss	RR	1.92 (0.73, 5.06)	2.85 (0.65, 12.53)	2.85 (0.65, 12.53)	--	2.87 (1.03, 8.02)*	--
	aRR	2.01 (0.76, 5.34)	3.47 (0.76, 15.91)	3.47 (0.76, 15.91)	--	3.67 (1.25, 10.77)*	--
Preterm Birth <37 weeks	RR	2.21 (0.37, 13.03)	--	--	--	--	3.74 (0.74, 18.94)
	aRR	1.93 (0.31, 12.01)	--	--	--	--	3.14 (0.55, 17.81)
Preeclampsia	RR	1.41 (0.22, 9.04)	--	--	--	--	3.21 (0.59, 17.64)
	aRR	1.17 (0.19, 7.23)	--	--	--	--	1.99 (0.39, 10.1)
SGA	RR	2.73 (0.45, 16.4)	--	--	--	6.74 (1.57, 28.89)*	--
	aRR	3.63 (0.56, 24.43)	--	--	--	7.63 (1.54, 37.88)*	--

Data are reported as risk ratio and 95% confidence interval

---Odds ratio calculated when risk ratio models would not converge.

Some results are missing due to no observation in one group. Adjustment model includes maternal age, BMI, number of previous losses, number of previous live births, and aspirin allocation. Models for pregnancy loss, preterm birth, preeclampsia, and SGA were weighted using inverse probability weights to account for potential bias due to restricting to pregnant women.

Table 4

Description of each subject with +aPL and +hCG.

Age (years)	# Previous Losses	# Previous Live Births	Pregnancy Outcome*	Pregnancy Complications
21.96	1	0	Live birth	None
31.57	2	1	Preclinical loss	Pregnancy loss
39.39	1	1	Clinical loss	Pregnancy loss
27.82	2	1	Live birth	None
30.78	2	1	Clinical loss	Pregnancy loss
23.89	1	0	Clinical loss	Pregnancy loss
21.80	1	0	Live birth	None
21.27	1	0	Live birth	None
31.91	1	1	Live birth	Preterm birth, preeclampsia

* Clinical losses are defined as pregnancy loss after ultrasound identification of intrauterine pregnancy. Preclinical loss is pregnancy loss prior to ultrasound visualization of gestation.