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Predictors of Pregnancy Outcome in a Prospective, Multiethnic Cohort of Lupus Patients

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Abstract

Background—Since systemic lupus erythematosus (SLE) affects women of reproductive age, pregnancy is a major concern.

Objective—To identify predictors of adverse pregnancy outcome (APO) in inactive or stable active SLE patients

Design—Prospective Cohort

Setting—Multicenter

Patients—385 patients (49% non-Hispanic White; 31% prior nephritis) with SLE in PROMISSE. Exclusion criteria were: proteinuria >1000 mg/24 hour, creatinine >1.2 mg/dL, prednisone >20 mg/day, or multi-fetal pregnancy.

Measurements—APO included: fetal/neonatal death; birth <36 weeks due to placental insufficiency, hypertension, or preeclampsia; and small for gestational age (SGA) <5%. Disease activity was assessed by SLEPDAI and physician's global assessment (PGA).

Results—APO occurred in 19.0% (95% CI: 15.2% - 23.2%) of pregnancies, fetal death (4%), neonatal death (1%), preterm delivery (9%), and SGA (10%). Severe flares in the second and third trimester occurred in 2.5% and 3.0%, respectively. Baseline predictors of APO included lupus anticoagulant positive (OR = 8.32, 95% CI: 3.59-19.26), antihypertensive use (OR = 7.05, 95% CI: 3.05 - 16.31), PGA>1 (OR = 4.02, 95% CI: 1.84 - 8.82) and platelets (OR = 1.33 per 50K decrease, 95% CI:1.09-1.63); non-Hispanic White was protective (OR = 0.45, 95% CI: 0.24-0.84). Maternal flares, higher disease activity, and smaller increase in C3 later in pregnancy also predicted APO. Among women without baseline risk factors, the APO rate was 7.8%. For those either LAC positive, or LAC negative but non-White or Hispanic and taking antihypertensives, APO rate was 58%; fetal/neonatal mortality 22%.

Limitations—Excluded patients with high disease activity.

Conclusions—In pregnant SLE patients with inactive or stable mild/moderate disease, severe flares are infrequent, and absent specific risk factors, outcomes are favorable.

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Introduction

Systemic lupus erythematosus (SLE) primarily affects women of childbearing age. Absent treatment with cytotoxic agents, SLE does not adversely impact fertility (1, 2), but fetal and maternal health during pregnancy are a concern. Advice regarding safety and timing of pregnancy requires identification of clinical and laboratory parameters that predict outcomes.

It has been suggested that SLE pregnancies result in high rates of preterm birth, preeclampsia, and fetal loss compared to pregnancies in healthy women (3-10). Previous

studies have identified active disease, hypocomplementemia, anti-ds DNA antibodies, prior nephritis, and antiphospholipid antibodies (aPL) (6-8, 10-13) as risk factors for adverse pregnancy outcomes (APO). Effects of pregnancy on SLE activity and contribution of disease activity to APO remain unclear (10, 14-18). Currently, SLE patients are advised to consider pregnancy during periods of minimal and stable disease (19). However, data supporting this advice are based on retrospective or prospective single-center studies involving few patients, have limited generalizability to multi-ethnic populations, and are controversial (3-10).

To develop more robust data to inform patients and their physicians regarding pregnancy in SLE, we leveraged the **PROMISSE** Study (**P**redictors of p**R**egnancy **O**utcome: bio**M**arker**I**n antiphospholipid antibody **S**yndrome and **S**ystemic lupus **E**rythematosus). PROMISSE is the largest multi-center, multi-ethnic and multi-racial study to prospectively assess the frequency of APO, clinical and laboratory variables that predict APO, and pregnancy-associated flare rates in SLE women with inactive or mild/moderate activity at conception.

Methods

Study Design

PROMISSE is a multicenter, prospective observational study of pregnancies in women with SLE (≥4 revised ACR criteria) (20), SLE and aPL, aPL alone, and healthy women at low risk of APO (≥1 successful pregnancy, no prior fetal death, and <2 miscarriages <10 weeks' gestation). Criteria for the healthy controls were designed to minimize factors unrelated to SLE that might impact outcome. This paper focuses on the SLE patients with or without aPL (Appendix Figure 1). Patients with aPL were previously reported (21).

Patient Population

Pregnant patients were enrolled between September 2003 and December 2012 at 8 U.S. and 1 Canadian site. Institutional review boards approved the protocol and consent forms; written informed consent was obtained from patients. Consecutive pregnant women meeting inclusion criteria were recruited up to 12 weeks' gestation precluding ascertainment of first trimester losses. Only one pregnancy for each patient was included.

Enrollment inclusion criteria were: singleton intrauterine pregnancy; age 18-45 years; hematocrit >26%. Since the overall goal of PROMISSE was to identify risk factors for and mechanisms of APO specifically attributable to lupus and/or aPL, other potential causes of APO were excluded: prednisone >20 mg/day; urine protein (mg)/creatinine (gram) ratio ≥1000; erythrocyte casts on urinalysis; serum creatinine >1.2 mg/dL; diabetes mellitus; blood pressure ≥140/90 mmHg at screening.

Definition of SLE Disease Activity and Flares during Pregnancy

Investigators used the Systemic Lupus Erythematosus Pregnancy Disease Activity Index (SLEPDAI), an instrument incorporating history, physical exam, and laboratory measures to

gauge lupus activity. The SLEPDAI was modified to discount physiologic changes of pregnancy that mimic disease activity to assure attribution to lupus (19, 22, 23).

A flare composite was used to define mild/moderate or severe flares, similar to that used in the SELENA (Safety of Estrogens in Lupus Erythematosus, National Assessment) trial, except SLEPDAI was substituted for SELENA SLEDAI (24) instrument. The composite includes: a) SLEPDAI score on the instrument; b) assessment of new or worsening disease activity, medication changes, and hospitalizations not captured on the SLEPDAI score; and c) physician's global-assessment (PGA) (range 0 to 3, with 0 indicating inactive disease and 3 severe disease). Study investigators were trained with “paper” pregnant SLE patients and case-report forms prepared by JPB (gold standard). The average correlation between investigator responses with the gold standard was 0.89 (95% CI: 0.83-0.95) and mean scores were all within ±15% of the gold standard. Inter-rater reliability estimated by the intraclass correlation coefficient was also high: 0.78 (95% CI: 0.61-0.89). In some situations, SLEPDAIs and PGAs were not completed because required serologic data and/or complete blood count (CBC) were unavailable. Flare status was then based on review of medical records and evidence of a clinical change and/or addition of new medications.

Adverse Pregnancy Outcomes

APO included one or more of the following: 1) fetal death after 12 weeks' gestation unexplained by chromosomal abnormalities, anatomic malformation, or congenital infection; 2) neonatal death prior to hospital discharge due to complications of prematurity and/or placental insufficiency (e.g. abnormal fetal surveillance test(s), abnormal Doppler flow velocimetry waveform analysis suggestive of fetal hypoxemia, oligohydramnios (25); 3) preterm delivery or termination of pregnancy <36 weeks due to gestational hypertension, preeclampsia, or placental insufficiency; 4) small for gestational age (SGA) neonate, defined as birth weight <5th percentile absent anatomical or chromosomal abnormalities.

Screening and Follow-Up Visits

Screening evaluation included history, ACR criteria, physical examination, CBC, comprehensive metabolic panel, urinalysis, and random or 24-hour urine collection for protein/creatinine ratio (if dipstick >1+). Serological profiles (anti-dsDNA, anti-SSA/Ro, SSB/La, and C3 and C4) were determined at local laboratories. Tests for aPL included anticardiolipin antibodies (IgG, IgM, and IgA), anti-β2 glycoprotein I (IgG, IgM), and lupus anticoagulant (LAC) and were performed at core laboratories (21).Tests were repeated each trimester. SLEPDAI and PGA were scored at screening, second trimester (20-23 weeks) and third trimester (32-35 weeks) visits.

Statistical Analysis

Bivariate associations of APO status and each predictor variable were evaluated with chi-square and Fisher's exact tests for categorical variables and T-test for continuous variables. Multivariable analyses were conducted using logistic regression models. Three separate models were fit to allow for greater flexibility in modeling the potentially time-varying relationship between predictors that were measured repeatedly during pregnancy and APO. Model 1 included variables measured at screening to identify baseline characteristics that are

predictive of an APO occurring at any time. Model 2 considered these baseline variables plus variables measured at 20-23 weeks to predict APO after 23 weeks, and Model 3 considered additional variables measured at 32-35 weeks to predict late APO. Decisions regarding variable selection at each step of model development were based on both clinical factors and statistical significance. For example, change in C3 is routinely monitored in SLE patients and was therefore prioritized for inclusion in models 2 and 3. When a continuous variable such as PGA yielded similar results whether dichotomized using a clinically justified cut point or in the original scale, the more clinically interpretable binary form was chosen. Ethnicity/race was dichotomized to non-Hispanic White versus all other groups because of sample size and clinical considerations. Potential confounding by enrollment site was also evaluated. The c-statistic was computed to assess the model's ability to discriminate between patients with and without APO. Leave-one-out cross-validation was conducted to evaluate the degree of over-fitting the model to the data (26).

Four patients who were lost to follow-up were excluded. Missing data in the predictor variables was addressed using the Markov chain Monte Carlo multiple imputation approach in the SAS procedure, PROC MI. The rates of missing data were 0% – 7% for baseline variables, 2% - 24% for 20-23 week variables and 5% - 27% for 32-35 week variables. The imputation model included outcome, all predictors in each logistic regression model, variables with missing values at the relevant visit for that model, and the following auxiliary variables deemed to influence the missing data value: past history of renal disease, thrombosis, thrombocytopenia, fetal death and heparin use for model 1, and platelet count, PGA, SLEPDAI, and C3 at the prior visits for models 2 and 3. Forty imputed data sets were generated for each model and results were combined with PROC MIANALYZE. To evaluate the robustness of our results, sensitivity analyses were conducted using the complete case approach for handling missing data, simpler imputation models that included final predictors and outcome variable only, and more complex imputation models. All analyses were performed using SAS software version 9.4 (SAS Institute, Inc., Cary, NC). Statistical significance was defined as a two-sided P-value <0.05.

Role of Funding Source

The funding source had no role in design, conduct, analysis, and decision to submit this manuscript for publication.

Results

Study Population and Pregnancy Outcomes

Of 741 pregnant women screened for PROMISSE, 385 SLE patients with documented outcomes were included (Appendix Figure 1). Patients were recruited from 9 sites. Forty-eight percent of patients were Non-Hispanic White, and 35% were African American or Hispanic White. Patients were inactive or had stable mild/moderate activity at entry, with a mean SLEPDAI of 2.8 (SD=3.0) and mean PGA of 0.39 (SD=0.54). In 91%, entry urine protein excretion was <500mg/day. Among 120 patients with a history of renal disease, available biopsy results included 19 Class III, 29 Class IV, 21 Class V, 8 Class III and V, and 2 Class IV/V.

One or more APO occurred in 19.0% (95% CI: 15.2% - 23.2%) of SLE patients. Fetal death occurred in 4%, neonatal death in 1%, indicated preterm delivery in 9%, and SGA neonate in 10% (Figure 1,Table 1). Seventeen patients (4.4%) had more than one outcome. Preeclampsia after 36 weeks (not included in the PROMISSE APO definition) occurred in 2%.APO rates were 15.4% (95% CI: 11.7% - 19.7%) in SLE patients without aPL and 43.8% (95% CI: 29.5% - 58.8%) in those with aPL. In contrast, 3% (95% CI: 1.1% - 6.4%) of PROMISSE controls had one or more APO. Congenital heart block (CHB) occurred in 1/154 anti-Ro exposed fetuses. Neonatal outcomes are presented in Appendix Table 1.

Bivariate Analyses of Risk Factors of APO

Demographic and Past Medical History—Mothers with APO were more likely to be African-American, to have BMI >30, prior fetal demise >10 weeks of gestation, past renal disease, and prior thrombosis, compared to mothers without APO (Table 2). APO rates also differed according to site of enrollment, reflecting inherent differences in the clinical and demographic characteristics of patients treated at those centers.

Laboratory Values at Screening Visit—The proportion of mothers classified as aPL-positive was higher in patients with APO compared to those without APO. Mothers with APO were more likely, at screening to have positive LAC, low platelet count, and low complement level (C3, C4, or CH50 below laboratory normal), although overall mean levels of C3 and C4 were in the normal range and not significantly different between those with or without APO. The proportions of patients with anti-ds DNA antibodies, anti-Ro, anti-La and urinary protein >500 mg/day were also similar across groups.

Medications and Disease Activity at Screening Visit—Baseline SLEPDAI and PGA were significantly higher in those with APO. Use of antihypertensive medications and heparin was also more common among patients with APO. Of 33 patients receiving antihypertensive medications, 13 had no evidence of prior nephritis and 28 had no proteinuria; of 83 patients receiving any type of heparin, 29 met study criteria for aPL positivity and 26 had prior thrombosis. Glucocorticoids were not associated with APO.

Maternal Disease Activity during Follow-Up—Table 3 summarizes disease activity measures and laboratory parameters obtained at 20-23 weeks on 370 patients still pregnant at 23 weeks, and variables measured at 32-35 weeks for 318 patients at 35 weeks. Among patients with known flare status, 12.7% (95% CI: 9.4% - 16.5%) had a mild/moderate flare and 2.5% (95% CI: 1.1% - 4.7%) had a severe flare at 20-23 weeks; 9.6% (95% CI: 6.5% - 13.5%) had a mild/moderate flare and 3.0% (95% CI: 1.4% - 5.6%) had a severe flare at 32-35 weeks. Severe flares included nephritis (9), pleuritis (6), arthritis (5), thrombocytopenia (3), and cerebritis, myositis, and pericarditis (1 each) with some patients having more than one organ system involved.

At both 20-23 weeks and 32-35 weeks, smaller increases in C3 from baseline, higher SLEPDAI, and higher PGA scores were observed in patients with APO. Platelet counts were also significantly lower at 20-23 weeks in those with APO. Patients with APO were more likely to have flared in second or third trimesters. Albeit rare, an increase in proteinuria of

>500 mg/day from the prior visit during second or third trimesters was not associated with subsequent APO. Anti-dsDNA antibodies and C4 levels in the second or third trimester did not differ between patients with or without APO.

Multivariable Analyses for Risk Factors of APO

Baseline variables which were independently predictive of APO at any time included LAC, antihypertensive use, PGA score>1, and lower platelet count. Non-Hispanic White ethnicity/race was associated with a lower risk of APO, compared to the other race/ethnic groups combined. LAC status and antihypertensive use on risk of APO were strongly related to risk of APO. Similar baseline predictors of APO were identified in analyses restricted to primigravid patients (results not shown).

Variables at screening that predicted APO after 23 weeks were identical to predictors of APO at any time: antihypertensive use, LAC, PGA score >1, and lower platelet count, with non-Hispanic White ethnicity/race associated with lower risk of APO (Table 4 Model 2). In addition, maternal flares in second trimester, increase in SLEPDAI score, and less of an increase in C3 level from baseline, predicted APO after 23 weeks. Adjusted odds of an APO was nearly 6-fold higher among women who had a severe flare compared to those who did not.

Many baseline and second trimester variables associated with risk of APO were also predictive of APO after 35 weeks, but reduced sample size and number of events diminished power (Table 4 Model 3). Statistically significant predictors were antihypertensive use at screening, LAC status, lower platelet count, and occurrence of severe flare between 32-35 weeks. The magnitudes of the effects of Non-Hispanic White ethnicity/race, PGA>1 and change in C3 on risk of APO were similar to those in models 1 and 2, but not did reach statistical significance. The limited sample size and number of events may not support a model with this number of covariates; thus, these results should be interpreted cautiously.

In sensitivity analyses using alternative approaches for handling missing data, the main results and inferences remained the same for models 1 and 2 (Appendix Table 2). Model 3 was more sensitive to how missing data were handled, but baseline antihypertensive and low platelet count, and severe flare in third trimester were consistently predictive of APO after 35 weeks across the different approaches considered.

Among 129 women known to be non-Hispanic White, not on antihypertensive therapy, LAC negative, PGA ≤1 at screening, and platelet count >100,000, only 10 (7.8%, 95% CI: 3.8% - 13.8%) had an APO at any time and fetal or neonatal death rate was 3.9% (95% CI: 1.3% - 8.8%). In comparison, APO rate was 58.0% (95% CI: 43.2% - 71.8%) and fetal/neonatal death rate 22.0% (95% CI: 11.5% - 36.0%) in the combined group of 50 women known to be either LAC positive, or LAC negative but non-White or Hispanic and treated with antihypertensive medications. Seven of 8 LAC positive patients with either PGA >1, on antihypertensive medication or with platelet counts <100,000 at screening experienced an APO.

Discussion

In our large cohort of prospectively followed SLE patients with inactive or stable mild/moderate activity at conception, 81% of pregnancies were uncomplicated, 5% ended in fetal or neonatal death, and severe maternal flares occurred in <3%. Importantly, the rate of APOs was <8%, with fetal or neonatal deaths accounting for fewer than half of these events in non-Hispanic White women with a PGA score ≤1, negative LAC, no antihypertensives, and platelet count >100,000. The frequency of CHB was half the reported rate of 2% (29, 30) perhaps due to a protective effect of hydroxychloroquine (31, 32).

Physicians often use anti-dsDNA antibodies and complement to anticipate clinical outcome. In this study, anti-dsDNA positivity was not associated with APO. However, patients with APO had baseline complement levels below normal ranges more often, although first trimester mean C3 and C4 values were in the normal range and not predictive of APO. Despite mean levels of C3 and C4 remaining in the normal range as pregnancy progressed, less of an increase in C3 levels from baseline to second trimester was predictive of an APO after 23 weeks. Interpretation of complement is confounded in pregnancy because circulating complement reflects both synthesis (enhanced by estrogen), and consumption (33). The absence of an increase in complement during pregnancy suggests increased complement activation with generation of anaphylatoxins which drive poor placental vascularization and trophoblast injury (34).

Other studies of pregnant women with SLE have assessed serological variables. In a single-center study of 40 pregnancies in women with mild/moderate lupus activity, clinical and laboratory variables evaluated between 20-28 weeks revealed 9 of 38 live births were preterm with low C4, the only marker associated with this outcome (19). A retrospective study of 267 pregnancies in 203 non-Hispanic SLE patients, one third of whom had APO, showed clinical and serologic activity (positive anti-dsDNA or low complement)in the second trimester was associated with fetal loss and preterm birth, even in those with low clinical activity (11). Our observations suggest that low complement levels in second and third trimesters were not helpful, but those with an APO had less of an increase in C3 later in pregnancy compared to baseline.

Findings from PROMISSE suggest that there is an increased risk of APO in patients with history of nephritis, although the association was not significant in multivariable analyses. A retrospective study of 107 pregnancies in 83 SLE patients found higher frequencies of preterm delivery (30%) and preeclampsia (28%) in women with past nephritis compared to 11% and 16%, respectively, in women without prior nephritis (11). Other retrospective studies did not find a relationship between previous nephritis and APO, and inclusion of more than one pregnancy in the same patient detracts from their reliability (7, 35). While a recent prospective study limited to patients with past lupus nephritis concluded that patients with quiescent disease at conception had favorable pregnancy outcomes (36), a meta-analysis of 37 studies with 1,842 patients showed that prior nephritis was associated with higher rates of preeclampsia (37).

Limitations of this study are acknowledged. The predictive models have not been externally validated and the number of adverse events in model 3 was limited. Given the timing of recruitment, PROMISSE did not address first trimester losses. Additional biomarkers should be evaluated to identify high risk patients and define mechanisms of APO in SLE patients.

Our study is the largest prospective study to date investigating pregnancy in SLE. In patients with inactive or stable mild/moderate activity, pregnancy is safer for mother and child than was considered in the past, with good outcomes in 81% of patients. Because women with high activity (e.g. active nephritis or prednisone >20 mg/day) were excluded, our findings may not apply to these individuals. Importantly, in the absence of baseline features indicative of risk (LAC positive, antihypertensive medications, PGA >1, Hispanic or non-White ethnicity/race, low platelet count), pregnancy outcomes are highly favorable. Patients with risk factors identified for APO should be monitored more closely and considered for future interventional trials to prevent APO.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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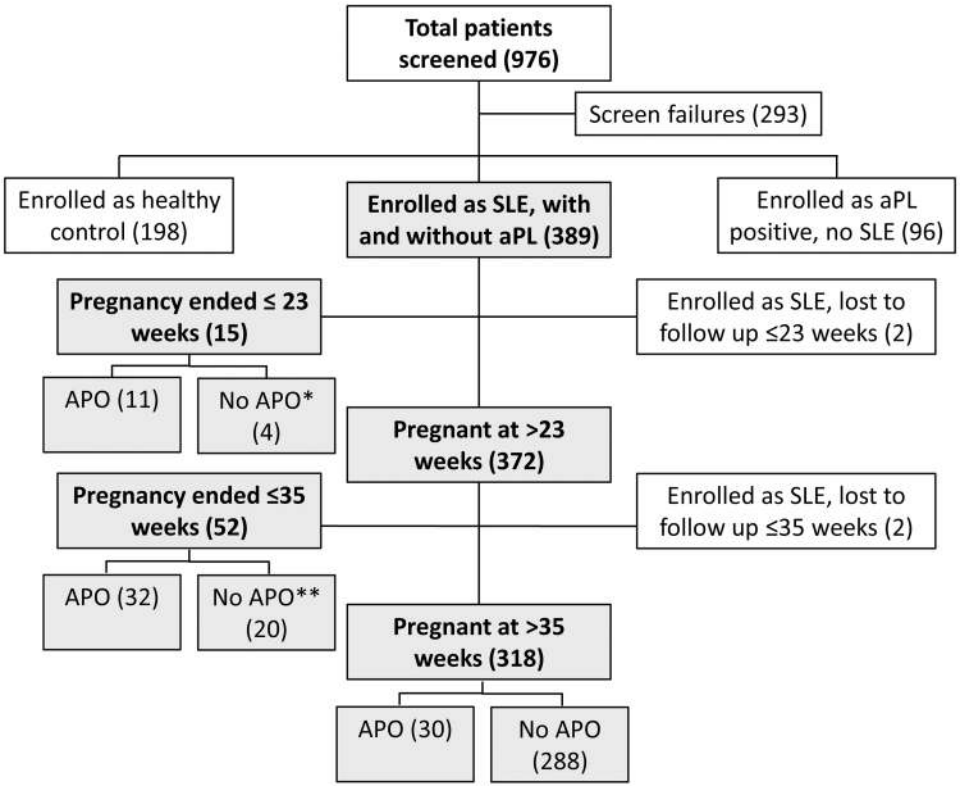
Appendix



Appendix Figure 1. Patient enrollment and classification for the PROMISSE Study

Pregnant women at <12 weeks' gestation with antiphospholipid antibody (aPL) positivity and systemic lupus erythematosus (SLE) and healthy controls were screened. Exclusion criteria included: multifetal pregnancy, prednisone >20 mg/day, blood pressure ≥140/90 mm Hgurine protein (mg)/creatinine (gram) ratio ≥1,000 mg protein/gm creatinine on 24-hour urine or spot urine collection, serum creatinine >1.2 mg/dl, screened too late in pregnancy, and previously enrolled in PROMISSE. Healthy pregnant women were enrolled if they had ≥ one successful pregnancy, no history of fetal death, and no more than 1 miscarriage <10 weeks' gestation and no antiphospholipid antibodies. The current study included all PROMISSE patients who met American College of Rheumatology criteria for systemic lupus erythematosus (SLE). Number of subjects is shown in parenthesis.

*Four patients whose pregnancy ended at <23 weeks did not meet study criteria for primary study outcome: elective termination (1), incompetent cervix (2), PPROM (1).See Table 1.

**Twenty patients whose pregnancy ended at <35 weeks did not meet study criteria for primary study outcome: indicated delivery for poor obstetric history (1), for SLE flare (1), for bleeding placental abruption (1); termination for complete heart block (1); fetal death due to trisomy 18 (1); PPROM and/or premature labor (15).See Table 1.

APO = adverse pregnancy outcome; aPL = antiphospholipid antibodies; PPROM = premature preterm rupture of membranes

Appendix Table 1
Neonatal Outcomes (includes only live-born neonates)

	Gestational Age of Pregnancy Outcome in Completed Weeks	
	>23 to ≤35 weeks (N)	**>35 weeks (N)**
Live births from pregnancies with PROMISSE Study-defined APOs	27	28
5 minute Apgar <7	40.7% (27) *	3.8% (26)
5 minute Apgar <5	40.7% (27)	3.8% (26)
Need for ventilator support (CPAP or intubation)	84.2% (19)	10.5% (19)
Neonatal hospitalization >5 days (in neonates living to hospital discharge)	88.2% (17)	21.7% (23)
Neonatal death prior to discharge due to complications of prematurity	5[a]	0
Other neonatal complications	1[b]	1[d]
Live births from pregnancies from pregnancies without PROMISSE Study-defined APOs	20	288
5 minute Apgar <7	5.6% (18)	0.4% (229)
5 minute Apgar <5	0% (18)	0.4% (229)
Need for ventilator support (CPAP or intubation)	41.7% (12)	2.6% (229)
Neonatal hospitalization >5 days	71.4% (14)	2.6% (229)
Other neonatal complications	1[c]	4[e]

[a] Includes 5 cases of extreme prematurity, including 2 cases with sepsis and 1 case with respiratory distress syndrome

[b] 1 case of sepsis

[c] 1 case of blindness

[d] 1 case of sepsis and respiratory distress syndrome

[e] Includes 1 case of tachycardia, 1 case of hydronephrosis, 1 case of pneumothorax and 1 case of Tetralogy of Fallot with severe pulmonary atresia

* % subjects who are positive for the parameter; N=total number of patients with available data for the specific parameter

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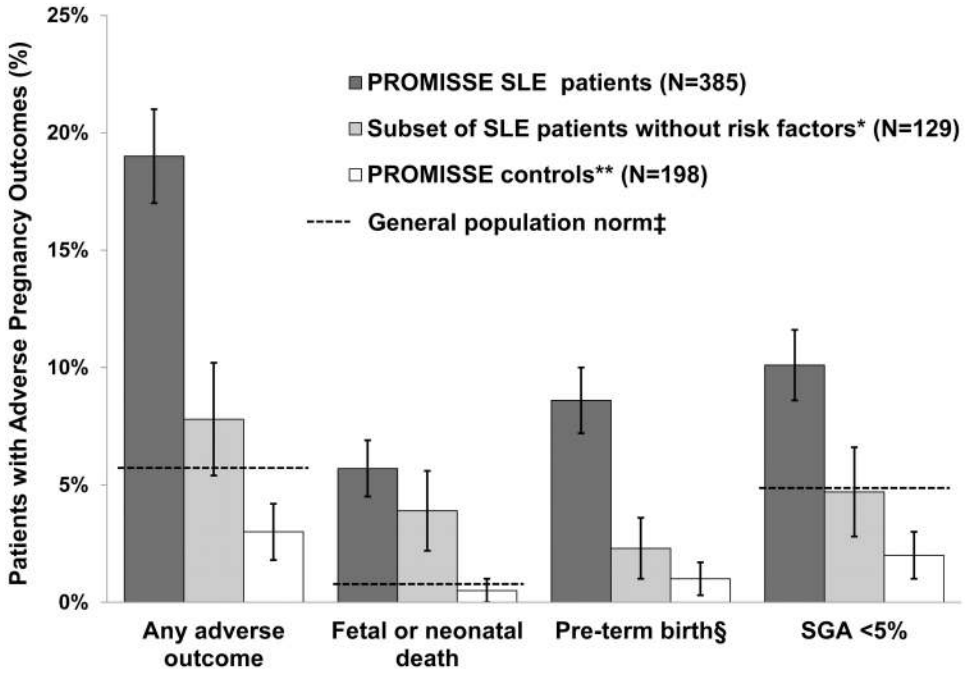

Figure 1. Frequency of Adverse Pregnancy Outcomes in Patients and Healthy Controls

Error bars represent 95% confidence bounds.

*SLE patients with no risk factors are non-Hispanic White, LAC negative, PGA ≤1, platelet count >100,000 and not treated with antihypertensive medications at baseline. They constitute a subset of "All SLE".

† Because women enrolled in the PROMISSE control group had at least one successful pregnancy, no history of fetal death, no more than 1 miscarriage <10 weeks' gestation, and no underlying medical problems requiring treatment, it was anticipated that their pregnancy outcomes would be better than those in unselected healthy patients, particularly nulliparous women. In addition to the APOs in the bar graph, the healthy control patients had 10 (5.1%) adverse outcomes that did not meet the study primary outcome definition: ≤23 weeks: 2 genetic terminations; >23 to ≤35 weeks: 3 premature preterm rupture of membranes and/or spontaneous preterm births, 2 placental abruptions, 1 delivery for fetal indications (supraventricular tachycardia and hydrops); >35 weeks: 3 premature preterm rupture of membranes and/or spontaneous preterm births (event numbers may add to more than total because some women had more than one adverse outcome).

‡ When available, pregnancy outcomes in the general population are represented by the broken line (27, 28). No general population norm line is available for the study definition used for pre-term birth (see below).

§ Pre-term birth is defined as delivery at <36 weeks and indicated by gestational hypertension, preeclampsia, or placental insufficiency.

SGA = small for gestational age

Table 1

Pregnancy outcomes in SLE patients*

	Gestational Age of Pregnancy Outcome in Completed Weeks		
	≤23 weeks	>23 to ≤35 weeks	>35 weeks
Pregnancies with PROMISSE Study-defined Adverse Pregnancy Outcomes**	11	32	30
Average gestational age at end of pregnancy (weeks)	18.2	29.6	37.7
Study APOs			
Fetal death	11	5	2
Neonatal death	0	5	0
Birth < 36 wks due to placental insufficiency, gestational hypertension, or preeclampsia	4	27	2
Small-for-gestational age (birthweight <5th percentile). Patients with SGA had the following other pregnancy complications:	3	9	27
a) Premature preterm rupture of membranes and/or premature labor	0	0	4
b) Delivery > 35 weeks with GHTN/PE, oligohydramnios	0	0	3[e]
Pregnancies with outcomes that were not in the PROMISSE Study definitions**	4	20	52
Average gestational age at end of pregnancy (weeks)	19.6	32.1	38.7
Termination of pregnancy	1[a]	2[b]	0
Incompetent cervix	2	0	0
Premature preterm rupture of membranes and/or premature labor	1	14	14
Delivery > 35 weeks with GHTN/PE, oligohydramnios	0	0	28[f]
Delivery for other obstetric indications	0	2[c]	5[g]
Delivery for maternal indications	0	2[d]	6[h]
Uncomplicated pregnancies	0	0	236

*See Figure 1 for pregnancy outcomes in healthy control population

**May add up to more than the total because patients may have multiple outcomes.

[a]Elective

[b]1 CHB, 1 Trisomy 18

[c]1 placental abruption, 1 poor obstetric Hx

[d]2 SLE flares

[e]2 PE/GHTN>36W, 1 oligohydramnios

[f]12 PE/GHTN>36W, 16 oligohydramnios

[g]3 chorioamnionitis, 2 poorobstetricHx

[h]5 thrombocytopenia, 1 congestive heart failure

Table 2

Characteristics of Pregnant SLE Patients at Baseline and Their Association with Adverse Pregnancy Outcome

	Patient Characteristic	Total N=385 (%)	No AP0 N=312 (%)	APO N=73 (%)	P-value*
Demographic	Site, N (%)				0.033
	NYU	95 (24.7)	82 (26.3)	13 (17.8)	
	Toronto	95 (24.7)	77 (24.7)	18 (24.7)	
	Johns Hopkins	86 (22.3)	75 (24.0)	11 (15.1)	
	Hospital for Special	47 (12.2)	33 (10.6)	14 (19.2)	
	Surgery	29 (7.5)	23 (7.4)	6 (8.2)	
	University of Utah	22 (5.7)	14 (4.5)	8 (11.0)	
	Oklahoma	8 (2.1)	6 (1.9)	2 (2.7)	
	University of Chicago	2 (0.5)	1 (0.3)	1 (1.4)	
	Columbia	1 (0.3)	1 (0.3)	0 (0.0)	
	Northwestern				
	Ethnicity/Race, N (%)				0.053
	Non-Hispanic White	184 (47.8)	157 (50.3)	27 (37.0)	
	Hispanic White	58 (15.1)	43 (13.8)	15 (20.6)	
	African American	78 (20.3)	58 (18.6)	20 (27.4)	
	Asian	42 (10.9)	36 (11.5)	6 (8.2)	
	Other	10 (2.6)	10 (3.2)	0 (0.0)	
	Don't know/Refused to answer	13 (3.4)	8 (2.6)	5 (6.9)	
	BMI, N (%)				0.048
	<25	217 (60.3)	183 (62.9)	34 (49.3)	
	25-30	82 (22.8)	65 (22.3)	17 (24.6)	
	>30	61 (16.9)	43 (14.8)	18 (26.1)	
	Missing	25	21	4	
	Mean Age (SD), N=385	30.93(4.9)	31.04 (4.8)	30.49 (5.3)	0.39
Clinical History	Pregnancy Number, N (%)				0.36
	1	159 (41.3)	135 (43.3)	24 (32.9)	

	Patient Characteristic	Total N=385 (%)	No AP0 N=312 (%)	APO N=73 (%)	P-value*
	2	102 (26.5)	82 (26.3)	20 (27.4)	
	3	66 (17.1)	51 (16.4)	15 (20.6)	
	4+	58 (15.1)	44 (14.1)	14 (19.2)	
	Renal Disease, N (%)				0.042
	No	265 (68.8)	222 (71.2)	43 (58.9)	
	Yes	120 (31.2)	90 (28.9)	30 (41.1)	
	Platelets <100,000, N (%)				0.058
	No	319 (82.9)	264 (84.6)	55 (75.3)	
	Yes	66 (17.1)	48 (15.4)	18 (24.7)	
	Prior Thrombosis, N (%)				0.014
	No	354 (92.0)	292 (93.6)	62 (84.9)	
	Yes	31 (8.1)	20 (6.4)	11 (15.1)	
	Prior Fetal Death > 10 weeks, N (%)				0.002
	No	344 (89.4)	286 (91.7)	58 (79.5)	
	Yes	41 (10.7)	26 (8.3)	15 (20.6)	
	Prior Premature Birth <34 weeks, N (%)				0.104
	No	378 (98.2)	308 (98.7)	70 (95.9)	
	Yes	7 (1.8)	4 (1.3)	3 (4.1)	
Laboratory Values	Anti-dsDNA, N (%)				0.51
	Negative	219 (58.4)	180 (59.2)	39 (54.9)	
	Positive	156 (41.6)	124 (40.8)	32 (45.1)	
	Missing	10	8	2	
	aPL ***, N (%)				<0.001
	Negative	337 (87.5)	285 (91.4)	52 (71.2)	
	Positive	48 (12.5)	27 (8.7)	21 (28.8)	

Patient Characteristic	Total N=385 (%)	No AP0 N=312 (%)	APO N=73 (%)	P-value*
LAC, N (%)				<0.001
Negative	351 (91.2)	297 (95.2)	54 (74.0)	
Positive	34 (8.8)	15 (4.8)	19 (26.0)	
Anti-Ro, N (%)				0.21
Negative	221 (59.1)	175 (57.6)	46 (65.7)	
Positive	153 (40.9)	129 (42.4)	24 (34.3)	
Missing	11	8	3	
Anti-La, N (%)				0.57
Negative	311 (84.3)	253 (83.8)	58 (86.6)	
Positive	58 (15.7)	49 (16.2)	9 (13.4)	
Missing	16	10	6	
Protein > 500mg/day, N (%)				0.40
No	339 (91.1)	277 (91.7)	62 (88.6)	
Yes	33 (8.9)	25 (8.3)	8 (11.4)	
Missing	13	10	3	
Platelets				
Mean (SD), N=379	253.04 (84.3)	259.13 (85.8)	226.17(71.6)	0.003
< 100,000, N (%)				0.065
No	370 (97.6)	304 (98.4)	66 (94.3)	
Yes	9 (2.4)	5 (1.6)	4 (5.7)	
Missing	6	3	3	
Low Complement**, N (%)				0.019
No	252 (66.0)	213 (68.7)	39 (54.2)	
Yes	130 (34.0)	97 (31.3)	33 (45.8)	
Missing	3	2	1	
Mean C3 in g/L (SD), N=364	1.05 (0.3)	1.05 (0.3)	1.02 (0.3)	0.31
Mean C4 in g/L (SD), N=358	0.20 (0.1)	0.20 (0.1)	0.19 (0.1)	0.60

	Patient Characteristic	Total N=385 (%)	No APO N=312 (%)	APO N=73 (%)	P-value*
Disease Activity	SLEPDAI				
	Mean (SD), N=381	2.79 (3.0)	2.58 (2.9)	3.68 (3.2)	0.005
	> 4				0.009
	No	311 (81.6)	260 (84.1)	51 (70.8)	
	Yes	70 (18.4)	49 (15.9)	21 (29.2)	
	Missing	4	3	1	
	PGA				
	Mean (SD), N=367	0.39 (0.5)	0.35 (0.5)	0.59 (0.6)	0.005
	> 1				0.003
	No	328 (89.4)	275 (91.7)	53 (79.1)	
	Yes	39 (10.6)	25 (8.3)	14 (20.9)	
	Missing	18	12	6	
Current Medications	Glucocorticoids, N (%)				0.29
	No	232 (60.3)	192 (61.5)	40 (54.8)	
	Yes	153 (39.7)	120 (38.5)	33 (45.2)	
	Hydroxychloroquine, N (%)				0.38
	No	136 (34.3)	107 (34.3)	29 (39.7)	
	Yes	249 (64.7)	205 (65.7)	44 (60.3)	
	Azathioprine, N (%)				0.184
	No	316 (82.1)	260 (83.3)	56 (76.7)	
	Yes	69 (17.9)	52 (16.7)	17 (23.3)	
	Heparin, N (%)				0.009
	No	302 (78.4)	253 (81.1)	49 (67.1)	
	Yes	83 (21.6)	59 (18.9)	24 (32.9)	
	Aspirin, N (%)				0.48
	No	250 (64.9)	200 (64.1)	50 (68.5)	
	Yes	135 (35.1)	112 (35.9)	23 (31.5)	
	Antihypertensives, N (%)				< 0.001

	Patient Characteristic	Total N=385 (%)	No AP0 N=312 (%)	APO N=73 (%)	P-value*
	No	352 (91.4)	295 (94.6)	57 (78.1)	
	Yes	33 (8.6)	17 (5.5)	16 (21.9)	

APO = adverse pregnancy outcome; anti-dsDNA = anti-double stranded DNA; LAC = lupus anticoagulant; SLEPDAI = Systemic Lupus Erythematosus Pregnancy Disease Activity Index; PGA = physician's global assessment

*P-values based on available data; proportion of missing data < 10% for all variables

**Low is defined as C3 and/or C4 below normal value in the local laboratory

***APL is defined as aCL IgG ≥40 GPL units; IgM ≥40 MPL units and/or positive LAC: RVVT, Kaolin, dilute TTI or PTT LA and/or anti-β2GPI IgG ≥40 GPL units; IgM ≥40 MPL units at least twice between 6 weeks and 5 years apart of which one must be during the PROMISSE pregnancy at a core lab, as previously described (21).

Table 3

Association of Laboratory Parameters and Maternal Lupus Disease Activity During Pregnancy with Adverse Outcomes

20 – 23 Week Measures*	Total N=370 (%)	No APO N=308 (%)	APO N=62 (%)	P-value**
Anti-dsDNA				
Negative	188 (60.5)	162 (61.8)	26 (53.1)	0.25 (0.45)
Positive	123 (39.6)	100 (38.2)	23 (46.9)	
Missing	59	46	13	
Change in protein > 500mg/day from baseline				0.22 (0.27)
No	346 (97.2)	290 (97.6)	56 (94.9)	
Yes	10 (2.8)	7 (2.4)	3 (5.1)	
Missing	14	11	3	
Mean Platelets (SD), N=318	241.90 (76.9)	246.87 (75.4)	218.64 (80.6)	0.013(0.004)
<100,000, N (%)				
No	308 (96.9)			0.079 (0.063)
Yes	10 (3.1)	256 (97.7)	52 (92.9)	
Missing	52	6 (2.3)	4 (7.1)	
		46	6	
Low complement				
No	226 (72.2)	195 (74.1)	31 (62.0)	0.079 (0.167)
Yes	87 (27.8)	68 (25.9)	19 (38.0)	
Missing	57	45	12	
C3				
Mean in g/L (SD), N=300	1.14 (0.3)	1.17 (0.3)	1.03 (0.3)	0.002(0.007)
Mean increase from baseline (SD),N=289	0.10 (0.2)	0.11 (0.2)	0.04 (0.2)	0.025(0.009)
C4				
Mean in g/L (SD), N=295	0.20 (0.1)	0.20 (0.1)	0.20 (0.1)	0.96(0.79)
Mean increasefrom baseline (SD),N=281	0.00 (0.1)	0.00 (0.0)	0.01 (0.1)	0.71(0.73)
Mean SLEPDAI (SD), N=319	2.22 (2.5)	1.93 (2.1)	3.67 (3.4)	<0.001(<0.001)
>4				
No	280(87.8)	241 (90.9)	39 (72.2)	<0.001(<0.001)
Yes	39 (12.2)	24 (9.1)	15 (27.8)	
Missing	51	43	8	
Mean PGA (SD), N=301	0.38 (0.5)	0.34 (0.5)	0.57 (0.6)	0.015(0.009)
> 1				
No	277 (92.0)	234 (94.0)	43 (82.7)	0.011(0.019)
Yes	24 (8.0)	15 (6.0)	9 (17.3)	
Missing	69	59	10	

20 – 23 Week Measures*	**Total N=370 (%)**	**No APO N=308 (%)**	**APO N=62 (%)**	**P-value****
Flare				
No	308 (84.9)	269 (88.5)	39 (66.1)	<0.001 (<0.001)
Mild/moderate	46 (12.7)	30 (9.9)	16 (27.1)	
Severe	9 (2.5)	5 (1.6)	4 (6.8)	
Unknown	7	4	3	
32 – 35 Week Measures*	**TotalN=318 (%)**	**No APON=288 (%)**	**APON=30 (%)**	**P-value****
Anti-dsDNA				
Negative	160 (65.3)	146 (65.5)	14 (63.6)	0.86 (0.93)
Positive	85 (34.7)	77 (34.5)	8 (36.4)	
Missing	73	65	8	
Change in protein > 500mg/day from second trimester				
No	285 (97.3)	261 (97.8)	24 (92.3)	0.152(0.104)
Yes	8 (2.7)	6 (2.3)	2 (7.7)	
Missing	25	21	4	
Mean Platelets (SD), N=258	233.98 (75.6)	234.65 (75.4)	227.46 (79.2)	0.66(0.61)
<100,000, N (%)				
No	254 (98.5)			0.32(0.46)
Yes	4 (1.6)	231 (98.7)	23 (95.8)	
Missing	60	3 (1.3)	1 (4.2)	
		54	6	
Low complement				
No	191 (77.0)	177 (78.3)	14 (63.6)	0.118(0.120)
Yes	57 (23.0)	49 (21.7)	8 (36.4)	
Missing	70	62	8	
C3				
Mean in g/L (SD), N=241	1.25 (0.3)	1.26 (0.3)	1.13 (0.4)	0.147(0.027)
Mean increase from baseline (SD), N=234	0.19 (0.2)	0.20 (0.2)	0.14 (0.2)	0.18(0.019)
C4				
Mean in g/L (SD), N=239	0.21 (0.1)	0.22 (0.1)	0.21 (0.1)	0.90(0.80)
Mean increase from baseline (SD), N=231	0.01 (0.1)	0.01 (0.1)	0.01 (0.1)	0.96(0.59)
Mean SLEPDAI (SD), N=265	1.99 (2.7)	1.83 (2.5)	3.74 (4.4)	0.051(<0.001)
>4, N (%)				
No	239 (90.2)	221 (91.3)	18 (78.3)	0.060(0.006)
Yes	26(9.8)	21 (8.7)	5 (21.7)	
Missing	53	46	7	
Mean PGA (SD), N=262	0.31 (0.5)	0.30 (0.4)	0.44 (0.6)	0.31 (0.038)
>1, N (%)				

20 – 23 Week Measures*	Total N=370 (%)	No APO N=308 (%)	APO N=62 (%)	P-value**
No	247 (94.3)	228 (95.0)	19 (86.4)	0.120 (0.047)
Yes	15 (5.7)	12 (5.0)	3 (13.6)	
Missing	56	48	8	
Flare				
No	264 (87.4)	249 (89.3)	15 (65.2)	<0.001 (<0.001)
Mild/moderate	29 (9.6)	25 (9.0)	4 (17.4)	
Severe	9 (3.0)	5 (1.8)	4 (17.4)	
Unknown	16	9	7	

APO = adverse pregnancy outcome; anti-dsDNA = anti-double stranded DNA; SLEPDAI = Systemic Lupus Erythematosus Pregnancy Disease Activity Index; PGA = physician's global assessment

*20-23 week data are based on patients who had not delivered by 23 weeks and 32-35 week data are based on patients who had not delivered by 35 weeks.

**Top p-value based on available data, bottom p-value in () based on multiply imputed data (see Statistical Analysis).

Table 4

Predictors of Adverse Pregnancy Outcomes from Logistic Regression models

Predictor Variable	Model 1: APO at any time during pregnancy (N=385, Events = 73)		Model 2: APO after 23 weeks (N=370, Events = 62)		Model 3: APO after 35 weeks (N = 318, Events = 30)	
Baseline	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Non-Hispanic White : Yes vs No	0.45 (0.24-0.84)	0.013	0.44 (0.21-0.93)	0.032	0.40 (0.15-1.08)	0.071
Current Antihypertensive Use: Yes vs No	7.05 (3.05-16.31)	<0.001	13.14 (4.79-36.04)	<0.001	7.69 (2.37-24.96)	<0.001
LAC status: Positive vs Negative	8.32 (3.59-19.26)	<0.001	7.80 (2.83-21.45)	<0.001	4.04 (1.05-15.61)	0.043
PGA: > 1 vs ≤1	4.02 (1.84-8.82)	<0.001	3.78 (1.47-9.73)	0.006	3.20 (0.93-10.96)	0.064
Platelet Count (per 50,000 decrease)	1.33 (1.09-1.63)	0.006	1.41 (1.12-1.78)	0.003	1.35 (1.01-1.82)	0.046
20-23 weeks						
Flare:						
Mild/Moderate vs None			3.14 (1.25-7.90)	0.0150		
Severe vs None			5.87 (1.15-29.96)	.033		
Change in C3 from baseline (per 0.10 g/L decrease)			1.24 (1.03-1.50)	0.025		
SLEPDAI (per 2 point increase)			1.43 (1.06-1.94)	0.020		
32-35 weeks						
Flare:						
Mild/Moderate vs None					1.95 (0.55-7.00)	0.30
Severe vs None					9.60 (1.95-47.35)	0.006
Change in C3 from baseline (per 0.10 g/L decrease)					1.21 (0.97-1.50)	0.087
C-statistic	0.78 (95% CI: 0.71-0.84)		0.84 (95% CI: 0.77-0.90)		0.79 (95% CI: 0.70 – 0.89)	
Cross-validated C-statistic	0.76 (95% CI: 0.69 – 0.83)		0.81 (95% CI: 0.74-0.88)		0.75 (95% CI:0.64-0.85)	

LAC = lupus anticoagulant; PGA = physician's global assessment; SLEPDAI = Systemic Lupus Erythematosus Pregnancy Disease Activity Index; Missing data for predictor variables was addressed using multiple imputation (see Statistical Analysis)