HHS Public Access

Author manuscript

Clin Rheumatol. Author manuscript; available in PMC 2017 July 01.

Published in final edited form as:

Clin Rheumatol. 2016 July ; 35(7): 1725–1732. doi:10.1007/s10067-016-3270-5.

Organ-Specific Systemic Lupus Erythematosus Activity during Pregnancy is Associated with Adverse Pregnancy Outcomes

Sara K. Tedeschi, MD, **Hongshu Guan, PhD**, **Alexander Fine, BS**, **Karen H. Costenbader, MD, MPH***, and **Bonnie Bermas, MD***

Brigham and Women's Hospital, Harvard Medical School, Department of Medicine, Division of Rheumatology, Immunology and Allergy, Boston, USA

Abstract

BACKGROUND—Systemic lupus erythematosus (SLE) is a disease of reproductive-age women and thus questions regarding how disease influences pregnancy outcomes arise. We investigated whether five specific types of SLE activity during the six months before conception or during pregnancy (nephritis, cytopenias, skin disease, arthritis, serositis) were associated with adverse pregnancy outcomes.

METHODS—We performed a retrospective cohort study of pregnancy outcomes among women with SLE at the Brigham and Women's Hospital Lupus Center. Adverse pregnancy outcomes included pre-eclampsia, preterm delivery, elective termination due to SLE, spontaneous miscarriage at weeks 12–20, and stillbirth. SLE and obstetric history, laboratories, and medications were obtained from electronic medical records. Generalized linear mixed models adjusting for potential confounders were used to identify predictors of any adverse pregnancy outcome.

RESULTS—Most pregnancies resulted in a live, term delivery (76.5%). After adjustment for Hispanic ethnicity, prior adverse pregnancy outcome and medication use six months before conception, nephritis during pregnancy (OR 3.6, 95% CI [1.0–12.8]), cytopenias during pregnancy (OR 3.9, 95% CI [1.3–11.4]), and serositis during pregnancy (OR 5.9, 95%CI [1.0–34.0]) were significantly associated with adverse pregnancy outcome.

CONCLUSIONS—Specific types of SLE disease activity during pregnancy were related to adverse pregnancy outcome. Nephritis, cytopenias and serositis carried a higher risk of adverse pregnancy outcome, suggesting that these abnormalities should be carefully monitored during pregnancy.

Keywords

SLE; disease activity; epidemiology

Corresponding author: Sara K. Tedeschi, MD, Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115 USA, stedeschi1@partners.org, Telephone: +1-617-732-5325.

*co-senior authors

Conflicts of interest The authors declare they have no conflicts of interest

INTRODUCTION

Systemic lupus erythematosus (SLE) is a disease of reproductive-age women and thus questions regarding how SLE affects pregnancy outcomes frequently arise. In the past, women with SLE were often counseled to avoid pregnancy due to concern for the mother's health and because of poor pregnancy outcomes. Adverse pregnancy outcomes in women with SLE include fetal loss, pre-eclampsia, preterm delivery, and intra-uterine growth retardation. Prior studies have demonstrated that active SLE (by a composite disease activity measure such as the SLE- Pregnancy Disease Activity Index,[1] BILAG-P,[2] and Lupus Activity Index-Pregnancy[3]) during the six months prior to conception, active disease during pregnancy, any history of lupus nephritis, and the presence of antiphospholipid antibodies are associated with worse pregnancy outcomes. Additionally, a recent study suggested that low platelet count during pregnancy may contribute to poor pregnancy outcome.[4]

We previously reported that specific types of SLE activity six months before conception were associated with continued or worsened SLE activity of the same type during pregnancy.[5] Specifically, we demonstrated that nephritis, cytopenias, serositis, and skin disease in the six months prior to conception predicted the same type of SLE disease activity during pregnancy whereas arthritis symptoms in the six months before conception did not. In the present study, we investigated whether these same types of organ-specific SLE activity in the six months before conception or during pregnancy were likewise associated with adverse pregnancy outcomes. Based on previous reports, we hypothesized that active nephritis and cytopenias prior to and during pregnancy would be associated with a higher risk for adverse pregnancy outcomes.

METHODS

Study design

We performed a retrospective cohort study of women who all had a diagnosis of SLE, with four or more 1997 American College of Rheumatology (ACR) classification criteria,[6] and who were followed at the Brigham and Women's Hospital (BWH) Lupus Center. SLE diagnosis was confirmed via electronic medical record review by a second rheumatologist. Of the 1127 women with more than two visits to the BWH Lupus Center between 1990 and 2013, we identified those with one or more pregnancies during the study period, and with clinical and laboratory data available in the six months prior to conception and during pregnancy. The Department of Obstetrics and Gynecology at BWH is one of the oldest and largest, and performs 8000 deliveries per year. Thus, the majority of women included in our study delivered at BWH. We restricted our analyses to include pregnancies that progressed past 12 weeks gestation.

Adverse pregnancy outcome was defined as occurrence of one or more of the following: pre-eclampsia,[7, 8] preterm delivery (<37 weeks),[7, 9, 10] elective termination due to SLE activity, spontaneous miscarriage ≥12 weeks to <20 weeks, or stillbirth (fetal loss ≥20 weeks).[9, 11] Sensitivity analyses defined preterm as live birth <34 weeks gestation, given that live birth at 34–37 weeks is considered "late preterm" and may be more favorable than

delivery <34 weeks.[12, 13] As in another recent SLE pregnancy cohort, we did not consider pregnancy loss before 12 weeks as an adverse pregnancy outcome related to SLE.[4] Elective terminations due to SLE activity as documented in the medical record were treated as an exception, and were included regardless of gestational age, given that omitting these women with the most severe SLE disease activity—which resulted in pregnancy termination to protect the woman's health—could bias our results.

Data collection

For each pregnancy, we recorded the date of conception as documented in the electronic medical record; if not clearly documented in the medical record, this date was calculated based on the gestational age at completion of pregnancy. Using the date of conception as the index date, we determined the six-month period prior to the date of conception. We reviewed the electronic medical record from the time of the woman's initial visit to the BWH Lupus Center through the duration of pregnancy, and recorded information on demographics (age at SLE diagnosis, age at conception, self-reported race/ethnicity), medication use (whether a range of individual SLE-related medications had been prescribed ever, within six months of conception, and/or during pregnancy), laboratory data (SLE serologies and antiphospholipid antibodies [APLAb] collected prior to conception; complete blood counts, complement levels, and urinalysis with sediment at each assessment during the six months prior to conception and during pregnancy).

SLE clinical history was collected from records of clinic visits for the six months prior to conception and during pregnancy, and was categorized into five organ-specific types of SLE activity: cytopenias (WBC <4000/mm^3 not attributed to medication; hemolytic anemia; or platelet count <100×10^9/L),[6] nephritis (new-onset or worsening proteinuria >0.5g/24h; >5 WBC/hpf or >5 RBC/hpf in the absence of infection or stone; or granular or cellular casts),[14] skin disease (malar rash or discoid lesions),[6] arthritis (synovitis in >1 joint),[6] and serositis (pleurisy or pleural effusion; or pericarditis or pericardial effusion).[6] The threshold for leukopenia was chosen with the consideration that WBC <4000/mm^3 is the cutoff in the 1997 ACR classification criteria,[6] and that the lower limit of WBC is 5600/mm^3 during normal pregnancy.[15] Sensitivity analyses defined leukopenia as WBC <3000/mm^3, per the SLE Pregnancy Disease Activity Index (SLEPDAI).[1] Thrombocytopenia was attributed to SLE activity after excluding medication-related thrombocytopenia and pre-eclampsia based on a detailed review of the medical record.

Lupus nephritis and pre-eclampsia can be difficult to distinguish, thus we took the following approach based on chart review: If new-onset or worsened proteinuria (>0.5g/24h) occurred during the first trimester, this was attributed to lupus nephritis. If new or worsened proteinuria occurred in the second or third trimesters, we assessed whether this was attributable to lupus nephritis or pre-eclampsia by incorporating information about C3 and C4 levels (low values supporting lupus nephritis; normal or high values supporting pre-eclampsia), blood pressure (>140/90 on two or more occasions suggesting pre-eclampsia), the presence of urinary casts (supporting lupus nephritis, with the absence of casts suggesting pre-eclampsia), and elevated serum uric acid (supporting pre-eclampsia). Lupus nephritis was characterized as mild in the presence of non-nephrotic-range proteinuria, few

RBC or WBC, and no cellular casts; and as moderate-to-severe in the presence of new nephrotic-range proteinuria, many RBC or WBC on urinary sediment, or cellular casts.

We recorded each specific type of SLE activity as present or absent at any point before conception, during the six-month period before conception, and at any point during pregnancy. If a type of SLE activity was present during pregnancy, we classified it as new, recurrent, stable, or worsened.

Pregnancy outcomes were classified first as live birth, spontaneous miscarriage, elective termination, or stillbirth. Weeks of gestation at the time of pregnancy completion were recorded for all pregnancies. Live births were described as term (≥37 weeks) or preterm (<37 weeks gestation). We made note of congenital heart block and neonatal lupus if documented in the woman's medical record.

Statistical methods

Baseline characteristics of women with and without adverse pregnancy outcome were compared with Chi-square or Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. We calculated the proportion of women that was prescribed each SLE-related medication six months prior to conception and during pregnancy. Pregnancy outcomes were tabulated in the categories above.

We employed generalized linear mixed models in both univariable and multivariable analyses to account for correlated data among 114 women carrying a total of 149 pregnancies. From the generalized linear mixed models, we obtained odds ratios (OR) with 95% confidence intervals (CI) for adverse pregnancy outcome. Univariable analyses evaluated the effect of each specific type of SLE activity (nephritis, cytopenias, skin disease, arthritis, and serositis) prior to conception and then during pregnancy, as well as other patient traits including year of conception, on adverse pregnancy outcome. Those patient traits that were significantly related to adverse outcome in univariable analyses were then added to multivariable models, which were predetermined to include a maximum of four covariates (in addition to the specific type of SLE activity) based on 40 adverse outcomes. Given our finding that Hispanic ethnicity was associated with adverse pregnancy outcome in univariable models, we investigated differences in SLE manifestations by ethnicity using Fisher's exact tests.

Multivariable analyses were performed including one specific type of SLE activity either in the six months before conception or during pregnancy as the predictor variable. The first models were adjusted for ethnicity (Hispanic vs. non-Hispanic) and prior adverse pregnancy outcome given that these were significantly related to adverse outcome in univariable analyses. The second models included these variables and additionally adjusted for corticosteroid and/or azathioprine (AZA) six months before conception and hydroxychloroquine (HCQ) six months before conception. These medications were *a priori* specified to be included in the multivariable model; corticosteroid and/or AZA prescription in the months prior to conception was considered a marker for active SLE in one or more organ system, but was also expected to decrease SLE activity via immunosuppression. Therefore, we considered corticosteroid and/or AZA prescription within the six months prior

to conception to be a bidirectional confounder of organ-specific SLE activity during pregnancy. The decision to include HCQ use in the six months before conception in our models was based on literature supporting a protective role for HCQ on the risk of adverse pregnancy outcome.[11, 16] As we were interested in specific types of SLE activity during pregnancy rather than aggregate disease activity as risk factors for adverse pregnancy outcome, we did not additionally include biomarkers of SLE activity such as anti-dsDNA and complements in our models.

In sensitivity analyses, the composite definition of adverse pregnancy outcome was modified to include preterm delivery <34 weeks, rather than <37 weeks. Further sensitivity analyses of cytopenia defined leukopenia as WBC <3000/mm^3. Univariable and multivariable generalized linear mixed models were repeated, using this modified definition of adverse pregnancy outcome.

Analyses were performed using SAS (version 9.4, Cary, NC). Two-sided p values of <0.05 were considered statistically significant. The Partners Healthcare Institutional Review Board approved all aspects of this study.

RESULTS

Pregnancy characteristics

Characteristics of the 114 women included in this analysis are summarized in Table 1. Median age at SLE diagnosis was 23.7 years (interquartile range [IQR] 19.9 to 26.8 years). At the time of SLE diagnosis, women had a median of five ACR Classification Criteria[17] (range 4 to 11). All women had a positive ANA titer defined as >1:40. 67.5% were White, 14.9% Hispanic, 10.5% African-American, and 7.0% Asian. Pre-gestation antiphospholipid antibody (APLAb) assays were positive in 43 pregnancies; 12 with lupus anticoagulant (LAC), 10 with anticardiolipin (ACL) IgM, and 33 with ACL IgG. Six women tested positive for both LAC and either ACL IgM or ACL IgG. A history of secondary antiphospholipid antibody syndrome (APS) was present in seven (4.7%) pregnancies. Among the 103 parous women, 23 had one or more prior adverse pregnancy outcomes: nine had a prior history of pre-eclampsia, 12 had a prior preterm delivery, nine had a prior spontaneous miscarriage ≥12 weeks, and five had a history of stillbirth. 36.2% of women had one or more types of organ-specific SLE activity during the six months prior to conception.

SLE-related medications are summarized in Table 2. 54.4% of women took HCQ in the six months before conception, while 40.3% took HCQ during pregnancy. Corticosteroid use was observed in fewer than half of the women six months before conception and during pregnancy. Azathioprine was the most often used immunosuppressant, in approximately 10% of women before and during pregnancy; other immunosuppressants were used less frequently. While 14.1% of women used aspirin before conception, this increased to 22.8% of women during pregnancy.

The vast majority of pregnancies resulted in a live, term delivery (76.5%). (Table 3) Among the 40 adverse pregnancy outcomes, preterm delivery was the most common. Pre-eclampsia

developed in eight pregnancies (5.4%); of these, five progressed to term and three were delivered preterm. Stillbirth, spontaneous miscarriage at 12–20 weeks, and elective termination due to SLE disease activity were each uncommon; together these adverse outcomes occurred in less than 5% of pregnancies

Two pregnancies were electively terminated due to SLE disease activity for the following reasons: One woman had poor fetal prognosis due to absent diastolic flow at 17 weeks; the other woman had lupus nephritis requiring cyclophosphamide use at 10 weeks gestation.

Congenital heart block was documented during one pregnancy conceived in 1994, not treated with hydroxychloroquine during pregnancy, and delivered preterm at 34 weeks gestation. Neonatal lupus skin rash developed at two months of age in an infant conceived in 2000, delivered at term, whose mother stopped taking hydroxychloroquine during first trimester. Both women had high-titer Ro and La antibodies prior to and during pregnancy.

Specific types of SLE activity during pregnancy

One or more of the five specific types of SLE activity was active during 56 of 149 pregnancies. Cytopenia was most common and was observed during 15.4% of pregnancies. Nephritis (10.7%), skin disease (8.7%), arthritis (5.4%) and serositis (5.4%) were less common than cytopenias during pregnancy.

Predictors of adverse pregnancy outcome

Univariable analyses of specific types of SLE activity and pregnancy outcome are presented in Table 4. Nephritis in the six months prior to conception, nephritis during pregnancy, and cytopenias during pregnancy each conferred an increased risk of adverse pregnancy outcome. We also found that while race was not associated with adverse pregnancy outcome, Hispanic ethnicity was (OR 3.7, 95% CI [1.2–10.9]).

A history of prior adverse pregnancy outcome and corticosteroid and/or AZA use in the six months before conception were associated with adverse pregnancy outcome in univariable analyses, whereas age at SLE diagnosis, age at conception, year of conception (pre- or post-2006), HCQ use in the six months before conception, history of lupus nephritis at any time, history of APS, primigravida status, Ro positive, La positive, LAC positive, and APLAb positive were not significantly associated with pregnancy outcome.

In multivariable analyses, nephritis (OR 3.5, 95% CI [1.0–12.2]), cytopenias (OR 4.2, 95% CI [1.4–12.2]), and serositis (OR 5.7, 95% CI [1.1–30.3]) during pregnancy were each significantly associated with adverse pregnancy outcome, after adjusting for adjusted for Hispanic ethnicity and prior adverse pregnancy outcome. (Table 4) In the second multivariable model, including corticosteroid and/or AZA use and HCQ use six months before conception, these three specific types of SLE activity during pregnancy remained significantly associated with an increased risk for adverse pregnancy outcome.

Active nephritis in the six months prior to conception was more common among Hispanic than non-Hispanic women (19.1% vs. 4.7%, p=0.04). Cytopenias were present six months before conception in 23.8% of Hispanic pregnancies and 9.4% of non-Hispanic pregnancies

(p=0.07). The proportions of women with arthritis, skin disease, and serositis did not significantly differ between Hispanic and non-Hispanic women.

A detailed description of the 13 pregnancies with both an adverse pregnancy outcome and cytopenia during pregnancy is shown in Table 5. Among 11 of these 13 pregnancies (85%), cytopenia was the sole type of SLE activity during pregnancy. All of these women had a prior history of cytopenia during the course of their SLE. In five cases, the cytopenia was present within six months of conception and continued or worsened during the pregnancy. In eight pregnancies, cytopenia recurred during pregnancy with the majority (five) presenting during the first trimester, and three starting in either the second or third trimester. Among these women, leukopenia was the most common cytopenia that developed during pregnancy.

Sensitivity analyses

When we employed a modified definition of adverse pregnancy outcome, including preterm delivery at <34 weeks rather than <37 weeks, adverse pregnancy outcome occurred in 26 (17.5%) pregnancies. In univariable analyses, nephritis six months before conception, nephritis during pregnancy, cytopenia during pregnancy, and serositis during pregnancy were each associated with increased risk for the modified definition of adverse pregnancy outcome. (Supplemental Table 1) In fully-adjusted models, nephritis six months before conception and serositis during pregnancy were each associated with increased risk of adverse outcome.

When leukopenia was defined as WBC <3000/mm^3, cytopenia during pregnancy remained associated with elevated risk of adverse pregnancy outcome, using the original definition and the modified definition of adverse pregnancy outcome. Effect estimates were similar to those presented for cytopenia in Table 4 and Supplemental Table 1.

DISCUSSION

In our population of 114 women with 149 pregnancies, women with nephritis, cytopenias, or serositis during pregnancy were more likely to have adverse pregnancy outcomes, including miscarriage between gestational weeks 12 and 20, stillbirth, SLE-related elective termination, pre-eclampsia or preterm birth. The presence of skin disease or arthritis during pregnancy was not associated with elevated risk of adverse pregnancy outcome in multivariable models. When we re-defined preterm delivery as <34 weeks in the adverse pregnancy outcome definition, nephritis during the six months before conception and serositis during pregnancy were each associated with an increased risk of adverse outcome. The widened confidence intervals in our sensitivity analyses reflect the smaller number of outcomes using the modified definition of adverse pregnancy outcome.

Our cohort, as previously described,[5] was composed of primarily Caucasian women. All were ANA positive, two-thirds were anti-dsDNA positive, and approximately one-third had a history of nephritis. Only 54% of patients received HCQ in the six months preceding conception and 40% during pregnancy, reflecting our study period. HCQ use during pregnancy prior to 2000 was not common practice, but increasing reports of its safety and efficacy during pregnancy have since changed prescribing patterns.[18] In our study, HCQ

use either prior or during pregnancy was not related to pregnancy outcome, nor was year of conception (pre- vs. post-2006).

In a recent publication by Buyon *et al.* evaluating pregnancy outcomes among 385 women with SLE (12.5% of whom had positive APLAb [LAC, high-titer ACL IgG or IgM, or high-titer beta-2-glycoprotein 1 IgG or IgM]) in the PROMISSE study, adverse pregnancy outcomes included fetal death after 12 weeks gestation, neonatal death, preterm delivery <36 weeks, and small for gestational age infants.[4] In that cohort, which excluded women using prednisone >20 mg/d, or with active renal disease (urine protein-creatinine ratio >1000 mg/g, RBC casts, creatinine >1.2 mg/dL), prior renal disease and baseline low platelet count were associated with adverse pregnancy outcome in univariable analyses. As in our cohort, the prevalence of adverse pregnancy outcome was low (19% in the PROMISSE study compared with 27% in our cohort), and prior fetal loss at >10 weeks was also associated with adverse pregnancy outcome in univariable analyses. In contrast to our findings, in the PROMISSE study prior thrombosis and the presence of APLAb were associated with adverse pregnancy outcome in univariable analyses; however, the prevalence of prior thrombosis (8.1%) was higher in their population compared to our cohort (4.7% with history of APS). In addition, our study used a lower threshold for APLAb positivity (>20 units) than the PROMISSE Study (>40 units), which prevents direct comparison of the prevalence of APLAb positivity.

Another recent study, conducted in Italy, reported predictors of adverse pregnancy outcomes among 96 women with 132 pregnancies (11% of which were carried by women with APS).[19] Each of the following adverse pregnancy outcomes was analyzed separately as a dependent variable: pregnancy loss (any pregnancy not resulting in a live infant past 28 days), spontaneous miscarriage ≤10 weeks, fetal loss >10 weeks, preterm delivery <37 weeks, intrauterine growth restriction, small for gestational age, pre-eclampsia, premature rupture of membranes (PROM) and preterm PROM. Potential predictors of adverse pregnancy outcomes included APLAb, APS, anti-dsDNA, corticosteroid use, hypertension, renal disease and the European Consensus Lupus Activity Measurement (ECLAM) score modified for pregnancy. However, these variables were only assessed in the six months prior to conception and not during pregnancy.

Our findings are novel in several ways. First, they emphasize that organ-specific disease activity in the six months prior to and during pregnancy is related to pregnancy outcomes. Second, in addition to the known risk of nephritis, cytopenias—particularly leukopenia and thrombocytopenia during pregnancy—carried a higher risk of adverse pregnancy outcome suggesting that these abnormalities should be carefully monitored during pregnancy. However, the findings regarding thrombocytopenia should be interpreted in light of the potential difficulty in distinguishing between gestational thrombocytopenia, gestational idiopathic thrombocytopenic purpura (ITP), and the thrombocytopenia secondary to SLE flare. None of the women in our study had HELLP syndrome, although one woman had thrombotic thrombocytopenic purpura (TTP) during pregnancy. Only one woman developed thrombocytopenia during the third trimester, when HELLP typically occurs. Therefore, it is unlikely that misclassification of these two conditions occurred in this study. In only two of 13 described pregnancies did thrombocytopenia occur in the absence of thrombocytopenia in

the six months before conception. Furthermore, all patients with the observed adverse pregnancy outcomes and cytopenia had a prior cytopenia either during the pre-conception period or in the past. This suggests that the observed cytopenias were SLE-related and not due to pregnancy alone. In our cohort, leukopenia, present in isolation in eight pregnancies, did not result in a change in SLE therapy, further suggesting that adverse pregnancy outcomes were not due to medication adjustments.

These data are limited as they are representative of our predominantly Caucasian SLE patient population evaluated and followed at a large urban academic medical center. While the data were recorded prospectively in the medical record, they were collected retrospectively for the present analysis. Clinic visits occurred at varying intervals and therefore data were limited to those collected as part of routine clinical practice. The small numbers of women with each type of clinical activity during pregnancy limited our ability to associate a specific type of clinical disease activity with a specific type of adverse pregnancy outcome. Additionally, the small numbers led to wide confidence intervals for our point estimates of adverse pregnancy outcome. Our report of two elective SLE-related terminations during the study period is likely an underestimation of the total number of elective terminations among women in this cohort, given that many elective terminations occur in the first trimester[20] and may not be recorded in the medical record.

Our findings need to be replicated in different SLE populations, in particular those with higher proportions of African American and Hispanic patients. Larger populations would also help delineate the specific impact of the different hematologic abnormalities on different adverse pregnancy outcome and suggest potential therapeutic interventions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

The investigators would like to thank the funding sources supporting this work: NIH T32 AR007530, K24 AR066109, R01 AR057327

References

1. Buyon JP, Kalunian KC, Ramsey-Goldman R, et al. Assessing disease activity in SLE patients during pregnancy. Lupus. 1999; 8(8):677–684. [PubMed: 10568906]
2. Yee CS, Akil M, Khamashta M, et al. The BILAG2004-Pregnancy index is reliable for assessment of disease activity in pregnant SLE patients. Rheumatology (Oxford). 2012; 51(10):1877–1880. [PubMed: 22763989]
3. Ruiz-Irastorza G, Khamashta MA, Gordon C, et al. Measuring systemic lupus erythematosus activity during pregnancy: validation of the lupus activity index in pregnancy scale. Arthritis Rheum. 2004; 51(1):78–82. [PubMed: 14872459]
4. Buyon JP, Kim MY, Guerra MM, et al. Predictors of Pregnancy Outcomes in Patients With Lupus: A Cohort Study. Ann Intern Med. 2015; 163(3):153–163. [PubMed: 26098843]
5. Tedeschi SK, Massarotti E, Guan H, et al. Specific systemic lupus erythematosus disease manifestations in the six months prior to conception are associated with similar disease manifestations during pregnancy. Lupus. 2015; 24(12):1283–1292. [PubMed: 25972367]

6. Rheumatology ACo. https://www.rheumatology.org/Practice/Clinical/Classification/SLE/1997_Update_of_Revised_Systemic_Lupus_Erythematosus/.
7. Saavedra MA, Cruz-Reyes C, Vera-Lastra O, et al. Impact of previous lupus nephritis on maternal and fetal outcomes during pregnancy. Clin Rheumatol. 2012; 31(5):813–819. [PubMed: 22278163]
8. Kwok LW, Tam LS, Zhu T, et al. Predictors of maternal and fetal outcomes in pregnancies of patients with systemic lupus erythematosus. Lupus. 2011; 20(8):829–836. [PubMed: 21543513]
9. Ko HS, Ahn HY, Jang DG, et al. Pregnancy outcomes and appropriate timing of pregnancy in 183 pregnancies in Korean patients with SLE. Int J Med Sci. 2011; 8(7):577–583. [PubMed: 22022210]
10. Cavallasca JA, Laborde HA, Ruda-Vega H, et al. Maternal and fetal outcomes of 72 pregnancies in Argentine patients with systemic lupus erythematosus (SLE). Clin Rheumatol. 2008; 27(1):41–46. [PubMed: 17516127]
11. Al Arfaj AS, Khalil N. Pregnancy outcome in 396 pregnancies in patients with SLE in Saudi Arabia. Lupus. 2010; 19(14):1665–1673. [PubMed: 20947541]
12. Andrade R, Sanchez ML, Alarcon GS, et al. Adverse pregnancy outcomes in women with systemic lupus erythematosus from a multiethnic US cohort: LUMINA (LVI) [corrected]. Clin Exp Rheumatol. 2008; 26(2):268–274. [PubMed: 18565248]
13. Kramer MS, Demissie K, Yang H, et al. The contribution of mild and moderate preterm birth to infant mortality. Fetal and Infant Health Study Group of the Canadian Perinatal Surveillance System. JAMA. 2000; 284(7):843–849. [PubMed: 10938173]
14. Dooley MA, Aranow C, Ginzler EM. Review of ACR renal criteria in systemic lupus erythematosus. Lupus. 2004; 13(11):857–860. [PubMed: 15580982]
15. Branch, DWWL., editor. Normal pregnancy, pregnancy complications and obstetric management. New York: Springer; 2014.
16. Clowse ME, Magder L, Witter F, et al. Hydroxychloroquine in lupus pregnancy. Arthritis Rheum. 2006; 54(11):3640–3647. [PubMed: 17075810]
17. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997; 40(9):1725.
18. Leroux M, Desveaux C, Parcevaux M, et al. Impact of hydroxychloroquine on preterm delivery and intrauterine growth restriction in pregnant women with systemic lupus erythematosus: a descriptive cohort study. Lupus. 2015; 24(13):1384–1391. [PubMed: 26082465]
19. Borella E, Lojacono A, Gatto M, et al. Predictors of maternal and fetal complications in SLE patients: a prospective study. Immunol Res. 2014; 60(2–3):170–176. [PubMed: 25398639]
20. Strauss LT, Gamble SB, Parker WY, et al. Abortion surveillance--United States, 2003. MMWR Surveill Summ. 2006; 55(11):1–32.

Table 1

Characteristics of Women with SLE and their Pregnancies, 1990–2013

149 pregnancies	Total, n=149	Adverse pregnancy outcome*, n=40	Favorable pregnancy outcome, n=109	p value
Age at conception, years	31.3 (27.7–35.0)	30.1 (26.2–33.1)	32.3 (28.2–35.5)	**0.03**
Race/ethnicity#				
Caucasian	77 (67.5)	19 (59.4)	58 (70.7)	
African American	12 (10.5)	3 (9.4)	9 (11.0)	0.99
Asian	8 (7.0)	2 (6.3)	6 (7.3)	
Hispanic	17 (14.9)	8 (25.0)	9 (11.0)	0.08
Planned pregnancy	57 (38.3)	15 (37.5)	42 (38.5)	0.99
Gravida				
1	46 (30.9)	15 (37.5)	31 (28.4)	
2	45 (30.2)	13 (32.5)	32 (29.4)	0.61
3	25 (16.8)	5 (12.5)	20 (18.4)	
≥4	33 (22.2)	7 (17.5)	26 (23.9)	
History of adverse pregnancy outcome**	23 (22.3)	13 (52.0)	10 (12.8)	<**0.01**
History of APS	7 (4.7)	1 (2.5)	6 (5.5)	0.68
History of lupus nephritis	49 (32.9)	17 (42.5)	32 (29.4)	0.17
Serologies prior to conception				
Anti-dsDNA elevated	99 (66.4)	33 (82.5)	66 (60.6)	**0.01**
Anti-La	25 (16.8)	9 (22.5)	16 (14.7)	0.32
Anti-Ro	42 (28.2)	12 (30.0)	30 (27.5)	0.84
APLAb positive	43 (28.9)	13 (32.5)	30 (27.5)	0.55

Presented as median (IQR) for continuous variables and n (%) for categorical variables

Bonferroni-adjusted p values from Wilcoxon rank-sum tests and Fisher's exact or Chi-square tests

*Adverse pregnancy outcome: pre-eclampsia, preterm delivery (<37 weeks), termination due to SLE disease activity, spontaneous abortion ≥12 weeks to <20 weeks, or stillbirth (fetal loss ≥20 weeks)

#Presented as percentage of 114 unique women (32 with adverse outcome and 82 with favorable outcome)

**Presented as percentage of 103 non-primigravida pregnancies (25 with adverse outcome and 78 with favorable outcome)

APS = antiphospholipid antibody syndrome
APLAb = antiphospholipid antibodies (anti-cardiolipin, lupus anticoagulant, and/or beta-2-glycoprotein 1)

Table 2

Medications six months before conception and during 149 pregnancies

Medication*	Six months before conception	During pregnancy
Hydroxychloroquine	81 (54.4)	60 (40.3)+
Corticosteroid	54 (36.2)	56 (37.6)
Median prednisone equivalent [IQR], mg	10 [5, 12.5]	20 [10, 35]
Azathioprine	14 (9.4)	16 (10.7)
Sulfasalazine	1 (0.7)	0
Cyclosporine	0	3 (2.0)
Mycophenolate	3 (2.0)	0
Rituximab	2 (1.3)	1 (0.7)
Methotrexate	1 (0.7)	0
Cyclophosphamide	1 (0.7)	0
Anticoagulant	6 (4.0)	15 (10.1)
Aspirin	21 (14.1)	34 (22.8)

*n (%) unless otherwise indicated

+Among these 60 women, eight initiated HCQ while pregnant

Table 3

Outcomes of 149 pregnancies

Outcome	N (%)
Term delivery	114 (76.5)
Adverse pregnancy outcome	40 (26.9)
Preterm delivery (<37 weeks)	28 (18.8)
Preterm delivery (<34 weeks)	14 (9.4)
Pre-eclampsia *	8 (5.4)
Stillbirth (≥20 weeks)	3 (2.0)
Spontaneous miscarriage (12 to 20 weeks)	2 (1.3)
Elective termination due to SLE activity	2 (1.3)

* Three preterm live deliveries and five live term deliveries

Table 4

Odds ratios for adverse pregnancy outcome (n=40) among 149 pregnancies

Predictor	Number of occurrences	Univariable OR (95% CI)	Model 1* OR (95% CI)	Model 2# OR (95% CI)
Organ-specific activity six months prior to conception				
Cytopenia	17	2.6 (0.8–8.5)	1.8 (0.5–6.0)	1.6 (0.5–5.4)
Nephritis	10	**7.3 (1.5–35.2)**	4.6 (0.9–23.4)	3.3 (0.6–17.9)
Skin disease	15	1.0 (0.3–3.9)	1.3 (0.4–5.0)	1.2 (0.3–4.8)
Arthritis	13	0.8 (0.2–3.6)	0.7 (0.1–3.2)	0.7 (0.1–3.0)
Serositis	5	1.8 (0.2–14.1)	1.6 (0.2–12.7)	1.0 (0.1–7.8)
Organ-specific activity during pregnancy				
Cytopenia	23	**4.8 (1.7–14.0)**	**4.2 (1.4–12.2)**	**3.9 (1.3–11.4)**
Nephritis	16	**4.4 (1.3–14.9)**	**3.5 (1.0–12.2)****	**3.6 (1.0–12.8)**$
Skin disease	13	1.9 (0.5–7.1)	1.3 (0.3–5.4)	1.3 (0.3–5.2)
Arthritis	8	3.2 (0.6–16.2)	3.7 (0.8–18.5)	3.9 (0.8–19.7)
Serositis	8	4.8 (0.9–25.5)	**5.7 (1.1–30.3)**	**5.9 (1.0–34.0)**++

Adverse pregnancy outcome: pre-eclampsia, preterm <37 weeks, miscarriage (fetal loss at 12–20 weeks gestation), stillbirth (fetal loss at ≥20 weeks gestation), SLE-related elective termination

OR and 95% CI from generalized linear mixed models to account for correlated data among 114 women carrying a total of 149 pregnancies

*Model 1: adjusted for ethnicity (Hispanic/non-Hispanic) and prior adverse pregnancy outcome

#Model 2: model 1 + corticosteroid and/or azathioprine use six months before conception, and hydroxychloroquine use six months before conception

**p=0.046

$p=0.045

++p=0.049

Table 5

Detailed description of 13 pregnancies with adverse outcome and cytopenia during pregnancy

Pregnancy	Cytopenia category	Timing of cytopenia	SLE medications during pregnancy	Other manifestations during pregnancy	Adverse outcome
A*	Leukopenia	Continued from 6 months pre-conception	HCQ (newly started)		pre-eclampsia, emergent pre-term delivery at 31 weeks
B#	Thrombocytopenia	Continued from 6 months pre-conception	HCQ (continued), prednisone 30mg (continued)		pre-term at 33 weeks
C**	Leukopenia	Continued from 6 months pre-conception	HCQ (continued), AZA (continued), prednisone 20mg before conception → 40mg		pre-term at 36 weeks
D#	Thrombocytopenia	Continued from 6 months pre-conception	HCQ (continued), prednisone 20mg due to ITP		pre-term at 36 weeks
E	Thrombocytopenia, Leukopenia	Continued from 6 months pre-conception	HCQ (continued), prednisone 20mg (newly started)		stillbirth at 32 weeks
F	Thrombocytopenia, Hemolytic anemia	Started in 1st trimester	Prednisone 60mg (new in 1st trimester), tapered to 20mg		pre-term at 31 weeks
G*	Leukopenia	Started in 1st trimester	HCQ (newly started)		pre-term at 30 weeks
H	Leukopenia	Started in 1st trimester	HCQ (continued), AZA (continued), prednsione 7.5mg (continued)		pre-term at 33 weeks
I	Leukopenia	Started in 1st trimester	None		miscarriage at 16 weeks
J	Leukopenia	Started in 1st trimester	AZA (newly started), prednisone 60mg (newly started)	New-onset Class III lupus nephritis, arthritis, skin disease	pre-term at 34 weeks
K**	Leukopenia	Started in 2nd trimester	HCQ (continued), AZA (continued), prednisone 15mg before conception → 60mg	Pleuritis, skin disease	pre-term at 33 weeks
L	Thrombocytopenia	Started in 2nd trimester	Prednisone 10mg at conception → 60mg		stillbirth at 28 weeks
M	Thrombocytopenia	Started in 3rd trimester	HCQ (continued), aspirin (newly started)		pre-term at 36 weeks

Pregnancies carried by the same woman are indicated by * or # or **

Leukopenia: WBC <4000/mm^3 not attributed to medication. Thrombocytopenia: platelet count <100×10^9/L

Cell counts presented in thousands per cubic millimeter. HCQ: hydroxychloroquine. AZA: azathioprine.