

Adverse pregnancy outcomes in women with systemic lupus erythematosus from a multiethnic US cohort: LUMINA (LVI)

R. Andrade^{1*}, M.L. Sanchez^{1*}, G.S. Alarcón^{1*}, B.J. Fessler¹, M. Fernández¹,
A.M. Bertoli¹, M. Apte¹, L.M. Vilá³, A.M. Arango², J.D. Reveille²,
for the LUMINA Study Group.

From the ¹Department of Medicine (Division of Clinical Immunology and Rheumatology), School of Medicine, The University of Alabama at Birmingham, Birmingham, Alabama; ²Department of Medicine (Division of Rheumatology), The University of Texas Health Science Center at Houston, Houston, Texas; ³Department of Internal Medicine (Division of Rheumatology), The University of Puerto Rico Medical Sciences Campus, San Juan, Puerto Rico.

Abstract

Objective

To study the factors associated with an adverse pregnancy outcome in women with systemic lupus erythematosus (SLE).

Methods

SLE women from LUMINA of Hispanic, African American and Caucasian ethnicity were studied. Adverse pregnancy outcome was a miscarriage or abortion (<20 weeks), a stillbirth (≥ 20) and/or a moderate to severe preterm-baby (<34 weeks); good outcome was either a mild preterm-baby (≥ 34 weeks) or a full-term baby [C-section or vaginal delivery (38-42 weeks)]. Pregnancies occurring after SLE diagnosis (TD) were included; pregnancy outcome was the unit of analyses. The relationship between selected variables and pregnancy outcomes was examined by univariable and multivariable analyses.

Results

Adverse outcomes occurred in 63.7% of 102 pregnancies. In the univariable analyses, Texan Hispanic and African American ethnicities, fewer years of education, higher number of ACR criteria, renal involvement, glucocorticoid exposure and the maximum dose of glucocorticoids used prior to the pregnancy outcome were associated with an adverse pregnancy outcome. Renal involvement was independently associated with an adverse pregnancy outcome [Odds ratio (OR)=5.219 (95% Confidence Interval (CI) 1.416-19.239, $p=0.0131$)] as were the maximum dose of glucocorticoids used prior to the pregnancy outcome (OR=1.028; CI:1.002-1.054; $p=0.0315$) and fewer years of education (OR=1.204; CI:1.006-1.472; $p=0.0437$). Ethnicity was not retained in the multivariable model.

Conclusions

Renal involvement, the maximum dose of glucocorticoids used prior to pregnancy and fewer years of education were associated with adverse pregnancy outcomes. These data have implications for the management of women with lupus planning to become pregnant.

Key words

Pregnancy, SLE, adverse outcome, miscarriages, premature births, stillbirths, abortions, pregnancy loss.

Rosa Andrade, MD; Martha L. Sanchez, MD, MPH; Graciela S. Alarcón, MD, MPH; Barri J. Fessler, MD; Mónica Fernández, MD; Ana M. Bertoli, MD; Mandar Apte, MD; Luis M. Vilá, MD; Ana M. Arango, MD, John D. Reveille, MD.

*Dr. Andrade, Dr. Sanchez and Dr. Alarcón contributed equally to this study.

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Please address correspondence to and reprint requests to: Graciela S. Alarcón, MD, MPH, 830 Faculty Office Tower, 510 20th Street South, Birmingham, Alabama 35294-3408, USA.

E-mail: graciela.alarcon@ccc.uab.edu

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Introduction

Previous studies have shown that women with systemic lupus erythematosus (SLE) maintain fertility, although once they become pregnant, they have an increased frequency of adverse pregnancy outcomes including pregnancy losses, intrauterine growth restrictions and preterm births (1-6). Multiple factors have been associated with these outcomes including increased lupus activity, lupus nephritis, hypertension and the presence of antiphospholipid antibodies (1-3, 6-10). In addition, women who exhibit anti-Ro/SSA and/or anti-La/SSB antibodies are more likely to have a child with congenital heart block than those who do not (11). The available literature is based mostly on Caucasian and African American lupus patients. However, in the last 40 years, the demographic composition of the US population has changed. Indeed, as per the 2000 census, Hispanics now constitute the largest and the fastest growing minority group (12). As we have previously shown, Hispanic lupus patients, particularly those of Mexican and Central American ancestry (residing in Texas), have an overall worse prognosis than Caucasians and their disease course resembles that of African American patients (13-15). Therefore determining if the inclusion of Hispanics in lupus studies changes the spectrum of fetal outcomes among SLE patients is quite relevant.

We have now conducted such a study by examining the impact of socioeconomic-demographic, clinical, immunological and behavioral factors on the outcome of pregnancy in SLE patients from LUMINA (LUpus in MInorities, NAture versus Nurture), a multiethnic US cohort.

Methods

Patients

The LUMINA study is being performed under the guidelines of the declaration of Helsinki for the use of human subjects in research and was approved at the three participating institutions. Details about the constitution of the cohort have been previously published, and they are

now briefly summarized. LUMINA is a multiethnic [Hispanic (from Texas and from the Island of Puerto Rico), African American and Caucasian] longitudinal study of outcome in SLE (14) and it is a collaborative effort between the University of Alabama at Birmingham (UAB), the University of Texas Health Science Center at Houston, and the University of Puerto Rico Medical Sciences Campus. Only patients meeting ACR criteria for the classification of SLE (16), at least 16 years of age, with disease duration at enrollment (T0) of five years or less, and of defined ethnicity (all grandparents of the same ethnicity) are eligible to participate in LUMINA. Visits are conducted every six months during the first year and annually thereafter. Time of diagnosis (TD, herein) is defined as the time at which patients meet four of the ACR criteria for SLE. Disease duration is the interval between TD and T0, follow-up time is the interval between T0 and pregnancy outcome, whereas total disease duration is defined as the interval between TD and pregnancy outcome.

By June 1st, 2005, the LUMINA cohort was constituted by 611 patients; of them, 548 were women. Three hundred and fifty-nine of these 548 women had reported having had at least one pregnancy during their life span, with a total of 985 pregnancy outcomes. Only pregnancies that occurred after TD (n=102) were included in these analyses.

Variables

As previously described, the LUMINA database includes variables from the following domains: socioeconomic-demographic, clinical, immunological, genetic and behavioral and psychological. Only the variables included in these analyses will now be described.

Socioeconomic-demographic variables included are age, ethnicity, marital and health insurance status, education and poverty (as defined by the US Federal government adjusted for the number of members in the household). Health-related behaviors such as smoking, drinking, not exercising, and using recreational drugs are also included.

Competing interests: none declared.

Clinical variables included are onset type [acute (accrual of four ACR criteria within one month) versus insidious if otherwise], total disease duration in months (from TD to the time of pregnancy outcome), pregnancy duration in weeks, disease activity [ascertained with the Systemic Lupus Activity Measure-Revised (17) or SLAM-R herein at TD using all available medical records as described by Wluka *et al.* (18)], clinical manifestations (ACR criteria and others), the presence of anti-phospholipid aPL (abnormal IgG isotype > 13 GPL U/mL and/or IgM isotype > 13 MPL U/mL) detected by enzyme-linked immunoabsorbent assay (ELISA) technique (19) and/or the lupus anticoagulant (LAC) (Stacot test, Diagnostica Stago 92600, Asnières-Sur-Seine, France) (20) and of anti-Ro//SSA and anti-La//SSB antibodies (detected by counterimmunoelectrophoresis against human spleen and calf thymus extract) (21) prior to the pregnancy outcome. Thrombotic events were either arterial [myocardial infarction, definite or classic angina and/or vascular procedure for myocardial infarction (coronary artery bypass graft), stroke, intermittent claudication and/or peripheral arterial thrombosis] or venous (peripheral and/or visceral). Renal involvement was defined as present if patients met the ACR renal disorder criterion (16) and/or had biopsy-proven World Health Organization (WHO) Class II or higher for lupus nephritis, and/or 2+/3+ proteinuria and/or protein in urine > 500 mg in 24-hours.

Exposure to glucocorticoids (prednisone equivalent), hydroxychloroquine, cyclophosphamide, cyclosporine A, azathioprine and low-dose aspirin prior to the pregnancy outcome was also included. The maximum dose of glucocorticoid ever used (calculated in mg per day) prior to the pregnancy outcome was also recorded for each patient.

Analyses

The unit of analysis was the pregnancy outcome, not the patient. For the purpose of this study, adverse pregnancy outcomes included a miscarriage or an abortion (<20 weeks), a stillbirth (≥20 weeks) and/or moderate to severe premature birth (<34 gestational weeks) (22). Abortions whether therapeutic or not, were considered adverse pregnancy outcomes as the biological purpose of a pregnancy (*i.e.*, a live birth) was not achieved. A good outcome was defined either as having a mild premature birth (34-37 gestational weeks) or a full-term birth (either by a C-section or by vaginal delivery between 38 and 42 weeks). The outcome of the previous pregnancy was also considered in these analyses. The relationship between pregnancy outcome and variables from the different domains was then examined using standard descriptive statistical tests, the Student's *t*-test for continuous variables and the Chi-square test for the categorical variables. Variables with a $p \leq 0.10$ in these analyses as well as age and ethnicity were then entered into a logistic regression model to determine factors independently associated with

the occurrence of an adverse pregnancy outcome.

All analyses were done with the SAS program, version 9.1 (SAS Institute, Cary, NC, USA).

Results

From a total of 985 pregnancies, only the 102 which occurred after TD were included in these analyses. Of them, 52 pregnancies occurred between TD and T0 and 50 occurred after T0. As noted in Table I, of the 102 pregnancies included in these analyses, 65 (63.7%) had an adverse outcome. Patients of African American (73.5%) and Hispanic-Texan (68.8%) ethnicities experienced adverse outcomes more frequently than patients in the other groups; however, Hispanics (Texan and Puerto Rican) experienced frequent severe premature births (36.4% and 50.0%, respectively) while African Americans experienced more abortions (44.0%) and Caucasians more miscarriages (85.7%).

Adverse pregnancy outcomes

Univariable analyses. Comparison of the socioeconomic-demographic, clinical, obstetric and behavioral and psychological variables between women who experienced an adverse pregnancy outcome and those who did not are shown in Table II. Age, poverty, marital status and health insurance were comparable in both groups. In contrast African Americans and Hispanic-Texans and those with fewer years of formal education were overrepresented among those with adverse pregnancy outcomes.

Table I. Pregnancy outcome type in LUMINA patients as a function of ethnic group*.

Adverse pregnancy outcome	Hispanic				African American		Caucasian		All	
	Texan		Puerto Rican		n=34	%	n=24	%	n=102	%
	n=32	%	n=12	%						
No [†]	10	31.2	8	66.7	9	26.5	10	41.7	37	36.3
Yes	22	68.8	4	33.3	25	73.5	14	58.3	65	63.7
Miscarriage	6	27.3	1	25.0	2	8.0	12	85.7	21	32.3
Abortion	7	31.8	0		11	44.0	2	14.3	20	30.8
Moderate to severe premature birth [‡]	8	36.4	2	50.0	9	36.0	0		19	29.2
Stillbirth	1	4.5	1	25.0	3	12.0	0		5	7.7

*Differences between groups are not statistically significant; [†]mild premature birth (34-37 gestational weeks) and full term (38-42 gestational weeks); [‡]<34 gestational weeks.

Table II. Selected socioeconomic-demographic and clinical characteristics of LUMINA patients as a function of their pregnancy outcome (102 pregnancies).

Features	Adverse pregnancy outcome		<i>p</i> value*
	Yes n = 65	No n = 37	
Age at outcome, years, mean (SD)	26.6 (6.3)	27.7 (5.5)	
Ethnicity, %			
Texan Hispanic	34	27	0.0175
Puerto Rican Hispanic	6	22	
African American	38	24	
Caucasian	22	27	
Poverty [†] , below, %	44	26	
Education, years, mean (SD)	12.2 (3.3)	13.9 (3.3)	0.0122
Married/living together, %	61	74	
Health insurance, %	76	84	
Smoking and/or drinking and/or using recreational drugs, %	22	16	
Total disease duration at outcome, months, mean (SD)	28.7 (30.5)	27.1 (23.3)	
Disease onset, acute %	29	24	
ACR [‡] criteria number, mean (SD)	6.0 (1.5)	5.3 (1.3)	0.0106
SLAM-R [§] at diagnosis, mean (SD)	8.6 (5.5)	7.1 (4.0)	
Previous adverse pregnancy outcome	37.0	30.0	
Renal involvement, %	48	14	0.0005
Hypertension, %	34	11	0.0106
Thrombotic events [¶] , %	3	0	
Antiphospholipid antibodies ^{**} , %	22	22	
Anti-Ro//SSA	14	16	
Anti-La//SSB	0	0	
Glucocorticoid exposure use, %	88	71	0.0360
Maximum glucocorticoid dose ^{††} , mean (SD)	26.2 (26.9)	15.1 (22.4)	0.0371
Hydroxychloroquine use, %	52	54	
Cyclophosphamide use, %	22	11	
Cyclosporine A use, %	2	0	
Azathioprine use, %	14	3	
Low dose aspirin use, %	12	19	

*Only $p \leq 0.10$ are shown; [†]As per the US Federal government guidelines; [‡]American College of Rheumatology; [§]Systemic Lupus Activity Measured-Revised; [¶]Arterial and/or venous; ^{**}IgG and/or IgM and/or the lupus anticoagulant; ^{††}in mg of prednisone or equivalent.

Health-related behaviors (smoking and/or drinking and/or using recreational drugs) were numerically higher among the adverse pregnancy outcome group than among those with a good outcome (22% vs. 16%), but this difference was not statistically significant.

Total disease duration, acute onset type and disease activity at TD were found to be comparable in the two pregnancy outcome groups. The number of ACR criteria at diagnosis was higher in the adverse pregnancy outcome group [6.0 (1.5) vs. 5.3 (1.3); $p = 0.0106$]. The proportion of previous adverse pregnancy outcomes was numerically higher in those with an adverse pregnancy out-

come than in those without it but the differences did not reach statistical significance (37% vs. 30%). Renal involvement prior to pregnancy outcome was more frequent among those in the adverse pregnancy outcome group than among those with a good outcome (48% vs. 14%; $p = 0.0005$). Likewise, hypertension prior to pregnancy outcome occurred more frequently in the adverse pregnancy outcome group (34%) than in those with a good outcome (11%; $p = 0.0106$). The occurrence of thrombotic events prior to the outcome of the first pregnancy as well as the presence of anti-Ro//SSA and anti-La//SSB antibodies and of aPL antibodies occurred

at comparable frequencies in both groups.

The use of glucocorticoids (88% vs. 71% $p = 0.0360$) and the maximum dose of glucocorticoids ever used prior to pregnancy were significantly higher among the adverse pregnancy outcome group [prednisone 26.2 (26.9) vs. 15.1 (22.4) mg, $p = 0.0371$]. In contrast, hydroxychloroquine (52% vs. 54%), cyclophosphamide (22% vs. 11%), cyclosporine A (2% vs. 0%), azathioprine (14% vs. 3%) and low-dose of aspirin (12% vs. 19%) were comparable between the two groups.

As expected, pregnancy duration was shorter among the adverse pregnancy outcome group [21.8±(22.1) vs. 38.3±(1.9) weeks; $p < 0.001$].

Multivariable analyses. As shown in Table III, the predictors of the occurrence of an adverse pregnancy outcome were renal involvement [OR=5.219; 95% Confidence Interval (CI) 1.416-19.239; $p = 0.0131$], the maximum glucocorticoid dose used prior to the pregnancy outcome (OR=1.028; 95% CI: 1.002-1.0058; $p = 0.0315$) and fewer years of education (OR=1.204; 95% CI 1.006-1.472; $p = 0.0437$). No protective factors were identified.

Discussion

Over the last decade our LUMINA cohort has allowed us to delve into several important issues closely related to the long-term prognosis and quality of life of SLE patients (15, 23-25) including the effect of pregnancy itself in damage accrual (26). Herein, we give an insight on the effects of SLE on pregnancy outcome in this large multiethnic cohort. The vast early literature on SLE and pregnancy is based on Caucasian and African American patient groups (2, 3, 5, 6, 9); this does not reflect the current population structure of the US (12). Indeed, Hispanics now constitute the largest and fastest growing minority group in our country. Improvement in the health care system over the last 40 years and increased emphasis on patient education have both contributed positively to the overall long-term survival and, in this par-

Table III. Variables associated with the occurrence of adverse pregnancy outcomes in LUMINA patients by Multivariable Logistic Regression Analyses*.

Feature	Odds ratio	(95% Confidence interval)	p value
Fewer years of education	1.204	1.006 – 1.472	0.0437
Maximum glucocorticoid dose	1.028	1.002 – 1.054	0.0315
Renal involvement	5.219	1.416 – 19.239	0.0131

*Adjusted for age at outcome, ethnicity, number of ACR criteria prior to pregnancy outcome, and hypertension. Only variables with $p \leq 0.10$ are shown.

ticular case, to the pregnancy outcomes in SLE patients (27); however, paucity of studies on Hispanics residing in the US still remains. Therefore, our study sought to determine if there are any demonstrable differences in pregnancy outcomes among patients from these ethnic groups.

Unlike previous publications, we found over sixty percent of adverse pregnancy outcomes occurred in our cohort. The inclusion of abortions among adverse pregnancy outcomes might account for this high frequency. The nature of our database, however, prevented us from distinguishing between elective and therapeutic abortions; given that a pregnancy is ultimately expected to culminate in a live birth, we decided to include abortions in the group of adverse outcomes (28). However, even if we had excluded them from our analyses, the frequency of adverse pregnancy outcomes would have accounted for about 54% of all outcomes, which is still high (data not shown). The high frequency of adverse pregnancy outcomes that we found strikingly contrasts with data from the meta-analysis published by Clark *et al.* (27) and the associated comment by Buyon (29). Therein, Clark *et al.* reported an overall decrease in the frequency of pregnancy losses among SLE patients in the last 40 years, with current rates among SLE women being similar to those of the general population (17%). In this meta-analysis, premature births and pregnancy losses were considered as two separate categories. Of note, these authors decided to exclude those “outlier” studies whose results differed significantly from the ones selected for their meta-analysis (<25th or >75th

percentile). However, even studies published subsequent to this meta-analysis support the notion that adverse pregnancy outcomes occur more frequently in lupus patients than in the general population (4). Excluding such studies may have allowed Clark *et al.* to support the conclusions reached. Another possible explanation for the divergent results between our study and theirs is the fact that these authors did not consider the socioeconomic-demographic or behavioral features of the patients from the studies included in their meta-analysis. More importantly, although, we had not specifically recorded in the database whether our patients received specialized care in a high-risk obstetric-rheumatology setting, we suspect that many of our patients had no access to such care based on their overall socioeconomic features but precise figures cannot be provided.

We have shown previously that Hispanics are usually younger when diagnosed with SLE, therefore more likely to be in their childbearing years during the course of their disease; they also experience higher degrees of disease activity, which may have suggested that their pregnancy outcomes may not be satisfactory (30). However, ethnicity was not found to be a determinant of adverse pregnancy outcomes when other patients’ characteristics were adjusted for in the multivariable analyses. It appears that other factors, over and above ethnicity or highly correlated with ethnicity (fewer years of education), are more important determinants of pregnancy outcome in patients with lupus.

Our analyses showed that renal involvement, the maximum dose of glucocor-

ticoids ever used before the pregnancy outcome and fewer years of education were independently associated with adverse pregnancy outcomes. In general, our results are in agreement with the current literature (7, 9, 31); indeed, renal involvement in SLE has been recognized as a strong predictor of adverse pregnancy outcomes in lupus patients (7, 9, 31, 32). However, the dose of glucocorticoids used has never been associated with adverse pregnancy outcomes in SLE patients although its use at conception has been associated with prematurity but not with other adverse pregnancy outcomes (33). In our study, this negative effect of glucocorticoids is demonstrated. In the past, the use of glucocorticoids in low doses throughout the pregnancy had been recommended to prevent disease exacerbations (1); this practice, however, has largely been abandoned since (34). High doses, on the other hand, have been recommended perinatally in women receiving glucocorticoids throughout their pregnancies and assumed to have adrenal suppression (35).

This study is not without limitations. Firstly, as already noted, these patients were not followed during their pregnancies. Thus, we are unable to determine specific maternal and fetal characteristics associated with each trimester of pregnancy (*i.e.*, intrauterine growth restriction, disease activity per domains, setting of pregnancy care, continuity of treatment during pregnancy, dose and time of exposure to medications) hampering our efforts to determine more specifically the factors that could be associated with adverse pregnancy outcomes. Secondly, we were not able to distinguish between therapeutic and elective abortions since this information is not an element of our database. Conversely, some miscarriages may go unnoticed by the patient, particularly during the first six weeks of pregnancy or the patient may not want to disclose or forget to disclose a therapeutic abortion precluding the proper ascertainment of all adverse pregnancy outcomes with the consequent underestimation of its rate in these patients.

Thirdly, the time of exposure to high doses of glucocorticoids in relation to the pregnancy could not be exactly determined as this information was not part of the database. Finally, given that LUMINA is not an inception cohort, disease activity at TD was ascertained by review of all available medical records except in those patients who were enrolled within few weeks of disease onset. Although this is less than ideal, the method has been found to be reliable and thus the scores obtained are a reasonable approximation of the ones we would have obtained if disease activity had been ascertained during study visits (18).

Despite these limitations, the data presented allow us to conclude that ethnicity *per se* does not appear to influence the outcome of pregnancy in the lupus patient; rather, fewer years of education seems to be more important determinant of this outcome. In addition, the maximum dose of glucocorticoids (probably reflecting disease activity) and overall systemic involvement (renal, primarily) that these patients experience over the course of their disease, but particularly immediately prior to pregnancy, may determine whether the outcome of a pregnancy is favorable or not. Although, based on our data we cannot specifically recommend that lupus patients receive comprehensive obstetric care, this seems entirely reasonable based on the literature accrued to date (36).

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