Predictors of post-partum damage accrual in systemic lupus erythematosus: data from LUMINA, a multiethnic US cohort (XXXVIII)


Objective. To determine the impact of pregnancy on systemic lupus erythematosus (SLE) outcome.

Methods. SLE patients, age ≥16 yrs, disease duration ≤5 yrs at enrolment in LUMINA, a multiethnic cohort (Hispanics, African-Americans and Caucasians), were studied. The first pregnancy after SLE diagnosis was examined. A good pregnancy outcome was a full-term delivery; an adverse outcome was a miscarriage, abortion, premature birth or stillbirth. Dependent variables were disease activity (Systemic Lupus Activity Measure-Revised, SLAM-R) and damage accrual [Systemic Lupus International Collaborating Clinics (SLICC) Damage Index, SDI]. Differences in these variables between the visit immediately prior to, and the first visit after, pregnancy and their relationship with pregnancy outcome were examined. Damage accrual due to pregnancy exposure was examined by a case-crossover design.

Results. Sixty-three SLE women from all ethnic groups were included. The mean (s.d.) age and disease duration at pregnancy outcome were 27.6 (6.5) yrs and 18.3 (22.5) months, respectively. Adverse pregnancy outcomes occurred in 76.2% women. The SLAM-R and SDI scores were statistically different after pregnancy (P = 0.050 and P < 0.001, respectively); the SDI score was independent of pregnancy outcome but strongly associated with pregnancy duration (P = 0.006), disease activity (P = 0.001), damage prior to pregnancy (P < 0.001) and total disease duration (P = 0.039) by multivariable analyses. Exposure to pregnancy itself did not impact on damage accrual in the case-crossover analyses of 142 patients (17 pregnancy exposures) (OR = 1.25; 95% CI 0.336–4.655; P = 0.480).

Conclusions. Pregnancy duration, total disease duration, disease activity and damage immediately prior to pregnancy decisively impact on damage accrual after pregnancy in patients with SLE.

Key words: Pregnancy, Outcome, SLE, Damage, Predictors.

Introduction

Systemic lupus erythematosus (SLE) is known to occur predominantly in women and in their childbearing years. When pregnancy occurs, an increased exposure to oestrogens is expected. Given the known deleterious effects of exposure to oestrogens in SLE [1–3], pregnancy would reasonably be expected to have an overall negative impact on its course and progression. Moreover, as a dynamic process, the effects of pregnancy do not end right after the delivery. As a matter of fact, uterine involution does not occur until 6 weeks after delivery, mood changes and post-partum depression can be detected as late as 6 months post partum and bone mass and quality can take up to 2 yrs to recover [4]. In this setting, it is plausible that the exposure to pregnancy in SLE patients might exert long-term effects on the course of the disease.

Most studies on SLE pregnancy have been primarily focused on the immediate outcome of pregnancy [5–8] and the acute exacerbation of disease activity during pregnancy and in the immediate post-partum period [6–11] without further attempts to determine the aftermath of pregnancy in this group of patients later on.

We evaluated the impact of pregnancy on both, disease activity and damage accrual among SLE patients from LUMINA (Lupus in Minorities: Nature vs Nurture), a multiethnic cohort.

Patients and methods

Patients

The LUMINA cohort has been previously described [12]. Briefly, LUMINA is a longitudinal study of outcome in SLE patients...
from three different ethnic groups [Hispanic [of Mexican and Central American (Texas) or Puerto Rican ancestry], African-American and Caucasian] at three institutions (the University of Alabama at Birmingham, The University of Texas Health Science Center at Houston and The University of Puerto Rico Medical Sciences Campus). This study was approved by the Institutional Review Boards for the Protection of Human Subjects of the participating institutions and is conducted according to the Declaration of Helsinki’s guidelines.

Patients meeting ≥4 of the American College of Rheumatology (ACR) revised criteria for SLE, 16 yrs of age and older, with disease duration ≤5 yrs at study entry, who are followed-up at any of the three institutions, are eligible for inclusion in the LUMINA cohort. Patients are seen at recruitment or baseline (T0), at 6 and 12 months (T0.5 and T1, respectively) and yearly thereafter [T2, T3, etc. to TL (last visit available)]. Cumulative data prior to enrollment in the LUMINA cohort were obtained from their medical records upon informed consent for medical information release. All visits include medical records review, interviews and questionnaires, physical examination and ancillary laboratory studies. The time of diagnosis (TD) was defined as the time at which patients met four of the ACR criteria for SLE. Total disease duration was defined as the interval between TD and the time of pregnancy outcome. For the purpose of this study, only women that, in theory, the ultimate expected result of a pregnancy is a live birth, abortions, whether therapeutic or the patient’s decision to stop her pregnancy, were also considered adverse pregnancy outcomes. Only pregnancies that occurred after SLE diagnosis (TD) were considered.

Variables
As described previously, the LUMINA database includes variables from the socioeconomic-demographic, clinical and other domains. These variables are measured at T0 and at every subsequent visit. Only variables included in this study will be described.

Variables from the socioeconomic-demographic domain included were age, ethnicity, poverty (as defined by the US Federal Government adjusted for the number of subjects in the household), marital status and health insurance. Clinical variables included were total disease duration, disease activity and damage. Disease activity was ascertained with the Systemic Lupus Activity Measure-Revised (SLAM-R). The SLAM-R is a validated instrument that includes 23 clinical manifestations and seven laboratory parameters present some time during the preceding month and attributable to SLE. Disease accrual was measured with the Systemic Lupus International Collaborating Clinics (SLICC) Damage Index (SDI). This index documents cumulative and irreversible damage irrespective of its cause in 12 different organ systems. To be scored, each manifestation must be present for at least 6 months, unless otherwise noted in the instructions accompanying the instrument.

Pregnancies, their duration (in weeks) and outcomes were recorded at each study visit. A full-term delivery (>37 weeks; vaginal or C-section) was considered a good outcome. Adverse outcomes, including miscarriages (<20 weeks), premature births (≥37 weeks) and stillbirths (≥20 weeks) were considered. Given that, in theory, the ultimate expected result of a pregnancy is a live birth, abortions, whether therapeutic or the patient’s decision to stop her pregnancy, were also considered adverse pregnancy outcomes. Only pregnancies that occurred after SLE diagnosis (TD) were considered.

Study design and statistical analyses
In order to determine the impact of pregnancy on SLE progression, our study was divided into two parts.

In the first part, only the first pregnancy occurring after SLE diagnosis was included. In order to prevent disease duration from becoming a confounding factor in our analyses, pregnancies that occurred more than 2 yrs prior to T0 were excluded. In addition to determining the general socioeconomic-demographic and clinical features of the patients included, these characteristics were also examined as a function of pregnancy duration and of pregnancy outcome. Thus, changes in disease activity and damage at the visit immediately prior to the first pregnancy after SLE diagnosis and its corresponding first post-partum visit were examined. When appropriate, multivariable models were examined.

In the second part of the study, we addressed the effect of exposure to pregnancy per se in damage accrual as a measure of progression of SLE. We examined this relationship using a case-crossover design. This design self-matched each patient for ethnicity, socioeconomic-demographic and other characteristics that might play a role as confounding variables. For design purposes, an interval was the unit of analysis defined as the period between two consecutive study visits. Hence, in the LUMINA cohort, each patient has a series of intervals. A control interval is one in which no damage accrual as per the SDI occurred, whereas a case interval is one wherein a change in the SDI has taken place. One case and one control interval were randomly selected for each patient. Only women in whom both types of intervals had occurred could be included in these analyses. Women in whom menopause was reported before the randomly selected case and control intervals, with only one visit, or with only one type of interval were excluded. Pregnancy occurring within an interval was considered a positive exposure and an interval without it a negative one. The odds of developing damage accrual if exposure to pregnancy had occurred and its 95% confidence interval were then calculated.

Results
In the first part of the study, 63 women with one or more pregnancies after SLE diagnosis were included out of 544 women from the LUMINA cohort. All ethnic groups were represented. Overall, 35.0% were Hispanics from Texas, 9.5% Hispanics from Puerto Rico, 39.5% African-Americans and 16.0% Caucasians. The mean (s.d.) age among these patients was 27.6 (6.5) yrs; the mean duration (s.d.) of disease at the time of pregnancy outcome was 18.3 (22.5) months and the mean duration (s.d.) of disease at the time of first post-partum visit was 31.7 (23.9) months (Table 1). All other socioeconomic-demographic and clinical characteristics are shown in Table 1 for all women included in the study by ethnic group.

Pregnancy outcomes
Over half of the pregnancies considered in this part of the study occurred in women who had not been pregnant before, thus they were first pregnancies (32/63; 50.8%). Pregnancy outcomes by ethnic group are presented in Table 2. Overall, 48 of 63 pregnancies had an adverse outcome (76.2%).

Disease activity and damage accrual
In terms of disease activity, there was a significant decrease in SLAM-R scores after pregnancy (mean SLAM-R score before: 10.1, mean SLAM-R score after: 8.4, P = 0.0500) (Table 3). In contrast, the SDI score after pregnancy was significantly higher than before it (mean SDI score before: 0.19; mean SDI score after: 0.60, P < 0.0001) (Table 3).

Predictive factors of post-partum damage accrual
Given that the only outcome which appeared to be adversely impacted by the occurrence of pregnancy was that of damage accrual, a multivariable analysis was performed. Variables entered in the model were the following: age at pregnancy
outcome, ethnicity, pregnancy outcome type, pregnancy duration, disease activity prior to pregnancy outcome, total disease duration at first post-partum visit and SDI score prior to pregnancy outcome. Damage accrual was strongly associated with pregnancy duration, disease activity and damage accrual at the visit immediately prior to the pregnancy outcome (P = 0.006, P = 0.001 and P < 0.001, respectively), and moderately associated with total disease duration (P = 0.039) (Table 4). The variance ($R^2$) explained in this model was 57.8%. Age at outcome, ethnicity and pregnancy outcome were not found to independently contribute to damage accrual in these patients. No interactions between pregnancy outcome type and pregnancy duration and between SDI score immediately prior to pregnancy and total disease duration at first post-partum visit were found.

### Case-crossover design

In this set of analyses, 142 patients with 284 intervals were included. All ethnic groups were represented; however, the group was predominantly African-American women. The mean (s.d.) age at the intervals selected was 35.4 (9.7) yrs. Within these intervals, 17 exposures to pregnancy were identified.

### Table 1. Socioeconomic–demographic and clinical characteristics of LUMINA patients as a function of their ethnic group

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hispanic</th>
<th>Texas (n = 22)</th>
<th>Puerto Rico (n = 6)</th>
<th>African-American (n = 25)</th>
<th>Caucasian (n = 10)</th>
<th>All (n = 63)</th>
<th>P-value*$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at outcome (yrs), mean (S.D.)</td>
<td>27.3 (5.9)</td>
<td>25.5 (5.5)</td>
<td>27.5 (7.1)</td>
<td>30.0 (7.0)</td>
<td>27.6 (6.5)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Marital status (married/together), %</td>
<td>50.0</td>
<td>100.0</td>
<td>44.0</td>
<td>90.0</td>
<td>59.0</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Poverty, below line, %</td>
<td>55.0</td>
<td>17.0</td>
<td>38.0</td>
<td>10.0</td>
<td>37.0</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Health insurance, %</td>
<td>47.4</td>
<td>100.0</td>
<td>84.0</td>
<td>100.0</td>
<td>76.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease duration (months), mean (S.D.)</td>
<td>At pregnancy outcome</td>
<td>22.9 (27.6)</td>
<td>10.5 (7.0)</td>
<td>16.8 (22.7)</td>
<td>16.8 (14.5)</td>
<td>18.3 (22.5)</td>
<td></td>
</tr>
<tr>
<td>At first post-partum visit</td>
<td>34.3 (29.0)</td>
<td>26.9 (14.4)</td>
<td>30.4 (23.5)</td>
<td>36.2 (18.0)</td>
<td>32.3 (23.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pregnancy duration (weeks), mean (S.D.)</td>
<td>29.0 (19.7)</td>
<td>34.0 (6.2)</td>
<td>30.4 (23.5)</td>
<td>25.9 (29.6)</td>
<td>29.6 (21.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLAM-R$^a$ prior to pregnancy, mean (S.D.)</td>
<td>10.5 (5.6)</td>
<td>9.3 (5.4)</td>
<td>11.3 (5.0)</td>
<td>6.1 (3.0)</td>
<td>10.0 (5.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLAM at first post-partum visit, mean (S.D.)</td>
<td>10.0 (5.3)</td>
<td>5.8 (4.2)</td>
<td>8.8 (4.9)</td>
<td>6.6 (4.3)</td>
<td>8.6 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDI$^b$ prior to pregnancy, mean (S.D.)</td>
<td>0.3 (1.0)</td>
<td>0.2 (0.4)</td>
<td>0.1 (0.4)</td>
<td>0.1 (0.3)</td>
<td>0.2 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDI at first post-partum visit, mean (S.D.)</td>
<td>0.5 (1.1)</td>
<td>0.6 (0.8)</td>
<td>0.8 (1.0)</td>
<td>0.3 (0.5)</td>
<td>0.6 (0.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$^a$Only P ≤ 0.05 are shown; $^b$Systemic Lupus Activity Measure-Revised; $^c$Systemic Lupus International Collaborating Clinics (SLICC) Damage Index.

### Table 2. Pregnancy outcome type in LUMINA patients as a function of Ethnic group*$^a$

<table>
<thead>
<tr>
<th>Hispanic</th>
<th>Texas</th>
<th>Puerto Rico</th>
<th>African-American</th>
<th>Caucasian</th>
<th>All</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy outcome type</td>
<td>n = 22 (%)</td>
<td>n = 6 (%)</td>
<td>n = 25 (%)</td>
<td>n = 10 (%)</td>
<td>n = 63 (%)</td>
</tr>
<tr>
<td>Good</td>
<td>6</td>
<td>27.3</td>
<td>3</td>
<td>50.0</td>
<td>4</td>
</tr>
<tr>
<td>Adverse</td>
<td>16</td>
<td>72.7</td>
<td>3</td>
<td>50.0</td>
<td>21</td>
</tr>
</tbody>
</table>

$^a$Differences between groups are not statistically significant.

### Table 3. Univariable analyses of disease activity and damage accrual as a function of pregnancy in LUMINA patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before</th>
<th>After</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease activity (SLAM-R$^a$ score, SD)</td>
<td>10.1 (5.2)</td>
<td>8.4 (5.0)</td>
<td>0.0500</td>
</tr>
<tr>
<td>Disease damage (SDI$^b$ score, SD)</td>
<td>0.19 (0.69)</td>
<td>0.60 (0.96)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

$^a$Systemic Lupus Activity Measure-Revised; $^b$Systemic Lupus International Collaborating Clinics (SLICC) Damage Index.

### Table 4. Multivariable analyses of damage accrual in pregnant women from LUMINA

<table>
<thead>
<tr>
<th>Variable</th>
<th>F-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at outcome</td>
<td>0.024</td>
<td>0.878</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>1.316</td>
<td>0.257</td>
</tr>
<tr>
<td>Total disease duration at first post-partum visit</td>
<td>3.383</td>
<td>0.039</td>
</tr>
<tr>
<td>Pregnancy outcome type (adverse)</td>
<td>1.109</td>
<td>0.297</td>
</tr>
<tr>
<td>Pregnancy duration, weeks</td>
<td>8.051</td>
<td>0.006</td>
</tr>
<tr>
<td>Disease activity prior to pregnancy outcome</td>
<td>12.172</td>
<td>0.001</td>
</tr>
<tr>
<td>Damage accrual prior to pregnancy outcome</td>
<td>17.790</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

$R^2$ for model, 57.8%.

Exposure to pregnancy did not increase the risk of damage accrual post-partum (OR = 1.25; 95% CI 0.336–4.655; P = 0.480).

### Discussion

Little is known about the overall effect of pregnancy on SLE progression. To date, the vast majority of studies have emphasized the effect of pregnancy on disease activity during pregnancy and the immediate fetal and maternal outcomes. We have assessed the
impact of pregnancy on SLE progression in the LUMINA cohort. Herein, we have found that over 70% of adverse pregnancy outcomes among the first pregnancies occurring after the diagnosis of SLE, decreased post-partum disease activity and a significant post-partum damage accrual. This last observation contradicts the accepted knowledge that pregnancy does not greatly influence the long-term course of SLE [13]. We have also shown that the effect on post-partum damage accrual is not due to pregnancy per se but due to pregnancy duration, disease activity levels and the degree of damage prior to pregnancy and total disease duration. Notably, this is the first study that describes the overall effect of pregnancy in SLE patients of Hispanic ancestry, given the multiethnic nature of our cohort that comprises patients from two Hispanic subgroups [one of Mexican ancestry (from Texas) and a second one from the Island of Puerto Rico] as well as Caucasians and African-Americans.

Disease activity [14, 15] and damage scores [16, 17] best depict the overall course and progression of SLE, respectively. Indeed, we have previously shown that Hispanics from Texas and African-Americans have higher SLAM-R and SDI scores when compared with Caucasians and Hispanics from Puerto Rico [18–20]. As a reflection of this intrinsic characteristic of our cohort, these two first ethnic groups had higher disease activity scores, both prior to pregnancy and after pregnancy, although these differences did not reach statistical significance. Overall and independent of the disease activity, disease activity decreased rather than increased after pregnancy. Therefore, we can surmise that pregnancy does not induce post-partum SLE flares, concurring with earlier observations made by Lockshin et al. [7] and Kiss et al. [21] but not with those of Petri [6] and Ruiz-Irastorza et al. [9].

In contrast to activity, damage accrual significantly increased after pregnancy. Given this latter finding and the critical overall effect of damage accrual on the long-term outcome of SLE, we assessed the predictors of post-partum damage at the first pregnancy immediately after the diagnosis of SLE through multivariable analyses. Variables were selected based on findings from the univariable analyses (disease activity and damage accrual prior to pregnancy), those known to have an effect on damage accrual (age and ethnicity) [19], and pregnancy characteristics that were felt could exert a major effect on SLE progression (pregnancy duration as an expression of oestrogen exposure [1–3], and pregnancy outcome type) and total disease duration at first post-partum visit (which is known to relate to damage accrual). Our model was fairly robust, accounting for nearly 60% of its variance. Post-partum damage accrual as a measure of SLE progression was strongly predicted by the degree of damage present prior to pregnancy which concurs with previous observations from our group and others on the predictive effect of initial damage and further damage accrual [20, 22, 23]. Furthermore, we have previously demonstrated that protective effects of drugs such as hydroxychloroquine are accomplished mainly in the patient without any damage at treatment initiation [24]. Despite the fact that ethnicity did not predict post-partum damage accrual in our model, it is important to note that some Hispanic subgroups accrue damage earlier during the course of their SLE, as shown by us previously [20].

Our model also showed that higher degrees of disease activity prior to pregnancy are strong predictors of post-partum damage accrual. This finding reinforces the current notion that accomplishing and maintaining SLE quiescence prior to pregnancy is the best approach to prevent further damage after pregnancy in SLE patients [11, 13, 25]. Total disease duration was found to be a moderate predictor of further post-partum damage. Although some may argue that time per se accounts for the damage accrual observed in our patients, it is noteworthy that other variables were retained in the model over and above disease duration.

Finally, longer pregnancy duration, as an expression of prolonged oestrogen exposure, remarkably predicts further damage accrual. This is the first time that the relationship between pregnancy duration and further damage accrual in SLE women has been shown. Although the deleterious effects of oestrogens on SLE are well known [1–3, 11, 13, 25], this finding should by no means be interpreted as an indication to discourage pregnancy in SLE women. Instead, our data, as a whole, suggest the important role of disease management, family planning counsel and appropriate patient education in order to prevent the thoroughly described adverse maternal and fetal outcomes pregnant lupus patients may experience [7, 11, 13, 20, 25, 26]. Indeed, the second part of our analyses allowed us to delve into the real impact of pregnancy per se on damage accrual as an indication of SLE progression. The case-crossover design best applies if the exposure is intermittent, the effect or risk is immediate and transient and the outcome is abrupt [27]. Indeed, pregnancy considered as an exposure of this nature (intermittent) best fits the purpose to validate our previous conclusions. Foremost, a case-crossover design allows for a perfect match of each participating subject, controlling for potential confounders such as ethnicity, socioeconomic factors and behavioural features which are hard to control in a traditional case-control design. Using this approach, we did not find any increased risk of accruing damage when exposed to pregnancy per se. Therefore, these complementary analyses, along with the results from the multivariable analyses, lead us to conclude that it is neither pregnancy outcome type nor pregnancy per se that determines a negative impact on SLE progression after pregnancy.

This study is not without some limitations. Due to the nature of the LUMINA cohort, we do not have precise information related to the pregnancy itself; whether this information might better predict post-partum damage accrual should be a matter of further studies. In addition, post-partum damage was not assessed at the same time in all patients (average post-partum time: 14.4 months); however, in order to circumvent this, time of disease duration at the first post-partum visit was included in our multivariate model. Indeed, total disease duration appeared to predict post-partum damage to some extent, although less remarkably than pregnancy duration, disease activity and damage prior to pregnancy.

Despite these limitations, our study is quite relevant as it demonstrates for the first time the progression of SLE after pregnancy; in addition it contributes to the understanding of pregnancy in SLE women of Hispanic ethnicity, which, in the last decade, has become the largest ethnic minority in the USA [28]. Finally, our study reinforces the current recommendations for SLE management and maintenance of quiescent disease as the treatment goals for all lupus patients but particularly for women of childbearing age with SLE planning to become pregnant.

<table>
<thead>
<tr>
<th>Rheumatology</th>
<th>Key messages</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Strong predictors of further post-partum damage accrual in SLE are higher disease activity levels and occurrence of damage prior to pregnancy.</td>
<td></td>
</tr>
<tr>
<td>- Pregnancy should not be discouraged in the lupus patient, but should occur when the disease is quiescent to minimize the risk of post-partum damage accrual.</td>
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</tbody>
</table>

Acknowledgements

The authors would like to acknowledge all LUMINA patients without whom this study would not be possible, our supporting staff (Ellen Sowell at UAB, Carmine Prinths-Diaz, MT at UPR and Robert Sandoval BA at UTH) for their efforts in securing our patients’ follow-up and performing other LUMINA-related tasks.
The authors have declared no conflicts of interest.

References