Increased risk of adverse pregnancy outcomes for hospitalisation of women with lupus during pregnancy: a nationwide population-based study

C.-Y. Chen¹,², Y.-H. Chen³, H.-C. Lin⁴,⁵, S.-F. Chen², H.-C. Lin²

¹Graduate Institute of Health Care Organization Administration, National Taiwan University, Taipei, Taiwan; ²School of Health Care Administration, ³School of Public Health, Taipei Medical University, and ⁴Division of Infectious Disease, ⁵Department of Paediatric Infections, Taipei Medical University Hospital, Taipei, Taiwan.

Abstract

Objective

Using a nationwide population-based dataset to examine the risk of adverse pregnancy outcomes in women with systemic lupus erythematosus (SLE), with and without SLE hospitalisation during pregnancy.

Methods

We identified 1,010 pregnant women who had SLE during 2001~2003 as the study cohort and 5,050 randomly selected pregnant women (five for every woman with SLE) as a comparison cohort. Conditional logistic regression analyses were performed to explore the relationship between women with and without SLE and the risk of low birth weight (LBW), preterm birth, and babies small for gestational age (SGA), after adjusting for the characteristics of the infant, mother, and father.

Results

We found that there were significant differences in the risk of LBW (14.9% vs. 7.2%), preterm birth (14.4% vs. 8.5%), and SGA (28.5% vs. 17.5%) for women with SLE compared to women without. In addition, the adjusted odds of LBW, preterm birth, and SGA babies for women who had SLE during pregnancy were 6.15 (95% CI=4.15-9.13), 4.19 (95% CI=2.77-6.36), and 4.25 (95% CI=2.95-6.11) times, respectively, compared to women without any chronic illness. The adjusted odds of LBW, preterm birth, and SGA babies for women who had SLE but were not hospitalized during pregnancy were 1.80 (95% CI=1.43-2.26), 1.62 (95% CI=1.30-2.03), and 1.63 (95% CI=1.38-1.94) times, respectively, compared to unaffected mothers.

Conclusion

We conclude that SLE can impact the pregnancy outcomes, especially if hospitalisation occurs during the pregnancy.

Key words

Systemic lupus erythematosus, pregnancy outcome, low birth weight.
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Chia-Yu Chen, MA
Yi-Hua Chen, PhD
Hsiu-Chen Lin, MD
Shu-Fen Chen, MA
Herng-Ching Lin, PhD

Please address correspondence and reprints requests to:
Dr Herng-Ching Lin,
School of Health Care Administration,
Taipei Medical University,
250 Wu-Hsing St.,
Taipei 110, Taiwan.
E-mail: henry1111@tmu.edu.tw

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Introduction
Systemic lupus erythematosus (SLE) is an autoimmune disease that affects primarily women of childbearing age. It is commonly believed that SLE is exacerbated during pregnancy. Cervera reviewed prior studies and concluded that the lupus flare rates during pregnancy range from 13 to 60% (1). Although the chance of lupus flares during pregnancy can be reduced by avoiding pregnancy when the disease is active and continuing appropriate medication (2), many researchers still suggest that women with SLE during pregnancy should be considered high-risk.

Numerous studies consistently report that SLE is associated with adverse obstetric outcomes, including foetal wastage (3, 4), preterm birth (3, 5-8), low birth weight (9, 10), and intrauterine growth restriction (4, 8). However, there is no agreement about the relationship between SLE flares during pregnancy and adverse obstetric outcomes (11-19). For example, Clark et al. (11) found preterm deliveries were associated with disease activity. In contrast, studies by Georgiou et al. (13) and Lima et al. (14) found no significant relationship between SLE flares and preterm birth and miscarriage. Whether or not a flare of SLE in pregnancy is a risk factor for a poor obstetric outcome remains unclear.

Furthermore, several such studies on pregnancy outcomes for women with SLE have relied only on descriptive analysis and lacked the means to compare the risk of adverse pregnancy outcomes among mothers with SLE and the general healthy population (6, 8-10). In addition, almost no studies have used a nationwide population-based database to examine the relationship between SLE and the risk of adverse pregnancy outcomes, so findings cannot be generalised to a population as a whole.

Therefore, we analysed the risk of adverse pregnancy outcomes for women who had SLE hospitalisation during pregnancy and women who did not, using a general healthy population via Taiwan’s National Health Insurance Research Database (NHIRD). The National Health Insurance program in Taiwan was initiated in 1995. The NHIRD currently includes all inpatient and ambulatory care medical claims data on over 22 million citizens, representing over 98% of the island’s population. Thus, the NHIRD is one of the largest and most complete nationwide population-based datasets in the world, and offers a unique opportunity to estimate the risk of adverse pregnancy outcomes among women experiencing SLE hospitalisation during pregnancy.

Methods
Database
This study used two nationwide datasets. First, we used data from the NHIRD covering the years 1996 to 2003. The NHIRD provides a registry of contracted medical facilities, registry of board-certified physicians, registry of catastrophically ill patients, monthly summaries of inpatient claims, monthly summaries of ambulatory care claims, details of inpatient orders, details of ambulatory care orders, and expenditures for prescriptions dispensed at contracted pharmacies. One principal diagnosis from the ‘International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM)’ codes and up to four secondary diagnoses are listed for each patient.

Second, we used the 2001-2003 birth certificate registry published by the Ministry of the Interior in Taiwan that included birth certificate data such as birthdates of both infants and their parents, gestational week at birth, birth weight, gender, parity, place of birth, parental educational level, and maternal marital status. In Taiwan, birth registration is mandatory, so birth certificate data are believed to be very accurate and comprehensive.

With assistance from the Bureau of National Health Insurance (NHI) in Taiwan, the mother’s and infant’s unique personal identification numbers provided links between the NHIRD and birth certificate data. All personal identifiers were encrypted by the Bureau of NHI before release to the researchers. Confidentiality assurances were thus addressed by abiding by the data regulations of the Bureau of NHI. Since the NHIRD consists of de-identified secondary data released to the public for research purposes, this study was ex-
empt from full review by the Internal Review Board.

Study sample
The study sample for this research initially comprised 588,499 singleton births between January 1, 2001 and December 31, 2003 in Taiwan. If a mother had more than one singleton birth during the study period, we only selected the first for the study sample in order to avoid potential bias using the pregnancy outcomes from the same mother. A total of 473,529 mothers with 473,529 singleton live births fulfilled our initial selection criteria.

The study cohort and comparison cohort were extracted from the set of 473,529 mothers. The women included in the study cohort were identified with a principal diagnosis of systemic lupus erythematosus (ICD-9-CM code 710.0) within two years prior to the indexed delivery (n=1,974), based either on inpatient or ambulatory care claims. Because administrative databases have a bad reputation regarding coding validity, we included only patients who had at least two consensus SLE diagnoses in the study cohort in order to ensure the validity of the diagnoses. In addition, we excluded pregnant women who had been diagnosed with renal diseases that might affect the pregnancy outcome (n=102), leaving 1,010 mothers with SLE in the study cohort; 126 (12.5%) of these experienced hospitalisation for SLE during their indexed pregnancy. We thus examined non-renal SLE patients exclusively.

Our comparison cohort was selected from the remaining pregnant women. We excluded women diagnosed with renal disease between 1996 and 2003. Then, 5,050 pregnant women were randomly selected (five for every woman with SLE) and matched with the study group in terms of age (<20, 20-24, 25-29, 30-34 and ≥35 years) and the year of delivery to comprise our comparison cohort.

Variables of interest
In this study, women with SLE were categorised as having or not having been hospitalised for SLE treatment during pregnancy. Hospitalisation for disease during pregnancy was identified from the NHIRD by selecting women hospitalised with a principal diagnosis of SLE during pregnancy. The classification is justifiable because a principle diagnosis is the diagnosis most likely to be the chief focus of treatment. The outcome variables were all dichotomous, including low birth weight (<2500 g), preterm birth (<37 weeks), and small for gestational age babies (SGA) (birth weights below the tenth percentile for gestational age).

We also took other possible confounding factors into consideration. These factors included characteristics of the mother (age, highest educational level and marital status), infant (gender and parity), father (age and highest educational level), and family monthly income (including mother and father monthly income). Parental ages were defined as each parent’s age, in years, at the time of the infant’s birth. Parity was categorized into the following three categories: 1, 2, and ≥3. Maternal and paternal highest education levels were categorized into four levels: elementary school or lower, junior high school, senior high school, and college or above. Family monthly income was grouped into four categories: <NT$15,000, NT$15,000-NT30,000, NT30,001-NT50,000, and ≥NT50,001.

Statistical analysis
The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform the analyses in this study. Chi-square tests were carried out to examine the differences in the characteristics of the infant, mother, and father, comparing unaffected women and women with SLE. Conditional logistic regression analyses which were conditioned on maternal age and year of delivery were also used to explore the relationship between women with and without SLE and the risk of LBW, preterm birth, and SGA, after adjusting for the possible confounding factors. Since we found a strong co-linearity between maternal and paternal age, we kept only maternal age in the regression model. In addition, since prior studies have documented a significant relationship between parental age differences and adverse pregnancy outcomes, we added age differences between parents into the regression model for adjustment. Adjusted odds ratios (OR) are presented with 95% confidence intervals (CI). A two-sided p-value of <0.05 was considered statistically significant for this study.

Results
Details of the distribution for characteristics of infants, mothers, and fathers according to the cohorts are given in Table I. Pearson χ² tests show that there were significant differences among the cohorts in terms of infant parity (p<0.001), maternal age (p<0.001), highest maternal educational level (p<0.001), family monthly income (p<0.015), and highest paternal educational level (p<0.001). Women who experienced SLE hospitalisation during pregnancy (mean age=27.3 years) were likely to be younger than unaffected women (mean age=29.1 years) or women with SLE who did not experience hospitalisation during pregnancy (mean age=29.4 years). The distributions in infant gender, marital status, and paternal age did not differ significantly among the cohorts.

Among 1,010 mothers with non-renal SLE, 31% displayed adverse pregnancy outcomes (not shown in the tables). Table II describes the distribution and crude odds ratios of LBW, preterm birth, and SGA among the cohorts. The χ² tests show that there were significant differences in LBW (14.9% vs. 7.2%), preterm birth (14.4% vs. 8.5%), and SGA (28.5% vs. 17.5%) (all p-values <0.001) between women with SLE and unaffected women. The regression analyses also reveal that, compared to unaffected mothers, women who experienced SLE hospitalisation during pregnancy were more likely to have LBW infants (OR=6.34, 95% CI=3.19-9.33), preterm birth (OR=4.15, 95% CI=2.76-6.23), and SGA babies (OR=4.32, 95% CI=3.02-6.18). Similarly, women with SLE who experienced no hospitalisation during pregnancy had higher odds than unaffected women of LBW infants (OR=2.25, 95% CI=1.84-2.76), preterm birth (OR=1.86, 95% CI=1.48-2.22), and SGA babies (OR=1.89, 95% CI=1.62-2.20).
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Table I. Comparisons of the maternal, paternal, and infant characteristics of women with SLE, with and without SLE hospitalisation during pregnancy and women without SLE in Taiwan, 2001–2003 (n=6,060).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mothers with SLE</th>
<th>Mothers without SLE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregnant women</td>
<td>No hospitalisation</td>
</tr>
<tr>
<td></td>
<td>without SLE</td>
<td>for SLE treatment</td>
</tr>
<tr>
<td></td>
<td>n=5,050</td>
<td>during pregnancy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>n=884</td>
</tr>
<tr>
<td></td>
<td>Total n.</td>
<td>Total n.</td>
</tr>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
</tbody>
</table>

Infant characteristics

Gender
- Male: 2704 (53.5) vs. 2346 (46.5)
- Female: 467 (52.8) vs. 417 (47.2)

Parity
- 1: 2465 (48.8) vs. 514 (58.1)
- 2: 1778 (35.2) vs. 263 (29.8)
- 3 or more: 807 (16.0) vs. 107 (12.1)

Maternal characteristics

Age
- <20: 100 (2.0) vs. 15 (1.7)
- 20-24: 705 (14.0) vs. 110 (12.4)
- 25-29: 1920 (38.0) vs. 333 (37.7)
- 30-34: 1665 (33.0) vs. 304 (34.4)
- >34: 660 (13.0) vs. 122 (13.8)

Education level
- Elementary school or lower: 108 (2.1) vs. 13 (1.5)
- Junior high school: 778 (15.4) vs. 96 (10.9)
- Senior high school: 3384 (69.0) vs. 586 (66.3)
- College or above: 780 (15.5) vs. 189 (21.4)

Marital status
- Married: 4912 (92.3) vs. 864 (97.7)
- Others: 138 (2.7) vs. 20 (2.3)

Diabetes
- Yes: 35 (0.7) vs. 9 (1.0)
- No: 5007 (99.0) vs. 875 (99.0)

Hypertension
- Yes: 523 (1.0) vs. 15 (1.7)
- No: 4998 (9.3) vs. 869 (98.3)

Family monthly income
- <NT$15,000: 1526 (30.2) vs. 279 (31.6)
- NT$15,000-30,000: 1311 (26.0) vs. 223 (25.2)
- NT$30,001-50,000: 1432 (28.4) vs. 223 (25.2)
- >NT$50,000: 781 (15.5) vs. 159 (18.0)

Paternal characteristics

Age
- <30: 29 (0.6) vs. 1 (0.1)
- 30-34: 3581 (70.9) vs. 614 (69.5)
- >34: 1440 (28.5) vs. 269 (30.4)

Education level
- Elementary school or lower: 84 (1.7) vs. 7 (0.8)
- Junior high school: 887 (17.6) vs. 136 (15.4)
- Senior high school: 3079 (61.0) vs. 504 (57.0)
- College or above: 1000 (19.7) vs. 237 (26.8)

Table II illustrates the details of the adjusted OR for the risk of LBW, preterm birth, and SGA among the groups. It shows that after adjusting for the infant’s gender, parity, maternal age, hypertension and diabetes, highest maternal and paternal educational level (separately), parental age difference, and mothers’ marital status and family monthly income, the odds for unaffected women of LBW, preterm birth, and SGA babies for women who experienced SLE hospitalisation during pregnancy were 6.15 (95% CI=4.15-9.13), 4.19 (95% CI=2.77-6.36), and 4.25 (95% CI=2.95-6.11) times, respectively. Likewise, the odds of LBW, preterm birth, and SGA babies for women with SLE who had no flares during pregnancy were 1.80 (95% CI=1.43-2.26), 1.62 (95% CI=1.30-2.03), and 1.63 (95% CI=1.38-1.94) times, respectively. Finally, as compared to SLE women without hospitalisation during pregnancy, those with SLE hospitalisation had a 3.77 (95% CI=2.41-5.89), 2.79 (95% CI=1.75-4.46), and 2.78 (95% CI=1.86-4.14) times increased risk of having LBW babies, preterm birth, and SGA babies, respectively, (not shown in the tables).

Discussion

Our nationwide population-based study shows that adverse pregnancy outcomes occurred in 31% of 1,010 mothers with non-renal SLE. More specifically, we found that after adjusting for possible confounders, women with SLE were 2.23, 1.89, and 1.87 times more likely to have LBW, preterm birth, and SGA, respectively, than unaffected women (not shown in tables). This finding is consistent with prior studies reporting that women with SLE have increased risk of preterm birth (3, 7, 20, 21) and LBW babies (9, 10, 18, 22) compared to unaffected women. Nevertheless, except for the study by Wolfberg et al. (20), several studies comparing women with and without SLE have also failed to observe significant differences in having SGA babies (3, 12, 18, 22). Possible explanations for the discrepancy in findings may include: a small sample size or data collection from only a few hospitals or sub-populations of patients and the availability and use of modern obstetric care and foetal monitoring. Furthermore, we found that at least one hospitalisation during pregnancy occurred in 12.5% of women with SLE in our study, and the relationship between SLE and adverse pregnancy outcomes was even more pronounced when women experienced SLE hospitalisation during pregnancy. We found that compared to mothers without SLE, women who had SLE hospitalisation...
during pregnancy were four to six times more likely to have adverse pregnancy outcomes. In addition, compared to SLE women who were not hospitalised during pregnancy, women with SLE who had been hospitalised during pregnancy were two to three times more likely to have adverse pregnancy outcomes. Our findings are consistent with a study by Clowse et al., which reported that moderate to severe lupus activity during pregnancy significantly increased the rate of preterm birth compared to women with mild lupus activity or none at all (12). In addition, Mintz et al. (15) and Petri (23) both observed a significant relationship between SLE flares and preterm birth. In contrast to our findings, several other studies have failed to observe an association between adverse pregnancy outcomes and pregnancy with or without a flare of SLE (13, 14, 16, 17).

These differences could be due to the lack of a universal standard for diagnosing lupus flares. Although different researchers have attempted to standardise the criteria defining lupus flares (24, 25), these measures are meant for research purposes and do not focus specifically on pregnant lupus patients, making their application in pregnancy difficult. Some prior studies have even considered patients at the mild end of lupus activity as having a flare. Nevertheless, as our study categorised women with SLE as experiencing or not experiencing hospitalisation for SLE treatment during pregnancy, the second group might identify women with medium-severe flares.

One study by Cavallasca et al. indicated that although maternal age at conception was similar overall, women having three or more pregnancies accounted for approximately 40% of SLE patients with mild flares (9). However, only about 13% of indexed pregnancies among mothers with more severe SLE were on their third or higher pregnancy. In this present study, we failed to observe an association between maternal and paternal educational level and adverse pregnancy outcomes. In contrast to our findings, several other studies have found a significant relationship between paternal and maternal educational level and adverse pregnancy outcomes among SLE patients.

**Table II.** Crude odds ratios for LBW, preterm birth, and SGA among non-SLE women, women with SLE as having or not having experienced hospitalisation for SLE treatment during pregnancy, 2001–2003.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pregnant Women without SLE n=5,050</th>
<th>Pregnant women with SLE n=1,010</th>
<th>No hospitalisation for SLE treatment during pregnancy n=884</th>
<th>Hospitalisation for SLE treatment during pregnancy n=126</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n. %</td>
<td>n. %</td>
<td>n. %</td>
<td>n. %</td>
</tr>
<tr>
<td>Low birth weight</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>363 7.2</td>
<td>150 14.9</td>
<td>108 12.2</td>
<td>42 33.3</td>
</tr>
<tr>
<td>No</td>
<td>4,687 92.8</td>
<td>860 85.2</td>
<td>776 87.8</td>
<td>84 66.7</td>
</tr>
<tr>
<td>Crude OR* (95% CI)</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Preterm birth</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>427 8.5</td>
<td>145 14.4</td>
<td>111 12.6</td>
<td>34 27.0</td>
</tr>
<tr>
<td>No</td>
<td>4,623 91.5</td>
<td>865 85.6</td>
<td>773 87.4</td>
<td>92 73.0</td>
</tr>
<tr>
<td>Crude OR* (95% CI)</td>
<td>1.00</td>
<td>1.86*** (1.48-2.22)</td>
<td>1.55*** (1.24-1.93)</td>
<td>4.15*** (2.76-6.23)</td>
</tr>
<tr>
<td>Small for gestational age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>882 17.5</td>
<td>288 28.5</td>
<td>227 25.7</td>
<td>61 48.4</td>
</tr>
<tr>
<td>No</td>
<td>4,168 82.5</td>
<td>722 71.5</td>
<td>657 74.3</td>
<td>65 51.6</td>
</tr>
<tr>
<td>Crude OR* (95% CI)</td>
<td>1.00</td>
<td>1.89*** (1.62-2.20)</td>
<td>1.64*** (1.39-1.94)</td>
<td>4.32*** (3.02-6.18)</td>
</tr>
</tbody>
</table>

**Notes:**
- *Crude odds ratios (OR) were calculated by conditional logistic regressions which were conditioned on maternal age and the year of delivery.
- *Crude OR* **(95% CI)**
- ***p<0.001;** p<0.01; * p<0.05.
tases. These factors may increase the risk of adverse pregnancy outcomes. Secondly, we were unable to appropriately assess the flare status of women with SLE during pregnancy. However, by categorising mothers with SLE by their hospitalisation status in our study, women in the group of “hospitalisation for SLE treatment during pregnancy” might experience medium-severe flares. Thirdly, because this was a retrospective analysis, we were not able to assess any casual relationship between SLE and pregnancy outcomes. Finally, our study did not consider the effects of medication during pregnancy. Several treatments such as corticosteroids, non-steroidal anti-inflammatory drugs, and hydroxychloroquine are frequently used to prevent SLE flares during pregnancy. Stopping hydroxychloroquine during pregnancy is specifically associated with increased degrees of lupus activity (29). However, women with SLE in Taiwan are likely to discontinue any medication after becoming pregnant out of concern of adverse consequences for the developing foetus. Thus, the association between SLE and pregnancy outcomes found in our study was largely based upon the assumption of women not receiving SLE treatment during pregnancy.

In conclusion, our study showed a significant relationship between adverse pregnancy outcomes and SLE in pregnant women, especially in mothers with a hospitalisation for SLE treatment during pregnancy. The SLE hospitalisation rate seemed relatively high for non-renal patients, possibly reflecting the tendency to stop medication during pregnancy. We suggest that women with SLE regularly visit both rheumatologists and obstetricians and prevent increases in disease activity before and during pregnancy. Mild increases in disease activity should be identified and treated before a severe flare occurs. Appropriate medication is available (30) and should be continued through pregnancy in women who require it for symptom control.

Acknowledgements
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References