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### Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study

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| Complete List of Authors: | WU, JIAYUE; Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China, Department of Obstetrics and Gynecology  
MA, Jinghang; Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China, Department of Obstetrics and Gynecology  
BAO, Chunde; Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China, Department of Rheumatology  
Zhang, WeiHong; International Centre for Reproductive Health (ICRH), Ghent University, ICRH  
DI, WEN; Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China, Department of Obstetrics and Gynecology |
| Primary Subject Heading: | Obstetrics and gynaecology |
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| Keywords: | Fetal outcomes, Maternal outcomes, Systemic lupus erythematosus, Pregnancy |
Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study

Jiayue WU, MD 1,2, 5 Jinghang MA, MS1,2; Chunde BAO, MD3,4; Wei-Hong ZHANG, MD, MPH, PhD, 5, ∆; Wen DI, MD, PhD 1,2, ∆

1. Department of Obstetrics and Gynecology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China;
2. Shanghai Key Laboratory of Gynecologic Oncology, Shanghai, China;
3. Department of Rheumatology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China;
4. Shanghai Institute of Rheumatology, Shanghai, China.
5. International Centre for Reproductive Health (ICRH), Ghent University, 9000, Ghent, Belgium

∆ Co-corresponding authors

Correspondence to China:
Wen DI, Department of Obstetrics and Gynecology, Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China.

Email: diwen163@163.com

Correspondence to Europe:
Wei-Hong ZHANG, International Centre for Reproductive Health (ICRH), Ghent University, 9000, Ghent, Belgium;

E-mail: WeiHong.Zhang@UGent.be
Abstract

Objective: To completely and quantifiably determine the effect of SLE on pregnancy outcomes in Chinese cohorts.

Design: A retrospective cohort study.

Setting: Data was collected in a tertiary medical center, located in Shanghai, China, from September 2011 to May 2017.

Participants: We assigned 338 pregnancies with SLE to the study cohort and 1014 randomly selected pregnancies without SLE (three for every woman with SLE) to a comparison cohort. The relevant medical records of all pregnancies were retrospectively reviewed. Cases of multiple pregnancy and those in which artificial abortion was performed for personal reasons were excluded.

Primary and secondary outcome measures: Maternal and fetal outcomes were primary outcomes and managements of antenatal care were secondary outcomes.

Results: The risk of spontaneous abortion (OR=4.42, 95%CI=1.52-12.80), therapeutic abortion (OR=16.57, 95%CI=5.80-47.35), pregnancy-induced hypertension (OR=2.68, 95%CI=1.75-4.09) and preeclampsia (OR=3.13, 95%CI=1.95-5.03) was significantly different between women with and without SLE. Women with SLE were more likely to have postpartum infections. Gestational diabetes was negatively associated with SLE in pregnant women (OR=0.49,
95%CI=0.28-0.85). Pregnant women with SLE had significantly fewer live births (OR=0.10, 95%CI=0.05-0.20) and a higher risk of having a still (OR=14.70, 95%CI=1.65-131.00) or preterm birth (OR=3.15, 95%CI=2.21-4.50), intrauterine growth restriction (OR=2.20, 95%CI=1.35-3.58), small for gestational age (OR=1.86, 95%CI=1.11-3.13), low birth weight (OR=3.86, 95%CI=2.59-5.75), a cesarean section birth (OR=4.73, 95%CI=3.30-6.80), or a NICU admission (OR=3.48, 95%CI=2.21-5.48) than was observed in the women in the non-SLE population after the analysis was adjusted for confounding factors.

**Conclusions:** In this study, we found that SLE significantly increased the risk of adverse pregnancy outcomes. Therefore, a pre-conception assessment and close antenatal monitoring by both rheumatologists and obstetricians should be performed in pregnant women with SLE.

**Keywords:** Fetal outcomes; Maternal outcomes; Pregnancy; Systemic lupus erythematosus;
Strengths and limitations to this study

1. This is the first Chinese cohort study to compare maternal and fetal outcomes between pregnant women with and without SLE.

2. Additionally, the present study included large samples of both SLE patients and controls that consisted of over 1350 individuals in all, and no data was missing for any of these patients.

3. Furthermore, the maternal and fetal outcomes evaluated in this study were comprehensive and reflect almost every key aspect of pregnancy.

4. One limitation was that as a retrospective study, this study has inherent biases, and these include selection bias and information bias.

5. Second limitation was the clinical records lacked some details regarding baseline population characteristics, e.g. education, body mass index, and family income of some of the included participants.

Competing interests

The authors have declared that no competing interests exist.

Funding

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Data sharing statement

No additional data are available.

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Introduction

Systemic lupus erythematous (SLE) is an autoimmune disease that involves multiple organs and is most common in young women, in whom it has an incidence of 90/100,000\(^1\). Women with SLE have a normal fertility rate,\(^1\) and pregnancy is therefore a frequent subject of interest in these patients. In past decades, SLE was viewed as a contraindication for pregnancy. However, in the last 50 years, as treatments for affected patients have improved and increasingly involved multidisciplinary management, pregnancy outcomes have dramatically improved.\(^2\) While numerous studies have reported that SLE is associated with adverse obstetric outcomes, including preterm birth, fetal growth restriction, pre-eclampsia, and fetal loss, most such studies have used descriptive methods to evaluate SLE cohorts and have failed to compare results with the general population.\(^3-6\) In addition, while a limited number of studies have compared pregnancy outcomes between women with SLE and the general population,\(^7-10\) almost no studies have done so in a Chinese cohort. Therefore, we have compared maternal and fetal outcomes between women with SLE and those in the general population to completely and quantifiably clarify the effect of SLE on pregnancy outcomes in a Chinese cohort.

Materials and Methods

Study sample

This is a retrospective cohort study performed in a single center. Our study cohort consisted of pregnant patients with SLE who were treated in Ren Ji Hospital,
Shanghai Jiao Tong University School of Medicine between September 2011 and May 2017. Cases of multiple pregnancy and in which an artificial abortion was performed for personal reasons were excluded. SLE was diagnosed according to the revised criteria for the classification of SLE developed by the American College of Rheumatology.  

Our comparison cohort was randomly selected from singleton pregnancies without SLE and matched with the study group by delivery time (three controls were selected for every woman with SLE).

Variables of interest

Medical records from both cases and controls were retrospectively reviewed, and pregnancy outcomes were systematically evaluated.

1. Population characteristics

The baseline characteristics of the population were recorded to identify potentially confounding factors. These factors included maternal age at delivery, region, whether the pregnancy is nulliparous, spontaneous abortion and comorbidities. Region was categorized as city and country. Spontaneous abortion was categorized as 0, 1, and ≥2. Comorbidities included a pre-pregnancy diagnosis of hypertension or diabetes. None of the women in the study population was a smoker or a drinker, and lifestyle (e.g., smoking and drinking) was therefore not analyzed in the study.
2. Maternal outcomes

All outcome variables were dichotomous. The abstracted maternal outcomes and definitions were as follows:

- Spontaneous abortion: spontaneous termination of a pregnancy prior to 28 weeks of gestation.
- Therapeutic abortion: abortion for therapeutic reasons because the pregnancy might be a threat to maternal health.
- Premature rupture of membranes (PROM): a rupture of the amniotic sac at < 24 h prior to the onset of labor.
- Maternal death: the death of a woman while pregnant or within 42 days of the termination of a pregnancy, regardless of the duration or site of the pregnancy, of any cause related to or aggravated by the pregnancy or its management but not of any accidental or incidental cause.\(^\text{12}\)
- Postpartum hemorrhage (PPH): was defined as a blood loss of 500 ml or more within 24 h after birth.\(^\text{13}\)
- Postpartum infection: an infection that occurs following childbirth.
- Pregnancy-induced hypertension (PIH): an increase in blood pressure to $\geq 140/90$ mmHg on at least two occasions $\geq 6$ h apart that arises *de novo* after the 20th week of pregnancy.
- Preeclampsia: pregnancy-induced hypertension with proteinuria $> 0.3$ g/L/d in the absence of a urinary tract infection or the abrupt onset of hypertension and
proteinuria after 20 weeks of gestation. Seizures were required for a diagnosis of eclampsia.

- **Gestational diabetes (GDM):** was defined as any degree of glucose intolerance with onset or first recognition during pregnancy.\(^ {14} \)

- **HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome:** the presence of hemolysis, high levels of lactate dehydrogenase or total bilirubin >12 mg/L, elevated alanine aminotransferase levels of greater than twofold the upper normal value, and thrombocytopenia < 100×10\(^9 \)/L.

### 3. Fetal outcomes

All outcome variables were dichotomous and continuous. The abstracted fetal outcomes and definitions were as follows:

- **Live birth:** the birth of a living child.

- **Stillbirth or intrauterine fetal death:** any baby born without signs of life at greater than or equal to 28 completed weeks of gestation.\(^ {15} \)

- **Preterm birth:** delivery <37 weeks of gestation.

- **Neonatal death:** live birth during the first 28 completed days of life.\(^ {16} \)

- **Intrauterine growth restriction (IUGR):** factors that limit the potential for the intrauterine growth of the fetus.\(^ {17} \)

- **NICU:** neonates who required intensive medical attention and were admitted into a special area of the hospital called the Neonatal Intensive Care Unit (NICU).
Small for gestational age (SGA): infants whose weight was lower than the lower 10% limit of the CI of the normal curve for gestational weight.\textsuperscript{18}

Low birth weight (LBW): infants with a birth weight \( \leq 2500 \text{ g} \) regardless of gestational age and circumstances.\textsuperscript{19}

Method of childbirth: cesarean section or vaginal birth.

Congenital malformation: all types of congenital malformation.

Neonatal gender: male and female.

One-minute and 5-minute Apgar scores: an Apgar score \( >7 \) was defined as normal, while a score \( <7 \) was considered indicative of moderate or severe hypoxia.\textsuperscript{20}

Birth weight: neonatal birth weight is presented in grams.

Gestational days: neonatal gestational days is presented in days.

\textbf{Statistical analysis}

Descriptive data are showing with the mean \( \pm \) SD or as a frequency. Categorical variables were analyzed using the chi-square test or Fisher’s exact probability test as appropriate. Continuous variables were analyzed using Student’s t test.

The denominator used in the analyses of all maternal outcomes in addition to still births and live births was all reported pregnancies. For all other fetal outcomes (excluding still births and live births), the denominator was all live births.

Logistic regression analyses were performed to compute crude ORs with 95% CIs for maternal and fetal outcomes. The logistic regression models were adjusted for
potential confounding factors, including maternal age, region, nulliparity, history of spontaneous abortion and comorbidities. These analyses yielded new adjusted ORs with 95% CIs. All tests were two-tailed, and p < 0.05 was considered statistically significant. All analyses were performed using SPSS version 22.0.

**Ethics statement**

The research protocol used in this study was reviewed and approved by the Medical Ethical Committee of Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine. Because this is a retrospective observational study, the Medical Ethical Committee granted a waiver for informed consent for this study. Approval to obtain clinical data from the database was received from the office of the medical director of the hospital. All patient information was kept confidential.

**Results**

**Population characteristics**

A total of 338 pregnancies with SLE (cases) and 1014 pregnancies without SLE (controls) that occurred between September 2011 and May 2017 were included. The distributions of population baseline characteristics are shown in Table 1. Mean ages was not significantly different between the two cohorts. Women with SLE were more likely than the controls to reside in a city, and most of the SLE pregnancies were nulliparous. A history of spontaneous abortion, especially ≥ 2 times, was more common in SLE women. There was no significant difference in comorbid conditions
between the women with SLE and the controls. The proportion of women in whom diabetes and/or hypertension was diagnosed prior to pregnancy was not significantly different between the SLE and non-SLE populations.

**Maternal outcomes**

The rate of adverse maternal outcomes was several-fold higher in women with SLE than in the non-SLE population during pregnancy. Of the women with SLE, 3.3% had experienced a spontaneous abortion, while 6.2% had undergone a therapeutic abortion. PIH and preeclampsia/eclampsia were diagnosed in 19.2% and 14.2%, respectively, of the women with SLE. After adjusting for confounding factors, the risk of having a spontaneous abortion (OR=4.42, 95%CI=1.52-12.80), therapeutic abortion (OR=16.57, 95%CI=5.80-47.35), PIH (OR=2.68, 95%CI=1.75-4.09) or preeclampsia (OR=3.13, 95%CI=1.95-5.03) remained high. The absolute risk of infection was low, and postpartum infections occurred in 0.9% of the women with SLE and none of those without (p=0.016). Interestingly, the rate of GDM was lower in women with SLE than in the controls, and the OR remained unchanged after adjusting for confounding factors (OR=0.49, 95%CI=0.28-0.85). There was no significant difference in other maternal outcomes, including PROM, PPH and HELLP syndrome, between the two cohorts. There were no maternal deaths in either population. (Table 2)

**Fetal outcomes**
Women with SLE had a lower live birth rate (OR=0.10, 95%CI=0.05-0.20) and a higher risk of still birth (OR=14.70, 95%CI=1.65-131.00) than were observed in the non-SLE population after adjusting for confounding factors. Among women who achieved a live birth, the rates of preterm and cesarean births were 3.15-fold and 4.73-fold higher, respectively, in the pregnant women with SLE than in those without. The rate of NICU for neonates was also higher in SLE population. IUGR, SGA, LBW occurred in 12.3%, 10.0%, 22.7% of SLE pregnancies, respectively. The adjusted ORs were 2.20, 1.86 and 3.86, respectively, for each outcome (all p-values <0.05). Furthermore, we also found that neonatal birth weights (2763.7±588.7 g) and gestational days (259.3±16.2d) were lower in SLE pregnancies (both p<0.01). There were no neonatal deaths in either group. Finally, there was no significant difference in the rate of congenital malformations, neonatal gender, or the proportion of low Apgar scores between the cohorts (Table 3).

Comments

Principal findings of the study

In this study, we show that compared to pregnant women without SLE, pregnant women with SLE have a higher risk of adverse maternal outcomes, such as spontaneous abortion, therapeutic abortion, postpartum infection, PIH, and preeclampsia/eclampsia. Furthermore, SLE was also associated with adverse fetal outcomes, including a lower rate of live births; higher rates of preterm births, cesarean
sections, and NICU admissions and a significantly higher number of infants with
growth restriction (e.g., IUGR, SGA or LBW). The elevated risk that SLE confers to
each of these factors indicates that it a preconception assessment and antenatal
monitoring are both important in pregnant women with SLE.

**Comparison with previous studies**

In our cohort, there were differences in several baseline demographic features
between the women with SLE and those without. The women with SLE were more
likely than the non-SLE group to reside in a city and to be nulliparous. Importantly,
the women with SLE more frequently experienced a spontaneous abortion, and this
may potentially be associated with the high rate of adverse pregnancy outcomes
observed in SLE.¹⁰ There was no difference in the pre-pregnancy incidence of chronic
disease between the women with and without SLE. This finding was also reported in
two previous cohort studies.²¹,²²

SLE is an important risk factor for fetal loss, including spontaneous abortion,
therapeutic abortion and stillbirth. This finding was also reported in several previous
cohort studies performed in other settings.³⁴,⁷,¹⁰,²¹,²³-²⁵ In this study, the rates of still
birth and spontaneous abortion were 2.0% and 3.3%, respectively, in the SLE group.
These rates are much lower than those reported in other studies. This might have been
caused by differences in the terms used to define outcomes. However, in this study,
the rate of therapeutic abortion was higher in the SLE group (6.2% in SLE vs 0.5% in
non-SLE). Few previous studies have reported this outcome. One systemic review reported the rate of elective abortion and found that the OR was not significant (OR=1.19, 95%CI=0.76-1.88), but their definition for elective abortion were not the same as that used in this study. In our study, therapeutic abortion was defined as those performed for a therapeutic reason but not elective abortions based on the mother’s will. This definition may have contributed to the low rates of spontaneous abortion and stillbirth that were observed in our study because some severe cases of SLE were terminated using therapeutic abortion during an early trimester to maintain the health of the mother.

The results of our study confirm that PIH and preeclampsia are significant problems in SLE pregnancies. In our study, nearly one-fifth of SLE pregnancies were complicated with significant hypertension and preeclampsia, whereas only 5.8% to 9.0% of the pregnancies in healthy women were affected by these conditions. The OR remained significant even after adjusting for confounding factors. It is both important and difficult to recognize SLE flares and preeclampsia in pregnant SLE patients because both are associated with proteinuria, deteriorating renal function, and hypertension. Some common laboratory tests, such as tests to examine full blood cells or the erythrocyte sedimentation rate, have also become viewed as less reliable. Uncontrolled hypertension has been shown to predict poor pregnancy outcomes, and implementing measures to control blood pressure are recommended in these patients.
While few cases of postpartum infection were reported in either cohort, the SLE group had a significantly higher rate of infection. Clowse et al.\textsuperscript{9} and Nili et al.\textsuperscript{29} reported similar results. This effect may be related to the nature of the immune dysregulation observed in SLE or associated with the immunosuppressive nature of treatments for SLE.

Interestingly, we noticed that the rate of GDM was significantly lower in the women with SLE than in the controls (5.6\% vs 11.5\%) even after adjusting for confounding factors. Only one previous study reported the same result. In that study, McGrory et al. reported that no patients in their SLE group developed GDM, whereas 12\% of their non-SLE group developed GDM.\textsuperscript{26} Clowse et al. reported that their SLE cohort had a higher rate of pre-gestational diabetes potentially because these patients were administered corticosteroids during pregnancy.\textsuperscript{9} Further studies performed using larger populations should be performed.

The rate of cesarean section surgeries was surprisingly high in this study (SLE vs non-SLE: 85\% vs 55.6\%) and far higher than the rates reported in previous studies. A national U.S. population-based study performed in 2000-2003 reported a 36.6\% cesarean rate in SLE.\textsuperscript{9} Two studies conducted in northern Europe reported cesarean rates of 32-39\% in SLE pregnancies and 16-24\% in non-SLE pregnancies.\textsuperscript{8,30} While one study reported the converse result (SLE vs non-SLE: 30\% vs 53\%), the authors
recruited patients post-renal transplantation, and this may have contributed to the
difference in their results. Although the absolute rate was high in both groups in our
study, SLE was still a risk factor for cesarean section. The extremely high cesarean
section rate observed in our study reflects the true clinical situation in China. The
WHO suggested in 2008 that nearly half of all births in China are delivered via
caesarean section. Some of the potential reasons for this high rate include a fear of
pain and accidents during vaginal birth, an uneasy doctor–patient relationship, the fact
that caesarean sections are financially profitable for the hospital, and increases in the
number of babies with macrosomia at birth and the number of pregnancies in older
women.

In our study, the percentage of neonates who were diagnosed with IUGR, SGA, and
LBW and mean birth weight were each significantly higher in the SLE group than in
the control group. All three of these terms (IUGR/SGA/LBW) were used as indicators
of fetal growth restriction, but each involves a different mechanism. The definitions
we used for these terms are provided in the methods section. Our findings are in
agreement with previous studies that reported growth restriction rates of 10%-28% in
SLE populations. The risk of neonatal death is three-fold higher in
growth-restricted neonates than in those with a normal weight. These infants also
have high risk of developing other severe conditions, such as cardiovascular disease,
infection, and neurodevelopmental retardation. The risk of preterm birth was also 3-fold
higher in our SLE cohort, consistent with previous studies. The underlying
reason for this effect might be the fact that immune complexes cause vascular
inflammation, which contributes to a hypercoagulable state and consequently reduces
placental and umbilical artery blood flow and decreases placental perfusion and villus
structure, thereby affecting fetal growth.¹⁷,³⁷ Not surprisingly, the higher rates of
prematurity and growth restriction observed in the SLE group led to a higher NICU
admission rate. However, there was no difference in the Apgar scores of the neonates
at either 1 or 5 minutes, and the absolute incidence of moderate or severe hypoxia was
very low in both cohorts. This finding is in contrast to the result described in
Wallenius et al.³⁰, but this may be because the size of the SLE population was small
in this study.

There were four live births with congenital malformations in the SLE cohort and ten
in the controls, but there was no significant difference between the two groups.
Among the four infants with congenital malformations in the SLE cohort, two had
renal problems, and one had polydactyly. Additionally, three cases of malformation in
the SLE cohort were detected before 28 weeks, and these included one case of
dextrocardia and two cases of maldevelopment of cardiac anatomy. These three cases
were treated with therapeutic abortion. Compared to previous studies, in our study, we
reported a relatively low rate of congenital malformations. Wallenius et al.³⁰ and Liu J
et al.³⁸ reported a rate of malformation of approximately 6-7% in SLE neonates born
from approximately 2008-2009, and Rahman et al. reported a rate of 2% from
1970-1995.³⁹ One potential reason for these differences in the incidence of congenital
malformation is the fact that so many improvements have been made in the prenatal diagnosis and antenatal management of these patients.

Strengths and limitations

The present study is noteworthy for several reasons. While it has been previously reported in other studies that pregnancy is risky for SLE women, who have high rates of cesarean deliveries, infections, gestational hypertension and preeclampsia. This is the first Chinese cohort study to compare maternal and fetal outcomes between pregnant women with and without SLE. A nationwide population-based cohort was evaluated in Taiwan in 2010, but that study focused on only three fetal outcomes. Additionally, the present study included large samples of both SLE patients and controls that consisted of over 1350 individuals in all, and no data was missing for any of these patients. Furthermore, the maternal and fetal outcomes evaluated in this study were comprehensive and reflect almost every key aspect of pregnancy.

Nevertheless, our study has some limitations. First, as a retrospective study, this study has inherent biases, and these include selection bias and information bias. Second, the clinical records lacked some details regarding baseline population characteristics. These included the level of education, body mass index, and family income of some of the included participants. These factors may be confounding factors in the study. Finally, we did not consider the effect of medication during pregnancy even though medications can influence outcomes.
Research and clinical implications

In conclusion, in this study, we show that the risk of gestational hypertension, preeclampsia, postpartum infection and cesarean birth is higher, while the risk of gestational diabetes is lower in pregnant women with SLE than in those without. Additionally, we found that SLE contributes to higher rates of fetal loss, prematurity, fetal growth restriction and NICU admission. We therefore suggest that women with SLE should have full access to pre-conception counseling, choose an optimal time for pregnancy, and be provided close monitoring during antenatal care by both rheumatologists and obstetricians. Future large cohort studies should focus on antenatal management, including laboratory assessment and medication use, in pregnant women with SLE.

Acknowledgment

Not applicable.

Author contributions

JY.W., JH.M., CD.B., WH.Z., and W.D. were each responsible for the conception and design of the study; and JY.W., JH.M., and W.D. had full access to all of the data in the study. JY.W. and JH.M. collected the data. JY.W. and WH.Z. analyzed and interpreted the data; JY.W. and JH.M. drafted the initial manuscript; and WH.Z.,
CD.B., and W.D. revised the manuscript. All authors read and approved the final version of the manuscript.
### Tables

#### Table 1. Baseline clinical characteristics of pregnancy in SLE and non-SLE patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SLE cases (n=338)</th>
<th>Non-SLE cases (n=1014)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td><strong>Age (years)±SD</strong></td>
<td>29.53±4.0</td>
<td>29.67±4.3</td>
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<tr>
<td><strong>Region</strong></td>
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<tr>
<td>City (%)</td>
<td>237(70.1%)</td>
<td>318(31.4%)</td>
<td>0.000**</td>
</tr>
<tr>
<td>Rural(%)</td>
<td>101(29.9)</td>
<td>695(68.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Nullipara (%)</strong></td>
<td>291(86.1%)</td>
<td>706(69.6%)</td>
<td>0.000**</td>
</tr>
<tr>
<td><strong>Spontaneous abortion</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>265(78.4%)</td>
<td>903(89.1%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>46(13.6%)</td>
<td>64(6.3%)</td>
<td>0.000**</td>
</tr>
<tr>
<td>≥2</td>
<td>27(8.0%)</td>
<td>47(4.6%)</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>1(0.3%)</td>
<td>4(0.4%)</td>
<td>1.000</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>10(3.0%)</td>
<td>21(2.1%)</td>
<td>0.345</td>
</tr>
</tbody>
</table>

* p<0.05; ** p<0.01;
Table 2. Maternal outcomes in SLE and non-SLE patients

<table>
<thead>
<tr>
<th>Maternal outcomes</th>
<th>SLE cases (n=338)</th>
<th>Non-SLE cases (n=1014)</th>
<th>Crude OR 95% CI</th>
<th>Adjusted OR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous abortion (%)</td>
<td>11(3.3%)</td>
<td>7(0.7%)</td>
<td>4.84 (1.86-12.59)**</td>
<td>4.42 (1.52-12.80)**</td>
</tr>
<tr>
<td>Therapeutic abortion (%)</td>
<td>21(6.2%)</td>
<td>5(0.5%)</td>
<td>13.37(5.00-35.74)**</td>
<td>16.57(5.80-47.35)**</td>
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<td>PIH (%)</td>
<td>65(19.2%)</td>
<td>91(9.0%)</td>
<td>2.42(1.71-3.41)**</td>
<td>2.68(1.75-4.09)**</td>
</tr>
<tr>
<td>Pre-eclampsia/eclampsia (%)</td>
<td>48(14.2%)</td>
<td>59(5.8%)</td>
<td>2.68(1.81-4.10)**</td>
<td>3.13(1.95-5.03)**</td>
</tr>
<tr>
<td>HELLP (%)</td>
<td>1(0.3%)</td>
<td>2(0.2%)</td>
<td>1.50(0.14-16.11)</td>
<td>2.35(0.18-31.60)</td>
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<td>GDM (%)</td>
<td>19(5.6%)</td>
<td>117(11.5%)</td>
<td>0.46(0.28-0.75)**</td>
<td>0.49(0.28-0.85)*</td>
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<tr>
<td>PROM (%)</td>
<td>67(19.8%)</td>
<td>157(15.5%)</td>
<td>1.35(0.98-1.85)</td>
<td>1.35(0.95-1.92)</td>
</tr>
<tr>
<td>PPH (%)</td>
<td>8(2.4%)</td>
<td>18(1.8%)</td>
<td>1.34(0.58-3.11)</td>
<td>1.39(0.54-3.53)</td>
</tr>
<tr>
<td>Postpartum infection (%)</td>
<td>3(0.9%)</td>
<td>0(0.0%)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* p<0.05; ** p<0.01;

NA = Not applicable;

\(^\text{Adjusted odds ratios (ORs) were calculated using a logistic regression analysis and were adjusted for maternal age, region, nulliparity, history of spontaneous abortion, history of diabetes, and history of hypertension.}\)
Table 3. Fetal outcomes in SLE and non-SLE patients

<table>
<thead>
<tr>
<th>Fetal outcomes</th>
<th>SLE cases (n=338)</th>
<th>Non-SLE cases (n=1014)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Still birth (%)</td>
<td>6(1.8%)</td>
<td>1(0.1%)</td>
<td>18.31(2.20-152.62)**</td>
<td>13.25(1.49-118.11)*</td>
</tr>
<tr>
<td>Live birth (%)</td>
<td>300 (88.8%)</td>
<td>1001 (98.7%)</td>
<td>0.10(0.05-0.20)**</td>
<td>0.10(0.05-0.20)**</td>
</tr>
<tr>
<td>IUGR (%)</td>
<td>37(12.3%)</td>
<td>57(5.7%)</td>
<td>2.33(1.51-3.60)**</td>
<td>2.20(1.35-3.58)**</td>
</tr>
<tr>
<td>SGA (%)</td>
<td>30(10.0%)</td>
<td>53(5.3%)</td>
<td>1.99(1.25-3.17)**</td>
<td>1.86(1.11-3.13)*</td>
</tr>
<tr>
<td>LBW (%)</td>
<td>68(22.7%)</td>
<td>81(8.1%)</td>
<td>3.33(2.34-4.74)**</td>
<td>3.86(2.59-5.75)**</td>
</tr>
<tr>
<td>Preterm birth (%)</td>
<td>86(28.7%)</td>
<td>133(13.3%)</td>
<td>2.62(1.92-3.58)**</td>
<td>3.15(2.21-4.50)**</td>
</tr>
<tr>
<td>Cesarean section (%)</td>
<td>255(85%)</td>
<td>557(55.6%)</td>
<td>4.51(3.21-6.35)**</td>
<td>4.73(3.30-6.80)**</td>
</tr>
<tr>
<td>Congenital malformation (%)</td>
<td>4(1.3%)</td>
<td>10(1.0%)</td>
<td>1.34(0.42-4.30)</td>
<td>1.60(0.43-5.97)</td>
</tr>
<tr>
<td>Neonatal gender (boys) (%)</td>
<td>149(49.7%)</td>
<td>548(54.7%)</td>
<td>0.82(0.63-1.06)</td>
<td>0.84(0.63-1.11)</td>
</tr>
<tr>
<td>NICU (%)</td>
<td>48(16.0%)</td>
<td>66(6.6%)</td>
<td>2.70(1.81-4.01)**</td>
<td>3.48(2.21-5.48)**</td>
</tr>
<tr>
<td></td>
<td>Apgar 1&lt; 7 (%)</td>
<td>Apgar 5&lt; 7 (%)</td>
<td>Birth weight (g)±SD</td>
<td>Gestational Days (d)±SD</td>
</tr>
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<td>--------------------------</td>
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<td>------------------------</td>
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<tr>
<td></td>
<td>3(1.0%)</td>
<td>6(0.6%)</td>
<td>2763.7±588.7</td>
<td>259.3±16.2</td>
</tr>
<tr>
<td></td>
<td>0(0.0%)</td>
<td>2(0.2%)</td>
<td>3211.3±592.8</td>
<td>269.7±15.3</td>
</tr>
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</tr>
</tbody>
</table>

* p<0.05; ** p<0.01;

NA = Not applicable

Adjusted odds ratios (OR) were calculated by logistic regressions, which were adjusted for maternal age, region, nullipara, history of spontaneous abortion, history of diabetes, history of hypertension.
References


cohort from a stable referral population followed during 1990-2010.


22. Chen CY, Chen YH, Lin HC, Chen SF, Lin HC. Increased risk of adverse pregnancy outcomes for hospitalisation of women with lupus during...


34. Garite TJ, Clark R, Thorp JA. Intrauterine growth restriction increases...


<table>
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<th>Item #</th>
<th>Recommendation</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Title and abstract</strong></td>
<td>1</td>
<td>(a) Indicate the study’s design with a commonly used term in the title or the abstract</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(b) Provide in the abstract an informative and balanced summary of what was done and what was found</td>
<td>2</td>
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<tr>
<td><strong>Introduction</strong></td>
<td></td>
<td></td>
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<tr>
<td>Background/rationale</td>
<td>2</td>
<td>Explain the scientific background and rationale for the investigation being reported</td>
<td>5</td>
</tr>
<tr>
<td>Objectives</td>
<td>3</td>
<td>State specific objectives, including any pre-specified hypotheses</td>
<td>5</td>
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<tr>
<td><strong>Methods</strong></td>
<td></td>
<td></td>
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<tr>
<td>Study design</td>
<td>4</td>
<td>Present key elements of study design early in the paper</td>
<td>5</td>
</tr>
<tr>
<td>Setting</td>
<td>5</td>
<td>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</td>
<td>6</td>
</tr>
<tr>
<td>Participants</td>
<td>6</td>
<td>(a) <strong>Cohort study</strong>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Case-control study</strong>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Cross-sectional study</strong>—Give the eligibility criteria, and the sources and methods of selection of participants</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>(b) <strong>Cohort study</strong>—For matched studies, give matching criteria and number of exposed and unexposed</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Case-control study</strong>—For matched studies, give matching criteria and the number of controls per case</td>
<td></td>
</tr>
<tr>
<td>Variables</td>
<td>7</td>
<td>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</td>
<td>6</td>
</tr>
<tr>
<td>Data sources/ measurement</td>
<td>8</td>
<td>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</td>
<td>7</td>
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<tr>
<td>Bias</td>
<td>9</td>
<td>Describe any efforts to address potential sources of bias</td>
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<tr>
<td>Study size</td>
<td>10</td>
<td>Explain how the study size was arrived at</td>
<td>6</td>
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<tr>
<td>Quantitative variables</td>
<td>11</td>
<td>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</td>
<td>6-9</td>
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<tr>
<td>Statistical methods</td>
<td>12</td>
<td>(a) Describe all statistical methods, including those used to control for confounding</td>
<td>9</td>
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<tr>
<td></td>
<td></td>
<td>(b) Describe any methods used to examine subgroups and interactions</td>
<td>9</td>
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<tr>
<td></td>
<td></td>
<td>(c) Explain how missing data were addressed</td>
<td>9</td>
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<tr>
<td></td>
<td></td>
<td>(d) <strong>Cohort study</strong>—If applicable, explain how loss to follow-up was addressed</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Case-control study</strong>—If applicable, explain how matching of cases and controls was addressed</td>
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<tr>
<td>Results</td>
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<td></td>
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<tr>
<td>Participants</td>
<td>13*</td>
<td></td>
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<tr>
<td>(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed</td>
<td>10</td>
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<tr>
<td>(b) Give reasons for non-participation at each stage</td>
<td>NA</td>
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<tr>
<td>(c) Consider use of a flow diagram</td>
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<tr>
<td>Descriptive data</td>
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<tr>
<td>(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders</td>
<td>10</td>
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<tr>
<td>(b) Indicate number of participants with missing data for each variable of interest</td>
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<tr>
<td>(c) Cohort study—Summarise follow-up time (eg, average and total amount)</td>
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<tr>
<td>Outcome data</td>
<td>15*</td>
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<tr>
<td>(a) Report numbers of outcome events or summary measures over time</td>
<td>11-12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(b) Case-control study—Report numbers in each exposure category, or summary measures of exposure</td>
<td></td>
<td></td>
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<tr>
<td>(c) Cross-sectional study—Report numbers of outcome events or summary measures</td>
<td></td>
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<td></td>
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<tr>
<td>Main results</td>
<td>16</td>
<td></td>
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<tr>
<td>(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included</td>
<td>11-12</td>
<td></td>
<td></td>
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<tr>
<td>(b) Report category boundaries when continuous variables were categorized</td>
<td>11-12</td>
<td></td>
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<tr>
<td>(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period</td>
<td>11-12</td>
<td></td>
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<tr>
<td>Other analyses</td>
<td>17</td>
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<tr>
<td>Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses</td>
<td>11-12</td>
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<td></td>
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<tr>
<td>Discussion</td>
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<tr>
<td>Key results</td>
<td>18</td>
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<tr>
<td>Summarise key results with reference to study objectives</td>
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<tr>
<td>Limitations</td>
<td>19</td>
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<tr>
<td>Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias</td>
<td>18</td>
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<tr>
<td>Interpretation</td>
<td>20</td>
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<tr>
<td>Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence</td>
<td>13-18</td>
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<tr>
<td>Generalisability</td>
<td>21</td>
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<tr>
<td>Discuss the generalisability (external validity) of the study results</td>
<td>19</td>
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<td>Other information</td>
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<tr>
<td>Funding</td>
<td>22</td>
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<tr>
<td>Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based</td>
<td>4</td>
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</tbody>
</table>

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study

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<th>BMJ Open</th>
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<td>Research</td>
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<td>Date Submitted by the Author:</td>
<td>13-Feb-2018</td>
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| Complete List of Authors: | WU, JIAYUE; Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China, Department of Obstetrics and Gynecology  
MA, Jinghang; Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China, Department of Obstetrics and Gynecology  
BAO, Chunde; Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China, Department of Rheumatology  
DI, WEN; Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China, Department of Obstetrics and Gynecology  
Zhang, WeiHong; International Centre for Reproductive Health (ICRH), Ghent University, ICRH |
| Primary Subject Heading: | Obstetrics and gynaecology |
| Secondary Subject Heading: | Rheumatology, Obstetrics and gynaecology |
| Keywords: | Fetal outcomes, Maternal outcomes, Pregnancy, Systemic lupus erythematosus |
Pregnancy outcomes among Chinese women with and without systemic lupus erythematosus: a retrospective cohort study

Jiayue WU, MD¹,²,⁵; Jinghang MA, MS¹,²; Chunde BAO, MD³,⁴; Wen DI, MD, PhD¹,²,⁴; Wei-Hong ZHANG, MD, MPH, PhD⁵,∆

¹. Department of Obstetrics and Gynecology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China;
². Shanghai Key Laboratory of Gynecologic Oncology, Shanghai, China;
³. Department of Rheumatology, Renji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200127, China;
⁴. Shanghai Institute of Rheumatology, Shanghai, China.
⁵. International Centre for Reproductive Health (ICRH), Ghent University, 9000, Ghent, Belgium

∆ Co-corresponding authors

Correspondence to China:
Wen DI, Department of Obstetrics and Gynecology, Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai 200127, China.
Email: diwen163@163.com

Correspondence to Europe:
Wei-Hong ZHANG, International Centre for Reproductive Health (ICRH), Ghent University, 9000, Ghent, Belgium.
E-mail: WeiHong.Zhang@UGent.be
Abstract

Objective: To completely and quantifiably determine the effect of SLE on pregnancy outcomes in a Chinese cohort.

Design: A retrospective cohort study.

Setting: Data were collected at a tertiary medical center located in Shanghai, China, from September 2011 to May 2017.

Participants: We assigned 338 pregnant women with SLE to the study cohort and 1014 randomly selected pregnant women without SLE (three for every woman with SLE) to a comparison cohort. The relevant medical records of all pregnant women were retrospectively reviewed. Cases of multiple pregnancy and cases in which an artificial abortion was performed for personal reasons were excluded.

Primary and secondary outcome measures: Maternal and fetal outcomes were primary outcomes, and management of antenatal care was the secondary outcome.

Results: The risks of pregnancy-induced hypertension (odds ratio (OR)=2.68, 95% CI=1.75-4.09), preeclampsia (OR=3.13, 95% CI=1.95-5.03), and premature rupture of membranes (PROM) (OR=2.53, 95% CI=1.46-4.40) were significantly different between women with and without SLE. Gestational diabetes was negatively associated with SLE in pregnant women (OR=0.49, 95% CI=0.28-0.85). Pregnant women with
SLE displayed significantly higher rates of fetal loss (OR=10.23, 95% CI=5.08-20.59), including spontaneous abortion (OR=4.42, 95% CI=1.52-12.80), therapeutic abortion (OR=16.57, 95% CI=5.80-47.35), and stillbirth (OR=13.25, 95% CI=1.49-118.11), and a higher risk of preterm birth (OR=3.15, 95% CI=2.21-4.50), intrauterine growth restriction (OR=2.20, 95% CI=1.35-3.58), a child who was small for the gestational age (OR=1.86, 95% CI=1.11-3.13), a cesarean section (OR=4.73, 95% CI=3.30-6.80), or a NICU admission (OR=3.48, 95% CI=2.21-5.48) than women in the non-SLE population after adjusting for confounding factors.

Conclusions: In this study, SLE significantly increased the risk of adverse pregnancy outcomes. Therefore, a pre-conception assessment and close antenatal monitoring by both rheumatologists and obstetricians should be performed in pregnant women with SLE.

Keywords: Fetal outcomes; Maternal outcomes; Pregnancy; Systemic lupus erythematosus
Strengths and limitations of this study

1. This study represents the first comparison of maternal and fetal outcomes between pregnant women with and without SLE in a Chinese cohort.

2. Additionally, the present study included large samples of both patients with SLE and controls comprising a total of 1350 individuals, and no data were missing for any of these patients.

3. Furthermore, the maternal and fetal outcomes evaluated in this study were comprehensive and reflect almost every key aspect of pregnancy.

4. One limitation of this retrospective study was inherent biases, including selection bias and information bias.

5. The second limitation was the lack of some details regarding baseline population characteristics, e.g. education, body mass index, and family income, in the clinical records for some of the included participants.

Competing interests

The authors have no competing interests to declare.

Funding

The work was supported by funding from the Shanghai Municipal Health and Family Planning Commission (15GWZK0701).

Data sharing statement No additional data are available.

Word Counts: Abstract: 283  Main text: 4707
Introduction

Systemic lupus erythematos (SLE) is an autoimmune disease that involves multiple organs and most commonly occurs in young women, in whom it has an incidence of 90/100,000. Women with SLE have a normal fertility rate, and pregnancy is therefore a frequent subject of interest for these patients. As treatments for pregnant women with SLE have improved and increasingly involve multidisciplinary management, pregnancy outcomes have dramatically improved in recent decades.

Although several studies have compared pregnancy outcomes between women with SLE and the general population and reported that SLE is associated with adverse obstetric outcomes, few studies have examined these outcomes in a Chinese cohort. Therefore, we have compared maternal and fetal outcomes between women with SLE and women in the general population to completely and quantifiably clarify the effect of SLE on pregnancy outcomes in a Chinese cohort.

Materials and Methods

Study sample

This retrospective cohort study was performed in a single center. Our study cohort consisted of pregnant patients with SLE who were treated in Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine between September 2011 and May 2017. Multiple gestations and elective terminations for personal reasons were excluded. SLE was diagnosed according to the revised criteria for the classification of SLE developed by the American College of Rheumatology. All participants with
SLE were evaluated by an experienced gynecologist at least monthly and by a rheumatologist at least once per trimester. At each evaluation, a physical examination and laboratory tests were performed, and medications were adjusted as needed.

Our comparison cohort was randomly selected from women with singleton pregnancies who were not diagnosed with SLE and attended the same hospital.

Control participants were matched with the study group by delivery time (three controls were selected for every woman with SLE) and received regular, routine antenatal care.

Variables of interest

Medical records from both cases and controls were retrospectively reviewed, and pregnancy outcomes were systematically evaluated.

1. Population characteristics

The baseline characteristics of the population were recorded to identify potential confounding factors. These factors included maternal age at delivery, region, nulliparity, spontaneous abortion and comorbidities. Region was categorized as city and rural areas. A history of spontaneous abortion was categorized as 0, 1, and ≥2, according to the numbers of miscarriages. Comorbidities included a pre-pregnancy diagnosis of hypertension or diabetes. None of the women in the study population had ever smoked or used alcohol during pregnancy; therefore, these two variables were not included in the study. For the SLE cohort, the history of SLE, pre-gestational SLE
status, SLE clinical manifestations (including nephritis, mucocutaneous, hematological disorder, neurological disorder, arthritis, serositis and antiphospholipid syndrome (APS)), the laboratory test data and medications were also extracted. Laboratory data included a complete blood count, urinalysis, and levels of serum albumin, 24-hr urinary protein, complement 3 (C3), complement 4 (C4), antinuclear antibodies (ANA), anti-dsDNA antibodies (anti-dsDNA), anti-Smith antibodies (anti-Sm), anti-SSA/Ro antibodies, anti-SSB/La antibodies and antiphospholipid (aPL) antibodies, which included anticardiolipin antibodies (aCL), anti-2-glycoprotein I antibodies (anti-β2GPI), and lupus anticoagulant (LA). APS was defined according to the Sapporo criteria. All laboratory tests were performed using standardized methods.

The pre-gestational clinical status of patients with SLE was categorized into the remission stage, which was defined as a patient who took a low dose of or stopped prednisone treatment without clinical manifestations of SLE activity for more than 6 months prior to conception. The active stage was defined as patients presenting clinical manifestations of SLE activity, including central nervous system and renal involvement, vasculitis, arthritis, myositis, fever, rash, pleurisy, pericarditis, and hypocomplementemia. The initial onset during pregnancy was defined as a new onset of SLE during pregnancy.

2. Maternal outcomes
All outcome variables were dichotomous. The abstracted maternal outcomes and definitions are listed below.

- Pregnancy-induced hypertension (PIH): *a de novo* increase in blood pressure to $\geq 140/90$ mmHg on at least two occasions $\geq 6$ h apart observed after the 20th week of pregnancy.

- Preeclampsia: pregnancy-induced hypertension with proteinuria $>0.3$ g/L/d in the absence of a urinary tract infection or the abrupt onset of hypertension and proteinuria after 20 weeks of gestation. Seizures were required for a diagnosis of eclampsia.

- HELLP (hemolysis, elevated liver enzymes and low platelet count) syndrome: the presence of hemolysis, high levels of lactate dehydrogenase or total bilirubin $>12$ mg/L, alanine aminotransferase levels more than two-fold the upper normal value, and thrombocytopenia $<100 \times 10^9$ cells/L.

- Gestational diabetes (GDM) was defined as any degree of glucose intolerance with onset or first recognition during pregnancy.$^9$

- Premature rupture of membranes (PROM): a rupture of the amniotic sac $<24$ h prior to the onset of labor. We further divided this condition into term PROM (TPROM) and preterm PROM (PPROM), according to the neonatal gestational age.

- Postpartum hemorrhage (PPH) was defined as blood loss of 500 mL or more within 24 h after birth.$^{10}$
Peripartum infection was defined as an infection of the genital tract occurring at any time between the onset of membrane rupture or labor and the 42\textsuperscript{nd} postpartum day.\textsuperscript{11}

Maternal death: the death of a woman during pregnancy or within 42 days of the termination of a pregnancy, regardless of the duration or site of the pregnancy, of any cause related to or aggravated by the pregnancy or its management, but not any accidental or incidental causes.\textsuperscript{12}

An SLE flare was defined as a measurable increase in disease activity in one or more organ systems involving new or worsening clinical signs and symptoms and/or laboratory measurements that met the SLE diagnostic criteria ACR1997\textsuperscript{7}. The flare must be considered clinically significant by the assessor and a change or an increase in treatment is typically considered.\textsuperscript{13}

3. Fetal outcomes

All outcome variables were dichotomous and continuous. The abstracted fetal outcomes and definitions are listed below.

- Live birth: the birth of a living child.

- Fetal loss: defined as all pregnancies that did not end with a live birth,\textsuperscript{14} including spontaneous abortions, therapeutic abortions, stillbirths or intrauterine fetal deaths. Additional definitions were:

  - Spontaneous abortion: spontaneous termination of a pregnancy prior to 28 weeks of gestation.\textsuperscript{15} We further divided spontaneous abortions into <10
Therapeutic abortion: abortion for therapeutic reasons because the pregnancy might be a threat to maternal health, such as a life-threatening SLE flare or other severe obstetric complications, including severe thrombocytopenia or HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, etc., or fetal lethal malformations, including the maldevelopment of cardiac anatomy.

Stillbirth or intrauterine fetal death: any baby born without signs of life at ≥28 completed weeks of gestation.\textsuperscript{16}

Intrauterine growth restriction (IUGR): factors that limit the potential for the intrauterine growth of the fetus.\textsuperscript{17}

Small for gestational age (SGA): infants whose weight was lower than the lower 10\% limit of the CI of the normal curve for gestational weight.\textsuperscript{18}

Neonatal death: live birth that died during the first 28 completed days of life.\textsuperscript{19}

Preterm birth: was defined as delivery <37 weeks of gestation. We further divided this condition into very preterm (28-32 weeks) and moderate to late preterm (≥32 weeks), according to WHO definitions.\textsuperscript{20}

Method of childbirth: cesarean section or vaginal birth. We further divided cesarean section into elective and emergency cesarean section, according to the indications for cesarean section.\textsuperscript{21}

Congenital malformation: all types of congenital malformation.

Neonatal gender: male and female.
NICU: neonates who required intensive medical attention and were admitted into a special area of the hospital called the Neonatal Intensive Care Unit (NICU).

One-minute and 5-minute Apgar scores: an Apgar score >7 was defined as normal, whereas a score <7 was considered to indicate moderate or severe hypoxia.22

Birth weight: neonatal birth weight is presented in grams.

Gestational days: neonatal gestational days is presented in days.

Statistical analysis

Descriptive data are presented as means ± SD or as frequencies. Categorical variables were analyzed using the chi-square test or Fisher’s exact probability test, as appropriate. Continuous variables were analyzed using Student’s t test.

The denominator used in the analyses of all maternal outcomes, still births and live births was all reported pregnancies. For all other fetal outcomes (excluding still births and live births), the denominator was all live births.

Logistic regression analyses were performed to compute crude odds ratios (ORs) with 95% CIs for maternal and fetal outcomes. Logistic regression models were adjusted for potential confounding factors, including maternal age, region, nulliparity, a history of spontaneous abortion and comorbidities. These analyses yielded new adjusted ORs with 95% CIs. All tests were two-tailed, and p<0.05 was considered statistically significant. All analyses were performed using SPSS version 22.0.
**Ethics statement**

The research protocol used in this study was reviewed and approved by the Medical Ethical Committee of Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine. Because this study used a retrospective, observational design, the Medical Ethical Committee granted a waiver for informed consent for this study. Approval to obtain clinical data from the database was received from the Office of the Medical Director of the hospital. All patient information remained confidential.

**Results**

**Population characteristics**

338 pregnant women with SLE (cases) and 1014 pregnant without SLE (controls) who were monitored between September 2011 and May 2017 were included. The distributions of the baseline characteristics of the population are shown in Table 1. Mean ages were not significantly different between the two cohorts. Women with SLE were more likely to reside in a city than the controls, and most of the pregnancies in women with SLE were nulliparous. A history of spontaneous abortion, particularly ≥2 abortions, was more common in women with SLE. Significant differences in comorbid conditions were not observed between the women with SLE and the controls. The proportion of women in whom diabetes and/or hypertension was diagnosed prior to pregnancy was not significantly different between the SLE and non-SLE populations. Data for some variables, such as laboratory test data and SLE clinical manifestations, were not available for the non-SLE group because we do not
perform these laboratory tests on patients without SLE manifestations. Regarding the
SLE group, the mean duration of SLE was 5.6±4.3 years (range 0-20 years). Notably,
86.7% of pregnant women with SLE were in the remission stage, 1.8% were in the
active age and 11.5% of women were first diagnosed with SLE during pregnancy.
The most common SLE clinical manifestations were mucocutaneous lesions, which
were identified in 31.4% of patients, followed by lupus nephritis in 28.7%, arthritis in
20.7%, hematological disorders in 19.5%, serositis in 5.0% and neurological disorders
in 1.5%. APS was observed in 9.5% of the pregnant women with SLE. The mean
24-hr urinary protein level was 1.04±2.43 grams (range, 0.01 to 16.7 grams). Pregnant
women were positive for autoantibodies at the following frequencies: anti-ds DNA in
261 patients (77.2%), anti-Ro/SSA in 150 patients (44.4%), anti-La/SSB in 47
patients (13.9%), and anti-Sm in 20 patients (5.9%). Forty-six patients were positive
for aPL antibodies. C3 and C4 hypocomplementemia was present in 90 (26.6%) and 60
patients (17.8%), respectively (Table 1).

Maternal outcomes
The rate of adverse maternal outcomes was several fold higher in women with SLE
than in the non-SLE population during pregnancy. PIH and preeclampsia/eclampsia
were diagnosed in 19.2% and 14.2%, respectively, of the women with SLE. After
adjusting for confounding factors, the risks of PIH (OR=2.68, 95% CI=1.75-4.09) or
preeclampsia (OR=3.13, 95% CI=1.95-5.03) remained high. The proportion of
infection was low, and peripartum infections occurred in 0.9% (3/338) of the women
with SLE and none of the control women. Interestingly, the rate of GDM was lower in women with SLE than in the controls, and the OR remained unchanged after adjusting for confounding factors (OR=0.49, 95% CI=0.28-0.85). Although we did not observe a difference in PROM between the two groups, a significant difference in PPROM was observed, and the OR remained high, even after adjusting for confounding factors (OR=2.53, 95% CI=1.46-4.40). Significant differences in other maternal outcomes, including PPH and HELLP syndrome, were not observed between the two groups. The SLE flare rate was 24.0% in the SLE group. Maternal deaths did not occur in either group (Table 2).

**Fetal outcomes**

Women with SLE had a higher total fetal loss rate (OR=10.23, 95% CI=5.08-20.59) than the non-SLE population after adjusting for confounding factors. Among the causes of fetal loss in women with SLE, 3.3% experienced a spontaneous abortion, whereas 6.2% underwent a therapeutic abortion and 1.8% had a still birth. Furthermore, most of the spontaneous abortions occurred at ≥10 weeks, regardless of the group. After adjusting for confounding factors, the risks of a spontaneous abortion (OR=4.42, 95% CI=1.52-12.80), therapeutic abortion (OR=16.57, 95% CI=5.80-47.35), or a still birth (OR=13.25, 95% CI=1.49-118.11) were still high. Among women who achieved a live birth, the rates of preterm were 3.15-fold higher in the pregnant women with SLE than in the controls. Both the very preterm and moderate to late preterm sub-groups had higher adjusted ORs of 3.57
(95%CI=1.65-7.72) and 2.76 (95%CI=1.90-4.03), respectively. Cesarean births
occurred at a 4.73-fold higher rate in the SLE group, and 77% of patients with SLE
tended to undergo an elective cesarean section. The rate of NICU admission for
neonates was also higher in women with SLE. IUGR and SGA were observed in 12.3%
and 10.0% of pregnancies in women with SLE, respectively. The adjusted ORs were
2.20 and 1.86, respectively, for each outcome (all p-values <0.05). Furthermore, we
also observed lower neonatal birth weights (2763.7±588.7 g) and gestational days
(259.3±16.2 d) for pregnant women with SLE (both p<0.01). No neonatal deaths
occurred in either group. Finally, significant differences in the rates of congenital
malformations, neonatal genders, or the proportions of low Apgar scores were not
observed between the cohorts (Table 3). Only 2 cases of neonatal lupus occurred in
the women with SLE, both of which presented as mucocutaneous lesions.

Medications used during pregnancy by women with SLE

Medications were recorded for the SLE group and mainly included five kinds of
medicines. Of the 338 pregnant women with SLE, most (97.6%) were treated with
glucocorticoids, with a mean dose of 7.5 mg/d (range 2.5–40 mg). Approximately
75.4% and 74.6% of patients with SLE took hydroxychloroquine and low-dose aspirin
(25-75 mg), respectively. Only a small proportion of patients (3.8%) took
azathioprine, and 22.2% of the patients used low weight molecular heparin (LWMH)
during their pregnancy.
Discussion

Principal findings

In this study, pregnant women with SLE have a higher risk of adverse maternal outcomes, such as PIH, preeclampsia/eclampsia, PPROM and peripartum infection, than pregnant women without SLE. Furthermore, SLE was also associated with adverse fetal outcomes, including a high fetal loss risk, such as spontaneous abortion, particularly ≥10 weeks, therapeutic abortion and stillbirth; higher rates of preterm births, cesarean sections, mainly elective, and NICU admissions; and a significantly higher number of infants with growth restriction (e.g., IUGR or SGA). The elevated risk conferred by SLE on each of these factors indicates that preconception assessments and antenatal monitoring are both important in pregnant women with SLE.

Comparisons with previous studies

We observed differences in several baseline demographic features between the women with SLE and those without in our cohort. Women with SLE were more likely to reside in a city and to have a nulliparous pregnancy than women in the non-SLE group. Importantly, women with SLE more frequently experienced a spontaneous abortion, which may potentially be associated with the high rate of adverse pregnancy outcomes observed in women with SLE. Differences in the pre-pregnancy incidences of chronic diseases were not observed between the women with and without SLE. This finding was also reported in two previous cohort studies.23,24
SLE is an important risk factor for fetal loss, including spontaneous abortion, therapeutic abortion and stillbirth. This finding was also reported in several previous cohort studies performed in other settings. In the present study, the rates of still birth and spontaneous abortion in the SLE group were 1.8% and 3.3%, respectively. These rates are much lower than the rates reported in other studies. This finding might be due to the use of different terms to define outcomes. However, in the present study, a higher rate of therapeutic abortion was observed in the SLE group (6.2% in the SLE group vs 0.5% in the non-SLE group). Few previous studies have reported this outcome. One systemic review reported the rate of elective abortion, but the OR was not significant (OR=1.19, 95% CI=0.76-1.88). However, their definition of elective abortion differed from the definition used in the present study. In our study, therapeutic abortion was defined as an abortion performed for a therapeutic reason, but not elective abortions based on the mother’s will. This definition may have contributed to the low rates of spontaneous abortions and stillbirths observed in our study, because pregnancies were terminated in some patients with severe cases of SLE using therapeutic abortion during an early trimester to maintain the health of the mother. The results of our study confirm that PIH and preeclampsia are significant problems during pregnancy in women with SLE. In our study, nearly one-fifth of pregnant women with SLE experienced the complications of significant hypertension and
preeclampsia, whereas only 5.8% to 9.0% of the pregnancies in healthy women were affected by these conditions. The ORs remained significant, even after adjusting for confounding factors. SLE flares and preeclampsia are important and difficult to recognize in pregnant patients with SLE because both conditions are associated with proteinuria, deteriorating renal function, hypertension and sometimes even co-exist. Although several guidelines or biomarkers, such as placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), are available, they display limited utility in practical clinical settings. In our study, we considered several clinical manifestations together, including the onset time of hypertension, complement levels, anti-dsDNA levels, erythrocyte sedimentation rate (ESR), involvement of other organs and even responses to steroids. This differential diagnosis was a comprehensive process, and it was always assessed by an experienced gynecologist or a rheumatologist in our study. Uncontrolled hypertension has been shown to predict poor pregnancy outcomes, and guidelines recommend the implementation of measures to control blood pressure in these patients. In the present study, the rate of SLE flares was 24% and might have contributed to the adverse pregnancy outcomes, as reported previously. However, as the main goal of this article was to compare pregnancy outcomes between women with and without SLE, we did not further explore the effects of flares on pregnancy outcomes among the SLE group, which could be a future study direction.
Although a few cases of peripartum infections were reported in each group, the SLE group had a slightly higher proportion of infections. Clowse et al.\(^5\) and Nili et al.\(^{34}\) reported similar results. This effect may be related to the nature of the immune dysregulation observed in patients with SLE or may be associated with the immunosuppressive nature of treatments for SLE.

Interestingly, we noticed a significantly lower rate of GDM in women with SLE than in the controls (5.6\% vs 11.5\%), even after adjusting for confounding factors. Only one previous study reported the same result. In the study by McGrory et al., none of the patients in the SLE group developed GDM, whereas 12\% of patients in the non-SLE group developed GDM.\(^{30}\) Clowse et al. reported a higher rate of pre-gestational diabetes in the SLE group, potentially because these patients were administered corticosteroids during pregnancy.\(^5\) Further studies of larger populations should be performed.

The rate of cesarean section surgeries was surprisingly high in our study (SLE vs non-SLE: 85\% vs 55.6\%), and it was far higher than the rates reported in most previous studies. A national U.S. population-based study performed in 2000-2003 reported a 36.6\% cesarean rate in patients with SLE.\(^5\) Two studies conducted in northern Europe reported cesarean rates of 32-39\% in pregnant women with SLE and 16-24\% in non-SLE pregnant women.\(^{4,35}\) However, Saavedra MA et al reported a high cesarean rate (77.1-86.5\%) in a Latin American SLE group, consistent with our
result. The main explanations were Mexican sociocultural, economic, medical-legal, and biomedical factors. Although one study reported the opposite result (SLE vs non-SLE: 30% vs 53%), the authors recruited patients who had received a kidney transplant, which may have contributed to the difference in their results. Although the absolute rate was high in both groups in our study, SLE was still a risk factor for cesarean section. Furthermore, most patients with SLE tended to undergo an elective cesarean, mainly because doctors and patients tended to choose cesarean section to prevent complications related to SLE during delivery. The extremely high cesarean section rate observed in our study reflects the true clinical situation in China. In 2008, the WHO suggested that nearly half of all births in China are delivered via caesarean section. Some of the potential reasons for this high rate include a fear of pain and accidents during vaginal birth, an uneasy doctor–patient relationship, the profitability of caesarean sections for the hospital, and increases in the number of babies with macrosomia at birth and the number of pregnancies in older women.

In our study, the percentages of neonates who were diagnosed with IUGR or SGA and mean birth weights were significantly higher in the SLE group than in the control group. Both of these terms (IUGR/SGA) are used as indicators of fetal growth restriction, but each involves a different mechanism. The definitions we used for these terms are provided in the methods section. Our findings are consistent with previous studies reporting growth restriction rates of 10%-28% in SLE groups. The risk of neonatal death is three-fold higher in growth-restricted neonates than in neonates with
... for peer review only...

1 a normal weight. These infants also have high risk of developing other severe
2 conditions, such as cardiovascular disease, infection, and neurodevelopmental
3 retardation. The risk of preterm birth was also 3-fold higher in both the very preterm
4 or moderate to late preterm sub-groups of women with SLE in our study, consistent
5 with previous studies. Moreover, patients with SLE had a high risk of
6 PPROM, but not PROM, which has not been reported in previous studies. The
7 explanation for this finding might be that immune complexes cause vascular
8 inflammation that contributes to a hypercoagulable state and subsequently reduces
9 placental and umbilical artery blood flow and decreases placental perfusion and villus
10 structure, thereby affecting fetal growth and prematurity. Not surprisingly, the
11 higher rates of prematurity and growth restriction observed in the SLE group led to a
12 higher NICU admission rate. However, differences in the Apgar scores of the
13 neonates were not observed at either 1 or 5 minutes, and the absolute incidence of
14 moderate or severe hypoxia was very low in both group. This finding contrasts the
15 result described in the study Wallenius et al., but this discrepancy may be because
16 the size of the SLE group was small in the present study.

17 Four live births with congenital malformations occurred in the SLE group and ten
18 occurred in the control group, but the difference between the two groups was not
19 significant. Among the four infants with congenital malformations in the SLE group,
20 two had renal problems and one had polydactyly. Additionally, three cases of
21 malformation in the SLE group were detected before 28 weeks and included one case
of dextrocadia and two cases of maldevelopment of cardiac anatomy. These three cases were treated with a therapeutic abortion. Compared to previous studies, we reported a relatively low rate of congenital malformations in the present study.

Wallenius et al and Liu J et al. reported a rate of malformation of approximately 6-7% in neonates born to women with SLE from approximately 2008-2009, and Rahman et al. reported a rate of 2% from 1970-1995. One potential reason for these differences in the incidence of congenital malformations is the extensive improvements in the prenatal diagnosis and antenatal management of these patients.

As medication is an important contributor to the pregnancy outcomes in women with SLE, we also collected the medication data in the present study. Steroids were the most common medication used by patients with SLE, but the exposure should be minimized during pregnancy. However, short-term administration of high doses should be used during a disease flare, and doses must be administered at the time of delivery. Immunosuppressive therapy for SLE is often used to treat a flare.

Azathioprine is the most commonly used drug during pregnancy, because it has proven safe for use during pregnancy. Antimalarial agents are now a first-line therapy for SLE during pregnancy. They are safe for pregnant women, and are proven to be associated with a reduced risk of congenital heart block in neonates. Aspirin has been proven to prevent preeclampsia in women with SLE. LMWH is safe and easy to administer, and along with low-dose aspirin, LMWH is routinely used in obstetric patients with APS.
Strengths and limitations

The present study is noteworthy for several reasons. Pregnancy has been reported to be risky for women with SLE, due to the high rates of cesarean deliveries, infections, gestational hypertension and preeclampsia. However, this study is the first to compare maternal and fetal outcomes between pregnant women with and without SLE in a Chinese cohort. A nationwide population-based cohort was evaluated in Taiwan in 2010, but that study focused on only three fetal outcomes. Additionally, the present study included large samples of both patients with SLE and controls, comprising a total of 1350 individuals, and no data were missing for any of these patients. Furthermore, the maternal and fetal outcomes evaluated in this study were comprehensive and reflect almost every key aspect of pregnancy.

Nevertheless, our study has some limitations. First, as a retrospective study, this study has inherent biases, including selection bias and information bias. Second, the clinical records lacked some details regarding baseline population characteristics, including the level of education, body mass index, daily activity and family income, of some of the included participants. These factors may be confounding factors in the present study. Finally, data for some variables, such as 24-hr urinary protein, complement, auto-antibody and aPL antibody levels, were not available for the non-SLE group because we do not perform these laboratory tests on patients without SLE.
manifestations. Therefore, we were unable to compare these variables between the
two groups.

The generalisability of this study should be interpreted with caution due to this study
carried out in a single tertiary university hospital in China.

Conclusions

In conclusion, the risks of gestational hypertension, preeclampsia, peripartum
infection, PPROM and elective cesarean birth are higher and the risk of gestational
diabetes is lower in pregnant women with SLE than in women without SLE.

Additionally, SLE contributes to higher rates of fetal loss, prematurity, fetal growth
restriction and NICU admission. We therefore suggest that women with SLE should
have full access to pre-conception counseling, choose an optimal time for pregnancy,
and undergo close monitoring during antenatal care by both rheumatologists and
obstetricians. Future large cohort studies should focus on antenatal management,
including laboratory assessments and medication use, in pregnant women with SLE.

Acknowledgments

Not applicable.

Authors’ contributions
JY.W., JH.M., CD.B., WH.Z., and W.D. were each responsible for the conception and design of the study; JY.W., JH.M., and W.D. had full access to all of the data in the study. JY.W. and JH.M. collected the data. JY.W. and WH.Z. analyzed and interpreted the data; JY.W. and JH.M. drafted the initial manuscript; and WH.Z., CD.B., and W.D. revised the manuscript. All authors read and approved the final version of the manuscript.
## Tables

### Table 1. Baseline clinical characteristics of pregnant women with and without SLE

<table>
<thead>
<tr>
<th>Variables</th>
<th>SLE cases (n=338)</th>
<th>Non-SLE cases (n=1014)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yrs, mean±SD)</td>
<td>29.5±4.0</td>
<td>29.7±4.3</td>
<td>0.59</td>
</tr>
<tr>
<td>History of spontaneous abortion (frequency)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>265 (78.4%)</td>
<td>903 (89.1%)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>46 (13.6%)</td>
<td>64 (6.3%)</td>
<td>0.00**</td>
</tr>
<tr>
<td>≥2</td>
<td>27 (8.0%)</td>
<td>47 (4.6%)</td>
<td></td>
</tr>
<tr>
<td>History of SLE (yrs, mean±SD, range)</td>
<td>5.6±4.3</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Region</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>City</td>
<td>237 (70.1%)</td>
<td>318 (31.4%)</td>
<td>0.00**</td>
</tr>
<tr>
<td>Rural</td>
<td>101 (29.9%)</td>
<td>695 (68.6%)</td>
<td></td>
</tr>
<tr>
<td>Nulliparity</td>
<td>291 (86.1%)</td>
<td>706 (69.6%)</td>
<td>0.00**</td>
</tr>
<tr>
<td><strong>Clinical comorbidities</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-pregnancy diabetes</td>
<td>1 (0.3%)</td>
<td>4 (0.4%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Pre-pregnancy hypertension</td>
<td>10 (3.0%)</td>
<td>21 (2.1%)</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Pre-gestational SLE status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission stage</td>
<td>293 (86.7%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Active stage</td>
<td>6 (1.8%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Initial onset</td>
<td>39 (11.5%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td><strong>SLE clinical manifestation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephritis</td>
<td>97 (28.7%)</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Count</td>
<td>Percentage</td>
<td>Value</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------</td>
<td>------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Mucocutaneous</td>
<td>106</td>
<td>31.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Hematologic disorder</td>
<td>66</td>
<td>19.5%</td>
<td>NA</td>
</tr>
<tr>
<td>Neurologic disorder</td>
<td>5</td>
<td>1.5%</td>
<td>NA</td>
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<tr>
<td>Arthritis</td>
<td>70</td>
<td>20.7%</td>
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</tr>
<tr>
<td>Serositis</td>
<td>17</td>
<td>5.0%</td>
<td>NA</td>
</tr>
<tr>
<td>APS</td>
<td>32</td>
<td>9.5%</td>
<td>NA</td>
</tr>
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</table>

**Laboratory test during pregnancy**

<table>
<thead>
<tr>
<th>Test</th>
<th>Count</th>
<th>Percentage</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24-hr Urinary protein level</td>
<td></td>
<td></td>
<td>1.0±2.4</td>
</tr>
<tr>
<td>(g, mean±SD, range)</td>
<td></td>
<td></td>
<td>(0.0-16.7)</td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>261</td>
<td>77.2%</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-Ro/SSA</td>
<td>150</td>
<td>44.4%</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-La/SSB</td>
<td>47</td>
<td>13.9%</td>
<td>NA</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>20</td>
<td>5.9%</td>
<td>NA</td>
</tr>
<tr>
<td>aPL</td>
<td>46</td>
<td>13.6%</td>
<td>NA</td>
</tr>
<tr>
<td>Hypocomplementania-C₃</td>
<td>90</td>
<td>26.6%</td>
<td>NA</td>
</tr>
<tr>
<td>Hypocomplementania-C₄</td>
<td>60</td>
<td>17.8%</td>
<td>NA</td>
</tr>
</tbody>
</table>

NOTES: * p<0.05; ** p<0.01; NA=not applicable; APS=antiphospholipid syndrome
Table 2. Maternal outcomes in patients with SLE and non-SLE patients

<table>
<thead>
<tr>
<th>Maternal outcomes</th>
<th>SLE (n=338)</th>
<th>Non-SLE (n=1014)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PIH (%)</td>
<td>65 (19.2%)</td>
<td>91 (9.0%)</td>
<td>2.42 (1.71-3.41)**</td>
<td>2.68 (1.75-4.09)**</td>
</tr>
<tr>
<td>Preeclampsia/eclampsia (%)</td>
<td>48 (14.2%)</td>
<td>59 (5.8%)</td>
<td>2.68 (1.81-4.10)**</td>
<td>3.13 (1.95-5.03)**</td>
</tr>
<tr>
<td>HELLP (%)</td>
<td>1 (0.3%)</td>
<td>2 (0.2%)</td>
<td>1.50 (0.14-1.61)</td>
<td>2.35 (0.18-31.60)</td>
</tr>
<tr>
<td>GDM (%)</td>
<td>19 (5.6%)</td>
<td>117 (11.5%)</td>
<td>0.46 (0.28-0.75)**</td>
<td>0.49 (0.28-0.85)*</td>
</tr>
<tr>
<td>PROM (%)</td>
<td>67 (19.8%)</td>
<td>157 (15.5%)</td>
<td>1.35 (0.98-1.85)</td>
<td>1.35 (0.95-1.92)</td>
</tr>
<tr>
<td>TPROM (%)</td>
<td>38 (11.2%)</td>
<td>117 (11.5%)</td>
<td>0.97 (0.66-1.43)</td>
<td>0.94 (0.61-1.44)</td>
</tr>
<tr>
<td>PPROM (%)</td>
<td>29 (8.5%)</td>
<td>40 (3.9%)</td>
<td>2.29 (1.39-3.75)**</td>
<td>2.53 (1.46-4.40)**</td>
</tr>
<tr>
<td>PPH (%)</td>
<td>8 (2.4%)</td>
<td>18 (1.8%)</td>
<td>1.34 (0.58-3.11)</td>
<td>1.39 (0.54-3.53)</td>
</tr>
<tr>
<td>SLE flare (%)</td>
<td>81 (24.0%)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* p<0.05; ** p<0.01; NA=not applicable; PROM=premature rupture of membranes; TPROM=term PROM; PPROM=preterm PROM

Adjusted ORs were calculated using a logistic regression analysis and were adjusted for maternal age, region, nulliparity, history of spontaneous abortion, history of diabetes, and history of hypertension.
Table 3. Fetal outcomes in patients with SLE and non-SLE patients

<table>
<thead>
<tr>
<th>Fetal outcomes</th>
<th>SLE (n=338)</th>
<th>Non-SLE (n=1014)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR^2 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetal loss (%)</td>
<td>38 (11.2%)</td>
<td>13 (1.3%)</td>
<td>9.75 (5.13-18.55)^**</td>
<td>10.23 (5.08-20.59)^**</td>
</tr>
<tr>
<td>Spontaneous abortion (%)</td>
<td>11 (3.3%)</td>
<td>7 (0.7%)</td>
<td>4.84 (1.86-12.59)^**</td>
<td>4.42 (1.52-12.80)^**</td>
</tr>
<tr>
<td>&lt;10 weeks (%)</td>
<td>2 (0.6%)</td>
<td>0 (0.0%)</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>≥10 weeks (%)</td>
<td>9 (2.7%)</td>
<td>7 (0.7%)</td>
<td>3.94 (1.50-10.65)^**</td>
<td>3.79 (1.25-11.44)^*</td>
</tr>
<tr>
<td>Therapeutic abortion (%)</td>
<td>21 (6.2%)</td>
<td>5 (0.5%)</td>
<td>13.37 (5.00-35.74)^**</td>
<td>16.57 (5.80-47.35)^**</td>
</tr>
<tr>
<td>Still birth (%)</td>
<td>6 (1.8%)</td>
<td>1 (0.1%)</td>
<td>18.31 (2.20-152.62)^**</td>
<td>13.25 (1.49-118.11)^*</td>
</tr>
</tbody>
</table>

Live birth

<table>
<thead>
<tr>
<th>IUGR (%)</th>
<th>SLE (n=300)</th>
<th>Non-SLE (n=1001)</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR^2 (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>37 (12.3%)</td>
<td>57 (5.7%)</td>
<td>2.33 (1.51-3.60)^**</td>
<td>2.20 (1.35-3.58)^**</td>
</tr>
<tr>
<td>Category</td>
<td>Value 1</td>
<td>Value 2</td>
<td>Value 3</td>
<td>Value 4</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
<td>---------</td>
</tr>
<tr>
<td>SGA (%)</td>
<td>30 (10.0%)</td>
<td>53 (5.3%)</td>
<td>1.99 (1.25-3.17)**</td>
<td>1.86 (1.11-3.13)*</td>
</tr>
<tr>
<td>Preterm birth (%)</td>
<td>86 (28.7%)</td>
<td>133 (13.3%)</td>
<td>2.62 (1.92-3.58)**</td>
<td>3.15 (2.21-4.50)**</td>
</tr>
<tr>
<td>Very preterm (%)</td>
<td>15 (5.0%)</td>
<td>19 (1.9%)</td>
<td>2.72 (1.37-5.42)**</td>
<td>3.57 (1.65-7.72)**</td>
</tr>
<tr>
<td>Moderate to late preterm (%)</td>
<td>71 (23.7%)</td>
<td>114 (11.4%)</td>
<td>2.41 (1.73-3.36)**</td>
<td>2.76 (1.90-4.03)**</td>
</tr>
<tr>
<td>Cesarean section (%)</td>
<td>255 (85.0%)</td>
<td>557 (55.6%)</td>
<td>4.51 (3.21-6.35)**</td>
<td>4.73 (3.30-6.80)**</td>
</tr>
<tr>
<td>Elective cesarean (%)</td>
<td>231 (77.0%)</td>
<td>298 (29.7%)</td>
<td>8.37 (5.32-13.15)**</td>
<td>9.27 (5.65-15.21)**</td>
</tr>
<tr>
<td>Emergency cesarean (%)</td>
<td>24 (8.0%)</td>
<td>259 (25.8%)</td>
<td>0.12 (0.08-0.19)**</td>
<td>0.11 (0.07-0.18)**</td>
</tr>
<tr>
<td>Congenital malformation (%)</td>
<td>4 (1.3%)</td>
<td>10 (1.0%)</td>
<td>1.34 (0.42-4.30)</td>
<td>1.60 (0.43-5.97)</td>
</tr>
<tr>
<td>Neonatal gender (boys) (%)</td>
<td>149 (49.7%)</td>
<td>548 (54.7%)</td>
<td>0.82 (0.63-1.06)</td>
<td>0.84 (0.63-1.11)</td>
</tr>
<tr>
<td>NICU (%)</td>
<td>48 (16.0%)</td>
<td>66 (6.6%)</td>
<td>2.70 (1.81-4.01)**</td>
<td>3.48 (2.21-5.48)**</td>
</tr>
<tr>
<td>Apgar score at 1' &lt; 7 (%)</td>
<td>3 (1.0%)</td>
<td>6 (0.6%)</td>
<td>1.68 (0.42-6.74)</td>
<td>2.47 (0.55-11.14)</td>
</tr>
<tr>
<td>Apgar score at 5' &lt; 7 (%)</td>
<td>0 (0.0%)</td>
<td>2 (0.2%)</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
Birth weight (g)±SD

<table>
<thead>
<tr>
<th></th>
<th>Birth weight (g)±SD</th>
<th>Gestational days (d)±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2763.7±588.7</td>
<td>259.3±16.2</td>
</tr>
<tr>
<td></td>
<td>3211.3±592.8</td>
<td>269.7±15.3</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

* * p<0.05; ** p<0.01; NA=not applicable; SGA=small for gestational age; IURG=Intrauterine growth restriction;

Δ Adjusted ORs were calculated using logistic regression analyses, which were adjusted for maternal age, region, nulliparity, history of spontaneous abortion, history of diabetes, and history of hypertension.
References


11. WHO. World Health Organization recommendations for prevention and treatment of maternal peripartum infections. 2015;Publication date: September.


STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

<table>
<thead>
<tr>
<th>Section/Topic</th>
<th>Item #</th>
<th>Recommendation</th>
<th>Reported on page #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Title and abstract</td>
<td>1</td>
<td><em>(a)</em> Indicate the study’s design with a commonly used term in the title or the abstract <em>(b)</em> Provide in the abstract an informative and balanced summary of what was done and what was found</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td><em>Explain the scientific background and rationale for the investigation being reported</em></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td><em>State specific objectives, including any pre-specified hypotheses</em></td>
<td>3</td>
</tr>
<tr>
<td>Introduction</td>
<td>4</td>
<td><em>Present key elements of study design early in the paper</em></td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td><em>Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection</em></td>
<td>5</td>
</tr>
<tr>
<td>Methods</td>
<td>6</td>
<td><em>(a)</em> <strong>Cohort study</strong>—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <strong>Case-control study</strong>—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls <strong>Cross-sectional study</strong>—Give the eligibility criteria, and the sources and methods of selection of participants <em>(b)</em> <strong>Cohort study</strong>—For matched studies, give matching criteria and number of exposed and unexposed <strong>Case-control study</strong>—For matched studies, give matching criteria and the number of controls per case</td>
<td>5-6</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td><em>Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable</em></td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td><em>For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group</em></td>
<td>8-11</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td><em>Describe any efforts to address potential sources of bias</em></td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td><em>Explain how the study size was arrived at</em></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td><em>Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why</em></td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td><em>(a)</em> Describe all statistical methods, including those used to control for confounding <em>(b)</em> Describe any methods used to examine subgroups and interactions <em>(c)</em> Explain how missing data were addressed <em>(d)</em> <strong>Cohort study</strong>—If applicable, explain how loss to follow-up was addressed <strong>Case-control study</strong>—If applicable, explain how matching of cases and controls was addressed</td>
<td>12</td>
</tr>
</tbody>
</table>
Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy
(e) Describe any sensitivity analyses

Results

Participants 13*
(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
(b) Give reasons for non-participation at each stage
(c) Consider use of a flow diagram

Descriptive data 14*
(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
(b) Indicate number of participants with missing data for each variable of interest
(c) Cohort study—Summarise follow-up time (eg, average and total amount)

Outcome data 15*
Cohort study—Report numbers of outcome events or summary measures over time
Case-control study—Report numbers in each exposure category, or summary measures of exposure
Cross-sectional study—Report numbers of outcome events or summary measures

Main results 16
(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
(b) Report category boundaries when continuous variables were categorized
(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period

Other analyses 17
Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses

Discussion

Key results 18
Summarise key results with reference to study objectives

Limitations 19
Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias

Interpretation 20
Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence

Generalisability 21
Discuss the generalisability (external validity) of the study results

Other information

Funding 22
Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.