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

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Abstract

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

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

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

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

Key words
Systemic lupus erythematosus, pregnancy outcome, low birth weight.

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Introduction

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

Numerous studies consistently report that SLE is associated with adverse obstetric outcomes, including foetal wastage (3, 4), preterm birth (3, 5-8), low birth weight (9, 10), and intrauterine growth restriction (4, 8). However, there is no agreement about the relationship between SLE flares during pregnancy and adverse obstetric outcomes (11-19). For example, Clark *et al.* (11) found preterm deliveries were associated with disease activity. In contrast, studies by Georgiou *et al.* (13) and Lima *et al.* (14) found no significant relationship between SLE flares and preterm birth and miscarriage. Whether or not a flare of SLE in pregnancy is a risk factor for a poor obstetric outcome remains unclear. Furthermore, several such studies on pregnancy outcomes for women with SLE have relied only on descriptive analysis and lacked the means to compare the risk of adverse pregnancy outcomes among mothers with SLE and the general healthy population (6, 8-10). In addition, almost no studies have used a nationwide population-based database to examine the relationship between SLE and the risk of adverse pregnancy outcomes, so findings cannot be generalised to a population as a whole.

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

Methods

Database

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

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

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

empt from full review by the Internal Review Board.

Study sample

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

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

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

Variables of interest

In this study, women with SLE were categorised as having or not having been hospitalised for SLE treatment during pregnancy. Hospitalisation for

disease during pregnancy was identified from the NHIRD by selecting women hospitalised with a principal diagnosis of SLE during pregnancy. The classification is justifiable because a principle diagnosis is the diagnosis most likely to be the chief focus of treatment. The outcome variables were all dichotomous, including low birth weight (<2500 g), preterm birth (<37 weeks), and small for gestational age babies (SGA) (birth weights below the tenth percentile for gestational age).

We also took other possible confounding factors into consideration. These factors included characteristics of the mother (age, highest educational level and marital status), infant (gender and parity), father (age and highest educational level), and family monthly income (including mother and father monthly income). Parental ages were defined as each parent's age, in years, at the time of the infant's birth. Parity was categorized into the following three categories: 1, 2, and ≥3. Maternal and paternal highest education levels were categorized into four levels: elementary school or lower, junior high school, senior high school, and college or above. Family monthly income was grouped into four categories: <NT\$15,000, NT15,000-NT30,000, NT30,001-NT50,000, and ≥NT50,001.

Statistical analysis

The SAS statistical package (SAS System for Windows, Version 8.2) was used to perform the analyses in this study. Chi-square tests were carried out to examine the differences in the characteristics of the infant, mother, and father, comparing unaffected women and women with SLE. Conditional logistic regression analyses which were conditioned on maternal age and year of delivery were also used to explore the relationship between women with and without SLE and the risk of LBW, preterm birth, and SGA, after adjusting for the possible confounding factors. Since we found a strong co-linearity between maternal and paternal age, we kept only maternal age in the regression model. In addition, since prior studies have documented a significant relationship between parental age differences

and adverse pregnancy outcomes, we added age differences between parents into the regression model for adjustment. Adjusted odds ratios (OR) are presented with 95% confidence intervals (CI). A two-sided *p*-value of <0.05 was considered statistically significant for this study.

Results

Details of the distribution for characteristics of infants, mothers, and fathers according to the cohorts are given in Table I. Pearson χ^2 tests show that there were significant differences among the cohorts in terms of infant parity (*p*<0.001), maternal age (*p*<0.001), highest maternal educational level (*p*<0.001), family monthly income (*p*=0.015), and highest paternal educational level (*p*<0.001). Women who experienced SLE hospitalisation during pregnancy (mean age=27.3 years) were likely to be younger than unaffected women (mean age=29.1 years) or women with SLE who did not experience hospitalisation during pregnancy (mean age=29.4 years). The distributions in infant gender, marital status, and paternal age did not differ significantly among the cohorts.

Among 1,010 mothers with non-renal SLE, 31% displayed adverse pregnancy outcomes (not shown in the tables). Table II describes the distribution and crude odds ratios of LBW, preterm birth, and SGA among the cohorts. The χ^2 tests show that there were significant differences in LBW (14.9% *vs.* 7.2%), preterm birth (14.4% *vs.* 8.5%), and SGA (28.5% *vs.* 17.5%) (all *p*-values <0.001) between women with SLE and unaffected women. The regression analyses also reveal that, compared to unaffected mothers, women who experienced SLE hospitalisation during pregnancy were more likely to have LBW infants (OR=6.34, 95% CI=4.31-9.33), preterm birth (OR=4.15, 95% CI=2.76-6.23), and SGA babies (OR=4.32, 95% CI=3.02-6.18). Similarly, women with SLE who experienced no hospitalisation during pregnancy had higher odds than unaffected women of LBW infants (OR=2.25, 95% CI=1.84-2.76), preterm birth (OR=1.86, 95% CI=1.48-2.22), and SGA babies (OR=1.89, 95% CI=1.62-2.20).

Table I. Comparisons of the maternal, paternal, and infant characteristics of women with SLE, with and without SLE hospitalisation during pregnancy and women without SLE in Taiwan, 2001~2003 (n=6,060).

Variable	Pregnant women without SLE n=5,050		Mothers with SLE			
			No hospitalisation for SLE treatment during pregnancy n=884		Hospitalisation for SLE treatment during pregnancy n=126	
	Total n.	%	Total n.	%	Total n.	%
Infant characteristics						
Gender						
Male	2704	53.5	467	52.8	60	47.6
Female	2346	46.5	417	47.2	66	52.4
Parity						
1	2465	48.8	514	58.1	86	68.3
2	1778	35.2	263	29.8	24	19.1
3 or more	807	16.0	107	12.1	16	12.7
Maternal characteristics						
Age						
<20	100	2.0	15	1.7	5	4.0
20-24	705	14.0	110	12.4	31	24.6
25-29	1920	38.0	333	37.7	51	40.5
30-34	1665	33.0	304	34.4	29	23.0
> 34	660	13.0	122	13.8	10	7.9
Education level						
Elementary school or lower	108	2.1	13	1.5	4	3.1
Junior high school	778	15.4	96	10.9	14	11.1
Senior high school	3384	69.0	586	66.3	87	69.1
College or above	780	15.5	189	21.4	21	12.7
Marital status						
Married	4912	92.3	864	97.7	123	97.6
Others	138	2.7	20	2.3	3	2.4
Diabetes						
Yes	35	0.7	9	1.0	4	3.3
No	5007	99.0	875	99.0	122	96.7
Hypertension						
Yes	523	1.0	15	1.7	6	4.8
No	4998	9.3	869	98.3	120	95.2
Family monthly income						
<NT$15,000	1526	30.2	279	31.6	54	42.9
NT$15,000-30,000	1311	26.0	223	25.2	30	23.8
NT$30,001-50,000	1432	28.4	223	25.2	27	21.4
>NT$50,000	781	15.5	159	18.0	15	11.9
Paternal characteristics						
Age						
<30	29	0.6	1	0.1	2	1.6
20-34	3581	70.9	614	69.5	89	70.6
> 34	1440	28.5	269	30.4	35	27.8
Education level						
Elementary school or lower	84	1.7	7	0.8	3	2.4
Junior high school	887	7.6	136	15.4	22	17.5
Senior high school	3079	61.0	504	57.0	79	62.7
College or above	1000	19.7	237	26.8	22	17.5

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

Discussion

Our nationwide population-based study shows that adverse pregnancy outcomes occurred in 31% of 1,010 mothers with non-renal SLE. More specifically, we found that after adjusting for possible confounders, women with SLE were 2.23, 1.89, and 1.87 times more likely to have LBW, preterm birth, and SGA, respectively, than unaffected women (not shown in tables). This finding is consistent with prior studies reporting that women with SLE have increased risk of preterm birth (3, 7, 20, 21) and LBW babies (9, 10, 18, 22) compared to unaffected women. Nevertheless, except for the study by Wolfberg *et al.* (20), several studies comparing women with and without SLE have also failed to observe significant differences in having SGA babies (3, 12, 18, 22). Possible explanations for the discrepancy in findings may include: a small sample size or data collection from only a few hospitals or sub-populations of patients and the availability and use of modern obstetric care and foetal monitoring. Furthermore, we found that at least one hospitalisation during pregnancy occurred in 12.5% of women with SLE in our study, and the relationship between SLE and adverse pregnancy outcomes was even more pronounced when women experienced SLE hospitalisation during pregnancy. We found that compared to mothers without SLE, women who had SLE hospitalisation

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

Variable	Pregnant Women without SLE n=5,050		Pregnant women with SLE n=1,010		No hospitalisation for SLE treatment during pregnancy n=884		Hospitalisation for SLE treatment during pregnancy n=126	
	n.	%	n.	%	n.	%	n.	%
Low birth weight								
Yes	363	7.2	150	14.9	108	12.2	42	33.3
No	4,687	92.8	860	85.2	776	87.8	84	66.7
Crude OR[a] (95% CI)			1.002.25***(1.84-2.76)		1.80***(1.43-2.26)		6.34***(4.31-9.33)	
Preterm birth								
Yes	427	8.5	145	14.4	111	12.6	34	27.0
No	4,623	91.5	865	85.6	773	87.4	92	73.0
Crude OR[a] (95% CI)	1.00		1.86***(1.48-2.22)		1.55***(1.24-1.93)		4.15***(2.76-6.23)	
Small for gestational age								
Yes	882	17.5	288	28.5	227	25.7	61	48.4
No	4,168	82.5	722	71.5	657	74.3	65	51.6
Crude OR[a] (95% CI)	1.00		1.89***(1.62-2.20)		1.64***(1.39-1.94)		4.32***(3.02-6.18)	

***$p<0.001$; [a] Crude odds ratios (OR) were calculated by conditional logistic regressions which were conditioned on maternal age and the year of delivery.

during pregnancy were four to six times more likely to have adverse pregnancy outcomes. In addition, compared to SLE women who were not hospitalised during pregnancy, women with SLE who had been hospitalised during pregnancy were two to three times more likely to have adverse pregnancy outcomes. Our findings are consistent with a study by Clowse *et al.*, which reported that moderate to severe lupus activity during pregnancy significantly increased the rate of preterm birth compared to women with mild lupus activity or none at all (12). In addition, Mintz *et al.* (15) and Petri (23) both observed a significant relationship between SLE flares and preterm birth. In contrast to our findings, several other studies have failed to observe an association between adverse pregnancy outcomes and pregnancy with or without a flare of SLE (13, 14, 16, 17).

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

with SLE as experiencing or not experiencing hospitalisation for SLE treatment during pregnancy, the second group might identify women with medium-severe flares.

One study by Cavallasca *et al.* indicated that although maternal age at conception was similar overall, women having three or more pregnancies accounted for approximately 40% of SLE patients with mild flares (9). However, only about 13% of indexed pregnancies among mothers with more severe SLE were on their third or higher pregnancy. In this present study, we failed to observe an association between paternal education and adverse pregnancy outcomes, but we found that mothers with junior high school educational level had a higher risk of SGA compared to their counterparts with a senior high school educational level (OR=1.34). We further analysed the relationship between maternal and paternal highest educational level and adverse pregnancy outcomes among SLE women. However, we failed to find any significant relationship between highest maternal and paternal educational level and adverse pregnancy outcomes among SLE women. In contrast to our findings, one study by Andrade *et al.* (26) in the U.S. found that fewer years of education were associated with adverse pregnancy outcomes among SLE women. Further studies in other regions

or countries are still required to clarify the relationship between maternal educational level and pregnancy outcomes among SLE patients.

The mechanisms underlying the increased risk of adverse pregnancy outcomes among women with SLE remain unclear. The most common predisposing factor to adverse pregnancy outcomes in SLE is antiphospholipid antibodies (aPL). aPL are antibodies against phospholipids (substances in the lining of cells) that prevent blood clotting in a test tube. Studies have demonstrated that patients with aPL have an abnormally higher risk of maternal thrombosis, thrombocytopenia, and embryofetal demise (27). Therefore, aPL may play an important role in the increased risk of LBW and SGA found in our study (13, 28).

The strengths of our study include its large nationwide population-based sample size, the availability of data on patients with a wide range of demographic characteristics, and adjustment for comorbidities and other potential confounding factors.

Nevertheless, there are three limitations. Firstly, the NHIRD lacks detailed clinical and laboratory information and data on the severity of SLE. In addition, information such as mothers' smoking history, substance abuse, alcohol consumption, nutrition, and body mass index is not available in our da-

Table III. Adjusted odds ratios of LBW, preterm birth, and SGA for mothers without SLE, mothers with SLE as having or not having experienced hospitalisation for SLE treatment during pregnancy in Taiwan (n=6,060).

Variable	Low birth weight Adjusted OR[a], 95% CI	Preterm birth Adjusted OR[a], 95% CI	Small for gestational age Adjusted OR[a], 95% CI
Mothers			
with SLE (No hospitalisation for SLE treatment during pregnancy)	1.80[***] (1.43-2.26)	1.62[***] (1.30-2.03)	1.63[***] (1.38-1.94)
with SLE (Hospitalisation for SLE treatment during pregnancy)	6.15[***] (4.15-9.13)	4.19[***] (2.77-6.36)	4.25[***] (2.95-6.11)
without SLE	1.00	1.00	1.00
Maternal characteristics			
Diabetes	1.41 (0.83-2.41)	3.21[***] (2.17-5.21)	0.97 (0.62-1.42)
Hypertension	2.52[***] (1.21-3.28)	2.62[***] (2.20-3.52)	1.61 (0.92-2.15)
Education level			
Elementary school or lower	1.47 (0.81-2.67)	1.49 (0.87-2.57)	1.16 (0.73-1.85)
Junior high school	1.23 (0.94-1.60)	1.26 (0.98-1.61)	1.34[**] (1.11-1.62)
Senior high school	1.00	1.00	1.00
College or above	0.86 (0.63-1.17)	0.80 (0.59-1.08)	0.93 (0.75-1.15)
Marital status			
Married	1.00	1.00	1.00
Others	1.60 (0.98-2.58)	1.64[*] (1.04-2.59)	1.84 (1.30-2.62)
Infant characteristics			
Gender			
Male	0.82[*] (0.68-0.98)	1.13 (0.95-1.35)	0.75 (0.66-0.85)
Female	1.00	1.00	1.00
Parity			
1	1.00	1.00	1.00
2	0.82 (0.66-1.01)	1.14 (0.95-1.35)	0.80[**] (0.61-0.92)
3 or more	0.79 (0.59-1.07)	1.11 (1.04-2.59)	0.75[**] (0.61-0.92)
Family monthly income			
<NT$15,000	1.00	1.00	1.00
NT$15,000-30,000	1.14 (0.88-1.48)	1.21 (0.94-1.55)	1.24[*] (1.03-1.50)
NT$30,001-50,000	0.83 (0.63-1.11)	0.90 (0.69-1.18)	0.91 (0.74-1.11)
>NT$50,000	1.00 (0.72-1.39)	0.99 (0.72-1.35)	1.05 (0.83-1.32)
Parental age difference	0.99 (0.97-1.02)	0.99 (0.96-1.01)	0.99 (0.98-1.01)
Paternal characteristics			
Education level			
Elementary school or lower	0.68 (0.27-1.61)	0.99 (0.50-1.99)	0.77 (0.43-1.37)
Junior high school	1.67 (0.84-1.38)	1.00 (0.79-1.28)	1.04 (0.87-1.24)
Senior high school	1.00	1.00	1.00
College or above	0.99 (0.76-1.32)	1.09 (0.84-1.41)	1.02 (0.84-1.24)

* p<0.05; ** p<0.01; *** p<0.001; [a]Adjusted odds ratios (OR) were calculated by conditional logistic regressions which were conditioned on maternal age and the year of delivery.

tasets. These factors may increase the risk of adverse pregnancy outcomes. Secondly, we were unable to appropriately assess the flare status of women with SLE during pregnancy. However, by categorising mothers with SLE by their hospitalisation status in our study, women in the group of "hospitalisation for SLE treatment during pregnancy" might experience medium-severe flares. Thirdly, because this was a retrospective analysis, we were not able to assess any casual relationship between SLE and pregnancy outcomes. Finally, our study did not consider the effects of medication during pregnancy. Several treatments such as corticosteroids, non-steroidal anti-inflammatory drugs, and hydroxychloroquine are frequently used to prevent SLE flares during pregnancy. Stopping hydroxychloroquine during pregnancy is specifically associated with increased degrees of lupus activity (29). However, women with SLE in Taiwan are likely to discontinue any medication after becoming pregnant out of concern of adverse consequences for the developing foetus. Thus, the association between SLE and pregnancy outcomes found in our study was largely based upon the assumption of women not receiving SLE treatment during pregnancy.

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

References
1. CERVERA R, FONT J, CARMONA F et al.: Pregnancy outcome in systemic lupus erythematosus: good news for the new millennium. *Autoimmun Rev* 2002; 1: 354-9.
2. GORDON C: Pregnancy and autoimmune diseases. *Best Pract Res Clin Rheumatol* 2004; 18: 359-79.
3. JULKUNEN H, JOUHIKAINEN T, KAAJA R et al.: Fetal outcome in lupus pregnancy: a retrospective case-control study of 242 pregnancies in 112 patients. *Lupus* 1993; 2: 125-31.
4. RAHMAN P, GLADMAN DD, UROWITZ MB: Clinical predictors of fetal outcome in systemic lupus erythematosus. *J Rheumatol* 1998; 25: 1526-30.
5. KISS E, BHATTOA HP, BETTEMBUK P et al: Pregnancy in women with systemic lupus erythematosus. *Eur J Obstet Gynecol Reprod Biol* 2002; 101: 129-34.

6. KLEINMAN D, KATZ VL, KULLER JA: Perinatal outcomes in women with systemic lupus erythematosus. *J Perinatol* 1998; 18: 178-82.

7. PETRI M, ALLBRITTON J: Fetal outcome of lupus pregnancy: a retrospective case-control study of the Hopkins Lupus Cohort. *J Rheumatol* 1993; 20: 650-6.

8. RUBBERT A, PIMER K, WILDT L *et al.:* Pregnancy course and complications in patients with systemic lupus erythematosus. *Am J Reprod Immunol* 1992; 28: 205-7.

9. CAVALLASCA JA, LABORDE HA, RUDA-VEGA H *et al.:* Maternal and fetal outcomes of 72 pregnancies in Argentine patients with systemic lupus erythematosus (SLE). *Clin Rheumatol* 2008; 27: 41-6.

10. JOHNS KR, MORAND EF, LITTLEJOHN GO: Pregnancy outcome in systemic lupus erythematosus (SLE): a review of 54 cases. *Aust N Z J Med* 1998; 28: 18-22.

11. CLARK CA, SPITZER KA, NADLER JN *et al.*: Preterm deliveries in women with systemic lupus erythematosus. *J Rheumatol* 2003; 30: 2127-32.

12. CLOWSE ME, MAGDER LS, WITTER F *et al.:* The impact of increased lupus activity on obstetric outcomes. *Arthritis Rheum* 2005; 52: 514-21.

13. GEORGIOU PE, POLITI EN, KATSIMBRI P *et al.*: Outcome of lupus pregnancy: a controlled study. *Rheumatology* (Oxford) 2000; 39: 1014-9.

14. LIMA F, BUCHANAN NM, KHAMASHTA MA *et al.*: Obstetric outcome in systemic lupus erythematosus. *Semin Arthritis Rheum* 1995; 25: 184-92.

15. MINTZ G, NIZ J, GUTIERREZ G *et al.*: Prospective study of pregnancy in systemic lupus erythematosus. Results of a multidisciplinary approach. *J Rheumatol* 1986; 13: 732-9.

16. NOSSENT HC, SWAAK TJ: Systemic lupus erythematosus. VI. Analysis of the interrelationship with pregnancy. *J Rheumatol* 1990; 17: 771-6.

17. PETRI M, HOWARD D, REPKE J *et al.*: The Hopkins Lupus Pregnancy Center: 1987-1991 update. *Am J Reprod Immunol* 1992; 28: 188-91.

18. SURITA FG, PARPINELLI MA, YONEHARA E *et al.*: Systemic lupus erythematosus and pregnancy: clinical evolution, maternal and perinatal outcomes and placental findings. *Sao Paulo Med J* 2007; 125: 91-5.

19. UROWITZ MB, GLADMAN DD, FAREWELL VT *et al.*: Lupus and pregnancy studies. *Arthritis Rheum* 1993; 36: 1392-7.

20. WOLFBERG AJ, LEE-PARRITZ A, PELLER AJ *et al.*: Association of rheumatologic disease with preeclampsia. *Obstet Gynecol* 2004; 103: 1190-3.

21. YASMEEN S, WILKINS EE, FIELD NT *et al.*: Pregnancy outcomes in women with systemic lupus erythematosus. *J Matern Fetal Med* 2001; 10: 91-6.

22. DHAR JP, ESSENMACHER LM, AGER JW *et al.*: Pregnancy outcomes before and after a diagnosis of systemic lupus erythematosus. *Am J Obstet Gynecol* 2005; 193: 1444-55.

23. PETRI M: Systemic lupus erythematosus and pregnancy. *Rheum Dis Clin North Am* 1994; 20: 87-118.

24. PETRI M, BARR SG, ZOZNANA-NACH A *et al.*: Measures of disease activity, damage, and health status: the Hopkins Lupus Cohort experience. *J Rheumatol* 1999; 26: 502-3.

25. PETRI M, BUYON J, KIM M: Classification and definition of major flares in SLE clinical trials. *Lupus* 1999; 8: 685-91.

26. ANDRADE R, SANCHEZ ML, ALARCON GS *et al.*: LUMINA Study Group. Adverse pregnancy outcomes in women with systemic lupus erythematosus from a multiethnic US cohort: LUMINA (LVI). *Clin Exp Rheumatol*. 2008 Mar-Apr; 26: 268-74.

27. CLOWSE ME, JAMISON M, MYERS E *et al.*: A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol* 2008; 199: 127 e1-6.

28. RUIZ-IRASTORZA G, KHAMASHTA MA: Lupus and pregnancy: ten questions and some answers. *Lupus* 2008; 17: 416-20.

29. CLOWSE ME, MAGDER L, WITTER F *et al.*: Hydroxychloroquine in lupus pregnancy. *Arthritis Rheum* 2006; 54: 3640-7.

30. OSTENSEN M, KHAMASHTA M, LOCKSHIN M *et al.*: Anti-inflammatory and immunosuppressive drugs and reproduction. *Arthritis Res Ther* 2006; 8: 209.