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ORIGINAL ARTICLE

Clinical study of factors associated with pregnancy outcomes in pregnant women with systemic lupus erythematosus in the southern China

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ABSTRACT

Objectives: This study aims to estimate predicted factors for maternal and fetal outcomes in Hakka pregnant women with systemic lupus erythematosus (SLE) in the Southern China.

Patients and methods: Between June 2014 and February 2020, we retrospectively analyzed the data of a total of 123 singleton pregnant women with SLE (mean age: 27.1±4.1 years; range, 19 to 39 years) who were referred to our rheumatology clinic. Demographic, clinical, and laboratory data of the patients were recorded. Adverse pregnancy outcomes (APOs) were assessed.

Results: Multivariate logistic regression analysis revealed that preeclampsia was associated with the increased odds of APOs (odds ratios [OR]=9.538, 95% confidence interval [CI]: 2.055-44.271, p=0.004), premature birth (OR=14.289, 95% CI: 3.596-56.777, p<0.001) and low birth weight (OR=8.275, 95% CI: 2.117-32.345, p=0.002). Anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibody positivity was the predictor of APOs (OR=2.165, 95% CI: 1.034-4.532, p=0.040), premature birth (OR=2.849, 95% CI: 1.220-6.657, p=0.016) and pregnancy loss (OR=3.004, 95% CI: 1.086-8.305, p=0.034). The use of hydroxychloroquine and prednisone was associated with the decreased odds of APOs (OR=0.412, 95% CI: 0.198-0.860, p=0.018) and pregnancy loss (OR=0.304, 95% CI: 0.111-0.831, p=0.020).

Conclusion: Our study results indicate that preeclampsia, anti-dsDNA antibody positivity, and the use of hydroxychloroquine and prednisone are independent predictors of pregnancy outcomes.

Keywords: Adverse pregnancy outcomes, preeclampsia, systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a complex autoimmune disorder with an incidence of 20 to 70 per 100,000 person-years worldwide.[1] In particular, SLE is associated with a strong female predominance and diagnosed more frequently in their reproductive years.[2] It is currently well-documented that pregnancy in SLE-affected women encounter an increased risk of obstetric complications such as preeclampsia, miscarriage, preterm delivery, fetal growth restriction, and low fetal birth weight.[3,4] Indeed, pregnancy outcomes in pregnant women with SLE have dramatically improved due to meaningful management, including pre-pregnancy counseling, prenatal

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diagnosis, progression of immunosuppressive therapy, and family planning.[5,6] Nevertheless, the diagnosis and management of pregnant women with SLE have proven to be complicated and are still challenging either for physicians or patients.

Systemic lupus erythematosus is an inflammatory multi-system disease characterized by a broad range of clinical manifestations and prognosis.[7] Although several studies have shown that SLE has adverse effects on pregnant women and their offspring, the underlying pathogenesis contributing to pregnancy complications remains being actively investigated.[8] Identification of clinical and laboratory predictors of adverse pregnancy outcomes (APOs) have significantly reduced the maternal and fetal risks in pregnant women with SLE. Previous studies have demonstrated that disease-related factors such as active disease, renal involvement, high dose use of corticosteroid and cyclophosphamide have a great predictive value for the occurrence of APOs in pregnant women with SLE.[9-11] Moreover, other factors including socioeconomic status, behavior, and genetic factors have been also implicated in the major maternal, obstetrical, and neonatal complications.[12] Of particular interest is the fact that the results of these studies are controversial and vary according to region and ethnicity.[13,14] To the best of our knowledge, there is a paucity of data on the pregnancy of Hakka women with SLE in the literature. In this study, therefore, we aimed to identify predictors of maternal and fetal outcomes in Hakka pregnant women with SLE in the Southern China.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at the rheumatology clinic of the Meizhou People's Hospital of the Southern China between June 2014 and February 2020. The data of a total of 123 singleton pregnant women with SLE (mean age: 27.1±4.1 years; range, 19 to 39 years) who were referred to our clinic were analyzed. All pregnant women who underwent prenatal follow-up and diagnosed with SLE and met the Systemic Lupus International Collaborating Clinics (SLICC)/American College of Rheumatology (ACR) 2012 diagnostic criteria[15] were collected. Rheumatologists and fetal-maternal medicine specialists treated the patients regularly. Exclusion criteria were as follows: age <18 years, having a malignancy, having missing data, and those who were lost-to-follow-up or who did not give birth at our institution. A written informed consent was obtained from each patient. The study protocol was approved by the Meizhou People's Hospital, Ethics Committee (No: MPH-HEC 2014-A-02). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data collection and definitions

Using the hospital electronic database, the medical records of patients were comprehensively reviewed to collect demographic and clinical information and laboratory data. Recorded findings included maternal age at pregnancy age, gestational age at delivery, mode of delivery, disease duration of SLE, gravidity, previous pregnancy loss, blood pressure, type of current medications, lupus nephritis, thrombocytopenia, preeclampsia, diabetes, hypoalbuminemia, and Appearance, Pulse, Grimace, Activity and Respiration (APGAR) score at 1 min and 5 min. Disease activity scores were evaluated using the SLE Disease Activity Index (SLEDAI). Medication use during pregnancy was restricted to hydroxychloroquine, prednisone, and cyclosporine for the treatment of SLE. Hydroxychloroquine was prescribed to patients with a dose of 100 to 400 mg daily. Prednisone was prescribed 10 to 15 mg daily to patients with mild disease activity, 15 to 30 mg daily to patients with moderate disease activity, and over 30 mg daily to patients with high disease activity. Therapeutic doses of cyclosporine ranged from 25 to 100 mg twice daily. Laboratory parameters included serum levels of the antinuclear antibody (ANA), anti-phospholipid antibodies, anti-double-stranded deoxyribonucleic acid (anti-dsDNA) antibodies, anti-Sjögren syndrome antigen A (anti-SSA)/Ro antibodies, Sjögren syndrome antigen B (SSB)/La antibodies, complement 3, and complement 4. All laboratory tests were performed according to the manufacturer's protocols.

Preeclampsia was defined as a *de novo* persistent hypertension (blood pressure

>140/90 mmHg) with proteinuria >300 mg/24 h collection after 20 weeks of gestation. Premature birth was defined as births less than 37 weeks of pregnancy. Low-birth-weight was defined as weight at birth of <2,500 g. Fetal growth restriction (FGR) was defined as an estimated fetal weight below the 10th percentile for a given gestational age plus abnormal Doppler flow velocimetry waveform. Pregnancy loss included spontaneous abortions, therapeutic abortion, elective abortion, stillbirth, and neonatal death. Among these, stillbirth was defined as the occurrence of intrauterine fetal demise after at or 22 weeks of gestation. Neonatal death was defined as death within the first 28 days of birth. Adverse pregnancy outcomes were defined as the occurrence of one or more of the following: preterm delivery, low birth weight, pregnancy loss, FGR, and fetal distress.

Statistical analysis

Statistical analysis was performed using the PASW version 18.0 software (SPSS Inc., Chicago, IL, USA). Descriptive data were expressed in mean ± standard deviation (SD), median (min-max) or number and frequency. Continuous variables were compared using the Student t-test, while categorical variables were compared using the chi-square test or Fisher's exact test. Univariate and multivariate logistic regression analyses were performed to identify factors yielding odds ratios (ORs) and 95% confidence intervals (CIs). A p value of <0.05 was considered statistically significant.

Table 1. Maternal and pregnancy outcomes in pregnant women with SLE (n=123)

	Pregnant women with SLE		
	n	%	Mean±SD
Maternal outcomes			27.1±4.1
Maternal age at pregnancy (years)			37.3±2.9
Mean gestational age at delivery (weeks)			
Normal vaginal delivery	32/107	29.9	
Cesarean section	75/107	70.1	
Preeclampsia	17/123	13.8	
Diabetes	14/123	11.4	
Live birth			
Average birth weight (g)			2,582±615
Normal birth weight	62/107	57.9	
Low birth weight	45/107	42.1	
Full-term birth	74/107	69.2	
Premature birth	33/107	30.8	
Intrauterine growth retardation	7/107	6.5	
Fetal distress	12/107	11.2	
APGAR score			
1 min			9.25±1.72
5 min			9.75±0.96
Pregnancy loss			
Spontaneous abortion	4/123	3.3	
Therapeutic abortion	9/123	7.3	
Stillbirth	3/123	2.4	
Neonatal death	3/123	2.4	

SLE: Systemic lupus erythematosus; SD: Standard deviation; APGAR: Appearance, Pulse, Grimace, Activity and Respiration.

RESULTS

Maternal and pregnancy outcomes in pregnant women with SLE are summarized in Table 1. Among the patients, 32/107 (29.9%) had normal vaginal delivery and 75/107 (70.1%) had cesarean-section delivery, resulting in 62/107 (57.9%) had normal birth weight and 45/107 (42.1%) had low birth weight. In addition, 17/123 (13.8%) had preeclampsia and 14/123 (11.4%) had diabetes. The full-term birth and premature birth were calculated as 74/107 (69.2%) and 33/107 (30.8%), respectively. Our study showed 7/107 (6.5%) had FGR and 12/107 (11.2%) had fetal distress. In cases of pregnancy loss (n=19), four (3.3%) had spontaneous abortion, nine (7.3%) had therapeutic abortion, three (2.4%) had stillbirth, and three (2.4%) had neonatal death.

Demographic and baseline clinical characteristics of the patients with and without APOs are shown in Table 2. The frequencies of preeclampsia were 25.4% (n=15) for the

Table 2. Clinical characteristics of patients with and without APOs (n=123)

	With APOs (n=59)			Without APOs (n=64)			
	n	%	Mean±SD	n	%	Mean±SD	*p*
Maternal age at pregnancy (year)			26.4±3.7			27.7±4.3	0.093
SLE duration (year)			5.0±3.3			6.1±3.6	0.103
SLEDAI			4.6±2.7			3.9±2.6	0.108
Primigravida	34	57.6		31	48.4		0.367
Previous pregnancy loss	21	35.6		32	50.0		0.145
SLE activity during pregnancy							
Lupus flare	13	22.0		9	14.1		0.347
Lupus nephritis	6	10.2		4	6.3		0.520
Arthritis	0	0		1	1.6		1.000
Mucocutaneous	5	8.5		3	4.7		0.479
Serositis	4	6.8		4	6.3		1.000
Thrombocytopenia	4	6.8		1	1.6		0.196
Lupus flare	13	22.0		9	14.1		0.347
Lupus nephritis	6	10.2		4	6.3		0.520
Arthritis	0	0		1	1.6		1.000
Laboratory testing							
ANA positivity	41	69.5		37	57.8		0.195
Anti-phospholipid positivity	3	5.1		5	7.8		0.719
Anti-dsDNA antibody positivity	30	50.8		20	31.3		0.030
Anti-Sm antibody positivity	9	15.3		16	25.0		0.262
Anti-Ro/SSA antibody positivity	27	45.8		32	50.0		0.719
Anti-La/SSB antibody positivity	5	8.5		5	7.8		1.000
Hypoalbuminemia	12	20.3		6	9.4		0.125
Hypocomplementemia	29	49.2		32	50.0		1.000
Medication during pregnancy							
Hydroxychloroquine	26	44.1		43	67.2		0.012
Prednisone	37	62.7		50	78.1		0.075
Cyclosporine	4	6.8		2	3.1		0.425
Aspirin	3	5.1		5	7.8		0.719
Low-molecular weight heparin	3	5.1		3	4.7		0.721

APOs: Adverse pregnancy outcomes; SD: Standard deviation; SLE: Systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; ANA: Antinuclear antibody; Anti-dsDNA: Anti-double-stranded deoxyribonucleic acid.

Table 3. Univariate and multivariate analysis results

	Univariate logistic regression			Multivariate logistic regression		
	Crude OR	95% CI	*p*	Crude OR	95% CI	*p**
APOs						
Preeclampsia	10.167	2.213-46.710	0.003	9.538	2.055-44.271	0.004
Anti-dsDNA antibody positivity	2.150	1.033-4.475	0.041	2.165	1.034-4.532	0.040
Hydroxychloroquine	0.409	0.197-0.849	0.016	0.412	0.198-0.860	0.018
Premature birth						
Preeclampsia	13.524	3.486-52.460	<0.001	14.289	3.596-56.777	<0.001
Anti-dsDNA antibody positivity	2.836	1.216-6.619	0.016	2.849	1.220-6.657	0.016
Low birth weight						
Preeclampsia	7.152	1.882-27.175	0.004	8.275	2.117-32.345	0.002
Pregnancy loss						
Anti-dsDNA antibody positivity	2.977	1.080-8.208	0.035	3.004	1.086-8.305	0.034
Prednisone	0.300	0.110-0.819	0.019	0.304	0.111-0.831	0.020

OR: Odds ratio; CI: Confidence interval; APOs: Adverse pregnancy outcomes; Anti-dsDNA: Anti-double-stranded deoxyribonucleic acid; * Adjusted for age.

patients with APOs and 3.1% (n=2) for the patients without APOs, indicating a statistically significant difference (p=0.001). The rates of anti-dsDNA antibody positivity were significantly higher in patients with APOs, compared to those without APOs (50.8% *vs.* 7.9%, respectively; p=0.030). The rate of hydroxychloroquine use was significantly lower in patients with APOs than that without APOs (44.1% vs. 67.2%, respectively; p=0.012).

The univariate and multivariate logistic regression analyses of predictive factors for adverse maternal and fetal outcomes are shown in Table 3. After adjusting for age, preeclampsia was associated with the increased odds of APOs (OR=9.538, 95% CI: 2.055-44.271, p=0.004), premature birth (OR=14.289, 95% CI: 3.596-56.777, p<0.001) and low birth weight (OR=8.275, 95% CI: 2.117-32.345, p=0.002). Anti-dsDNA antibody positivity was the predictor of APOs (OR=2.165, 95% CI: 1.034-4.532, p=0.040), premature birth (OR=2.849, 95% CI: 1.220-6.657, p=0.016), and pregnancy loss (OR=3.004, 95% CI: 1.086-8.305, p=0.034). In contrast, the use of hydroxychloroquine and prednisone was associated with the decreased odds of APOs (OR=0.412, 95% CI: 0.198-0.860, p=0.018) and pregnancy loss (OR=0.304, 95% CI: 0.111-0.831, p=0.020).

DISCUSSION

Systemic lupus erythematosus is a multisystem autoimmune condition that commonly affects women of childbearing age.[2] Although substantial effort has been carried out to improve the prognosis of pregnancy in women with SLE, it is still associated with relatively poor pregnancy outcomes compared to pregnant women in the general population.[1] Evaluation of potential risk factors is of clinically utmost importance in establishing a treatment plan and understanding the prognosis for pregnant women with SLE. The true results, however, considerably vary depending on racial and ethnic differences.[13,14] The present study shed light into the need for identification of more detailed risk factors in a particular population. To the best of our knowledge, this study is the first to explore clinical and laboratory parameters for the prediction of pregnancy outcomes in pregnant women with SLE in the Hakka population in the Southern China. The main findings were that preeclampsia, anti-dsDNA antibody positivity, use of hydroxychloroquine and prednisone were the predictors of adverse fetal and maternal outcomes in our study cohort.

Currently, a higher risk of preeclampsia in pregnant women with SLE compared to the general population is well recognized.[16] Preeclampsia in patients with SLE are more likely to experience

undesired effects on maternal and infant health in varying degrees, such as cesarean-section delivery, preterm birth, spontaneous abortion, and FGR.[3,4] Our study showed that preeclampsia was a risk factor for adverse fetal outcomes, premature birth, and low birth weight, consistent with previous findings. Indeed, there are many complexities for predicting pregnancy outcomes in women with SLE, and most previous lupus studies have evaluated preeclampsia as a pregnancy outcome rather than a predictor. It is not clear why the presence of preeclampsia is increased in pregnant women with SLE. Alternatively, preeclampsia, itself, may be a risk factor for the development of pregnancy complications. The association between SLE and preeclampsia and pregnancy outcomes remains elusive. Despite the controversy, SLE women with preeclampsia should be closely monitored throughout pregnancy, which can provide the specialist physicians with more clinical information for the assessment of risk factors for poor obstetric outcomes among women with SLE. However, the precise pathophysiology and mechanisms of preeclampsia have not been completely clarified yet and, thus, this relationship urgently needs to be elucidated.

As reported previously, laboratory parameters such as low complement levels, antiphospholipid syndrome, anti-dsDNA antibodies, anti-SSA/Ro antibodies, and thrombocytopenia are proved to be reliable predictors of APOs, although the results vary among the studies.[17] Findings from earlier studies indicated that anti-dsDNA antibody positivity in pregnant women with SLE was a predictor of a potentially detrimental outcome for the future risk of fetal loss and preterm birth.[18] Similarly, in this study, higher rates of anti-dsDNA antibodies were found in pregnant women with APOs than those without. Further multivariate regression analysis revealed that concurrent anti-dsDNA antibodies positivity was highly associated with APOs, premature birth, and pregnancy loss, which are consistent with previous findings in the literature.[19,20] It is, therefore, evident that these patients should be informed about the risk of APOs.

It is also important to note that pregnant women need to avoid any risk of unnecessary treatment during pregnancy in the last few decades. Nevertheless, the part of the problem is certainly related to the drugs that the patients have to take to manage the active disease and reduce the risk of adverse maternal, fetal, and infant outcomes. There is a consensus on that the appropriate use of hydroxychloroquine is effective and safe during pregnancy, leading to fewer flares or lower disease activity in patients during pregnancy.[21,22] Several recent retrospective studies have reported that the use of hydroxychloroquine may also improve maternal and fetal outcomes.[23,24] Consistent with previous studies, our findings showed that hydroxychloroquine use could exert protective effects on pregnancy outcome. Moreover, in SLE, prednisone is commonly used to treat disease flares.[25,26] Currently, it is widely accepted that prednisone use in pregnancy poses a risk for preterm birth and a lower birth weight.[7,27] The results reported in our study differ somewhat from previous studies, showing that there were substantially lower odds for pregnancy loss in women taking prednisone throughout pregnancy. Therefore, we consider that this finding is not consistent with previous findings, probably due to lack of uniformity in the definitions, the different compositions of the cohorts, and differences in treatment regimens.[28,29] Considering these facts, pregnant SLE patients can be well-controlled based on the foundation of optimal management and medication adjustment. It should be noted, however, that currently available treatment options are largely still unstudied in this population.

The main limitation of our study is its relatively small sample size. Another limitation is its retrospective nature that we could not, therefore, exclude selection bias. Finally, residual confounding is still possible, such as educational status or financial situation, lifestyle. Nevertheless, our study provides some insights into the pregnancy outcomes of Hakka women with SLE in the Southern China.

In conclusion, our study suggests that preeclampsia, anti-dsDNA antibody positivity, use of hydroxychloroquine and prednisone are associated with adverse fetal and maternal outcomes. These findings highlight the importance that, considering the high risk of APOs in patients with SLE, pregnant women require an appropriate management of the disease and should be informed about the risks that may occur while receiving some medications, resulting in better clinical outcomes. Further

large-scale, prospective studies are warranted to confirm these preliminary findings.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

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