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Pregnancy outcomes among women with systemic lupus erythematosus: a retrospective cohort study from Thailand

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Objective: The objective of this paper is to compare adverse pregnancy outcomes between normal pregnancies and pregnancies with systemic lupus erythematosus (SLE), particularly focusing on uncomplicated SLE with remission. **Methods:** A retrospective cohort study was conducted by accessing the Maternal-Fetal Medicine (MFM) Unit database and the full medical records of the women. The records of singleton pregnancies with SLE and no underlying disease were assigned as the study group and their medical records were reviewed. The low-risk pregnancies were randomly selected as the controls. The adverse pregnancy outcomes were compared between the control group vs women with SLE, control group vs uncomplicated SLE, and between the subgroups within the study group. **Results:** Of 28,003 births during the study period, 1400 controls and 140 pregnancies with SLE were compared. The rates of fetal loss, preterm birth, small-for-date, low birth weight and preeclampsia were significantly higher in the study groups with a relative risk of 5.6 (95% CI: 2.9–10.9), 3.2 (95% CI: 2.5–4.1), 3.5 (95% CI: 2.4–4.9), 4.2 (95% CI: 3.4–5.3) and 2.9 (95% CI: 1.9–4.4), respectively. The increased rates of most adverse outcomes were still noted even in the cases of uncomplicated SLE. Among women with SLE, lupus nephritis, chronic hypertension, antiphospholipid syndrome, active disease at the onset of pregnancies, and proteinuria were significantly associated with such outcomes. **Conclusions:** Pregnancies with SLE, even in uncomplicated cases with remission, increase the risk of poor pregnancy outcomes. The presence of lupus nephritis, chronic hypertension, antiphospholipid syndrome, active disease at the onset of pregnancies, and proteinuria were significantly associated with such outcomes. *Lupus* (2017) **0,** 1–7.

Key words: Fetal loss; preeclampsia; pregnancy; preterm birth; small-for-date; systemic lupus erythematosus

Introduction

Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease that mainly affects women in their childbearing ages. As a consequence, pregnancies and its outcomes are of particular importance among women with SLE. The interaction between pregnancy and SLE remains controversial. Several studies have shown that the risk of flare of disease is more common during pregnancy. Unfavorable pregnancy outcomes have been shown to be increased among women complicated with SLE, including preeclampsia and gestational hypertension, fetal loss (miscarriage and stillbirth), preterm birth, small-for-gestational age or fetal growth restriction.[1–5] Additionally, the rate of flare of SLE is also increased, in the range of 13.5% to 65%.[1–3,6,7] The most recent meta-analysis shows a significantly higher rate of cesarean section and preeclampsia in women with SLE (relative risk (RR): 1.85, 95% confidence interval (CI): 1.63–2.10 and 1.91, 95% CI: 1.44–2.53, respectively).[4] Likewise, miscarriage, thromboembolic disease, post-partum infection, preterm birth, small-for-date and infants requiring neonatal intensive care unit were also significantly higher. Nevertheless, though several publications have shown SLE to have adverse consequences on fetal and maternal outcomes, the impacts on such outcomes seem to be varied from region to region and depend on many predictors associated with the baseline characteristics of SLE. There are limited data of pregnancy outcomes among Asian women. Moreover, the number of studies on predicting

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factors of such outcomes is very scanty, especially in Thailand and Asia-Pacific regions. This study aims to compare pregnancy outcomes as follows: (1) between women with SLE and normal controls, (2) between women with uncomplicated SLE with remission and normal controls, and (3) between SLE patients with and those without various risk factors including remission at the beginning of pregnancy, lupus nephritis, proteinuria, chronic hypertension, antiphospholipid syndrome (APS), etc.

Patients and methods

A retrospective cohort study was conducted at Chiang Mai University Hospital, a tertiary teaching school. The study complied with the Declaration of Helsinki Principles and was ethically approved by the institutional review boards. The study population was pregnant women who attended our antenatal care clinic and had delivery at Chiang Mai University Hospital, Thailand, between January 2001 and December 2015. The database of Maternal-Fetal Medicine (MFM) Unit was accessed to identify all consecutive cases during the study period. During the database development, the medical records of women with SLE were reviewed and digitally stored in a computer at the time of discharge. Firstly, all records were identified and categorized to be SLE or non-SLE patients. SLE patients with complications of twin pregnancies and other medical diseases were excluded. Likewise, in the control group, non-SLE patients with other underlying medical diseases or multi-fetal pregnancy were excluded. Additionally, women with incomplete data of the final outcomes in both groups were also excluded. Eligible cases for the controls were randomly recruited with a control-to-case ratio of 10:1, using a function of ''Random sample of cases'' in SPSS software (version 21). The medical records of women with medical or obstetric complications were reviewed. Nearly all the women were local residents in the northern part of Thailand and were of Thai ethnicity. The full medical records of the women in the study group were comprehensively reviewed; demographic, clinical and laboratory data were collected. Laboratory parameters included hemoglobin, complete blood cell and platelet counts, serum creatinine, blood urea nitrogen, albumin, glucose, uric acid, urinalysis, 24-hour urine protein, immunologic parameters including complement 3 (C3), complement 4 (C4), complement 50 (C50), immunoglobulin, Coomb's test, antinuclear antibodies (ANA), anti-double-stranded DNA antibodies (anti-dsDNA), anti-Smith antibodies, anti-Ro/SSA antibodies, anti-La/SSB antibodies, lupus anticoagulant, anticardiolipin antibodies (aCL), and anti-β2 glycoprotein 1 antibodies. The primary outcomes for comparisons were the rates of preterm birth (defined as delivery before 37 weeks of gestation), fetal growth restriction (birth weight of less than 10th percentile for each gestational week) and low birth weight (birth weight less than 2500 g). The secondary outcomes included the rates of fetal loss, including miscarriage (ending up at 20 weeks of gestation or less) and stillbirth, preeclampsia (new onset of blood pressure $\geq$ 140/90 mmHg or an increase $\geq$ 30/15 mmHg for the cases with pre-existing hypertension, together with 24-hour urine protein $>$ 300 mg), cesarean delivery, gestational diabetes mellitus (GDM), fetal macrosomia, and low Apgar scores (less than score 7). SLE disease activity was diagnosed based on the SLE Disease Activity Index 2000.[8]

Statistical analysis

The rates of pregnancy outcomes between the study group and the control group and between the women with uncomplicated SLE (remission of the disease, no renal involvement, no proteinuria, no hypertension, and no active hematologic disorders) and the control group were compared. Additionally, subgroup analyses were also performed among the women with SLE; those with and without renal involvement, active and non-active diseases, the presence and absence of chronic hypertension, etc. The statistical analysis was conducted using a commercial computer package (SPSS for Windows version 21.0, SPSS Inc, Chicago, IL, USA). Categorical variables were compared with the χ^2 test as well as RR with 95% CI calculation. Continuous variables were expressed as means $\pm$ SD and tested by the Student *t* test between the case and control groups.

Results

During the study period, 28,003 pregnancies were recorded in our MFM database. A total of 162 pregnancies with SLE were identified, accounting for 0.49% of the total birth in the tertiary center during the period. After excluding cases with incomplete data or other underlying disease, 140 cases were categorized in the study group and

1400 normal or low-risk pregnancies were assigned as the controls (Figure 1). While most baseline characteristics of both groups were not significantly different, as presented in Table 1, maternal weight as well as body mass index (BMI) were slightly, but significantly, lower in the study group. Notably, the number of prenatal care visits was significantly higher in the study group.

The rates of most adverse pregnancy outcomes, e.g. fetal loss, preeclampsia, preterm birth, early preterm birth (before 34 weeks of gestation), small-for-date, low birth weight, low Apgar scores and cesarean section, were significantly higher in the study group, as presented in Table 2, whereas the rates of gestational diabetes and macrosomia were similar. In the comparison of the adverse pregnancy outcomes between the normal controls and pregnancies with uncomplicated SLE, excluding cases with renal involvement, chronic hypertension and active disease (no remission) at the beginning of pregnancy, the rates of fetal loss, preterm birth before 37 weeks of gestation, and low birth weight in the study group were still significantly higher than the controls. Nevertheless, the adverse outcomes in uncomplicated SLE women were less pronounced or had relatively lower risks than those observed in all pregnancies with SLE. Furthermore, though the rates of preeclampsia, small-for-date and early preterm birth, tended to increase, they were not significantly higher in uncomplicated SLE. Notably, gestational age and birth weight were significantly lower in pregnancies with SLE, even in the uncomplicated cases.

The clinical and laboratory characteristics of pregnancies with SLE (study group), are presented in Table 3. Lupus nephritis was the most common complication in this series (47.9%), followed by chronic hypertension (29.3%). However, both complications were seen in the same patients in many cases. Note that about one-third of the study group had active diseases, no remission, at the onset of pregnancies and about one-third of them became active and had a flare-up during pregnancy. Half of them needed medications to control the disease

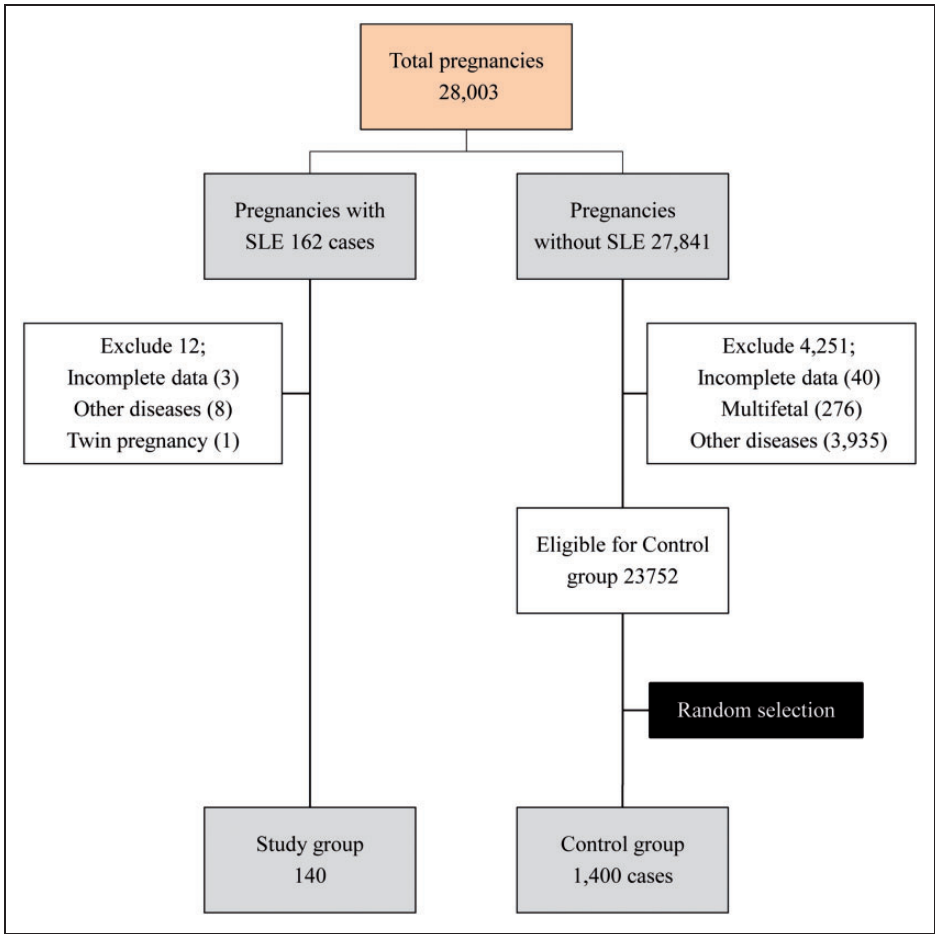

Figure 1 Groups and subgroups of the study population.

Table 1 Baseline characteristics of the patients

Characteristics	*Case (n = 140)*	*Control (n = 1400)*	p *value*
Quantitative data			
Maternal age	27.95 ± 5.76	27.38 ± 6.00	0.283
Maternal weight	51.33 ± 10.50	53.18 ± 10.47	0.046
Maternal BMI	21.34 ± 4.40	22.23 ± 4.98	0.044
Number of prenatal care visits	8.98 ± 3.77	7.70 ± 4.37	0.001
Categorical data			
Elderly gravida	20/140 (14.3%)	182/1400 (13.0%)	0.667
Nulliparity	77/140 (55.0%)	727/1399 (52.0%)	0.493
Prior preterm birth	7/140 (5.0%)	45/1400 (3.2%)	0.265
Occupations			0.452
• *Agriculture*	*11 (7.9%)*	*58 (4.1%)*	
• *Commercial*	*15 (10.7%)*	*151 (10.8%)*	
• *Employee*	*69 (49.3%)*	*728 (52.0%)*	
• *Housewife*	*23 (16.4%)*	*263 (18.8%)*	
• *Government/State officer*	*11 (7.9%)*	*95 (6.8%)*	
• *Others*	*11 (7.9%)*	*105 (7.5%)*	
Educational level			0.393
• *High*	*28 (27.1%)*	*310 (22.1%)*	
• *Intermediate*	*20 (14.3%)*	*224 (16.0%)*	
• *Low*	*82 (58.6%)*	*866 (61.9%)*	
Residency			0.638
• *Chiang Mai*	*99 (70.7%)*	*963 (68.8%)*	
• *Others*	*41 (29.3%)*	*437 (31.2%)*	

Results expressed in means ± standard deviation and compared with *t* test, or in % and compared with χ^2 test as indicated.
BMI: body mass index.

at the time of conception, prednisolone in most cases and multiple drugs in some cases, as presented in Table 3. Most cases still required medical treatment during pregnancy and some cases were first diagnosed and started drug treatment during pregnancy.

To evaluate the effect of major complications of the disease on pregnancy outcomes, comparisons of such outcomes between the women with and without the complications were performed. Pregnancy outcomes among women with respect to the presence or absence of such complications are presented in Table 4. Interestingly, lupus nephritis, chronic hypertension, active disease at the beginning of pregnancy and proteinuria were significantly associated with adverse outcomes (fetal growth restriction, preterm birth, low birth weight, fetal loss, preeclampsia and flare-up in late gestation). Note that the cases requiring medication were still significantly associated with higher rates of preterm birth and flare-up whereas the rates other complications were similar. Finally, we noted that the preterm birth rate among mothers with flare was significantly higher than that in those without flare (29/42: 69% vs 29/96: 30.2%, $p < 0.001$).

APS, SS-A/SS-B antibodies and thrombocytopenia also tended to increase adverse pregnancy outcomes but not consistently. Nevertheless the

Table 2 Comparisons of the pregnancy outcomes between pregnancies with SLE vs normal controls and pregnancies with uncomplicated SLE vs controls

Outcomes *Quantitative data*	*Control* *Mean ± SD*	*Case SLE* *Mean ± SD*	*Relative risk (95% CI)*	p *value*	*Case (uncomplicated SLE)* *Mean ± SD*	*Relative risk (95% CI)*	p *value*
Gestational weeks	38.1 ± 2.8	35.1 ± 5.3	–	< 0.001	36.5 ± 5.3	–	< 0.001
Birth weight (grams)	2944 ± 528 (52th centile for 38 weeks)	2216 ± 892 (36th centile for 35 weeks)	–	< 0.001	2504 ± 736 (49th centile for 36 weeks)	–	< 0.001
Categorical data	*n/N* (%)	*n/N* (%)			*n/N* (%)		
Fetal loss	23/1400 (1.6%)	13/140 (9.3%)	5.6 (2.9–10.9)	< 0.001	4/53 (7.5%)	4.6 (1.6–12.8)	0.002
GDM	67 (4.8%)	6/133 (4.5%)	0.9 (0.4–2.1)	0.879	0/52 (0.0%)	–	0.105
Preeclampsia	90/1394 (6.5%)	25/133 (18.8%)	2.9 (1.9–4.4)	< 0.001	7/53 (13.2%)	2.1 (0.99–4.2)	0.054
Cesarean delivery	187/1394 (13.4%)	35/133 (26.3%)	1.9 (1.4–2.7)	< 0.001	9/53 (17.3%)	1.3 (0.7–2.3)	0.421
Preterm birth < 37 wk	176/1394 (12.6%)	53/133 (39.8%)	3.2 (2.5–4.1)	< 0.001	14/53 (26.4%)	2.1 (1.3–3.3)	0.004
Preterm birth < 34 wk	57/1394 (4.1%)	25/133 (18.8%)	4.6 (3.0–7.1)	< 0.001	4/53 (7.7%)	1.9 (0.7–5.0)	0.204
Macrosomia	157/1394 (11.3%)	9/133 (6.8%)	0.6 (0.3–1.1)	0.112	4/52 (7.7%)	0.7 (0.3–1.8)	0.422
Small-for-date	97/1394 (7.0%)	33/133 (24.8%)	3.5 (2.4–4.9)	< 0.001	7/53 (13.2%)	1.9 (0.9–3.9)	0.084
Low birth weight	163/1394 (11.7%)	66/133 (49.6%)	4.2 (3.4–5.3)	< 0.001	20/53 (37.7%)	3.2 (2.2–4.7)	< 0.001
Apgar < 7 (1 min)	106/1394 (7.6%)	25/133 (18.8%)	2.5 (1.7–3.7)	< 0.001	3/52 (5.8%)	0.8 (0.2–2.3)	0.623
Apgar < 7 (5 min)	35/1393 (2.5%)	14/133 (10.5%)	4.2 (2.3–7.6)	< 0.001	3/52 (5.8%)	2.3 (0.7–7.2)	0.149

SLE: systemic lupus erythematosus; CI: confidence interval; GDM: gestational diabetes mellitus.

Table 3 Characteristics of the pregnant women with systemic lupus erythematosus

Characteristics	n/N	*Percentage*
Lupus nephritis	67/140	47.9
Chronic hypertension	41/140	29.3
Active disease	46/140	32.9
Thrombocytopenia	12/138	8.7
Anticardiolipin-IgM positive	4/114	3.5
Anticardiolipin-IgG positive	7/114	6.1
Lupus anticoagulant positive	12/89	13.5
Anti-Ro positive	29/121	24.0
Anti-La positive	6/120	5.0
Fever	1/137	0.7
Rash	14/138	10.1
Arthritis	3/139	2.2
Serositis	2/139	1.4
Neurological signs	2/139	1.4
Lung complication	2/139	1.4
Hematologic disorders	10/139	7.2
Vasculitis	1/139	0.7
Myositis	2/138	1.4
Flare during pregnancy	42/138	30.4
Proteinuria	33/136	24.3
Anti-DNA positive	21/87	24.1
On medications at the onset of conception	68/140	48.6
Prednisolone	*61/140*	*43.6*
Hydroxychloroquine	*37/140*	*26.4*
Azathioprine	*17/140*	*12.1*
Mycophenolate mofetil	*8/140*	*5.7*
Oral cyclophosphamide	*1/140*	*0.7*
Intravenous cyclophosphamide	*0/140*	*0.0*
On medications during pregnancy	72/140	51.4
Prednisolone	*68/140*	*48.6*
Hydroxychloroquine	*34/140*	*24.3*
Azathioprine	*11/140*	*7.9*
Mycophenolate mofetil	*0/140*	*0.0*
Oral cyclophosphamide	*0/140*	*0.0*
Intravenous cyclophosphamide	*8/140*	*5.7*

Ig: immunoglobulin.

sample size of the latter subgroups was relatively small. There was one case of fetal complete heart block, requiring postnatal pacemaker, in the mother with positive SS-A but negative SS-B antibody.

Discussion

Our results show that pregnancies with SLE still increase risk of unfavorable pregnancy outcomes even in uncomplicated cases or in remission. The presence of lupus nephritis, proteinuria, chronic hypertension, APS, and active disease at the onset of pregnancies were significantly associated with such outcomes. The bad outcomes among the SLE women with such risk factors were even more pronounced.

An important insight gained from this study is that pregnancies with SLE were still strongly associated with unfavorable maternal and fetal outcomes even in remission at the onset of the pregnancies and in the absence of any other SLE-related complications, like lupus nephritis or APS. This is in spite of the fact that these pregnant women with SLE had been taken care of with the multidisciplinary approach and were closely monitored throughout their pregnancies both by rheumatologists and the MFM team in the high-risk clinic. Perhaps, the effects of SLE on pregnancy outcomes are more complicated than expected. Possibly, several autoantibodies associated with the diseases and subtle inflammatory processes, which may cause only benign clinical manifestations, can cause serious effects on pregnancy outcomes, especially preterm birth, low birth weight and fetal growth restriction. Therefore, new special treatments or more strengthened and special approaches in monitoring the disease are needed, even in the uncomplicated cases with remission. More special care must be allocated to these women in order to manage adverse outcomes that might follow, and to improve successful pregnancy outcomes, especially to reduce low birth weight, preterm birth and growth-restricted infants born by mothers with SLE.

Different from most other studies,[1–5] including the large meta-analysis that focused mainly on the impacts of all cases of SLE on pregnancy outcomes,[4] we also determined whether SLE patients with remission and without serious complications were significantly associated with unfavorable outcomes when compared with the normal controls. Additionally, we also performed subgroup analysis within the study group to identify the significance of various risk factors such as lupus nephritis or chronic hypertension. Our findings were consistent with other previous studies. For examples, active disease at the time of conception, renal involvement, or proteinuria was at an increased risk of disease flares during pregnancy and adverse outcomes.[9–11]

The weaknesses of this study include the following: (1) The retrospective nature of the study certainly results in some missing data and significant difference in some baseline characteristics between the two groups, such as maternal age. (2) Though the sample size was adequate for many comparisons, it was probably too small to compare the rates of rare outcomes such as congenital anomalies

Table 4 Comparison of the major adverse pregnancy outcomes among the subgroups of pregnancies with SLE

Outcomes →		*FGR*	p *value*	*LBW*	p *value*	*PTB*	p *value*	*Fetal loss*	p *value*	*PE*	p *value*	*Flare*	p *value*
Lupus nephritis	Yes	21/67	<0.001	42/67	0.017	38/67	0.002	7/67	0.650	18/67	0.016	24/65	0.118
		31.3%		62.7%		56.7%		10.4%		26.9%		36.9%	
	No	12/73		31 /73		22/73		6/73		8/73		18/73	
		16.4%		42.5%		30.1%		7.2%		11.0%		24.7%	
Chronic hypertension	Yes	15/41	0.020	31/41	<0.001	30/41	<0.001	7/41	0.041	13/41	0.010	20/40	0.001
		36.6%		75.6%		73.2%		17.1%		31.7%		50.0%	
	No	18/99		42/99		30/99		6/99		13/99		22/98	
		18.2%		42.4%		30.3%		6.1%		13.1%		22.4%	
Active disease	Yes	16/46	0.029	31/46	0.012	26/46	0.022	4/46	0.866	14/46	0.012	20/44	0.009
(at the onset of pregnancy)		34.8%		67.4%		56.5%		8.7%		30.4%		45.5%	
	No	17/94		42/94		34/94		9/94		12/94		22/94	
		18.1%		44.7%		36.2%		9.6%		12.8%		23.4%	
Antiphospholipid syndrome	Yes	8/18	0.040	16/18	0.001	15/18	<0.001	4/18	0.053	3/18	0.455	14/17	<0.001
		44.4%		88.9%		83.3%		22.2%		16.7%		82.4%	
	No	15/72		33/72		25/72		5/72		18/72		16/71	
		20.8%		45.8%		34.7%		6.9%		25.0%		22.5%	
SS-A/SS-B antibodies	Yes	10/29	0.210	18/29	0.351	13/29	0.980	4/29	0.215	3/29	0.142	19/29	<0.001
		34.5%		62.1%		44.8%		13.8%		10.3%		65.5%	
	No	21/92		48/92		41/92		6/92		21/92		20/90	
		22.8%		52.2%		44.6%		6.5%		22.8%		22.2%	
Thrombocytopenia	Yes	4/12	0.423	8/12	0.293	8/12	0.080	0/12	0.263	5/12	0.034	9/11	<0.001
		33.3%		66.7%		66.7%		0.0%		41.7%		81.8%	
	No	29/126		64/126		51/126		12/126		21/126		33/125	
		23.0%		50.8%		40.5%		9.5%		16.7%		26.4%	
Proteinuria	Yes	10/33	0.352	24/33	0.007	26/33	<0.001	3/33	0.808	12/33	0.004	28/32	<0.001
(at the onset of pregnancy)		30.3%		72.7%		78.8%		9.1%		36.4%		87.5%	
	No	23/103		47/103		31/103		8/103		14/103		13/102	
		22.3%		45.6%		30.1%		7.8%		13.6%		12.7%	
Requiring medications	Yes	18/68	0.432	39/68	0.230	35/68	0.045	9/68	0.118	11/68	0.479	34/66	<0.001
		26.5%		57.4%		51.5%		13.2%		16.2%		51.5%	
	No	15/72		34/72		25/72		4/72		15/72		8/72	
		20.8%		47.2%		34.7%		5.6%		20.8%		11.1%	

SLE: systemic lupus erythematosus; FGR: fetal growth restriction; LBW: low birth weight; PTB: preterm birth; PE: preeclampsia.

and stillbirths. Additionally, we usually prescribed aspirin in cases of APS to prevent preeclampsia but the sample size was too small to assess its efficacy. (3) There was no comparison of the natural course of SLE during pregnancies and that prior to pregnancies or non-pregnant women with SLE. (4) The effects of treatment with medications on pregnancy outcomes may be less reliably interpreted since several confounding effects especially from underlying organ damages or the presence of specific antibodies could not be controlled.

The strengths of this study are as follows: (1) The relatively large study for comparisons of several primary outcomes. (2) Subgroup analysis to determine the significance of various potential risk factors was performed. (3) The data were based on the prospective database of high-risk pregnancies that we systematically recorded immediately after patients were discharged after delivery by the MFM team and also based on a comprehensive review of their full medical records.

This study reflects the real practice of management of SLE in pregnancies and suggests that even though we have developed a multidisciplinary approach in taking care of pregnancies with SLE, unfavorable outcomes were still very high even in cases of remission and without serious underlying complications. This study suggests that a more strengthened approach in taking care of pregnancies with SLE should be emphasized or that a new special care protocol needs to be sought.

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Authors' contributions are as follows:

- SP: Participated in the study design, data collection and manuscript writing.
- RS: Participated in data collection.
- PJ: Participated in data collection and helped to draft the manuscript.
- TT: Performed data analysis and drafting and editing of the manuscript.

Declaration of Conflicting Interests

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