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(Citation)
Journal of Reproductive Immunology,125:39-44

(Issue Date)
2018-02

(Resource Type)
journal article

(Version)
Accepted Manuscript

(URL)
https://hdl.handle.net/20.500.14094/90005834

Factors associated with adverse pregnancy outcomes in women with systematic lupus erythematosus

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Abstract

The aim of this prospective study was to determine clinical factors associated with adverse pregnancy outcomes in women with systematic lupus erythematosus (SLE). Fifty-six pregnancies from 46 women with SLE were enrolled. Risk factors for pregnancy loss, premature delivery, hypertensive disorders of pregnancy (HDP), and light-for-date neonate (LFD), were evaluated. Univariate and multivariate logistic regression analyses revealed a history of two or more pregnancy losses before 10 gestational weeks (GW) (OR 11.5, 95%CI 1.72–76.8) as a risk factor for pregnancy loss; low levels of blood complements (OR 7.55, 95%CI 1.10–51.9) and antiphospholipid syndrome (OR 26.5, 95%CI 3.17–219) as risk factors for premature delivery before 37 GW; SLEDAI score at conception (OR 1.68, 95%CI 1.05–2.68) and positive tests for two or more antiphospholipid antibodies (OR 6.89, 95%CI 1.13–41.9) as risk factors for premature delivery before 34 GW; prednisolone therapy >14 mg/day (OR 7.55, 95%CI 1.10–51.9) as a risk factor for HDP; and low dose aspirin therapy (OR 0.21, 95%CI 0.05–0.97) decreased the risk for LFD neonate. These results have important implications for clinicians managing SLE complicated pregnancy.

Key words: antiphospholipid antibodies, antiphospholipid syndrome, pregnancy complications, risk factor, systematic lupus erythematosus (SLE)

1. Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that mainly affects women of childbearing age. Pregnant women with SLE have high risks of premature delivery, hypertensive disorders of pregnancy (HDP), and serious complications including thrombosis, infection, thrombocytopenia, and cesarean delivery (Clowse et al., 2008). A meta-analysis of data from 2751 pregnant women with SLE has revealed that lupus nephritis and antiphospholipid antibody (aPL) are causally associated with adverse pregnancy outcomes such as premature delivery and HDP (Smyth et al., 2010). Other retrospective studies have determined risk factors for adverse pregnancy outcomes to be SLE disease activity (Liu et al., 2012), renal dysfunction (Saavedra et al., 2012), low levels of compliments (Kobayashi et al., 1999), and a positive test for anti-double stranded DNA antibody (dsDNA) in the second trimester (Clowse et al., 2013, 2011).

In this prospective study, we aimed to determine clinical factors associated with adverse pregnancy outcomes in women with SLE, whose disease activity was controlled by medications. aPLs were measured in all participants, and anticoagulation medicine was administered during pregnancy, where necessary.

2. Patients and Methods

This prospective cohort study was approved by the institutional review boards of Kobe University Hospital. Between April 2009 and March 2016, pregnant women with SLE who received perinatal management and medication at the university hospital were enrolled. They had been diagnosed as having SLE according to the 1997 update of the 1982 American College of Rheumatology (ACR) revised criteria for classification of systemic lupus erythematosus (Hochberg, 1997; Tan et al., 1982).

All women with SLE underwent the following blood tests; complete blood count, lupus anticoagulant (LA), IgG/IgM anti-cardiolipin (aCL), IgG ß2 glycoprotein I-dependent aCL (aCLß2GPI), antinuclear antigen (ANA), dsDNA, anti-Smith antibody (Sm), and complements (C3, C4, and CH50). A dilute Russell's viper venom time-based test (Gradipore LA Screen and LA Confirm, Gradipore Ltd., Australia) was used for LA measurements. Screen/Confirm clotting time ratio of 1.3 (99 percentile) was defined as a cut-off value of LA. IgG/IgM aCL was measured using an enzyme-linked immunosorbent assay for cardiolipin (MESACUP cardiolipin test IgG/IgM, MBL Co Ltd., Japan) with cut-off values of 40 GPL or MPL. IgG aCLß2GPI was measured using an enzyme immunoassay for ß2GPI (Yamasa kit, Yamasa Co., Japan) with a cut-off value of 3.5 unit/ml (+6SD). The data of IgG aCLß2GPI

were used as a substitute for IgG aß2GPI. IgM aCLß2GPI measurement is not commercially available in Japan. Antiphospholipid syndrome (APS) was diagnosed according to clinical and laboratory criteria defined in the updated Sydney classification criteria (Miyakis et al., 2006).

Rheumatologists assessed disease activity and managed SLE. Pregnant women with SLE were closely monitored by rheumatologists every four weeks and by obstetricians every two to three weeks until 24 gestational weeks (GW), every two weeks from 25 GW to 34 GW, and weekly from 35 GW to delivery. Women with APS received a therapy of low dose aspirin (LDA) plus unfractionated heparin (UFH), while women with aPLs who met laboratory criteria but not clinical criteria received LDA only, UFH only, or LDA+UFH. All treatment regimens were administered after informed consent was obtained. Prednisolone (PSL) dose was individually adjusted by rheumatologist, and was based on clinical findings of disease activity, such as joint pain, skin rash, proteinuria, levels of complements, and blood cell counts.

Data on clinical factors including maternal age, disease duration of SLE, systemic lupus erythematosus disease activity index (SLEDAI) score at conception, APS, histories of thrombosis, lupus nephritis and previous pregnancies; therapy modality, complete blood

count, IgG/IgM aCL, IgG aCLß2GPI, LA, ANA, dsDNA, Sm, and complements were assessed. Risk factors for pregnancy loss, premature delivery before 34 or 37 GW, HDP, and light-for-date (LFD) neonate were evaluated. HDP was defined as an in-hospital systolic blood pressure (sBP) of ≥140 mmHg and/or diastolic blood pressure (dBP) of ≥90 mmHg. HDP was subcategorized into early-onset (<34 GW) or severe HDP (sBP ≥160 mmHg and/or dBP ≥110 mmHg). LFD was defined as birth weight lower than 10 percentile. The cut-off values for white blood cell (WBC) and platelet counts were based on 1997 update of the 1982 ACR revised criteria of SLE. The cut-off dose of PSL was determined using maximum chi-squared test. Pregnancies that ended in artificially induced abortion or miscarriage due to abnormal chromosome karyotype of the fetus were excluded from the analysis.

Univariate and multivariate logistic regression analyses were performed to identify factors yielding odds ratios (OR) and 95% confidence intervals (CI). Covariates that were significant in univariate analyses ($p<0.05$) were subjected to multivariate analyses. When the sample number of one of the four comparative arms was zero in univariate analyses, p-values and OR were not calculated, and not subjected to multivariate logistic regression analyses. Statistical analyses were performed using R statistics software (version 3). A p-value <0.05 was considered significant.

3. Results

A total of 56 pregnancies from 46 women with SLE were enrolled in the present study. Maternal age (mean ± SD) at pregnancy was 33.9 ± 4.6 years. Median of SLEDAI score at conception was 0 (range 0-6). They had a history of median 1 (range 0-7) gravida, 0 (0-5) para, and 0 (0-6) pregnancy loss. Six pregnant women had a history of thrombosis. Four pregnancies were conceived through assisted reproductive technology. Fourteen pregnancies were complicated by APS. Fifty-one pregnant women received PSL (median 9, range 0-30 mg/day at the conception), and seven received tacrolimus (median 3, range 1.5-3.0 mg/day), and one received mizoribine (100 mg/day), while five received no medication for SLE. Twenty-two of 24 pregnant women with positive tests for aPLs received LDA or UFH, and 5 pregnant women with a history of pregnancy loss received LDA+UFH therapy.

Forty-nine of the 56 pregnancies ended in live births at median 37 GW (range 25-40 GW) with no early neonatal deaths or neonatal lupus. Two pregnancies ended in miscarriages with normal chromosome karyotype at 6 GW and 8 GW, while five ended in miscarriages with unknown chromosome karyotype at 6, 7, 12, 13, and 14 GW.

3.1 Risk factors for pregnancy loss

To identify risk factors associated with pregnancy loss in women with SLE, a stepwise logistic regression analysis was performed for 49 pregnancies that ended in live births and 7 pregnancies that ended in miscarriages.

Univariate logistic regression analyses identified a history of two or more pregnancy losses before 10 GW (OR 11.5, 95%CI 1.72-76.8, $p<0.05$) as a risk factor for pregnancy loss in the index pregnancy (Table 1). Because only one variable was identified as a risk factor for pregnancy loss, a multivariate logistic regression analysis was not performed.

3.2 Risk factors for pregnancy complications in women with SLE

Risk factors for pregnancy complications, including premature delivery, HDP, and LFD neonate were evaluated in 49 pregnancies that ended in live births after 24 GW.

3.2.1 Risk factors for premature delivery

Table 2 shows risk factors for premature delivery before 37 GW. Univariate logistic regression analyses identified, SLEDAI score at conception (OR 1.56, 95%CI 1.05-2.31, $p<0.05$), APS (OR 11.8, 95%CI 2.22-63.0, $p<0.01$), a history of one or more pregnancy losses at 10 GW or later (OR 13.5, 95%CI 1.51-120, $p<0.05$), PSL dose more than 14 mg/day at

conception (PSL>14 mg/day) (OR 16.6, 95%CI 1.88-147, p<0.05), LDA+UFH therapy (OR 5.96, 95%CI 1.69-21.0, p<0.01), positive tests for any aPLs (OR 11.5, 95%CI 2.97-44.5, p<0.01), two or more aPLs (OR 8.0, 95%CI 2.04-31.4, p<0.01), IgG aCLß2GPI (OR 8.00, 95%CI 1.48-43.2, p<0.05), LA (OR 9.75, 95%CI 2.46-38.6, p<0.05), WBC<4000/μL (OR 11.8, 95%CI 2.22-63.0, p<0.01), and low complements (OR 5.06, 95%CI 1.39-18.4, p<0.05) as risk factors for premature delivery before 37 GW. Multivariate logistic regression analyses demonstrated that low complements (OR 7.55, 95%CI 1.10-51.9, p<0.05) and APS (OR 26.5, 95%CI 3.17-219, p<0.01) were independent risk factors for premature delivery before 37 GW. The number of variables used in the final model of multivariable analyses was restricted to four covariates because of low case numbers, to avoid over-fitting during multivariable logistic regression analyses.

Univariate and multivariate logistic regression analyses identified SLEDAI score at conception (OR 1.68, 95%CI 1.05-2.68, p<0.05), positive tests for two or more aPLs (OR 6.89, 95%CI 1.13-41.9, p<0.05) as independent risk factors for premature delivery before 34 GW (Table 3).

3.2.2 Risk factors for hypertensive disorders of pregnancy

Table 4 shows risk factors for HDP. Univariate logistic regression analyses identified a history of lupus nephritis persisting 6 months before conception (OR 7.93, 95%CI 1.11-56.5, $p<0.05$) and PSL>14 mg/day (OR 8.75, 95%CI 1.74-44.0, $p<0.05$) as risk factors for HDP. Multivariate logistic regression analyses demonstrated that PSL>14 mg/day (OR 7.94, 95%CI 1.45-43.4, $p<0.05$) was an independent factor for HDP.

In addition, multivariate logistic regression analyses also demonstrated that PSL>14 mg/day (OR 18.0, 95%CI 1.28-253, $p<0.05$) was an independent factor for early onset HDP, and that PSL>14 mg/day (OR 19.0, 95%CI 1.67-216, $p<0.05$) and a history of lupus nephritis persisting 6 months before conception (OR 26.8, 95%CI 1.73-414, $p<0.05$) were independent risk factors for severe HDP.

3.2.3 Risk factors for light-for-date neonate

Table 5 shows risk factors for LFD neonate. Univariate logistic regression analyses identified LDA therapy (OR 0.21, 95%CI 0.05-0.97, $p<0.05$) as a factor that decreased a risk for LFD neonate.

4. Discussion

In the present cohort study, it was for the first time revealed that a history of two or more pregnancy losses before 10 GW was a risk factor for pregnancy loss in the subsequent pregnancies in women with SLE. Proteinuria, APS, thrombocytopenia, and hypertension early in pregnancy are reported as risk factors for pregnancy loss (Clowse et al., 2006). Active disease condition of SLE at conception is a strong predictor of adverse pregnancy outcomes (Lateef and Petri, 2013). In the present study, SLE disease activity was well-controlled using medications, and standard anticoagulation therapy for women with APS was provided from early pregnancy. Pregnancies that ended in miscarriages due to abnormal chromosome karyotype of the fetus were excluded from the analysis. Thus, in women with controlled SLE who received appropriate medications during pregnancy, a history of recurrent pregnancy loss was found to be a risk factor for pregnancy loss in the index pregnancy.

Univariate and multivariate logistic regression analyses revealed that low blood complements (low blood complements is included in the SLEDAI score) and APS were independent risk factors for premature delivery before 37 GW, while the SLEDAI score at conception and a positive test for two or more aPLs were risk factors for preterm delivery before 34 GW. The literatures show that active SLE, SLE flare, PSL use, low complements, lupus nephritis, HDP, and positive tests for aPLs or dsDNA are associated with premature

delivery (Al Arfaj and Khalil, 2010; Chakravarty et al., 2005; Clark et al., 2003; Clowse et al., 2011; Koh et al., 2015; Liu et al., 2012; Moroni et al., 2016; Smyth et al., 2010). Low complements may be associated with SLE disease activity and cause premature delivery before 37 GW, because PSL>14 mg/day at conception and SLEDAI score at conception were also found to be a risk factor for premature delivery before 37 GW by univariate analyses in the present study. It was for the first time revealed that a positive test for two or more aPLs was a risk factor for preterm delivery before 34 GW. This result suggests that aPL measurements must be performed in all women with SLE during early pregnancy, and that LDA+UFH therapy may be necessary to improve pregnancy outcomes in women who have positive tests for two or more aPLs but do not meet clinical criteria of APS.

In addition, PSL>14 mg/day was determined as a risk factor for HDP, early-onset HDP, and severe HDP. A history of lupus nephritis persisting 6 months before the conception was also found to be a risk factor for severe HDP. It has been reported that preeclampsia risk is three-fold higher in women with SLE than in the general population (Clowse et al., 2008). Thrombocytopenia during pregnancy (Chakravarty et al., 2005), active SLE, a history of lupus nephritis (Koh et al., 2015), and positive tests for aPLs (Smyth et al., 2010) are associated with HDP/preeclampsia in women with SLE. However, in the present study, APS

or a positive test for aPLs was not associated with HDP. A majority of women with positive tests for aPLs who did not meet clinical criteria of APS received LDA or UFH, and five women who had a history of pregnancy loss received LDA+UFH therapy. Standard LDA+UFH therapy was provided in women with APS. These anticoagulation therapies from early pregnancy may reduce risks for HDP in women with SLE and positive tests for aPLs. Indeed, LDA therapy is recommended to prevent preeclampsia in pregnancies complicated by SLE or APS (LeFevre and U.S. Preventive Services Task Force, 2014). LDA therapy has a preventive effect on severe adverse pregnancy outcomes in women with SLE (Imbasciati et al., 2008; Kim et al., 2016; Moroni et al., 2016).

LDA therapy was also determined as a factor that decreased a risk for LFD neonate. LFD neonate is an important adverse pregnancy outcomes in women with SLE (Al Arfaj and Khalil, 2010; Buyon et al., 2015; Lazzaroni et al., 2016; Liu et al., 2012; Madazli et al., 2014). We recently reported that LDA therapy decreased a risk of premature delivery before 34 GW in women with APS pregnancy (Deguchi et al., 2017). LDA therapy from early pregnancy in women with SLE also may reduce a risk of LFD neonate. Although hydroxychloroquine therapy reduces a risk of LFD neonate (Moroni et al., 2016), none of the participants received hydroxychloroquine in the present study.

The results presented here have important implications for clinicians managing SLE complicated pregnancy. However, this study has some potential limitations. The subjects of this study were from a mixed population with varied SLE-related background, although this study was designed as a prospective and all subjects had undergone workup for aPL. The number of variables in multivariable analyses was restricted to few covariates based on the case number. Covariates with high OR determined by univariate analyses might be related to risks for adverse pregnancy outcomes. Further prospective studies are necessary to confirm these conclusions.

Funding

This work was supported in part by a Grant-in-Aid from the Japan Society for the Promotion of Science (No. 26462489 and 25462593).

Conflict of interest

None of the authors have any conflicts of interest to declare.

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Table 1 Risk factors for pregnancy loss

Clinical factors	Pregnancy loss n=7 (%)	Live birth n=49 (%)	Univariate logistic regression *P*- value	OR (95%CI)
Maternal age at pregnancy (years, mean±SD)	32.9±5.5	33.1±4.5	0.911	0.99 (0.83–1.18)
Disease duration of SLE (years, mean±SD)	5.9±2.7	10.1±6.2	0.091	0.85 (0.70–1.03)
SLEDAI score at conception (mean±SD)	1.14±1.57	1.35±1.61	0.75	0.92 (0.54-1.55)
Anti-phospholipid syndrome	2 (28.6)	12 (24.5)	0.816	1.23 (0.21–7.20)
History of thrombosis, lupus nephritis and pregnancy				
History of thrombosis	1 (14.3)	5 (10.2)	0.745	1.47 (0.15–14.8)
Lupus nephritis persisting 6 months before conception	2 (28.6)	5 (10.2)	0.19	3.52 (0.54–23.1)
History of 2 or more pregnancy losses before 10 GW	3 (42.9)	3 (6.1)	0.012	11.5 (1.72–76.8)
History of 1 or more pregnancy losses at 10 GW or later	1 (14.3)	8 (16.3)	0.891	0.85 (0.09–8.09)
Therapy modality				
PSL >14 mg/day at conception	2 (28.6)	9 (18.4)	0.529	1.78 (0.30–10.7)
Increased PSL dose during pregnancy	0	23 (46.9)		
Coadministration of Tacrolimus or Mizoribine with PSL	2 (28.6)	6 (12.2)	0.264	2.87 (0.45–18.2)
LDA	2 (28.6)	29 (59.2)	0.146	0.28 (0.05–1.57)
LDA+UFH	1 (14.3)	19 (38.8)	0.233	0.26 (0.03–2.36)
Laboratory findings (at 1st trimester)				
Positive test for any anti-phospholipid antibodies	3 (42.9)	20 (40.8)	0.918	1.09 (5.40–0.22)
Positive test for 2 or more anti-phospholipid antibodies	1 (14.3)	8 (16.3)	0.891	0.85 (8.09–0.09)
Positive test for anti-double stranded DNA antibody	2 (28.6)	9 (18.4)	0.529	1.78 (0.30–10.7)
Positive test for antinuclear antibody	6 (85.7)	41 (83.7)	0.891	1.17 (0.12–11.1)
Positive test for anti-Smith antibodies	0	8 (16.3)		
Low complements	2 (28.6)	13 (26.5)	0.909	1.11 (0.19–6.43)
Laboratory findings (during pregnancy)				
WBC < 4000/μL	0	13 (26.5)		
PLT < 100000/μL	0	6 (12.2)		
Low complements	3 (42.9)	16 (32.7)	0.596	1.55 (0.31–7.75)

SLE, Systemic lupus erythematosus; SLEDAI, Systemic lupus erythematosus disease activity index; GW, gestational weeks; LDA, low dose aspirin, UFH, unfractionated heparin; PSL, prednisolone; HIVIg, a high dose intravenous immunoglobulin; WBC, white blood cell count; PLT, platelet count; OR, odds ratio; CI, confidence interval.

Table 2 Risk factors for premature delivery before 37 GW

Clinical factors	Delivery at 37 GW or later n=28 (%)	Premature delivery before 37 GW n=21 (%)	Univariate logistic regression			Multivariate logistic regression	
			P- value	OR (95%CI)		*P*- value	OR (95%CI)
Maternal age at pregnancy (years, mean±SD)	32.5±4.7	33.9±4.2	0.283	1.07 (0.94–1.23)			
Disease duration of SLE (years, mean±SD)	9.7±5.1	10.6±7.6	0.604	1.02 (0.93–1.12)			
SLEDAI score at conception (mean±SD)	0.89±1.42	1.95±1.69	0.029	1.56 (1.05-2.31)	*		
Anti-phospholipid syndrome	2 (7.1)	10 (47.6)	0.004	11.8 (2.22–63.0)		0.002	26.5 (3.17–219)
History of thrombosis, lupus nephritis and pregnancy							
History of thrombosis	1 (3.6)	4 (19)	0.111	6.35 (0.65–61.7)			
Lupus nephritis persisting 6 months before conception	1 (3.6)	4 (19)	0.111	6.35 (0.65–61.7)			
History of 2 or more pregnancy losses before 10 GW	1 (3.6)	2 (9.5)	0.407	2.84 (0.24–33.6)			
History of 1 or more pregnancy losses at 10 GW or later	1 (3.6)	7 (33.3)	0.02	13.5 (1.51–120)	*		
Therapy modality							
PSL >14 mg/day at conception	1 (3.6)	8 (38.1)	0.012	16.6 (1.88–147)		0.059	24.3 (0.88–666)
Increased PSL dose during pregnancy	10 (35.7)	13 (61.9)	0.073	2.92 (0.91–9.44)			
Coadministration of Tacrolimus or Mizoribine with PSL	3 (10.7)	3 (14.3)	0.707	1.39 (0.25–7.69)			
LDA	14 (50)	15 (71.4)	0.135	2.50 (0.75–8.32)			
LDA+UFH	6 (21.4)	13 (61.9)	0.006	5.96 (1.69–21.0)	*		
Laboratory findings (at 1st trimester)							
Positive test for any anti-phospholipid antibodies	5 (17.9)	15 (71.4)	0.0004	11.5 (2.97–44.5)	*		
Positive test for 2 or more anti-phospholipid antibodies	4 (14.3)	12 (57.1)	0.003	8.00 (2.04–31.4)	*		
IgG/IgM anti-cardiolipin	0	2 (9.5)					
IgG anti-cardiolipin β2 glycoprotein I	2 (7.1)	8 (38.1)	0.016	8.00 (1.48–43.2)			
Lupus anticoagulant	4 (14.3)	13 (61.9)	0.001	9.75 (2.46–38.6)			
Positive test for anti-double stranded DNA antibody	3 (10.7)	6 (28.6)	0.122	3.33 (0.72–15.3)			
Positive test for antinuclear antibody	23 (82.1)	18 (85.7)	0.738	1.30 (0.27–6.20)			
Positive test for anti-Smith antibodies	6 (21.4)	2 (9.5)	0.276	0.39 (0.07–2.14)			
Low complements	5 (17.9)	8 (38.1)	0.119	2.83 (0.77–10.5)			
Laboratory findings (during pregnancy)							
WBC < 4000/μL	11 (39.3)	2 (9.52)	0.03	0.16 (0.03-0.84)		0.065	0.11 (0.01–1.14)
PLT < 100000/μL	0	6 (28.6)					
Low complements	5 (17.9)	11 (52.4)	0.014	5.06 (1.39–18.4)		0.04	7.55 (1.10–51.9)

SLE, Systemic lupus erythematosus; SLEDAI, Systemic lupus erythematosus disease activity index; GW, gestational weeks; LDA, low dose aspirin, UFH, unfractionated heparin; PSL, prednisolone; HIVIg, a high dose intravenous immunoglobulin; WBC, white blood cell count; PLT, platelet count; OR, odds ratio; CI, confidence interval.

Table 3 Risk factors for premature delivery before 34 GW

Clinical factors	Delivery at 34 GW or later n=39 (%)	Premature delivery before 34 GW n=10 (%)	Univariate logistic regression		Multivariate logistic regression	
			P- value	OR (95%CI)	*P*- value	OR (95%CI)
Maternal age at pregnancy (years, mean±SD)	32.8±4.7	33.9±3.3	0.505	1.05 (0.90–1.23)		
Disease duration of SLE (years, mean±SD)	10.4±6	8.90±7.3	0.491	0.96 (0.85–1.08)		
SLEDAI score at conception (mean±SD)	1.08±1.46	2.4±1.84	0.03	1.63 (1.05-2.53)	0.029	1.68 (1.05-2.68)
Anti-phospholipid syndrome	8 (20.5)	4 (40)	0.21	2.58 (0.59–11.4)		
History of thrombosis, lupus nephritis and pregnancy						
History of thrombosis	4 (10.3)	1 (10)	0.981	0.97 (0.10–9.80)		
Lupus nephritis persisting 6 months before conception	3 (7.7)	2 (20)	0.269	3 (0.43–21.0)		
History of 2 or more pregnancy losses before 10 GW	2 (5.1)	1 (10)	0.573	2.06 (0.17–25.3)		
History of 1 or more pregnancy losses at 10 GW or later	5 (12.8)	3 (30)	0.203	2.91 (0.56–15.1)		
Therapy modality						
PSL > 14mg/day at conception	6 (15.4)	3 (30)	0.296	2.36 (0.47–11.8)		
Increased PSL dose during pregnancy	18 (46.2)	5 (50)	0.828	1.17 (0.29–4.69)		
Coadministration of Tacrolimus or Mizoribine with PSL	6 (15.4)	0				
LDA	24 (61.5)	5 (50)	0.51	0.63 (0.15–2.53)		
LDA+UFH	14 (35.9)	5 (50)	0.417	1.79 (0.44–7.25)		
Laboratory findings (at 1st trimester)						
Positive test for any anti-phospholipid antibodies	14 (35.9)	6 (60)	0.175	2.68 (0.64–11.1)		
Positive test for 2 or more anti-phospholipid antibodies	4 (10.3)	4 (40)	0.034	5.83 (1.14–29.9)	0.036	6.89 (1.13-41.9)
IgG/IgM anti-cardiolipin	1 (2.6)	1 (10)	0.325	4.22 (0.24–74.1)		
IgG anti-cardiolipin β2 glycoprotein I	6 (15.4)	4 (40)	0.097	3.67 (0.79–17.0)		
Lupus anticoagulant	11 (28.2)	6 (60)	0.069	3.82 (0.9–16.2)		
Positive test for anti-double stranded DNA antibody	8 (20.5)	1 (10)	0.454	0.43 (0.05–3.91)		
Positive test for antinuclear antibody	32 (82.1)	9 (90)	0.55	1.97 (0.21–18.2)		
Positive test for anti-Smith antibodies	7 (17.9)	1 (10)	0.55	0.51 (0.06–4.69)		
Low complements	8 (20.5%)	5 (50%)	0.07	3.88 (0.9–16.7)		
Laboratory findings (during pregnancy)						
WBC < 4000/μL	13 (33.3)	0 (0)				
PLT < 100000/μL	3 (7.7)	3 (30)	0.074	5.14 (0.86–30.9)		
Low complements	11 (28.2%)	5 (50%)	0.198	2.55 (0.61–10.6)		

SLE, Systemic lupus erythematosus; SLEDAI, Systemic lupus erythematosus disease activity index; GW, gestational weeks; LDA, low dose aspirin, UFH, unfractionated heparin; PSL, prednisolone; HIVIg, a high dose intravenous immunoglobulin; WBC, white blood cell count; PLT, platelet count; OR, odds ratio; CI, confidence interval.

Table 4 Risk factors for hypertensive disorders of pregnancy

Clinical factors	Hypertension in pregnancy		Univariate logistic regression		Multivariate logistic regression	
	Absent n=39 (%)	Present n=10 (%)	*P*- value	OR (95%CI)	*P*- value	OR (95%CI)
Maternal age at pregnancy (years, mean±SD)	32.7±4.5	34.4±4.5	0.291	1.09 (1.28–0.93)		
Disease duration of SLE (years, mean±SD)	9.3±5.9	13.0±7.0	0.106	1.10 (1.22–0.98)		
SLEDAI score at conception (mean±SD)	1.33±1.49	1.4±2.12	0.906	1.03 (0.67-1.58)		
Anti-phospholipid syndrome	10 (25.6)	2 (20.0)	0.712	0.73 (0.13–4.00)		
History of thrombosis, lupus nephritis and pregnancy						
History of thrombosis	5 (12.8)	0				
Lupus nephritis persisting 6 months before conception	2 (5.1)	3 (30.0)	0.039	7.93 (1.11–56.5)	0.084	6.74 (0.77–58.8)
History of 2 or more pregnancy losses before 10 GW	3 (7.7)	0				
History of 1 or more pregnancy losses at 10 GW or later	6 (15.4)	2 (20.0)	0.725	1.38 (0.23–8.13)		
Therapy modality						
PSL >14 mg/day at conception	4 (10.3)	5 (50.0)	0.008	8.75 (1.74–44.0)	0.017	7.94 (1.45–43.4)
Increased PSL dose during pregnancy	17 (43.6)	6 (60.0)	0.358	1.94 (0.47–7.99)		
Coadministration of Tacrolimus or Mizoribine with PSL	5 (12.8)	1 (10.0)	0.809	0.76 (0.08–7.31)		
LDA	24 (61.5)	5 (50.0)	0.51	0.63 (0.15–2.53)		
LDA+UFH	14 (35.9)	5 (50.0)	0.417	1.79 (0.44–7.25)		
Laboratory findings (at 1st trimester)						
Positive test for any anti-phospholipid antibodies	16 (41)	4 (40.0)	0.953	0.96 (0.23–3.95)		
Positive test for 2 or more anti-phospholipid antibodies	7 (17.9)	1 (10.0)	0.55	0.51 (0.06–4.69)		
WBC<4000	12 (30.8)	1 (10.0)	0.212	0.25 (0.03–2.20)		
PLT<100 thaosand	5 (12.8)	1 (10.0)	0.809	0.76 (0.08–7.31)		
Positive test for anti-double stranded DNA antibody	7 (17.9)	2 (20.0)	0.881	1.14 (0.20–6.59)		
Positive test for antinuclear antibody	34 (87.2)	7 (70.0)	0.203	0.34 (0.07–1.78)		
Positive test for anti-Smith antibodies	8 (20.5)	0				
Low complements	10 (25.6)	3 (30.0)	0.781	1.24 (0.27–5.75)		
Laboratory findings (during pregnancy)						
WBC < 4000/μL	12 (30.8)	1 (10.0)	0.212	0.25 (0.03–2.20)		
PLT < 100000/μL	5 (12.8)	1 (10.0)	0.809	0.76 (0.08–7.31)		
Low complements	11 (28.2)	5 (50)	0.198	2.55 (0.61–10.6)		

SLE, Systemic lupus erythematosus; SLEDAI, Systemic lupus erythematosus disease activity index; GW, gestational weeks; LDA, low dose aspirin, UFH, unfractionated heparin; PSL, prednisolone; HIVIg, a high dose intravenous immunoglobulin; WBC, white blood cell count; PLT, platelet count; OR, odds ratio; CI, confidence interval

Table 5 Risk factors for light-for-date neonate

Clinical factors	Appropriate for date neonate n=39 (%)	Light for date neonate n=10 (%)	Univariate logistic regression	
			P- value	OR (95%CI)
Maternal age at pregnancy (years, mean±SD)	33.6±4.2	31±5.2	0.111	0.87 (1.03–0.73)
Disease duration of SLE (years, mean±SD)	10.4±6.5	8.7±5.1	0.433	0.95 (1.08–0.84)
SLEDAI score at conception (mean±SD)	1.33±1.49	1.4±2.12	0.906	1.03 (0.67-1.58)
Anti-phospholipid syndrome	12 (30.8)	0		
History of thrombosis, lupus nephritis and pregnancy				
History of thrombosis	4 (10.3)	1 (10.0)	0.981	0.97 (0.10–9.80)
Lupus nephritis persisting 6 months before conception	4 (10.3)	1 (10.0)	0.981	0.97 (0.10–9.80)
History of 2 or more pregnancy losses before 10 GW	3 (7.7)	0		
History of 1 or more pregnancy losses at 10 GW or later	8 (20.5)	0		
Therapy modality				
PSL >14 mg/day at conception	7 (17.9)	2 (20.0)	0.881	1.14 (0.20–6.59)
Increased PSL dose during pregnancy	20 (51.3)	3 (30.0)	0.238	0.41 (0.09–1.81)
Coadministration of Tacrolimus or Mizoribine with PSL	6 (15.4)	0		
LDA	26 (66.7)	3 (30.0)	0.045	0.21 (0.05–0.97)
LDA+UFH	17 (43.6)	2 (20.0)	0.186	0.32 (0.06–1.73)
Laboratory findings (at 1st trimester)				
Positive test for any anti-phospholipid antibodies	18 (46.2)	2 (20.0)	0.149	0.29 (0.05–1.55)
Positive test for 2 or more anti-phospholipid antibodies	7 (17.9)	1 (10.0)	0.55	0.51 (0.06–4.69)
Positive test for anti-double stranded DNA antibody	7 (17.9)	2 (20.0)	0.881	1.14 (0.20–6.59)
Positive test for antinuclear antibody	34 (87.2)	7 (70.0)	0.203	0.34 (0.07–1.78)
Positive test for anti-Smith antibodies	5 (12.8)	3 (30.0)	0.203	2.91 (0.56–15.1)
Low complements	8 (20.5)	5 (50.0)	0.07	3.88 (0.90–16.7)
Laboratory findings (during pregnancy)				
WBC < 4000/μL	9 (23.1)	4 (40.0)	0.286	2.22 (0.51–9.65)
PLT < 100000/μL	4 (10.3)	2 (20.0)	0.41	2.19 (0.34–14.1)
Low complements	11 (28.2)	5 (50.0)	0.198	2.55 (0.61–10.6)

SLE, Systemic lupus erythematosus; SLEDAI, Systemic lupus erythematosus disease activity index; GW, gestational weeks; LDA, low dose aspirin, UFH, unfractionated heparin; PSL, prednisolone; HIVIg, a high dose intravenous immunoglobulin; WBC, white blood cell count; PLT, platelet count; OR, odds ratio; CI, confidence interval