Journal of Reproductive Immunology 125 (2018) 39–44

Contents lists available at ScienceDirect

Journal of Reproductive Immunology

journal homepage: www.elsevier.com/locate/jri

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

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ARTICLE INFO

Keywords:
Antiphospholipid antibodies
Antiphospholipid syndrome
Pregnancy complications
Risk factor
Systematic lupus erythematosus (SLE)

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.

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 β2 glycoprotein I-dependent aCL (aCLβ2GPI), 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 aCLβ2GPI was measured using an enzyme immunoassay for β2GPI (Yamasa kit, Yamasa Co., Japan) with a cut-off

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https://doi.org/10.1016/j.jri.2017.11.005
Received 29 August 2017; Received in revised form 25 October 2017; Accepted 27 November 2017

Table 1
Risk factors for pregnancy loss.

Clinical factors	Pregnancy loss	Live birth	Univariate logistic regression	
	n = 7 (%)	n = 49 (%)	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	0.750	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)	0.190	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 1 st 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; WBC, white blood cell count; PLT, platelet count; OR, odds ratio; CI, confidence interval.

value of 3.5 unit/ml (+6SD). The data of IgG aCLβ2GPI were used as a substitute for IgG aβ2GPI. IgM aCLβ2GPI 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 aCLβ2GPI, 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.