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Lupus Low Disease Activity State Achievement Is Important for Reducing Adverse Outcomes in Pregnant Patients With Systemic Lupus Erythematosus

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ABSTRACT. *Objective.* This study aimed to examine the frequency and risk factors of complications during pregnancy in women with systemic lupus erythematosus (SLE).

Methods. The medical records of patients with SLE and age-matched controls at Ajou University Hospital were collected. Clinical features and pregnancy complications in women with SLE were compared to those of the controls. Multivariate logistic regression analysis was performed to determine the predictors of adverse maternal and fetal outcomes.

Results. We analyzed 163 pregnancies in patients with SLE and 596 pregnancies in the general population; no significant differences regarding demographic characteristics were noted. Patients with SLE experienced a higher rate of stillbirth (OR 13.2), preeclampsia (OR 4.3), preterm delivery (OR 2.8), intrauterine growth retardation (OR 2.5), admission to neonatal intensive care unit (OR 2.2), and emergency cesarean section (OR 1.9) than the control group. Multivariate regression analysis revealed that thrombocytopenia, low complement, high proteinuria, high SLE Disease Activity Index (SLEDAI), low Lupus Low Disease Activity State (LLDAS) achievement rate, and high corticosteroid (CS) dose were associated with adverse pregnancy outcomes. In the receiver-operating characteristic curve analysis, the optimal cutoff value for the cumulative and mean CS doses were 3500 mg and 6 mg, respectively.

Conclusion. Pregnant women with SLE have a higher risk of adverse pregnancy outcomes. Pregnancies are recommended to be delayed until achieving LLDAS and should be closely monitored with the lowest possible dose of CS.

Key Indexing Terms: corticosteroid, fetal complications, lupus low disease activity state, maternal complications, pregnancy, systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease with multiorgan involvement and preferentially affects women of childbearing age[1]. In patients who wish to carry a child, pregnancy represents a challenge because the clinical course of SLE is variable and may be characterized by acute or chronic flares in remission status. Immunological, endocrine, and environmental factors are known to develop and control SLE disease activity; however, no clear mechanism has been identified so far[2,3]. Given that SLE is 9 times more prevalent in women than men, it is clear that sex hormones are partially attributed to the various causes that distinguish males and females in relation to autoimmunity[4]. Indeed, increased estrogen levels during pregnancy influence the immune system, leading to a greater number of patients experiencing disease flares during this period. Further, studies of women with active disease at conception have reported that the flare rates during pregnancy ranged from 45% to 70%, whereas the rates of flare in a quiescent disease state at conception were < 20%[5,6,7].

Although fertility is generally unimpaired by SLE, pregnancy is considered a high-risk situation; indeed, all pregnancy-related complications are higher in patients with SLE than in healthy women[8,9]. By using a systematic review and metaanalysis of pregnancy outcomes, patients with SLE were considered to have increased pregnancy complications including preterm labor, preeclampsia, intrauterine growth retardation (IUGR), and other problems, such as thrombosis and infection[10,11]. We now know that careful management of patients with SLE can lead to an improved pregnancy course; however, this does not mean that it will be uneventful[12]. Further, there is a lack of common treatment outcome states in SLE, such as the achievement of low disease activity (LDA) in rheumatoid arthritis using the Disease

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The authors declare no conflict of interest.

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Activity Score in 28 joints[13]. Numerous definitions of remission have been proposed in response to this unmet need; evidence has been increasing that achieving the Lupus Low Disease Activity State (LLDAS) is a potential tool to assess control of SLE[14]. However, few studies have examined pregnancy outcomes in patients with SLE who have reached LLDAS, whereas adverse outcomes in SLE pregnancies have been widely reported by many previous studies.

Therefore, we designed a retrospective study to identify the outcome of pregnancy among Korean patients with SLE who reached LLDAS, from our Ajou Lupus Cohort. Moreover, we investigated the maternal and fetal outcomes between women with SLE and those without and analyzed the risk and predicting factors of such outcomes. The effect of achieving LLDAS on pregnancy outcomes was also evaluated.

MATERIALS AND METHODS

Patients. A retrospective study of all pregnancies in patients with SLE followed at Ajou University Hospital during January 1999 to June 2019 was conducted. We found 163 pregnancies in 110 women diagnosed with SLE according to the 1997 American College of Rheumatology or the 2012 Systemic Lupus International Collaboration Clinic Classification criteria[15,16]. Demographic, clinical, serological, and therapeutic data related to SLE and pregnancy outcomes were gathered from medical records. Disease activities were assessed using the SLE Disease Activity Index 2000 (SLEDAI-2K) and the attainment of LDA was assessed using LLDAS[14,17]. LLDAS is achieved if all of the following are met: (1) SLEDAI-2K ≤ 4, with no activity in major organ systems (renal, central nervous system, cardiopulmonary, vasculitis, and fever) and excluding hemolytic anemia or gastrointestinal activity; (2) no new features of SLE disease activity compared with the previous assessment; (3) physician global assessment ≤ 1 (scale 0–3); (4) current prednisolone-equivalent dosage ≤ 7.5 mg daily; and (5) well-tolerated standard maintenance dosages of immunosuppressive drugs and approved biologic agents[14]. Exclusion criteria included patients diagnosed with SLE during and after pregnancy and those who had therapeutic abortions. Control pregnancies were selected from the registry of the same hospital records with a pregnancy-related code or delivery code (International Classification of Diseases, 10th revision codes O80-84). We matched 596 control pregnancies based on maternal age and parity. Baseline demographics, clinically relevant comorbidities, and pregnancy data were recorded. This study protocol was reviewed and approved by the institutional review board of Ajou University Hospital (AJIRB-MED-MDB-19-215).

Assessment of pregnancy outcomes. We studied the association of SLE with the following pregnancy-related outcomes. Maternal outcomes consisted of (1) disease flare during pregnancy, (2) preeclampsia, and (3) emergency cesarean section. Fetal outcomes included (1) miscarriages, (2) stillbirth, (3) preterm delivery, (4) IUGR, (5) low birthweight of infants, and (6) neonatal intensive care unit (NICU) admission. All the pregnancy outcomes were investigated in the control group, except for disease flare.

The following definitions were used for the outcomes. Disease flare: new signs or worsening of SLE disease activities requiring starting or increasing corticosteroids (CS) and/or immunosuppressive agents; preeclampsia: gestational hypertension with proteinuria; emergency cesarean section: nonelective cesarean section; miscarriage: spontaneous fetal loss before 20 weeks of gestation; stillbirth: intrauterine fetal death after 20 weeks of gestation; preterm delivery: delivery before 37 weeks of gestation; IUGR: birth weight < 10th percentile for the stated gestation; and low birthweight infants: a birth weight of ≤ 2500 g.

Statistical analysis. All statistical analyses were conducted using SPSS version 25.0 software (IBM Corp). To present data, we used mean ± SD, and 2-sided P values < 0.05 were considered statistically significant. Comparisons between the SLE and controls were performed using Pearson chi-square test or independent t-test. Categorical variables were analyzed by chi-square test and continuous variables were analyzed by unpaired 2-sample t-test. Binary logistic regression was used to determine the predictors of adverse maternal and fetal outcomes. OR and 95% CI were computed after adjusting for potentially confounding factors such as age, hypertension, diabetes mellitus (DM), BMI, and thyroid disease. Receiver-operating characteristic (ROC) curves were obtained to determine the optimal cutoff values of SLEDAI-2K and CS dose for patients with SLE that would not affect pregnancy outcomes.

RESULTS

Clinical characteristics of patients with SLE. A total of 163 pregnancies in 110 women were included in this study. The demographic composition of the patients with SLE was not different from that of the controls (Table 1). However, women with SLE had lower BMI compared to controls. Comorbid conditions such as hypertension, DM, and thyroid disease were similar in both groups.

The mean age at diagnosis of SLE was 26.2 ± 5.7 years and the mean follow-up period was 65.8 ± 61.3 months. In patients with SLE, the main clinical symptoms during pregnancy included arthritis (20.9%), malar rash (19%), photosensitivity (12.3%), alopecia (9.2%), and oral ulcer (7.4%). A total of 29 patients (17.8%) had lupus nephritis, and 2 (1.2%) had serositis. The laboratory findings were as follows: lymphopenia (19.6%), leukopenia (14%), thrombocytopenia (11.7%), and high proteinuria (13.5%). Antinuclear antibodies were positive in all cases except for 1, anti-dsDNA antibody was positive in 56 (34.4%), anti-Sm antibody was positive in 6 (3.7%), and antiphospholipid antibodies (aPL) were positive in 30 (18.4%). More than half of the patients (53.4%) had at least 1 abnormally low complement C3 (< 90 mg/dL) or C4 (< 10 mg/dL) level. The mean baseline SLEDAI-2K and SLE Pregnancy Disease Activity Index 2000 in pregnancy were 7.20 ± 5.04 and 3.80 ± 4.57, respectively, and LLDAS was achieved by 89 (54.6%) patients.

The majority of the patients (67.5%) were taking hydroxychloroquine and 43 (26.4%) were taking nonsteroidal antiinflammatory drugs. Daily low-dose acetylsalicylic acid (ASA) was taken by 51 (31.3%) of patients with SLE, and 15 (9.2%) received daily heparin therapy. The mean cumulative CS dose before pregnancy was 7.4 ± 12.24 g prednisone-equivalent, and the mean CS dose during pregnancy was 11.2 ± 78.4 mg prednisone-equivalent. Of the patients with SLE, 45 of the pregnancies received immunosuppressive agents and some were treated with more than 1 drug before conception. A total of 22 (13.5%) received azathioprine (AZA), 14 (8.6%) received mycophenolate mofetil, 24 (14.7%) received cyclophosphamide (CYC), and 8 (4.9%) received cyclosporine.

Pregnancy outcomes in patients with SLE. The pregnancy outcomes are listed in Table 2. Out of 163 pregnancies, there were 118 live births (72.4%), which was clearly lower than that in the controls (84.2%, $P < 0.001$). Women with SLE had a lower gestational age (37 ± 2.7 weeks vs 37.6 ± 2.3 weeks, $P = 0.004$) and birth weight (2808.5 ± 0.6 g vs 3111.9 ± 0.5 g, $P = 0.016$) than the controls. Compared to the controls, pregnant women with SLE had a higher risk of pregnancy-related complications

Table 1. General characteristics and treatments of pregnant women with and without SLE.

	SLE, n = 163	Controls, n = 596	*P*
Age at diagnosis, yrs	26.2 ± 5.7	NA	NA
Maternal age, yrs, mean ± SD	31.9 ± 4.3	31.8 ± 4.1	0.70
Follow-up period, months	65.8 ± 61.3	NA	NA
BMI, kg/m^2	20.9 ± 3.2	22.3 ± 4.3	0.007*
Comorbidities, n (%)			
Hypertension	1 (0.6)	15 (2.5)	0.14
Diabetes mellitus	0 (0)	11 (1.8)	0.08
Thyroid disorder	15 (9.2)	65 (10.9)	0.54
Assisted reproductive technology	10 (6.1)	37 (6.2)	0.61
Clinical manifestations, n (%)			
Oral ulcer	12 (7.4)	NA	NA
Malar rash	31 (19)	NA	NA
Photosensitivity	20 (12.3)	NA	NA
Alopecia	15 (9.2)	NA	NA
Arthritis	34 (20.9)	NA	NA
Lupus nephritis	29 (17.8)	NA	NA
Serositis	2 (1.2)	NA	NA
Laboratory finding			
Leukopenia, < 4000/mm^3, n (%)	22 (14)	2 (0)	< 0.001*
Lymphopenia, < 1000/mm^3, n (%)	32 (19.6)	27 (0.1)	< 0.001*
Thrombocytopenia, < 100,000/mm^3, n (%)	19 (11.7)	3 (0)	< 0.001*
Hemoglobin, g/dL	11.9 ± 1.56	12.1 ± 1.26	0.004*
ESR, mm/h	24 ± 17.4	23.4 ± 13.4	0.24
Serum creatinine, mg/dL	0.7 ± 0.15	0.57 ± 0.37	0.97
Immunologic finding, n (%)			
ANA positivity	162 (99.4)	NA	NA
Anti-dsDNA Ab positivity	56 (34.4)	NA	NA
Anti-Sm Ab positivity	6 (3.7)	NA	NA
aPL positivity	30 (18.4)	NA	NA
APS diagnosis	7 (4.3)	NA	NA
Low complements (C3 < 90 mg/dL or C4 < 10 mg/dL)	87 (53.4)	NA	NA
Urinalysis			
Proteinuria, mg/d	660.7 ± 2304.2	53.2 ± 617.9	< 0.001*
Proteinuria > 0.5 g/d, n (%)	22 (13.5)	6 (0)	< 0.001*
SLEDAI-2K, initial	7.20 ± 5.04	NA	NA
SLEPDAI-2K, at pregnancy	3.80 ± 4.57	NA	NA
LLDAS, n (%)	89 (54.6)	NA	NA
Treatment, n (%)			
Hydroxychloroquine	110 (67.5)	NA	NA
NSAID	43 (26.4)	14 (0)	< 0.001*
Acetylsalicylic acid	51 (31.3)	3 (0)	< 0.001*
Heparin	15 (9.2)	3 (0)	< 0.001*
Corticosteroid			
Cumulative dose before pregnancy, g (prednisone-equivalent)	7.4 ± 12.24	0 (0)	< 0.001*
Total dose 3 months before pregnancy, mg (prednisone-equivalent)	230.4 ± 394.7	0 (0)	< 0.001*
Mean dose during pregnancy, mg (prednisone-equivalent)	11.2 ± 78.4	0 (0)	< 0.001*
Immunosuppressant, n (%)	45 (27.6)	0 (0)	< 0.001*
Azathioprine	22 (13.5)	0 (0)	< 0.001*
Mycophenolate mofetil	14 (8.6)	0 (0)	< 0.001*
Cyclophosphamide	24 (14.7)	0 (0)	< 0.001*
Cyclosporine	8 (4.9)	0 (0)	< 0.001*
ACEi or ARB, n (%)	22 (13.5)	4 (0)	< 0.001*
Vitamin D, n (%)	60 (36.8)	16 (0)	< 0.001*

Values are mean ± SD unless otherwise indicated. * $P < 0.05$. Ab: antibody; ACEi: angiotensin-converting enzyme inhibitor; ANA: antinuclear antibody; aPL: antiphospholipid antibody; APS: antiphospholipid syndrome; ARB: angiotensin receptor blocker; ESR: erythrocyte sedimentation rate; LLDAS: Lupus Low Disease Activity State; NA: not applicable; NSAID: nonsteroidal antiinflammatory drug; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000; SLEPDAI-2K: SLE Pregnancy Disease Activity Index 2000.

Table 2. Pregnancy outcomes of patients with and without SLE.

	SLE, n = 163	Controls, n = 596	*P*
Pregnancy outcomes			
Live births, n (%)	118 (72.4)	502 (84.2)	< 0.001*
Gestational age, weeks	37 ± 2.7	37.6 ± 2.3	0.004*
Birth weight, g	2808.5 ± 0.6	3111.9 ± 0.5	0.016*
Elective cesarean section, n (%)	71 (43.6)	296 (49.7)	0.86
Sex, F/M, n	52/66	243/262	0.33
Adverse pregnancy outcomes, n (%)	90 (55.2)	215 (36.1)	< 0.001*
Length of hospitalization, days	7.6 ± 12.8	4.5 ± 3	< 0.001*
Apgar[a] score at 1 min	7.4 ± 1.3	7.7 ± 1.1	0.042*
Apgar[a] score at 5 min	8.6 ± 1	8.9 ± 0.9	0.02*
Maternal complications, n (%)			
Total	40 (24.5)	81 (13.6)	< 0.001*
Disease flare	15 (8.8)	NA	NA
Preeclampsia	5 (2.9)	5 (0.8)	0.027*
Emergency cesarean section	25 (15.3)	52 (8.7)	0.034*
GDM	11 (6.7)	33 (5.5)	0.56
Fetal complications, n (%)			
Total	81 (49.7)	187 (31.4)	< 0.001*
Miscarriages	33 (20.2)	91 (15.2)	0.13
Stillbirths	12 (7.4)	3 (0.5)	< 0.001*
Preterm deliveries	28 (16.4)	44 (7.4)	< 0.001*
IUGR	16 (9.8)	24 (4)	0.003*
Low birthweight infants, < 2500 g	26 (16)	38 (6.4)	< 0.001*
NICU admission	28 (17.2)	58 (9.7)	0.016*

Values are mean ± SD, unless otherwise indicated. [a] The Apgar score is a simple method of quickly assessing the health and vital signs of a newborn and is performed on a baby at 1 and 5 minutes after birth. The score comprises 4 components, each of which is given a score of 0, 1, or 2: heart rate, respiratory effort, muscle tone, reflex irritability, and color. * $P < 0.05$. GDM: gestational diabetes mellitus; IUGR: intrauterine growth retardation; NA: not applicable; NICU: neonatal intensive care unit; SLE: systemic lupus erythematosus.

(55.2% vs 36.1%, $P < 0.001$). Further, the length of hospital stay following childbirth was longer in patients with SLE than in the controls (7.6 ± 12.8 days vs 4.5 ± 3 days, $P < 0.001$). In terms of maternal complications, disease flare occurred in 15 patients with SLE (8.8%). The incidence of preeclampsia was 2.9% in patients with SLE and 0.8% in controls ($P = 0.027$), and women with SLE had a higher rate of emergency cesarean sections (15.3% vs 8.7%, $P = 0.034$) than controls. There were no statistical differences in miscarriages between the 2 groups. Other adverse fetal outcomes, including stillbirths, preterm deliveries, IUGR, low birthweight infants, and NICU admission have also been reported to be high in SLE pregnancies. We observed 12 stillbirths (7.4%, $P < 0.001$), 28 preterm deliveries (16.4%, $P < 0.001$), 16 cases of IUGR (9.8%, $P = 0.003$), 26 low birthweight infants (16.0%, $P < 0.001$), and 28 infants admitted to the NICU (17.2%, $P = 0.016$), which were significantly increased over the controls.

The results of the multivariate analysis of pregnancy outcomes are provided in Figure 1. Women with SLE had 2.3-fold more pregnancy-related complications after adjusting for potential confounders (OR 2.32, 95% CI 1.60–3.38). When we examined the association between SLE and specific pregnancy outcomes, patients with SLE had a remarkably higher prevalence of preeclampsia (OR 4.31, 95% CI 1.20–15.48), emergency cesarean section (OR 1.86, 95% CI 1.08–3.18), stillbirth (OR 13.24, 95% CI 3.62–48.36), preterm delivery (OR 2.75, 95% CI 1.62–4.92), IUGR (OR 2.48, 95% CI 1.25–4.92), low birthweight infants (OR 2.74, 95% CI 1.57–4.76), and NICU admission (OR 2.20, 95% CI 1.32–3.68).

Predictors of adverse maternal and fetal outcomes in patients with SLE. In Table 3, we compared the clinical characteristics and treatments of patients with or without maternal and fetal complications in pregnancies to analyze the risk factors of these complications. We found that the presence of thrombocytopenia, hemoglobin, complement, positivity of anti-dsDNA antibody, 24-h urine protein, SLEDAI, achievement of LLDAS, and mean CS dose during pregnancy were considerably different between SLE patients with and without complications. The frequencies of clinical features were not significantly different between both groups with the exception of arthritis. Pregnancies with maternal and fetal complications revealed a higher rate of thrombocytopenia (17.8% vs 4.1%, $P = 0.005$), lower hemoglobin (11.8 ± 1.7 g/dL vs 12 ± 1.3 g/dL, $P = 0.034$), and lower C3 and C4 levels (84.6 ± 22.7 mg/dL vs 109.2 ± 34.2 mg/dL, $P = 0.019$ and 17 ± 7.8 mg/dL vs 25.4 ± 11.2 mg/dL, $P = 0.019$, respectively). The anti-dsDNA antibody positivity rate was higher (42.2% vs 24.7%, $P = 0.015$) in patients with complications. Further, higher levels of 24-h urine protein excretion (1152.3 ± 3036.1 mg/d vs 70.8 ± 192 mg/d, $P < 0.001$),

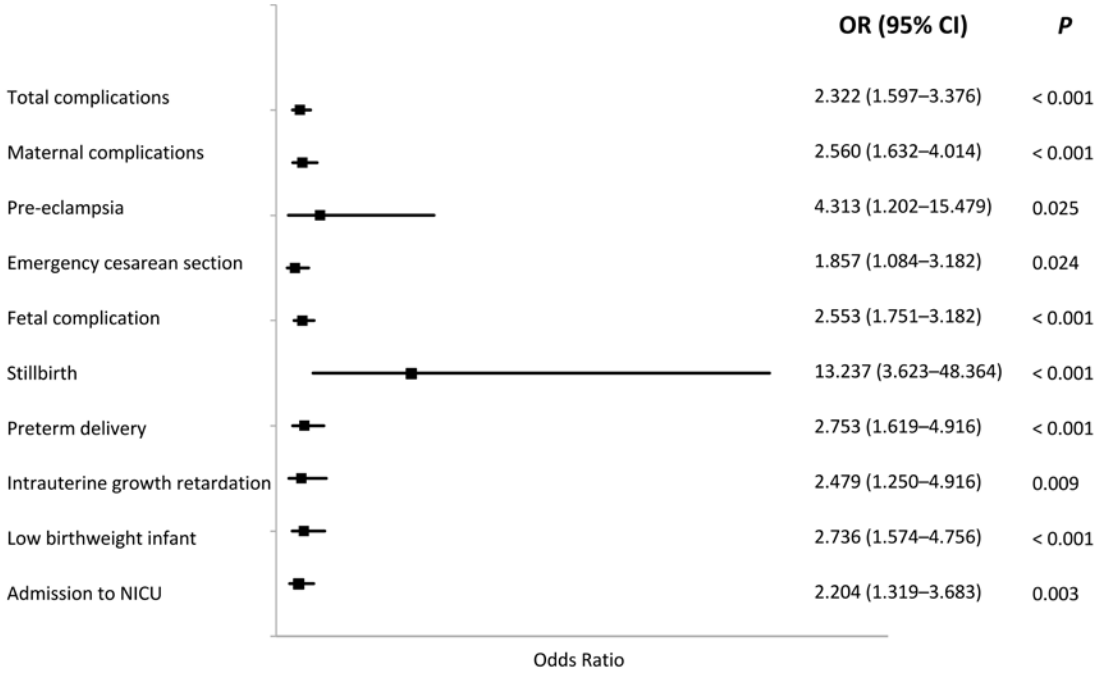

Figure 1. Multivariate analysis of maternal and fetal complications in patients with SLE. OR (95% CI) of the SLE vs non-SLE population for obstetric outcomes. The OR for obstetric outcomes listed on the left are plotted as dots; lines indicate 95% CI. All values were statistically significant ($P < 0.05$). Adjustment was made for age, BMI, and the presence of comorbid conditions such as hypertension, diabetes mellitus, and thyroid disease. SLE: systemic lupus erythematosus.

SLEDAI-2K score (5.4 ± 5.4 vs 1.9 ± 2.2, $P < 0.001$), and the mean dose of CS throughout pregnancy (19.4 ± 105.6 mg prednisone-equivalent vs 2 ± 4.4 mg prednisone-equivalent, $P = 0.049$) were observed in pregnancies with complications. The achievement of LLDAS (33.3% vs 80.8%, $P < 0.001$) was superior in pregnancies without complications. However, several factors were shown to only affect maternal complications. Patients who received a higher cumulative CS dose before conception and had a history of CYC treatment experienced more adverse maternal events (Table 4).

ROC curve analysis was performed in order to evaluate disease activity and CS dose that increases the risk of adverse events (Supplementary Figure 1, available with the online version of this article). The area under the curve (AUC) for the SLEDAI of maternal and fetal complications was 0.71 (95% CI 0.63–0.79). The optimal cutoff value was 4.5, with a sensitivity of 92% and a specificity of 56%. The best cutoff value of cumulative CS dose before conception for maternal complications was 3.5 g prednisone-equivalent, as determined from the AUC of 0.777 (95% CI 0.68–0.87). In terms of mean CS dose during pregnancy, the AUC was 0.761 (95% CI 0.69–0.84) and a cutoff value was 6 mg/d prednisone-equivalent.

After univariate logistic regression, various factors were identified as potential explanatory factors related to adverse maternal and fetal outcomes (Table 5). Among these factors, multiple logistic regression including the risk factors for maternal complications showed that high proteinuria, LLDAS achievement, and a cumulative CS dosage of > 3.5 g prednisone-equivalent were proven to be independent risk factors. Regarding fetal complications, thrombocytopenia, low complements, a SLEDAI score > 4, and LLDAS achievement were independent risk factors by multivariate analysis. Overall, the achievement of LLDAS had the most important influence on both maternal and fetal complications.

DISCUSSION

Over the past 40 years, improvements in disease care and regular prenatal monitoring have decreased adverse pregnancy outcomes[18]. Most pregnancies end in successful livebirths; nonetheless, women with SLE have more than twice the cumulative rate of pregnancy complications than the general population[19,20,21]. In this study, there was a noticeable difference in total pregnancy-related complications between patients with SLE and controls (55.2% vs 36.1%). Our findings were considerably higher than the rates reported in most previous studies (22.0–38.7%)[22,23]. One possible reason for the higher number of unsuccessful pregnancies in our data is the length of the study, in that some participants may not have received specialized close monitoring. However, the livebirth rate of patients with SLE was 72.4%, similar to rates in other studies in Korea[24]. Several Korean studies have reported livebirth rates ranging between 75% and 82%, which are comparable to those reported in Western countries[24,25,26]. Differences in the incidence of comorbidities and rates of cesarean section were not observed between women with and without SLE. These results are probably due to the need for referral of mothers without SLE having medical comorbidities to a tertiary medical center to reduce postpartum complications and mortality.

Table 3. Clinical characteristics and treatments of pregnancies with complications.

	Complications (Maternal and Fetal)		
	Yes, n = 90	No, n = 73	*P*
Age at diagnosis, yrs	25.7 ± 6	26.8 ± 5.3	0.167
Age at pregnancy, yrs	32 ± 4.5	32.3 ± 3.4	0.083
Time interval between diagnosis and pregnancy, months	69.8 ± 67	60.7 ± 53.5	0.21
Clinical manifestations			
Oral ulcer	8 (8.9)	4 (5.5)	0.407
Malar rash	22 (24.4)	9 (12.3)	0.05
Photosensitivity	9 (11)	11 (13.6)	0.878
Alopecia	8 (8.9)	7 (9.6)	0.402
Arthritis	26 (28.9)	8 (11)	0.005*
Nephritis	17 (18.9)	12 (16.4)	0.684
Serositis	2 (2.2)	0 (0)	0.2
Laboratory finding			
Leukopenia, < 4000/mm^3	12 (13.3)	10 (13.7)	0.991
Lymphopenia, < 1000/mm^3	19 (21.1)	13 (17.8)	0.658
Thrombocytopenia, < 100,000/mm^3	16 (17.8)	3 (4.1)	0.005*
Hemoglobin, g/dL	11.8 ± 1.7	12 ± 1.3	0.034*
ESR, mm/h	23 ± 17.8	25.1 ± 17	0.799
Serum creatinine, mg/dL	0.71 ± 0.16	0.68 ± 0.13	0.134
Immunologic finding			
C3, mg/dL	84.6 ± 22.7	109.2 ± 34.2	0.019*
C4, mg/dL	17 ± 7.8	25.4 ± 11.2	0.019*
Anti-dsDNA Ab positivity	38 (42.2)	18 (24.7)	0.015*
Anti-Sm Ab positivity	5 (5.6)	1 (1.4)	0.158
APA positivity	19 (21.1)	11 (15.1)	0.322
Urinalysis			
Proteinuria, mg/day	1152.3 ± 3036.1	70.8 ± 192	< 0.001*
Proteinuria > 0.5 g/d	19 (21.1)	3 (4.1)	0.001*
SLEDAI-2K, at pregnancy	5.4 ± 5.4	1.9 ± 2.2	< 0.001*
LLDAS	30 (33.3)	59 (80.8)	< 0.001*
Treatment			
Hydroxychloroquine	68 (75.6)	57 (78.1)	0.8
Steroid			
Cumulative dose before pregnancy, g (prednisone-equivalent)	10.2 ± 14.9	3.95 ± 6.35	< 0.001*
Total dose 3 months before pregnancy, mg (prednisone-equivalent)	270.2 ± 306.7	180.8 ± 480.4	0.629
Mean dose during pregnancy, mg (prednisone-equivalent)	19.4 ± 105.6	2 ± 4.4	0.049*
NSAID	20 (22.2)	23 (31.5)	0.195
Acetylsalicylic acid	24 (26.7)	27 (37)	0.158
Heparin	5 (5.6)	10 (13.7)	0.074
Immunosuppressants	33 (36.7)	12 (16.4)	0.004*
Azathioprine	16 (17.8)	6 (8.2)	0.076
Mycophenolate mofetil	10 (11.1)	4 (5.5)	0.194
Cyclophosphamide	19 (21.1)	5 (6.8)	0.01*
Cyclosporine	6 (6.7)	2 (2.7)	0.242
ACEi or ARB	16 (17.8)	6 (8.2)	0.071
Vitamin D	36 (40)	24 (32.9)	0.321

Values are mean ± SD or n (%). * $P < 0.05$. Ab: antibody; ACEi: angiotensin-converting enzyme inhibitor; APA: antiphospholipid antibody; ARB: angiotensin receptor blocker; ESR: erythrocyte sedimentation rate; LLDAS: Lupus Low Disease Activity State; NSAID: nonsteroidal antiinflammatory drug; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000.

The results of our study confirm that pregnancy-related complications are significant problems in patients with SLE compared to controls. Similar to previous studies, pregnancies in SLE show high rates of miscarriage, stillbirth, IUGR, NICU admission, preeclampsia, emergency cesarean section, and preterm delivery[11,27]. In a subgroup analysis, we observed 2.9% cases of preeclampsia, which is similar to that of previous studies involving Japan and other cohorts in Korea[26,28]. However, we noticed significantly lower rates of preeclampsia in our cohorts compared to Western countries. Several studies conducted in the US and Europe reported that the preeclampsia rates range from 12% to 35%[29,30]. In terms of fetal complications, we found a high rate of stillbirths (7.4% vs 0.5%), preterm deliveries (16.4% vs 7.4%), IUGR (9.8% vs 4.0%), low birthweight infants (16.0% vs

Table 4. Independent explanatory variables associated with maternal and fetal complications in patients with SLE.

	Maternal Complications			Fetal Complications		
	Yes, n = 40	No, n = 123	*P*	Yes, n = 73	No, n = 90	*P*
Thrombocytopenia	9 (22.5)	10 (8.1)	0.017*	16 (21.9)	3 (3.3)	0.001*
Hemoglobin, g/dL	11.3 ± 2.2	12.1 ± 1.2	< 0.001*	11.7 ± 1.8	12.1 ± 1.3	0.036*
C3 < 90 mg/dL + C4 < 10 mg/dL	14 (35)	18 (14.6)	< 0.001*	24 (32.9)	8 (8.9)	0.001*
Anti-dsDNA Ab positivity	20 (50)	36 (29.3)	0.033*	36 (49.3)	20 (22.2)	0.004*
Proteinuria, mg/d	2150.7 ± 4047.1	155.4 ± 805.5	< 0.001*	1089.8 ± 2844.1	242.7 ± 1520.5	< 0.001*
SLEDAI-2K, at pregnancy	7.2 ± 6.4	2.8 ± 3.3	< 0.001*	5.5 ± 5.5	2.2 ± 2.6	< 0.001*
LLDAS	5 (12.5)	84 (68.3)	< 0.001*	22 (30.1)	67 (74.4)	< 0.001*
Cumulative steroid dose before pregnancy, g (prednisone-equivalent)	15.14 ± 14.13	5.04 ± 10.59	< 0.001*	9.45 ± 14.81	6.03 ± 9.93	0.07
Mean steroid dose during pregnancy, mg (prednisone-equivalent)	38.3 ± 157.1	4.5 ± 13.3	0.001*	22.4 ± 111.2	3.3 ± 13.7	0.043*
Immunosuppressants	22 (55)	23 (18.7)	< 0.001*	27 (37)	18 (20)	0.09
Cyclophosphamide	14 (35)	10 (8.1)	< 0.001*	16 (21.9)	8 (8.9)	0.07

Values are mean ± SD or n (%). * $P < 0.05$. Ab: antibody; LLDAS: Lupus Low Disease Activity State; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000.

Table 5. Potential risk factors of complications in pregnancies with SLE.

	Maternal Complications					
	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Hemoglobin < 10 g/dL	17.7	3.63–86.25	< 0.001*	4.38	0.4–47.71	0.18
Thrombocytopenia	3.3	1.23–8.85	0.024*	2.12	0.46–9.61	0.34
C3 < 90 mg/dL + C4 < 10 mg/dL	4.41	1.9–10.26	< 0.001*	1.56	0.48–5.03	0.47
Anti-dsDNA Ab positivity	2.38	1.12–5.03	0.02*	0.86	0.25–2.94	0.81
Proteinuria > 0.5 g/d	9.82	3.61–26.7	< 0.001*	7.25	1.75–30.05	0.008*
SLEDAI-2K, at pregnancy > 4	4.61	2.08–10.23	< 0.001*	0.7	0.18–2.77	0.61
LLDAS	0.09	0.03 - 0.22	< 0.001*	0.18	0.04–0.74	0.016*
Cumulative steroid dose after diagnosis > 3500 mg	7.81	3.14–19.39	< 0.001*	3.99	1.25–12.77	0.024*
Mean steroid dose during pregnancy > 6 mg/d	6.63	2.95–14.89	< 0.001*	1.78	0.53–5.94	0.36
History of CYC treatment	6.33	2.52–15.88	< 0.001*	2.7	0.66–11.03	0.18

	Fetal complications					
	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*	OR	95% CI	*P*
Hemoglobin < 10 g/dL	5.91	1.23–28.29	0.029*	1.56	0.15–16.87	0.71
Thrombocytopenia	7.77	2.16–27.89	< 0.001*	18.42	2.09–162.63	0.009*
C3 < 90 mg/dL + C4 < 10 mg/dL	4.66	1.93–11.24	< 0.001*	4.57	1.46–14.33	0.017*
Anti-dsDNA Ab positivity	2.53	1.29–4.99	0.013*	1	0.36–2.784	0.99
Proteinuria > 0.5 g/d	3.71	1.37–10.09	0.01*	0.94	0.24–4.77	0.94
SLEDAI-2K, at pregnancy > 4	9.63	4.06–22.8	< 0.001*	2.93	0.75–11.5	0.004*
LLDAS	0.14	0.07–0.29	< 0.001*	0.21	0.06–0.65	0.01*
Mean steroid dose during pregnancy > 6 mg/d	3.59	1.63–7.92	0.035*	0.98	0.15–1.75	0.28

* $P < 0.05$. Ab: antibody; CYC: cyclophosphamide; LLDAS: Lupus Low Disease Activity State; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index 2000.

6.4%), and NICU admission (17.2% vs 9.7%) in patients with SLE; this was consistent with the results of previous studies[31]. However, there was no statistical difference in the incidence of miscarriages among women with SLE and controls (20.2% vs 15.2%, $P = 0.13$). These rates were similar considering that the miscarriage rate of pregnant Korean women is 14.0–23.0%[32].

We further analyzed the increased rates of adverse pregnancy outcomes after adjusting for important confounding factors. The OR for all complications proved to be higher in patients with SLE than in controls. The higher OR in our analysis was stillbirth (adjusted OR 13.2, $P < 0.001$) and preeclampsia (adjusted OR 4.3, $P = 0.025$). A previous metaanalysis by Bundhun, *et al*

supported tendencies similar to the present study[33]. However, there have been no published studies comparing the frequency of pregnancy complications between SLE and the general obstetric population in Korea.

As a result of investigating pregnancy-related complications, factors affecting complications were mostly consistent with other previous analyses conducted over the years[34,35]. One important difference is that a positive test for aPL was not an independent risk factor for adverse pregnancy outcomes[36]. This might be explained by the widespread consensus on the benefit of antithrombotic prophylaxis[37], as we adequately treated with ASA or low molecular weight heparin for the presence of aPL. We also found that some variables were only associated with maternal complications; these included a high cumulative CS dose during pregnancy and a history of CYC treatment. Among the various immunosuppressants, the only medication that demonstrated a meaningful relationship with adverse maternal outcomes was CYC. Despite possible teratogenic agents being discontinued in preparation for conception, ovarian failure and sustained amenorrhea might persist owing to a cumulative effect of CYC. As previously reported, the incidence of infertility by CYC was approximately 14.9–37.3%[38]; thus, it is recommended to limit the use of CYC in fertile women. For patients planning to continue CYC therapy, hormonal co-therapy during treatment is suggested to reduce the risk of ovarian insufficiency[39].

The reduction of adverse pregnancy outcomes by achieving LLDAS has not been studied previously. Even after validation in a multivariate model, the achievement of LLDAS was the only factor that affected both maternal and fetal complications. An agreement on the principles of the definition of remission in SLE has been proposed by several research groups over the years, which includes SLEDAI, and mostly coincided with SLEDAI ≤ 4[40,41]. In our analysis, to identify the SLEDAI that leads to better outcomes, we obtained similar results described in previous studies. However, many experts argue that the drawback of SLEDAI is that it does not reflect important systems such as hemolytic anemia or gastrointestinal activity, and treatment domains[14]. Indeed, currently there is a growing opinion that LLDAS has excellent validity and represents a much more attainable clinical target state[42]. In this regard, it is noteworthy that our study is the first study, to our knowledge, to analyze the relationship between LLDAS and pregnancy outcomes. Moreover, we investigated factors affecting LLDAS, and the results were largely consistent with factors affecting pregnancy outcomes (Supplementary Table 1, available with the online version of this article). When we compared the pregnancy-related complications between patients with SLE who achieved LLDAS and controls, there was no significant difference in the incidence of pregnancy-related complications other than stillbirth (Supplementary Table 2, available with the online version of this article). These results suggest that achieving LLDAS is important to preventing pregnancy-related complications in patients with SLE.

The areas with high disagreement on the validity of LLDAS are concerned with CS dose. The opinion that CS-related side effects generally occur at daily doses of ≥ 7.5 mg prednisone-equivalent is predominant, and this dosage is also used in the LLDAS criteria[43]. Contrary to the prevailing view, several studies reported that the CS dose accommodates daily doses of 10 mg prednisone-equivalent because this dosing has the benefit of rapid onset of action[44]. Further, CS are safe even during pregnancy; thus, this is the first-line therapy commonly used for acute flares throughout pregnancy. However, it is clear that CS are not innocuous because of the increased risk of congenital malformation and pregnancy outcomes[45]. The controversy over the safe maintenance CS dose of SLE pregnancies remains; thus, our available data analyzed the adequate CS doses and timing for pregnancy. Our study revealed that a mean CS dose during pregnancy of < 6 mg/day prednisone-equivalent was a reasonable value for reducing maternal and fetal risk. Cumulative CS doses exceeding 3.5 g prednisone-equivalent for women with SLE have contributed to the higher rate of adverse maternal outcomes, whereas CS doses taken 3 months before conception were not influential. Even in obstetric medicine, it is crucial to not exceed such doses while maintaining quiescent SLE. There is a general consensus that safe immunosuppressants such as AZA and tacrolimus can be administered by reducing CS to manage SLE flares in pregnant women[46].

The present study is relevant for several reasons. One of the strengths of this analysis is that it is the first study conducted in Korea to compare obstetric complications in patients with SLE with the general population, to our knowledge. Second, it is the first study to reveal that achieving LLDAS plays an important role in minimizing adverse pregnancy outcomes. Third, it is meaningful that our study has tried to determine the optimal CS dose, considering that we are uncertain what CS dose is best for mothers and babies.

We encountered some limitations in our attempt. First, this is a retrospective study in a single center, with selection and information bias. Additionally, as the general population was recruited from a tertiary care center, we may have recruited relatively high-risk pregnancies. Further, our study encompasses a vast period from 1999 to 2019, and during this period many advances in diagnostic criteria and medication use have changed the outcomes of the disease.

In conclusion, this study demonstrated adverse pregnancy outcomes are still higher in pregnant women with SLE than in the general population. A comprehensive analysis of risk factors and predictors of maternal and fetal complications was provided. Minimizing the occurrence of complications during pregnancy was strongly associated with achieving LLDAS and keeping daily steroid doses of prednisone < 6 mg/day. Targeting inactive disease and preventing a disease flare is important to allow for successful outcomes. Therefore, pregnancies in SLE should receive preconception counseling with a multidisciplinary team in a specialized center and choose an optimal time for pregnancy.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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