Adverse Pregnancy Outcomes in Patients With Systemic Lupus Erythematosus: A Retrospective Cohort Study

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Abstract- Systemic Lupus Erythematosus (SLE) is a complex autoimmune disease that may result in adverse pregnancy outcomes, posing a significant risk to both the mother and the fetus. The major purpose of the current study was to investigate the impact of SLE on the outcomes of pregnancy among women with SLE. This was a retrospective cohort study. Two groups of pregnant women, one with Systemic Lupus Erythematosus (SLE) and one without SLE, were included at the Gynecology and Obstetrics Clinic of Ayatollah Mousavi Hospital in Zanjan, Iran, from 2019 to 2020. Participants from both cohorts completed a checklist of study variables based on their medical records. The data were analyzed using binary logistic regression, chi-square test, analysis of variance, and independent samples t-test with SPSS software version 23. The research involved 400 pregnant women, with the mean age of the SLE and non-SLE groups being 36.68±4.90 and 29.46±6.56 years, respectively. The most prevalent adverse outcome was cesarean section (271 [67.8%]), significantly higher in the SLE group (54.5% vs. 10.0%, *P*=0.0001). The likelihood of experiencing spontaneous abortion, preterm labor, cesarean section, and LBW was increased by more than 6.5 times (odds ratio, 6.54; 95% CI, 2.22-19.27; *P*=0.001), 3.6 times (odds ratio, 3.67; 95% CI, 1.47-9.18; *P*=0.005), 18.9 times (odds ratio, 18.94; 95% CI, 6.46-55.49; *P*=0.0001), and 3 times (odds ratio, 3.04; 95% CI, 1.09-8.46; *P*=0.030) in individuals with SLE, respectively. Women with SLE have an increased likelihood of encountering spontaneous abortion, preterm labor, cesarean section, and delivering a low-birth-weight infant.

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Keywords: Systemic lupus erythematosus; Pregnancy; Cesarean section; Preterm labor; Spontaneous abortion; Low birth weight

Introduction

In relation to pregnancy and systemic lupus erythematosus (SLE), adverse pregnancy outcomes (APOs) cause concern. SLE is a systemic autoimmune inflammatory disease of unknown cause that affects different organs of the body. Patients with SLE present numerous clinical manifestations such as skin rashes, arthritis, anemia, thrombocytopenia, kidney involvement and seizures. SLE is also associated with low serum complement, antiphospholipid antibodies (APA), ANA (Antinuclear Antibody) and Anti-double-stranded deoxyribonucleic acid antibodies (dsDNA Abs) (1). According to epidemiological studies the prevalence of SLE ranges from 45.2 to 102.9 cases per 100,000 individuals, with an incidence rate of 2.4 to 7.2 cases per 100,000 individuals/year. Women are more commonly affected, with the highest incidence occurring during their reproductive years. The female to male prevalence ratio is approximately 7-9 to 1 (2).

The significant association between SLE and APOs has previously been endorsed. It has been found that

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pregnant women with SLE have a higher likelihood of experiencing new flares of the disease, preterm birth, intrauterine growth restriction (IUGR), cesarean section, preeclampsia, and fetal death (3,4). While there have been some improvement in these rates over the past decade, the incidence of complications in SLE pregnancies remains higher than that in the general population (4).

Pregnancy in women with SLE may lead to morbidities such as preeclampsia and cardiovascular disease (CVD) more likely than pregnancy in women without SLE (5). Pregnancy in individuals with SLE poses a significant risk, with a mortality rate 20 times higher than the general population. The main causes of maternal death have been shown to be infectious complications (40%), disease activity-related complications (30%), and thromboembolic events (6).

It has been revealed that there is a significant link between active SLE at the time of conception and disease flares throughout the pregnancy. Furthermore, a history of nephritis and high disease activity, as measured by the SLE Disease Activity Index (SLEDAI), may lead to unfavorable maternal outcomes during pregnancy (2). Moreover, pregnancy itself may have a negative impact on the immune system in mothers with SLE. Additionally, certain medications used to treat autoimmune diseases, such as cyclophosphamide, methotrexate, and mycophenolate mofetil, should be discontinued during pregnancy due to their potential for fetal toxicity (7).

In terms of fetal outcomes, prematurity has been reported to be the most common complication in pregnant women with SLE. Risk factors that can impact fetal prognosis include a history of LN, proteinuria exceeding 1 g/day, eGFR <90 mL/min, antiphospholipid syndrome (APS), hypocomplementemia, and high blood pressure at the time of conception (6).

The maternal and fetal outcomes among women with SLE have been ameliorated considerably over the recent decades (2). Formerly, patients with SLE were discouraged from getting pregnant due to a lack of information about medication compatibility and the risk factors involved. Despite past concerns, current evidence on managing SLE during pregnancy has improved maternal and fetal outcomes, making pregnancy a viable option for this population (2). Besides, there has been a remarkable improvement in overall fetal survival, with rates increasing from 57% in the 1960s to 85% in recent years (8). Nevertheless, the risk of developing APOs in pregnancies of women with SLE is still significantly higher than the general population.

Hence, it is still essential to further investigate APOs in the population of women with SLE to gain a deeper understanding of the influencing factors in order to secure an optimal disease management during pregnancy. Our study aimed at determining the effect of pregnancy on pregnant women with SLE, as well as identifying the factors that increase the likelihood of APOs for both the mother and fetus.

Materials and Methods

This study has a retrospective cross-sectional design. Medical records of 363 pregnancies in 200 SLE patients, who received care at Ayatollah Mousavi Hospital a tertiary referral center specializing in high-risk pregnancies affiliated with Zanjan University of Medical Sciences were examined between January 2010 and March 2020.

The comparison group, referred to as the “non-SLE group,” was composed of 200 healthy pregnant women with 415 pregnancies who referred to the same hospital within the same time frame. Participants in both groups presented to Ayatollah Mousavi Hospital, Zanjan, Iran for delivery. A checklist of various variables was completed for both sets of participants.

The research protocol underwent evaluation and received approval from the Ethics Committee at Zanjan University of Medical Sciences [IR.ZUMS.REC.1398.380]. We obtained written informed consent from all participants or their legal representatives, as applicable. We adhered to the requirements of Declaration of Helsinki.

Eligibility criteria

The cohort of women diagnosed with SLE encompassed all subjects who had received a verified SLE diagnosis based on the American College of Rheumatology (ACR) criteria or the Systemic Lupus International Collaborating Clinics (SLICC) criteria, irrespective of the duration of their illness and the existence of SLE-associated complications such as kidney failure and cardiovascular issues. Based on the SLEDAI-2K scoring system, we included all patients with mild disease activity (SLEDAI-2K $\leq$5). They had no prior history of other rheumatic diseases or non-SLE-related conditions that could potentially impact pregnancy outcomes, including cardiovascular diseases, high blood pressure, diabetes mellitus, thyroid, and kidney disorders.

The non-SLE group consisted of healthy pregnant

women with no history of any medical conditions affecting pregnancy outcomes and no prior use of specific medications.

Study variables

Data on the basic and clinical characteristics of the participants and pregnancy outcomes was extracted from the medical records. When required, this data was collected through in-person interviews with the participants or their doctors, or via phone calls.

The variables on maternal age, parity, education status, maternity hospital, dwelling, history of adverse pregnancy outcomes, and BMI (kg/m2), were included as basic characteristics of the participants. Preterm labor, spontaneous abortion, delivery mode (Normal vaginal delivery [NVD] or cesarean section [CS]), low birth weight (LBW), gestational hypertension, eclampsia, pre-eclampsia, still birth, fetal anomalies on the second-trimester anomaly scan, and overt congenital anomaly were considered the variables of adverse pregnancy outcomes.

Preterm labor was defined as delivery before the 37th week of pregnancy. LBW was characterized as birth weight less than 2500 grams. Spontaneous abortion was determined as miscarriage before week 20 of pregnancy. Still birth was defined as loss of a nonviable, intrauterine pregnancy at ≥20 weeks of gestation. Overt congenital anomaly was described as the presence of any fetal abnormalities at birth. Gestational hypertension was specified as blood pressure greater than 140/90 mm Hg after 20 weeks of pregnancy. Pre-eclampsia was defined as blood pressure greater than 140/90 mm Hg after 20 weeks of pregnancy along with the excretion of more than 500 mg of protein in the urine within 24 hours. Eclampsia was defined as meeting the criteria mentioned earlier in addition to developing seizures.

Statistical analysis

For numerical data, we presented descriptive statistics as the mean±standard deviation (SD) when the data followed a normal distribution, and as the median with the 25th and 75th quartiles when the data were not normally distributed. Categorical data were expressed as frequency (%). In terms of analytical statistics, we employed the chi-square test to compare categorical data among different groups. When comparing the means of numerical data between two groups, we employed an independent samples t-test. To compare the means of numerical data among three or more groups, we utilized Analysis of Variance (ANOVA). Logistic regression analysis was conducted to identify predictive variables for pregnancy outcomes. We considered a two-tailed *P* less than 0.05 as indicative of statistical significance. All graphs were illustrated using the R package ggplot2. The data were analyzed using SPSS software version 23.

Results

400 pregnant women (33.1±6.8 years, range, 17 to 47 years old) including 200 women with SLE (363 pregnancies, Min=1, Max=5) and 200 non-SLE women (415 pregnancies, Min=1, Max=7) were included in the study. The mean age of women with SLE and without SLE was found to be 36.68±4.90 and 29.46±6.56 years, respectively.

Regarding the basic characteristics of the patients, most of the participants were resided in urban areas (285 [71.3%]), gave birth in tertiary level maternity hospital (336[84.0%]), educated with high school diploma (HSD) (151[37.8%]), and with no history of adverse pregnancy outcomes (335[83.8%]) (Table 1).

Examining the basic characteristics of the participants through a $\chi 2$ test between the two groups indicated a statistically significant difference across all variables (All, $P<0.05$). The mean of maternal age, parity, and BMI were assessed through an independent samples t-test, revealing a significant distinction between the two groups (All, $P<0.05$) (Table 1).

Among all participants, 271 (67.8%) underwent cesarean section. Spontaneous abortion and preterm labor were the second and third most common outcomes, with 111 (27.8%) and 90 (22.5%) women experiencing them, respectively (Table 2).

Comparing the outcome variables between women with and without SLE using a chi-square test of independence revealed significant differences in terms of spontaneous abortion, preterm labor, delivery mode, and LBW.

The association between having SLE and experiencing spontaneous abortion was significant, X2 (1, N=400)=29.93, P=0.0001. Women diagnosed with SLE were more prone to undergoing spontaneous abortion compared to those without SLE (Table 2, Figure 1).

There was a significant relationship between having SLE and experiencing preterm labor. Women with SLE were more likely than non-SLE women to develop preterm labor, X2 (1, N=400) =25.29, P=0.0001 (Table 2, Figure 2).

The association between delivery method and low birth weight was notably significant. Women with SLE had a higher likelihood of opting for a C/S compared to

those without SLE (χ2 [1, N=400] =90.63, P=0.0001), and they were also more inclined to deliver a newborn with LBW (χ2 [1, N=400]=12.26, *P*=0.001) (Table 2, Figures 3 and 4).

The proportion of subjects who experienced still birth (X2 [1, N=400]=3.72), pre-eclampsia (X2 [1, N=400]=1.18), eclampsia (X2 [1, N=400]=0.33), congenital anomaly (X2 [1, N=400]=0.09), and 2nd-trimester anomaly (X2 [1, N=400]=0.20) did not significantly differ by SLE (All, P>0.05) (Table 2).

In logistic regression analysis, a significant association was found between SLE and spontaneous abortion (*P*=0.001), preterm labor (*P*=0.005), cesarean section (*P*=0.0001) and low birth weight (*P*=0.030). Furthermore, the odds ratios suggest that individuals with SLE have a higher likelihood of experiencing spontaneous abortion, preterm labor, cesarean section, and low birth weight, with increases of more than 6.5, 3.6, 18.9 and 3 times, respectively (Table 3).

Table 1. Comparisons of women with and without SLE according to socio-demographic characteristics

Variables		SLE group	Non-SLE group	t/ χ2	*P**
		N (%)/Mean±SD			
Maternal age, years		36.68 ± 4.90	29.46 ± 6.56	12.45	0.001[a]
Maternal education	**< HSD**	32 (16.0)	67 (33.5)	34.54	0.001[b]
	HSD	68 (34.0)	83 (43.5)		
	B.S.	25 (12.5)	17 (8.5)		
	B.S.	70 (35.0)	27 (13.5)		
	M.S.	5 (2.5)	6 (3.0)		
Parity		1.82 ± 0.83	2.08 ± 1.05	2.74	0.006[a]
Maternity Hospital	**Secondary level**	59 (29.5)	5 (2.5)	54.24	0.001[b]
	Tertiary level	141 (70.5)	195 (97.5)		
Dwelling	**Rural**	42 (21.0)	73 (36.5)	11.72	0.001[b]
	Urban	158 (79.0)	127 (63.5)		
History of adverse pregnancy outcomes	**Yes**	60 (30.0)	5 (2.5)	55.56	0.001[b]
	No	140 (70.0)	195 (97.5)		
BMI, kg/m2		22.52 ± 1.72	25.11 ± 2.13	13.24	0.001[a]

HSD: High School Diploma, B.S.: Bachelor's Degree, M.S.: Master's degree, BMI: Body Mass Index.
*$P < 0.05$
a *P* obtained from independent samples t-test
b *P* obtained from χ2 test

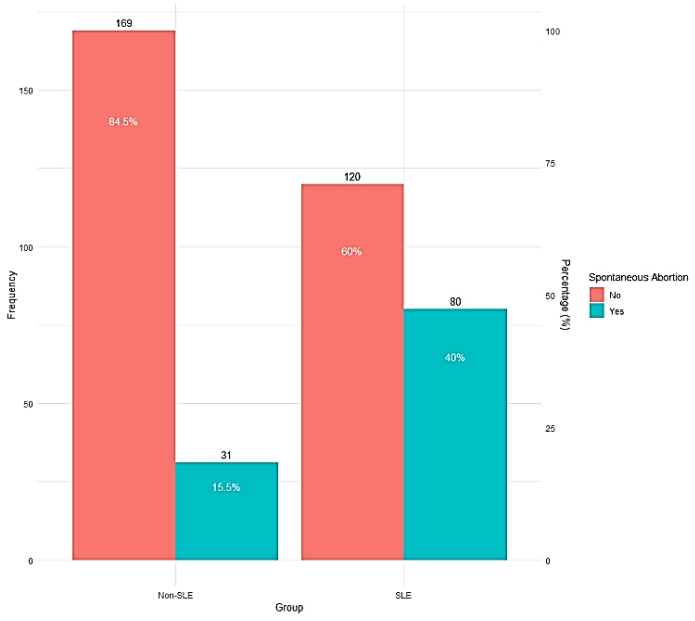

Figure 1. Spontaneous abortion among SLE and non-SLE women. SLE: Systemic Lupus Erythematosus

Table 2. Comparisons of women with and without SLE according to pregnancy outcomes

Outcome		SLE group	Non-SLE	Total	$\chi 2$	*P*
		N (%)				
Spontaneous abortion	**Yes**	80 (40.0)	31 (15.5)	111 (27.8)	29.93	0.0001
	No	120 (60.0)	169 (84.5)	289 (72.3)		
	Total	200 (100)	200 (100)	400 (100)		
Preterm labor	**Yes**	66 (33.0)	24 (12.0)	90 (22.5)	25.29	0.0001
	No	134 (67.0)	176 (88.0)	310 (77.5)		
	Total	200 (100)	200 (100)	400 (100)		
Still birth	**Yes**	13 (6.5)	5 (2.5)	18 (4.5)	3.72	0.054
	No	187 (93.5)	195 (97.5)	382 (95.5)		
	Total	200 (100)	200 (100)	400 (100)		
Pre-eclampsia	**Yes**	9 (4.5)	5 (2.5)	14 (3.5)	1.18	0.276
	No	191 (95.5)	195 (97.5)	386 (96.5)		
	Total	200 (100)	200 (100)	400 (100)		
Eclampsia	**Yes**	1 (0.5)	2 (1.0)	3 (0.8)	0.33	1.000*
	No	199 (99.5)	198 (99.0)	397 (99.3)		
	Total	200 (100)	200 (100)	400 (100)		
Congenital anomaly	**Yes**	6 (3.0)	5 (2.5)	11 (2.8)	0.09	0.760
	No	194 (97.0)	195 (97.5)	389 (97.3)		
	Total	200 (100)	200 (100)	400 (100)		
Fetal anomalies on the 2nd-trimester anomaly scan	**Yes**	2 (1.0)	3 (1.5)	5 (1.3)	0.20	1.000*
	No	198 (99.0)	197 (98.5)	395 (98.8)		
	Total	200 (100)	200 (100)	400 (100)		
Delivery mode	**CS**	109 (54.5)	20 (10.0)	271 (67.8)	90.63	0.0001
	NVD	91 (45.5)	180 (90.0)	129 (32.3)		
	Total	200 (100)	200 (100)	400 (100)		
LBW	**Yes**	46 (23.0)	20 (10.0)	66 (16.5)	12.26	0.001
	No	154 (77.0)	180 (90.0)	334 (83.5)		

The *P* marked in bold show they are statistically significant. CS: Caesarean Section, NVD: Normal Vaginal Delivery, LBW: Low Birth Weight

*Obtained from Fisher's exact test

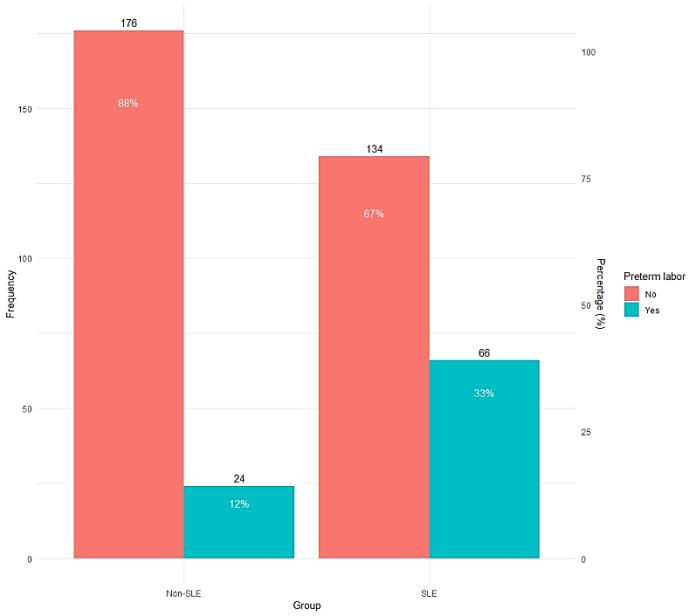

Figure 2. Preterm labor among SLE and non-SLE women. SLE: Systemic Lupus Erythematosus

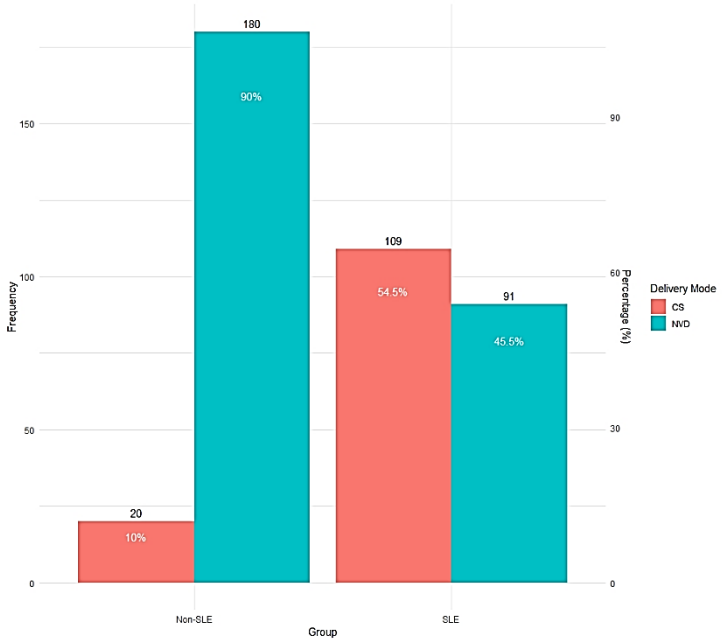

Figure 3. Delivery mode among SLE and non-SLE women. SLE: Systemic Lupus Erythematosus, CS: Caesarean Section, NVD: Normal Vaginal Delivery

Table 3. Multivariable and univariable logistic regression results*

Outcome variables	Multivariable logistic regression		Univariable logistic regression	
	Odds ratio (95% CI)	***P****	**Odds ratio (95% CI)**	***P*** **
Spontaneous abortion	6.54 (2.22, 19.27)	0.001	4.03 (2.49 , 6.52)	0.0001
Preterm labor	3.67 (1.47, 9.18)	0.005	5.01 (2.95 , 8.51)	0.0001
Still birth	2.72 (0.23, 32.10)	0.427	4.39 (1.18 , 9.73)	0.023
Pre-eclampsia	4.78 (0.42, 54.58)	0.200	1.85 (0.61 , 5.64)	0.275
Eclampsia	0	0.990	0.52 (0.14 , 5.85)	0.600
Congenital anomaly	3.16 (0.39, 33.87)	0.340	1.20 (0.32 , 4.01)	0.760
Fetal anomalies on the 2nd-trimester anomaly scan	0	0.997	0.73 (0.14 , 4.44)	0.730
Delivery mode	18.94 (6.46, 55.49)	0.0001	8.44 (4.94 , 15.10)	0.0001
LBW	3.04 (1.09, 8.46)	0.030	3.28 (1.84 , 5.83)	0.0001

The *P* marked in bold show they are statistically significant. LBW: Low Birth Weight, CI: Confidence Interval
*With the study group (presence or absence of SLE) as the predictor, level of education, place of delivery, dwelling, history of pregnancy outcomes, body mass index, maternal age, parity as confounding variables, in addition to pregnancy outcome variables
***P*< 0.05

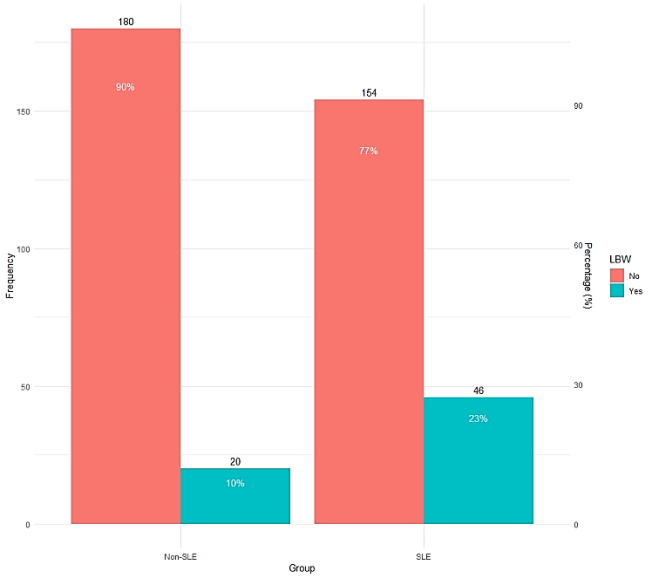

Figure 4. LBW among SLE and non-SLE women. SLE: Systemic Lupus Erythematosus, LBW: Low Birth Weight

Discussion

In the current investigation into adverse pregnancy outcomes among women with and without SLE, we have discovered significant findings. Our study demonstrated that women diagnosed with SLE face substantially higher risks of experiencing spontaneous abortion, preterm labor, cesarean section, and low birth weight, with increases surpassing 6.5, 3.6, 18.9, and 3 times, respectively.

As SLE typically manifests during young adulthood, pregnancies in individuals with this condition are common. While many pregnancies end favorably, it's imperative to classify all SLE patients as "high risk". On one hand pregnancy has the potential to exacerbate SLE activity. On the other hand, these pregnancies pose a heightened risk for both maternal and fetal complications, including spontaneous abortion, premature delivery, stillbirths, intrauterine growth retardation (IUGR), and the development of superimposed pre-eclampsia (8-10).

Existing evidence indicate that spontaneous abortion is the prevailing adverse pregnancy outcome among women diagnosed with SLE (11). In a cohort of pregnant women diagnosed with various autoimmune rheumatic disorders, a spontaneous abortion rate of 28.8% was documented which is lower (40%) than the rate found in our study. Nonetheless, preconception consultations with obstetricians and rheumatologists were found to significantly reduce the incidence of spontaneous abortions (12).

A Portuguese Case-Control Study confirmed that 12.4% of patients experienced preterm delivery, with an odds ratio of 1.72 compared to our study, where 33% of women with SLE underwent preterm delivery. They determined that being pregnant while having SLE led to a higher occurrence of negative results, despite the fact that the SLE patients in the study had their condition well managed (13). A retrospective cohort study conducted in the Netherlands identified preterm birth (19%) as the most common adverse pregnancy outcome in pregnancies impacted by SLE. Additionally, the study observed that stillbirth, preeclampsia, and cesarean section occurred in 4.2%, 10.4%, and 4.2% of the cases, respectively (14).

A recent systematic review revealed that the most prevalent obstetric outcomes experienced by women with SLE included preterm labor (70.8%), followed by preeclampsia (52%), and preterm rupture of membranes (20.8%) (15). The reported preterm labor rate exceeds that observed in our study.

Among sub-Saharan African women with SLE, significant adverse pregnancy outcomes included preterm birth (38.8%), low birth weight (29.8%), pregnancy loss (29.2%), and pre-eclampsia (24.8%). Nephritis and SLE flares were identified as the primary factors linked to these adverse pregnancy outcomes (16). Moreover, the presence of both SLE and antiphospholipid syndrome (APS) significantly contributes to adverse outcomes during pregnancy for individuals with APS. SLE increases the risk of preterm birth and preeclampsia (17).

In our study, 54.5% of women with SLE underwent cesarean section. Dur *et al*., noted a similar rate, with cesarean sections reported in 57.6% of pregnant women with SLE, aligning closely with our results (18). In a study conducted in Iran, involving 60 pregnancies among 55 patients with SLE, findings revealed 3 neonatal deaths, 3 spontaneous abortions, and 7 stillbirths. Additionally, 15% of the women experienced preeclampsia, while preterm delivery occurred in 11.6% of the pregnancies. The cesarean section rate was approximately 66% (19).

LBW was another pregnancy outcome we found to significantly differ between women with and without SLE. While prior research indicates that pregnancies in women with SLE considerably elevate the likelihood of preterm delivery (with an odds ratio of 8.87) and LBW (with an odds ratio of 10.35), our study suggests a comparatively lower odds ratio for LBW (20). Strong evidence indicates a link between preeclampsia/eclampsia, fetal loss, stillbirth, and abortion, with a significantly higher occurrence in pregnant women diagnosed with SLE. What's more, there has been an elevated likelihood of cesarean section among these patients. Regarding fetal complications like preterm birth, and LBW, the frequency was notably greater among babies born to mothers with SLE (21).

Attaining favorable pregnancy outcomes for individuals with SLE is achievable, thanks to evidence-based guidelines provided by the American College of Rheumatology (ACR). These guidelines underline the importance of a collaborative, multidisciplinary team comprising rheumatologists, obstetricians, and neonatal specialists, ensuring thorough monitoring throughout the entire journey from preconception to childbirth (2).

Limitations

This study faces several limitations that should be acknowledged. First, due to the retrospective design of the study establishing causality is restricted due to the inherent nature of analyzing past data. Second, since the study is conducted within a single center, the sample may not be representative of the broader population. This could limit the generalizability of the findings. Third, we gathered data from medical records of the participants. Reliance on medical records increases the risk of incomplete or missing data, which could affect the accuracy and reliability of the study results. Despite various investigations into the impact of SLE on pregnancy outcomes, conflicting results persist. The main limitations of these studies are attributed to their small sample sizes and retrospective methodologies (8). Nevertheless, our study incorporated a cohort of 200 SLE patients, comprising individuals from diverse backgrounds, expanding the sample size and encompassing a wider range of APOs could lead to findings that are more robust and applicable across populations. In addition to common APOs that has been frequently studied, research has indicated that maternal SLE is linked to developmental disorders in offspring, such as dyslexia, attention deficit, and speech disorders (21). Therefore, conducting additional prospective longitudinal studies to track offspring and investigate developmental issues is crucial for future research endeavors.

To conclude, our study illustrated that women diagnosed with SLE encounter significantly elevated risks of spontaneous abortion, preterm labor, cesarean section, and low birth weight, with spontaneous abortion being the most common APO. Obtaining knowledge about pregnancy outcomes in individuals with SLE would support clinicians in conducting regular monitoring and check-ups during pregnancy, thereby enhancing pregnancy outcomes within this population. Pre-conception counseling regarding potential risks, optimal timing for pregnancy, and a coordinated, multidisciplinary approach are essential in the management of SLE in patients contemplating pregnancy.

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