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Evaluation of Maternal and Fetal Outcomes of Pregnant Women with Systemic Lupus Erythematosus

Sistemik Lupus Eritematozuslu Gebe Kadınların Maternal ve Fetal Sonuçlarının Değerlendirilmesi

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ÖZ

Amaç: Bu çalışmada sistemik lupus eritematozuslu (SLE) gebelerin obstetrik ve perinatal sonuçlarını değerlendirmeyi amaçladık.

Gereç ve yöntemler: Bu çalışma 2010-2020 yılları arasında 35 SLE hastasının obstetrik sonuçlarını değerlendiren retrospektif bir çalışmadır. Lupus aktivitesi SLE Hastalık Aktivite İndeksi (SLEDAI) kriterlerine göre yapılmış ve gebelik sonuçları aktif ve inaktif SLE olarak gruplandırılarak değerlendirilmiştir.

Bulgular: Ortalama maternal yaş 29 (21-39) idi. Antifosfolipid sendromu ve aktif hastalık oranı sırasıyla %5 ve %40 idi. 30 canlı doğum oldu. Biri majör kardiyak anomalili, diğeri renal agenezili olmak üzere iki gebelik terminasyonu rapor edildi. Aktif SLE grubunda bir spontan abortus ve 2 ölü doğum gözlendi. İntrauterin büyüme geriliği, preeklampsi ve erken doğum oranları sırasıyla %8, %20 ve %26 idi. Aktif SLE grubunda fetal kayıp ve erken doğum anlamlı olarak daha yüksekti (p=0,018, p=0,023). Aktif SLE grubunda daha yüksek yenidoğan yoğun bakım ünitesine (YYBB) yatış oranı gözlendi (p=0,034) ancak Apgar skorları <8 ve umbilikal kord kanı pH'ı gruplar arasında benzerdi (p>0,05).

Sonuç: Bilimdeki gelişmelere rağmen, aktif SLE hastalığının, olumsuz gebelik sonuçlarına yol açma riski yüksektir. Yakın takip, özellikle erken doğumlar başta olmak üzere gebelik komplikasyonlarını azaltmaya yardımcı olabilir.

Anahtar Kelimeler: Sistemik lupus eritematozus, aktif hastalık, perinatal sonuçlar

ABSTRACT

Aim: To evaluate obstetrical and perinatal outcomes of pregnancies with systemic lupus erythematosus (SLE).

Materials and Method: This was a retrospective study evaluating obstetric outcomes of 35 patients with SLE who were followed up between 2010 and 2020. Lupus activity was based on SLE Disease Activity Index (SLEDAI) criteria and pregnancy outcomes were evaluated by grouping as active and inactive SLE.

Results: The mean maternal age was 29 (21-39). The rate of antiphospholipid syndrome and active disease was 5% and 40% respectively. There were 30 live births. Two elective abortions were reported, one with major cardiac anomaly and the other with renal agenesis. One spontaneous abortion and 2 stillbirths were observed in the active SLE group. Overall rates of intrauterine growth retardation, preeclampsia, and preterm delivery were 8%, 20%, and 26%, respectively. Fetal loss and preterm delivery were significantly higher in the active SLE group (p=0,018, p=0,023). A higher rate of neonatal intensive care unit (NICU) admission was observed in the active SLE group (p=0,034) but Apgar scores less than <8 and umbilical cord pH were similar between groups (p>0,05).

Conclusion: Despite advances in the medical sciences, an active disease with SLE has an elevated risk of inducing adverse pregnancy outcomes. Close follow-up could helps reduce pregnancy complications, especially preterm deliveries.

Keywords: Systemic lupus erythematosus, active disease, perinatal outcomes

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INTRODUCTION

Systemic lupus erythematosus (SLE) affects women of childbearing age, and a pregnancy with SLE carries a higher maternal and fetal risk than a pregnancy carried by a healthy woman (1). Conditions such as hypertension, hypocomplementemia, previous nephropathy, the presence of antiphospholipid antibodies (aPL), and the presence of active lupus (during pregnancy and up to six months before pregnancy) are associated with adverse perinatal outcomes (1–3). Studies show that patients with evidence of active SLE should postpone pregnancy for at least six months until the disease is well controlled (1,4). However, the effect of pregnancy on SLE activity is unclear, and adverse perinatal outcomes are also observed in cases in which disease activity is low or absent (5,6). In this study, we analyzed all available data on pregnant women with SLE who were followed up by our clinic. We evaluated the relationship between active SLE and adverse fetal and maternal outcomes.

MATERIALS AND METHODS

Data on pregnant women who were followed up by the Gazi University Hospital Fetal Medicine Unit between October 2010 and October 2020 was retrospectively evaluated. Thirty-five pregnant women diagnosed with SLE, based on the SLE classification criteria of the 1997 American College of Rheumatism, were included in the study. Approval for the study was obtained from the Gazi University Faculty of Medicine Clinical Research Ethics Committee with the ethics committee decision no: 186 dated:22.02.2021. The medical records of the study patients were investigated, with data from demographic notes, clinical findings related to SLE, laboratory results, medication, and perinatal outcomes taken into account. Patients with incomplete records were excluded from the study. The SLE Disease Activity Index (SLEDAI) criteria were used to evaluate disease activity, and cases with a score of four and above were classified as active disease. Pregnancy outcomes were categorized as either active and inactive SLE.

Statistical analysis

Statistical analysis was carried out using SPSS version 21.0. After performing descriptive statistics, data were presented as number (n), rate (%), mean and standard deviation (sd), or median where appropriate. Chi-square, Fisher exact and Mann-Whitney tests were used to compare pregnant women with active and inactive SLE. A p-value < 0.05 was considered statistically significant.

RESULTS

Thirty-five cases were analyzed in this study. Table 1 presents the demographics of the study population. The mean maternal age was 29 (21–39). Five patients had a coexisting systemic disease: familial Mediterranean fever in one case, and Hashimoto thyroiditis in four cases. Systemic involvement due to SLE was found in 4 (11%) patients, which involved the central nervous system (CNS), heart, and kidney. The rates of antiphospholipid syndrome (APS) and active disease were 5% and 40%, respectively. There were 30 live births. Two elective abortions were reported, one with a major cardiac anomaly and the other with renal agenesis. One spontaneous abortion and two stillbirths were recorded, two of which were in the active SLE group. As seen in Table 4, there was no significant difference between the active and inactive SLE groups in terms of abortions and stillbirths ($p < 0.05$). However, fetal loss—including spontaneous abortion and stillbirth—was significantly higher in the active SLE group (p=0,018). Table 2 shows the patients with positive antibodies and the drugs used. Anti-Ro, anti-La, and anti-double stranded DNA (anti-dsDNA) antibodies were positive in 23%, 4%, and 48% of patients, while low level of complement component 3 (C3) and complement component 4 (C4) were observed in 25% and 50% of the patients. The aPL in the APS classification criteria include anticardiolipin, anti-beta2-glycoprotein, and lupus anticoagulant (7). The prevalence of anticardiolipin and anti-β2 glycoprotein positivity were 33% ve 47%, respectively. However, there was no lupus anticoagulants positivity. While aPL positivity was 25%, the number of patients with APS—based on Sapporo classification—was 5% (7). The vast majority (97%) of the women in this study were using hydroxychloroquine (HCQ). The distribution of use of SLE-specific immunosuppressives was 14% prednisolone, 5% azathioprine, and 5% cyclosporine. Overall rates of intrauterine growth retardation, preeclampsia, and preterm delivery were 8%, 20%, and 26%, respectively. Preterm delivery was significantly higher in the active SLE group (p=0,023). The mean gestational age at birth was 37 ± 3 weeks, and the cesarean section (CS) birth rate was 63%. The number of patients with 1st and 5th minute Apgar scores of <8 were 5 (16%) and 1 (3%), respectively. Three (10%) newborns were admitted to the neonatal intensive care unit (NICU) due to prematurity. A higher rate of NICU admission was observed in the active SLE group (p=0,034), but Apgar scores of less than eight and umbilical cord pH were similar between the two study groups (p>0,05).

Table 1. Characteristics of patients with SLE

	Mean (min-max)
Maternal age	29 (21-39)
Gravida	2 (1-9)
Parity	1 (0-4)
Number of miscarrages	0 (0-2)
	N (%)
Coexisting disease	5 (14%)
System involvement	4 (11%)
Renal (LN)	2 (5%)
Central nervous system	1 (3%)
Cardiac disease (LSE)	1 (3%)
Antiphospholipid syndrome	2 (5%)
Active disease	14 (40%)

LN: lupus nephritis, LSE: Libman–Sacks endocarditis

Table 2. Antibodies and medications

Antibodies	n/N (%)
Anti-Ro	6/26 (23%)
Anti-La	2/25 (4%)
Anti-dsDNA	16/33 (48%)
C3 complement (low)	7/27 (25%)
C4 complement (low)	13/26 (50%)
Lupus anticoagulant	0/27
Anticardiolipin	11/33 (33%)
Anti-β2 glycoprotein	10/21 (47%)
Medications	**N (%)**
Hydroxychloroquine	34 (97%)
Prednisolone	5 (14%)
Azathioprine	2 (5%)
Cyclosporin	2 (5%)
Aspirin	22 (62%)
Thromboprophylaxis (LMWH)	18 (51%)

LMWH: Low-molecular-weight heparin

Table 3. Overall pregnancy outcomes with SLE.

Pregnancy outcome	N (%)
Livebirth	30 (85%)
Miscarriage	1 (3%)
Elective abortion*	2 (6%)
Stillbirth	2 (6%)
Obstetric complication	21 (60%)
Gestational hypertension	1 (2%)
Preeclampsia	7 (20%)
HELLP	1 (2%)
Intrauterin growth retardation	3 (8%)
Placenta previa	1 (2%)
Preterm delivery	8 (26%)
Delivery results in livebirth	**N (%)**
Gestational week at delivery	37±3
CS	19 (63%)
Birth weight	2702±756
1-min Apgar score <8	5 (16%)
5-min Apgar score <8	1 (3%)
Umbilical artery pH	7,34±0,07
Admissions to NICU	3 (10%)
Prematurity	3 (10%)

HELLP syndrome: hemolysis, elevated liver enzymes, low platelet syndrome, CS: caesarean section, NICU: neonatal intensive care unit * two for fetal abnormality

Table 4. Comparison of perinatal outcomes between active and inactive SLE pregnancies

	İnactive SLE (n=21)	Active SLE (n=14)	P value
Miscarriage	0 (0%)	1 (7,7%)	0,187
Stillbirth	0 (0%)	2 (15,4%)	0,058
Fetal loss	0 (0%)	3 (23,1%)	**0,018**
Hypertensive diseases of pregnancy	4 (18,1%)	5 (38,5%)	0,269
Intrauterin growth retardation	2 (9,1%)	1 (7,7%)	0,051
Preterm delivery	3 (13,6%)	5 (38,5%)	**0,023**
CS	14 (63,6%)	5 (38,5%)	0,076
1-min Apgar score <8	3 (13,6%)	2 (15,4%)	0,208
5-min Apgar score <8	0 (0%)	1 (7,7%)	0,090
Umbilical artery pH	7,35±0,06	7,33±0,09	0,593
Admissions to NICU	0 (0%)	3 (23,1%)	**0,034**

Hypertensive diseases of pregnancy was including in gestational hypertension, preeclampsia and HELLP, CS: caesarean section, NICU: neonatal intensive care unit

DISCUSSION

We reported the pregnancy outcomes of patients with SLE at our clinic. In women with SLE, pregnancy carries high maternal and fetal risks, including pregnancy loss, preeclampsia, and preterm labor, especially in the presence of active disease (8,9) . In this study, the rate of active disease was 34%, and we found that SLE activity during pregnancy was significantly associated with fetal loss, preterm labor, and neonatal intensive care needs.

SLE is a chronic autoimmune disease of unknown cause, and based on clinical findings, it can progress to involvements ranging from mild joint and skin involvement to life-threatening renal, hematological, or central nervous system involvement (10). Pregnancy in women with SLE occurs at a frequency of 82 per 100,000 deliveries (10,11). SLE affects women of childbearing age, and the median age in this study was 29 (21–39). Disease activity and major organ involvement are associated with adverse pregnancy outcomes. Patients with active SLE, especially lupus nephritis, should be advised to postpone getting pregnancy for at least six months until the disease is well controlled (1,12). In our study, systemic involvement was observed in 11% of the patients, predominantly those with renal disease. Preeclampsia developed in two patients who had a renal disease. The findings of a separate study, which included 385 pregnant SLE patients, suggest that there is an increased risk of adverse pregnancy outcomes in patients with a history of renal disease (13). A meta-analysis showed a prior case of renal disease was associated with high rates of preeclampsia (6,14) . Kalok et al. evaluated 71 pregnant women with SLE and observed that the frequency of APS was 32.4% (15). In another study, in which 102 patients were evaluated, aPL positivity was

found to be 29.4%, while the frequency of APS was 9.8% (16). Similarly, in our study, while aPL positivity was high, only 5% of the patients had APS. In another study, 43.8% of patients with aPL had negative pregnancy outcomes, while only 15.4% of those without aPL had negative pregnancy outcomes (13). In our study, all pregnant women who had stillbirths and spontaneous abortions were positive for aPL antibodies, but only one of the patients who had a stillbirth was diagnosed with APS. These findings confirm that aPL positivity is important for predicting the prognosis of pregnancies in patients with SLE. Many studies have been conducted on the effects of anti-Ro, anti-La, anti-dsDNA, and complement levels on pregnancy prognosis. In contrast to studies in which anti-dsDNA positivity, low C3, and C4 were found to be associated with high pregnancy loss and preterm birth(17–19), there are studies found these factors to not to be associated with adverse pregnancy outcomes (5,20). Clowse et al. reported that anti-dsDNA positivity, low C3, and lowC4 are associated with high pregnancy loss and preterm birth (19). Buyon et al. reported that anti-dsDNA and low complement levels in the second and third trimesters were not associated with adverse pregnancy outcomes (5). In our study, low C3 was detected in 25% of the patients, low C4 was detected in 50%, and anti-ds DNA positivity in 48%. Anti-Ro positivity was 23% and anti-La positivity was 4%, while fetal heart block was not observed. The prevalence of congenital heart block in prospectively followed newborns of women known to be anti-Ro positive in patients with SLE was found to be 2% (21). The use of HCQ has been shown to reduce the incidence of congenital heart block in at-risk fetuses of mothers with anti-Ro and anti-La antibodies (22). HCQ medication was administered to 97% of the patients. Low-dose aspirin use is recommended in pregnant women with SLE because it reduces preeclampsia (23). Sixty-two percent of our patients used aspirin.

The live birth rate was 85% and similar to the rate reported in other studies (9,15). The miscarriage rate was lower than expected, which is attributable to the study population being limited to only patients admitted to Gazi Universty Hospital. In the literatüre, the rate of the fetal loss, including spontaneous abortions and stillbirths, varies between 8% and 28% (9,17,18,20). Similarly, in our study, fetal loss rate was 9%. The overall rates of intrauterine growth retardation, preeclampsia, and preterm delivery were 8%, 20%, and 26%, respectively. These are the most common complications of lupus pregnancy, as demonsrated by several studies (1–3,13). Women with SLE had a two to four times higher rate of pregnancy complications than the non-SLE population (10). In addition, the rate of CS among SLE patients is higher than among the normal population (6,8,9). In our study, we determined the rate of CS to be 63%. The NICU requirement in this study was 10% and were all were due to prematurity. In another study, in which 71 pregnant women with SLE were evaluated, the need for NICU was 16% (15), a similar finding to that of our study.

It has been established that active disease in SLE is associated with adverse pregnancy outcomes, and our study findings occur with those of these other studies. One spontaneous abortion and two stillbirths were recorded in the active SLE group, and the fetal loss rate was significantly higher in this group. Liu et al. evaluated 111 pregnancies, and like our study, they found that the rate of fetal loss was significantly higher among active SLE patients (9). However, in a study in which active disease was observed in 33% of 85 pregnant women with SLE, no difference was observed between women with active disease and those with inactive diseases in terms of fetal outcomes (including abortion and stillbirth) (24). In our study, the rate of preterm birth and admission to the NICU due to prematurity were found to be significantly higher in the active SLE group. In another study—with 22% of the participants having active SLE—preeclampsia, fetal growth retardation, and preterm delivery were significantly higher in the active SLE group than in the inactive SLE group (9).

CONCLUSION

Despite advances in medical treatment, SLE patients have adverse pregnancy outcomes, especially in the cases of active disease. In our study, this risk was found to be significantly high. For these patients, preconception counseling and delaying pregnancy until after a remission period of at least six months are important for preventing adverse pregnancy outcomes. Close monitoring of the pregnancies of patients with SLE by a multidisciplinary team is an effective measure for preventing potential complications.

Study Limitations

This study has some limitations. First, it has a retrospective design, and the second, it was conducted at a single institution. Studies involving many health centers and evaluating many more patients will deepen our knowledge of SLE patients.

Authorship Contributions

Concept: D.K., A.T., E.T., Design: D.K., A.T., E.T., Data Collection or Processing: G.T., S.K., Analysis or Interpretation: S.K.,

G.T., Literature Search: D.K., E.T., Writing: E.T., H.K., D.K.

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