ORIGINAL ARTICLES
ОРИГИНАЛНИ СТАТИИ

Pregnancy outcomes in women with systematic lupus erythematosus: a matched cohort study of maternal and perinatal complications

K. Neykova, I. Shikova, S. Hitrova-Nikolova, P. Radulova, I. Kostov

"Maichin Dom" State University Hospital – Sofia

Бременност при системен лупус еритематозус: сравнителен анализ на майчините и феталните усложнения спрямо здрави бременни

К. Нейкова, И. Шикова, С. Хитрова-Николова, П. Радулова, И. Костов

УСБАЛАГ „Майчин Дом" – София

Abstract:

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease predominantly affecting women of reproductive age. Despite substantial advances in diagnostics, treatment and multidisciplinary care, pregnancies complicated by SLE remain associated with increased maternal and perinatal morbidity. **Objective.** To compare maternal and perinatal outcomes in pregnancies complicated by SLE with those of healthy pregnant controls and to quantify the risk of major obstetric and neonatal complications associated with the disease. **Materials and Methods.** A combined retrospective and prospective matched cohort study was conducted, including 75 pregnant women with SLE and 75 healthy pregnant controls. The groups were matched for maternal age, body mass index (BMI) and parity. Maternal outcomes included preeclampsia (PE), Caesarean delivery (CD) and termination of pregnancy for medical indications (TOP). Perinatal outcomes comprised preterm birth (PB), fetal growth restriction/small for gestational infants (FGR/SGA) and neonatal bradycardia (NB). Univariable logistic regression analysis was performed to estimate the odds ratios (ORs) for the major pregnancy complications. **Results.** No significant differences were observed between the study groups regarding maternal age, BMI or parity. Women with SLE had significantly higher rates of preeclampsia (17.3% vs. 0%; $p < 0.001$), preterm birth (35.2% vs. 1.3%; $p < 0.001$), FGR/SGA (21.3% vs. 1.3%; $p < 0.001$) and neonatal bradycardia (21.1% vs. 0%; $p < 0.001$). CD was performed significantly more frequently in women with SLE than in healthy controls (69.0% vs. 52.0%; $p = 0.036$). Univariable logistic regression demonstrated markedly increased risks of NB (OR = 41.43; 95% CI 5.37–5324.11), PB (OR = 40.22; 95% CI 5.27–306.95), PE (OR = 32.62; 95% CI 4.18–569.07) and FGR/SGA (OR = 20.07; 95% CI 2.59–155.74). **Conclusions.** Pregnancies complicated by SLE are associated with a substantially increased risk of major maternal and perinatal complications compared with healthy pregnancies. These findings highlight the importance of multidisciplinary prenatal care, individualized risk assessment and specialized maternal and fetal surveillance in women with SLE.

Key words:

systemic lupus erythematosus, pregnancy, preeclampsia, preterm birth, fetal growth restriction, small for gestational age, neonatal bradycardia

Address for correspondence:

Assoc. Prof. Konstantsa Neykova, MD, PhD, e-mail: neykovaconstantsa@yahoo.com

Резюме:

Системният лупус еритематозус (СЛЕ) е хронично автоимунно заболяване, засягащо предимно жени в репродуктивна възраст. Въпреки напредъка в диагностиката и лечението, бременността при пациентки със СЛЕ остава свързана с повишен риск от майчини и фетални усложнения. **Цел.** Да се сравни честотата на майчините и феталните усложнения при бременни със СЛЕ и здрави бременни контроли. **Материал и методи.** Проведено беше комбинирано ретроспективно и проспективно кохортно проучване, включващо 75 бременни със СЛЕ и 75 здрави бременни контроли, съпоставени по възраст, индекс на телесна маса (ИТМ) и паритет. Анализирани бяха честотата на преeклампсия (ПЕ), преждевременно раждане (ПР), вътреутробно изоставане в растежа на плода/малък за гестационната възраст плод (ИУРП/SGA), фетална брадикардия, плацентарно медиирани усложнения (ПМУ) и начин на родоразрешение. **Резултати.** В групата със СЛЕ беше установена значително по-висока честота на ПЕ (17.3% срещу 0%; p < 0.001), ПР (35.2% срещу 1.3%; p < 0.001), ИУРП/SGA (21.3% срещу 1.3%; p < 0.001), фетална брадикардия (21.1% срещу 0%; p < 0.001) и ПМУ (48.0% срещу 1.3%; p < 0.001). Цезаровото сечение (ЦС) беше значимо по-често при пациентките със СЛЕ (69.0% срещу 52.0%; p = 0.036). Най-висок риск беше установен за неонатална брадикардия (OR = 41.43), ПР (OR = 40.22) и ПЕ (OR = 32.62). **Заключение**. Бременността при пациентки със СЛЕ е свързана със значително повишен риск от майчини и фетални усложнения в сравнение със здрави бременни жени. Получените резултати подчертават необходимостта от специализирано проследяване и мултидисциплинарен подход при тези пациентки.

Ключови думи:

системен лупус еритематозус; бременност; преeклампсия; преждевременно раждане; IUGR; плацентарно медиирани нарушения

Адрес за кореспонденция:

Доц. д-р Констанца Нейкова, дм, e-mail: neykovaconstantsa@yahoo.com

Introduction

Systemic lupus erythematosus (SLE) is a chronic multisystem autoimmune disease characterized by the loss of immune tolerance, the production of pathogenic autoantibodies and immune-complex deposition, resulting in inflammation and damage to multiple organs [1, 2]. Because SLE predominantly affects women of reproductive age, pregnancy represents a major clinical challenge requiring close collaboration between rheumatologists, obstetricians and neonatologists [3].

Over the past decades, advances in disease monitoring, immunosuppressive therapy and multidisciplinary obstetric care have substantially improved maternal and fetal survival. Nevertheless, pregnancies complicated by SLE remain associated with significantly increased maternal and perinatal morbidity compared with the general obstetric population [3–5]. Current recommendations emphasize on pregnancy being planned during periods of sustained disease remission. However, adverse pregnancy outcomes continue to occur even in women with clinically quiescent disease [3, 6].

Numerous cohort studies and systematic reviews have demonstrated that women with SLE are at increased risk of preeclampsia (PE), preterm birth (PB), fetal growth restriction (FGR), delivery of small-for-gestational-age (SGA) infants and fetal loss [7–9]. In the international PROMISSE study, adverse pregnancy outcomes occurred despite relatively well-controlled disease activity, highlighting the multifactorial nature of pregnancy complications in SLE and suggesting that mechanisms beyond active clinical disease contribute to placental dysfunction and impaired fetal development [10].

The mechanisms responsible for adverse pregnancy outcomes in SLE are complex and include chronic systemic inflammation, endothelial dysfunction, complement activation, immune-mediated vascular injury and abnormal placentation [11–13]. These processes may impair uteroplacental perfusion, resulting in hypertensive disorders of pregnancy, fetal growth restriction and spontaneous preterm birth. In addition, maternal autoantibodies and immune activation may adversely influence fetal and neonatal outcomes through mechanisms that are only partially understood [14].

Despite the growing body of evidence regarding pregnancy in women with SLE, considerable variability exists in the reported incidence of obstetric and neonatal complications. Differences in disease severity, ethnicity, treatment strategies and obstetric management may explain much of this heterogeneity [7-10]. Furthermore, published data from Eastern Europe remain limited, and studies from Bulgarian populations are scarce.

Preliminary risk estimation associated with individual pregnancy complications is essential for appropriate preconception counselling, individualized antenatal surveillance and multidisciplinary pregnancy management. Comparative cohort studies including healthy pregnant controls provide an opportunity to quantify the excess risk attributable to SLE and to identify the complications that contribute most substantially to maternal and neonatal morbidity.

Therefore, the aim of the present study was to compare the frequency of major maternal and perinatal complications in pregnancies complicated by systemic lupus erythematosus with those observed in healthy pregnant controls and to quantify the risk associated with each individual complication.

Materials and methods

The present study was designed as a combined retrospective and prospective matched cohort study comparing maternal and perinatal outcomes in pregnancies complicated by systemic lupus erythematosus (SLE) with those of healthy pregnant women.

A total of 150 pregnant women were enrolled and allocated into two study groups. The study group (SG) consisted of 75 women with confirmed SLE, while the control group (CG) included 75 healthy pregnant women without autoimmune diseases. Controls were matched to the SLE group according to their maternal age, body mass index (BMI) and parity.

Women were eligible for inclusion in the SLE group if they fulfilled the 2019 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) or the 2012 Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for SLE [15, 16]. Only pregnancies with complete obstetric follow-up and a documented pregnancy outcome were included. Healthy pregnant women with singleton pregnancies and no history of autoimmune diseases served as controls. Multiple pregnancies, pregnancies with incomplete medical documentation, unknown pregnancy outcomes and women with other systemic autoimmune disorders were excluded.

Maternal demographic, clinical and obstetric data were obtained from the available medical records. We analyzed demographic variables such as maternal age, body mass index (BMI) and parity. The analyzed obstetric variables included gestational age at delivery, mode of delivery, maternal complications, perinatal complications.

Maternal outcomes included preeclampsia (PE), Caesarean delivery (CD), termination of pregnancy for medical indications (TOP). Termination of pregnancy was analyzed as an independent maternal outcome and reflected pregnancies interrupted because of severe maternal disease progression and/or fetal compromise according to contemporary obstetric practice.

Perinatal outcomes included preterm birth (PB), fetal growth restriction/small for gestational age (FGR/SGA), neonatal bradycardia (NB). Preterm birth was defined as delivery before 37+0 weeks of gestation [17]. Fetal growth restriction and small-for-gestational-age fetuses were diagnosed according to the contemporary international criteria proposed by Figueras and Gratacós and the ISUOG Practice Guidelines [18, 19]. Neonatal bradycardia was defined as documented bradycardia diagnosed during the neonatal period on the basis of neonatal clinical assessment and medical documentation.

Continuous variables were expressed as the mean ± the standard deviation (Mean ± SD), whereas categorical variables were presented as absolute numbers (n) and percentages (%). Continuous variables were compared using the independent-samples t-test. Categorical variables were analyzed using Pearson's χ^2 test or Fisher's exact test, as appropriate. Univariable logistic regression analysis was performed to estimate the association between SLE and each maternal and perinatal complication. Results were expressed as odds ratios (ORs), 95% confidence intervals (95% CIs) and corresponding p-values. For outcomes containing zero cells, odds ratios and confidence intervals were estimated using penalized logistic regression (Firth correction) or continuity-corrected methods, as appropriate [20]. A two-sided p-value < 0.05 was considered statistically significant.

Results

A total of 150 pregnant women were included in the study and allocated into two groups: 75 women with SLE and 75 healthy pregnant controls.

Table 1. Baseline demographic and obstetric characteristics of the study groups

Variable	SLE group (n = 75)	Controls (n = 75)	p-value
Maternal age, years, Mean ± SD	31.45 ± 5.01	31.43 ± 5.03	0.98
BMI, kg/m², Mean ± SD	23.36 ± 3.39	23.35 ± 3.16	0.996
Primiparous women, n (%)	41/71 (57.7%)	43/75 (57.3%)	0.965

SLE – systemic lupus erythematosus; BMI – body mass index; SD – standard deviation.
Abbreviations: SLE – systemic lupus erythematosus; BMI – body mass index; SD – standard deviation.
Note: Parity was analyzed among completed pregnancies only (71 pregnancies in the SLE group, as four pregnancies were terminated for medical indications).

The two groups were comparable with respect to maternal age, body mass index (BMI) and parity. The mean maternal age was **31.45 ± 5.01 years** in the SLE group and **31.43 ± 5.03 years** in the control group (CG), *p* = 0.98. Likewise, no statistically significant differences were observed in BMI (23.36 ± 3.39 vs. 23.35 ± 3.16 kg/m²; p = 0.996) or parity (*p* = 0.965).

These findings indicate that both study groups were well-matched and that subsequent differences in pregnancy outcomes were unlikely to be attributable to demographic characteristics.

The frequencies of maternal and perinatal complications are summarized in Table 2 and illustrated in Fig.1.

Table 2. Maternal and perinatal outcomes in women with systemic lupus erythematosus and healthy pregnant controls

Outcome	SLE (n = 75)	Controls (n = 75)	p value
Maternal outcomes			
Preeclampsia, n (%)	13 (17.3)	0 (0.0)	< 0.001
Termination of pregnancy (TOP), n (%)	4 (5.3)	0 (0.0)	0.12
Caesarean delivery*, n (%)	49/71 (69.0)	39/75 (52.0)	0.037
Perinatal outcomes			
Preterm birth, n (%)	25/71 (35.2)	1 (1.3)	< 0.001
FGR/SGA, n (%)	16 (21.3)	1 (1.3)	< 0.001
Neonatal bradycardia, n (%)	15/71 (21.1)	0 (0.0)	< 0.001

**Calculated only among completed pregnancies.*
Abbreviations: SLE – systemic lupus erythematosus; TOP – termination of pregnancy for medical indications; PMD – placenta-mediated disorders; FGR – fetal growth restriction; SGA, small for gestational age.

PE occurred in **13 of 75 women (17.3%)** with SLE, whereas no cases were recorded among healthy pregnant controls (p < 0.001).

TOP was performed in **4 women (5.3%)** in the SLE group and in none of the controls (p = 0.12). In all four cases, pregnancy termination resulted from a combination of severe maternal disease progression, uncontrolled hypertension and evidence of early fetal growth restriction.

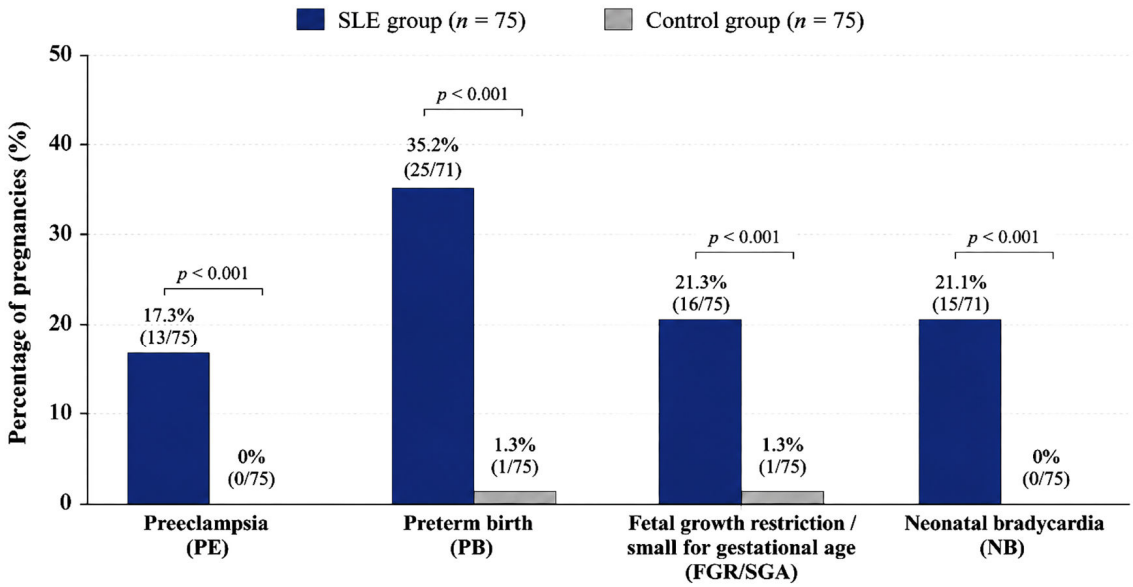
Among completed pregnancies, CD was performed significantly more frequently in women with SLE than in healthy controls **(69.0% vs. 52.0%; p = 0.037).**

Regarding perinatal outcomes, PB occurred in **25 of 71 pregnancies (35.2%)** among women with SLE compared with 1 of 75 pregnancies (1.3%) in the CG (*p* < 0.001).

Similarly, FGR/SGA was diagnosed in **16 of 75 pregnancies (21.3%)** among women with SLE compared with **1 of 75 pregnancies (1.3%)** among healthy pregnant controls (*p* < 0.001).

Neonatal bradycardia (NB) was documented in **15 of 71 neonates (21.1%)** born to mothers with SLE, whereas no cases were observed in the CG (*p* < 0.001).

Collectively, these findings demonstrate that pregnancies complicated by SLE were associated with a significantly higher frequency of both maternal and perinatal complications compared with healthy pregnancies.



Note: Percentages are calculated using the total number of pregnancies in each group.

Abbreviations: SLE, systemic lupus erythematosus; PE, preeclampsia; PB, preterm birth; FGR, fetal growth restriction; SGA, small for gestational age; NB, neonatal bradycardia.

Fig. 1. Maternal and perinatal complications in pregnancies complicated by SLE compared with healthy controls

The results of the univariable logistic regression analysis are summarized in Table 3 and illustrated in Fig. 2.

Women with SLE demonstrated significantly increased odds of all analyzed maternal and perinatal complications compared with healthy pregnant controls. The highest risk was observed for **NB** (OR = **41.4**; 95% CI **2.4–71**1; p < 0.001), followed by cases with **PB** (OR = **40.2**; 95% CI **5.3–303**; p < 0.001).

The odds of developing **PE** were more than thirty-fold higher among women with SLE than among healthy controls (OR = **32.6;** 95% CI **2.0–560**; *p* < 0.001).

Likewise, women with SLE had an approximately 20-fold increased risk of FGR/SGA compared with healthy pregnant women (OR = **20.1**; 95% CI **2.5–160**; *p* < 0.001).

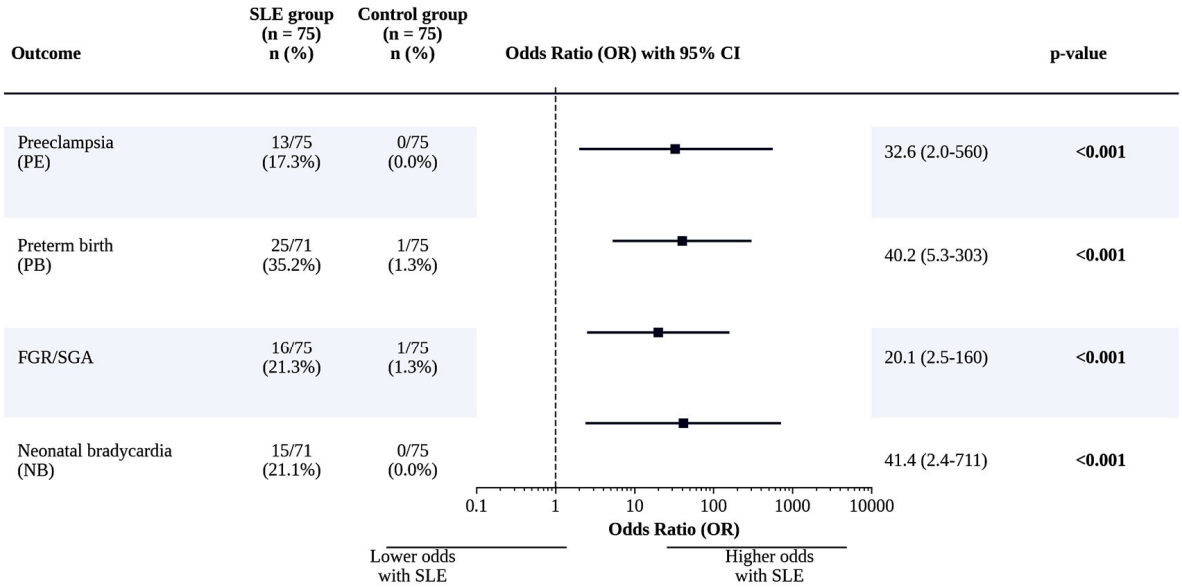
Although relatively wide confidence intervals were observed for PE and NB because of the limited number of events, all analyzed associations remained statistically significant.

Overall, the findings demonstrate that SLE is associated with a markedly increased risk of adverse maternal and perinatal outcomes.

Table 3. Risk of developing major maternal and perinatal complications in pregnancies complicated by systemic lupus erythematosus

Outcome	SLE	Controls	OR	95% CI	p-value
Preeclampsia (PE)	13/75	0/75	32.6	2.0–560	< 0.001
Preterm birth (PB)	25/71	1/75	40.2	5.3–303	< 0.001
FGR/SGA	16/75	1/75	20.1	2.5–160	< 0.001
Neonatal bradycardia (NB)	15/71	0/75	41.4	2.4–711	< 0.001

Abbreviations: SLE – systemic lupus erythematosus; OR – odds ratio; CI – confidence interval; PE – preeclampsia; PB – preterm birth; FGR – fetal growth restriction; SGA – small for gestational age; NB – neonatal bradycardia.
Note: For outcomes related to completed pregnancies and neonates, the denominator in the SLE group was 71. Odds ratios for outcomes with zero cells were estimated using penalized logistic regression or continuity-corrected methods, as appropriate.



Note: Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using univariable logistic regression.
For outcomes with zero cells, penalized logistic regression (Firth correction) was applied.

Abbreviations:SLE, systemic lupus erythematosus; PE, preeclampsia; PB, preterm birth; FGR, fetal growth restriction; SGA, small for gestational age; NB, neonatal bradycardia.

Fig. 2. Association between systemic lupus erythematosus (SLE) and major maternal and perinatal complications: univariable logistic regression analysis

Discussion

The present matched cohort study demonstrates that pregnancies complicated by SLE are associated with a substantially increased risk of adverse maternal and perinatal outcomes compared with healthy pregnant controls. Women with SLE experienced significantly higher rates of PE, PB, FGR/SGA infants and NB. These findings confirm that, despite considerable advances in disease monitoring and multidisciplinary obstetric care, SLE remains an important determinant of pregnancy-related morbidity.

One of the principal findings of the present study is the markedly increased incidence of PE. PE occurred in 17.3% of women with SLE, whereas no cases were

observed among healthy controls. This observation is consistent with the findings of the PROMISSE study, in which PE occurred in approximately 10–23% of pregnancies complicated by SLE, depending on maternal disease characteristics and baseline risk factors [10]. Similar results have been reported in a large meta-analysis by Bundhun et al., demonstrating that women with SLE have a significantly increased risk of hypertensive disorders of pregnancy compared with healthy pregnant women [7]. Chronic systemic inflammation, endothelial dysfunction, complement activation and immune-mediated vascular injury are considered the principal mechanisms responsible for the increased susceptibility to PE in these pregnancies [11-13].

PB represented another major adverse pregnancy outcome in the present cohort. More than one-third of pregnancies in women with SLE resulted in delivery before 37 completed gestational weeks, whereas only one PB occurred among healthy controls. The estimated odds ratio exceeding 40 emphasizes the strong association between SLE and premature delivery. Comparable rates have been reported by Smyth et al. in their meta-analysis of pregnancy outcomes in women with SLE and lupus nephritis [8], while Moroni and Ponticelli similarly observed that active disease and renal involvement substantially increase the likelihood of PB [9]. More recent systematic reviews continue to identify PB as one of the most frequent adverse outcomes in pregnancies complicated by SLE [3, 7].

The present study also demonstrated a significantly increased frequency of FGR and delivery of SGA infants among women with SLE. The observed incidence of 21.3% is comparable with the previously published data reporting frequencies ranging from 15% to 30% [3, 8, 9]. Immune-mediated vascular dysfunction, impaired trophoblast invasion and reduced uteroplacental perfusion are considered the principal mechanisms responsible for restricted fetal growth in pregnancies complicated by autoimmune disease [11–13]. These findings further support the concept that chronic maternal inflammation adversely affects placental function and fetal development even when pregnancy progresses beyond the first trimester.

A particularly noteworthy finding of the present study is the remarkably high frequency of NB. Neonatal bradycardia was documented in more than one-fifth of newborns delivered by mothers with SLE and represented the complication associated with the highest estimated odds ratio among all analyzed outcomes. Although congenital complete heart block has traditionally received the greatest attention in literature, NB has rarely been evaluated as an independent clinical endpoint. Previous studies have generally described cardiac rhythm abnormalities within the broader spectrum of neonatal lupus rather than investigating neonatal bradycardia separately [14–16]. The present findings, therefore, suggest that disturbances of neonatal cardiac rhythm may be more common than previously recognized and deserve greater attention during neonatal assessment and follow-up.

Another important observation is that all evaluated complications demonstrated markedly elevated odds ratios despite the relatively limited sample size. Although wide confidence intervals were observed for PE and NB because of the low number of events, the magnitude and consistency of the observed associations strongly support the clinical relevance of these findings. The use of a matched healthy CG further strengthens the interpretation by minimizing the influence of major demographic confounders such as maternal age, BMI and parity.

The principal strengths of the present study include the matched cohort design, the inclusion of a healthy control group and the simultaneous evaluation of several clinically relevant maternal and perinatal outcomes within the same population. These characteristics enabled a reliable quantitative assessment of the excess risk associated with SLE and provide contemporary data from a population for which published evidence remains limited.

Several limitations should also be acknowledged. First, the relatively limited sample size resulted in wide confidence intervals for some analyzed outcomes, particularly neonatal bradycardia and preeclampsia. Second, the study was conducted in a limited number of tertiary referral centres, which may affect the generalizability of the results to other populations. Finally, although the present study quantified the risk of major obstetric and neonatal complications, it was not designed to investigate the contribution of individual immunological factors or treatment strategies to pregnancy outcome. These questions require dedicated analyses and will be addressed in subsequent studies.

In conclusion, pregnancies complicated by systemic lupus erythematosus remain associated with substantially increased risks of preeclampsia, preterm birth, fetal growth restriction/small-for-gestational-age infants and neonatal bradycardia. These findings emphasize the importance of preconception counselling, individualized risk assessment and multidisciplinary maternal–fetal care. Furthermore, the high incidence of neonatal bradycardia observed in the present cohort indicates that neonatal cardiac rhythm disturbances deserve further investigation and may represent an important area for future research in pregnancies complicated by systemic lupus erythematosus.

References

1. Tsokos GC. Systemic lupus erythematosus. N Engl J Med. 2011;365:2110–2121.
2. Rees F, Doherty M, Grainge MJ, et al. The worldwide incidence and prevalence of systemic lupus erythematosus. Rheumatology (Oxford). 2017;56:1945–1961.
3. Sammaritano LR. Pregnancy in systemic lupus erythematosus. Best Pract Res Clin Obstet Gynaecol. 2020;64:24–35.
4. Clowse MEB. Lupus activity in pregnancy. Rheum Dis Clin North Am. 2007;33:237–252.
5. Lateef A, Petri M. Managing lupus patients during pregnancy. Best Pract Res Clin Rheumatol. 2013;27:435–447.
6. Sammaritano LR, Bermas BL, Chakravarty EE, et al. 2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases. Arthritis Care Res (Hoboken). 2020;72:461–488.
7. Bundhun PK, Soogund MZS, Huang F. Impact of systemic lupus erythematosus on maternal and fetal outcomes following pregnancy. Medicine (Baltimore). 2017;96:e6246.
8. Smyth A, Oliveira GHM, Lahr BD, et al. A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. Clin J Am Soc Nephrol. 2010;5:2060–2068.
9. Moroni G, Ponticelli C. Pregnancy in women with lupus nephritis. J Nephrol. 2016;29:193–205.
10. Buyon JP, Kim MY, Guerra MM, et al. Predictors of pregnancy outcomes in patients with lupus: a cohort study. Ann Intern Med. 2015;163:153–163.
11. Burton GJ, Redman CWG, Roberts JM, Moffett A. Pre-eclampsia: pathophysiology and clinical implications. BMJ. 2019;366:l2381.
12. Rana S, Lemoine E, Granger JP, Karumanchi SA. Preeclampsia: pathophysiology, challenges, and perspectives. Circ Res. 2019;124:1094–1112.
13. Staff AC. The two-stage placental model of preeclampsia: an update. Placenta. 2019;84:S32–S38.
14. Izmirly PM, Saxena A, Kim MY, et al. Maternal and fetal factors associated with mortality and morbidity in a multi-racial/ethnic registry of anti-SSA/Ro-associated cardiac neonatal lupus. Circulation. 2011;124:1927–1935.
15. Brito-Zerón P, Izmirly PM, Ramos-Casals M, Buyon JP. The clinical spectrum of autoimmune congenital heart block. Nat Rev Rheumatol. 2015;11:301–312.
16. Buyon JP, Clancy RM. Autoantibody-associated congenital heart block: biomarkers, mechanisms and management. Clin Rev Allergy Immunol. 2020;58:16–27.
17. Petri M, Orbai AM, Alarcón GS, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum. 2012;64:2677–2686.
18. Aringer M, Costenbader K, Daikh D, et al. 2019 European League Against Rheumatism/American College of Rheumatology Classification Criteria for Systemic Lupus Erythematosus. Ann Rheum Dis. 2019;78:1151–1159.
19. World Health Organization. WHO recommendations on interventions to improve preterm birth outcomes. Geneva: World Health Organization; 2015.
20. Figueras F, Gratacós E. Update on the diagnosis and classification of fetal growth restriction and proposal of a stage-based management protocol. Fetal Diagn Ther. 2014;36:86–98.
21. ISUOG Practice Guidelines: diagnosis and management of small-for-gestational-age fetus and fetal growth restriction. Ultrasound Obstet Gynecol. 2020;56:298–312.
22. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. Stat Med. 2002;21:2409–2419.

Received: July 8th 2026.