Received: 26 December 2023 | Revised: 24 April 2024 | Accepted: 6 May 2024

DOI: 10.1111/aogs.14880

AOGS Acta Obstetricia et Gynecologica Scandinavica

ORIGINAL RESEARCH ARTICLE

Pregnancy outcomes in patients with systemic lupus erythematosus compared to a high-risk tertiary cohort and to standard population from the Austrian birth registry

Klara Rosta[1] | Florian Heinzl[1] | Valerie Kuczwara[1] | Stefanie Schindler[1] | Veronica Falcone[1] | Anja Catic[1] | Marina Riedmann[2] | Hermann Leitner[2] | Elisabeth Simader[3] | Valentin Ritschl[4,5] | Tanja Stamm[4,5] | Alexandra Szlatinay[3] | Peter Mandl[3] | Antonia Mazzucato-Puchner[3]

[1]Department of Obstetrics and Gynecology, Clinical Division of Gynecological Endocrinology and Reproductive Medicine, Medical University of Vienna, Vienna, Austria

[2]Department of Clinical Epidemiology, Tyrolean Federal Institute for Integrated Care, Tirol Kliniken GmbH, Innsbruck, Austria

[3]Department of Internal Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria

[4]Center for Medical Data Science, Institute for Outcomes Research, Medical University of Vienna, Vienna, Austria

[5]Ludwig Boltzmann Institute for Arthritis and Rehabilitation, Vienna, Austria

Correspondence
Antonia Mazzucato-Puchner, Medical University of Vienna, Department of Internal Medicine III, Division of Rheumatology, Waehringer Guertel 18-20, Vienna 1090, Austria.
Email: antonia.mazzucato-puchner@meduniwien.ac.at

Funding information
UCB; Pfizer; Erasmus Plus COHRICE, Grant/Award Number: 2021-1-HU01-KA220-HED-000027613

Abstract

Introduction: Women with systemic lupus erythematosus (SLE) have a higher risk for fetal and maternal complications. We aimed to investigate maternal and fetal complications in pregnant women with SLE compared to a high-risk pregnancy cohort (HR) from a tertiary university center and a standard-risk general population (SR) from the Austrian Birth Registry.

Material and Methods: In this retrospective data analysis, we compared the incidence of fetal/neonatal and maternal complications of pregnancies and deliveries of women with SLE to age, body mass index and delivery date—matched high-risk pregnancies from the same department, a progressive tertiary obstetric center and to a group of women, who represent pregnancies with standard obstetric risk from the Austrian Birth Registry.

Results: One hundred women with SLE were compared to 300 women with high-risk pregnancies and 207039 women with standard-risk pregnancies. The incidence of composite maternal complications (preeclampsia, Hemolysis, Elevated Liver enzymes and Low Platelets [HELLP] syndrome, pregnancy-related hypertension, gestational diabetes mellitus, maternal death, thromboembolic events) was significantly higher in the SLE as compared to the SR group (28% vs. 6.28% SLE vs. SR, $p=0.001$). There was no difference between the SLE and the HR groups (28% vs. 29.6% SLE vs. HR group, $p=0.80$). The incidence of composite fetal complications (preterm birth before 37 weeks of gestation, stillbirths, birth weight less than 2500 g, fetal growth restriction, large for gestational age, admission to neonatal intensive care unit, 5-min Apgar <7) was also higher in the SLE than in the SR group (55% vs. 25.54% SLE vs. SR

Abbreviations: BMI, body mass index; C3c, proteolytic fragment of complement component 3; dsDNA, double-stranded DNA; HELLP, syndrome; Hemolysis, Elevated Liver enzymes, and Low Platelets; HR, high-risk; NICU, neonatal intensive care unit; SLE, systemic lupus erythematosus; SR, standard-risk; cohort from the Austrian Birth Registry.

$p < 0.001$) while the higher incidence of adverse fetal outcome was detected in the HR than in the SLE group (55% vs. 75% SLE vs. HR group, $p = 0.0005$).

Conclusions: Although composite fetal risk is higher in the SLE group than in the general population, it is still significantly lower as compared to high-risk pregnant women at a tertiary obstetric center. Prepregnancy counseling of women with SLE should put fetal and maternal risk in perspective, not only in relation to healthy, low risk cohorts, but also compared to mixed HR populations.

KEYWORDS
birth registry, high-risk pregnancy, obstetric risk, systemic lupus erythematosus

1 | INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune connective tissue disorder in the group of inflammatory rheumatic diseases. It is characterized by the loss of immunological tolerance to cellular nuclear antigens, through which the disease can affect various organ systems.[1] The diagnosis of SLE is based on the American College of Rheumatology/European League Against Rheumatism (EULAR) classification criteria from 2019.[2] Women are disproportionately more often affected, representing 85%–93% of individuals with SLE.[3] The most likely time of the diagnosis of the disease is between 15 and 55 years, which often overlaps with childbearing age and might influence family planning and the course of pregnancy.

Systemic lupus erythematosus in pregnancy increases the risk of maternal and fetal/neonatal complications. To date, the exact pathomechanism of the elevated incidence of complications, such as early abortions, stillbirth, preterm birth, fetal growth retardation, and preeclampsia, is not exactly known but is believed to be due to disturbed placentation through autoimmune and inflammatory processes.[4]

High-risk (HR) pregnancy is defined according to various national and international obstetric committees. A woman with HR pregnancy requires special care because of a problem with the pregnancy itself, a preexisting maternal health condition, or fetal congenital abnormalities or complication.[5] The definition of HR pregnancy is not defined unequivocally, but most definitions of HR pregnancy imply that the mother, her fetus, or both are at an increased risk for complications during pregnancy or delivery as compared to women with unremarkable pregnancies.[6] Patients who fall into this category tend to accumulate in obstetric centers with high-level neonatology units and specialized obstetric expertise to optimize the care for mother and child.

Reproductive trends in Europe show that childbearing age is increasing,[7] along with the number of pregnancies with comorbidities and predictable risks. Moreover, the widespread use of artificial reproductive technology also increases risk in pregnancies. For that reason, we have an ever-growing number of HR pregnancies, which, however, are increasingly accepted as a part of everyday care.

Obstetricians and internal specialists consider pregnancies with SLE as risk situations and pregnancy counseling might trigger overwhelming fears before or during pregnancies. Advances in therapy and preconceptional interdisciplinary counseling might improve obstetric and rheumatic outcome. Unfortunately, exact risk stratification is still not possible for women with SLE, and it is still not exactly predictable which pregnant women will experience adverse pregnancy outcome or flare of the underlying disease. Centers providing pregnancy or preconceptional care for women with autoimmune disease employ standardized screening of disease activity, fetal biometry, and Doppler ultrasound examinations as well as optional screening for congenital heart block to minimize risk and detect possible complications. Until we find biomarkers for better prediction of obstetric and rheumatic risk situations, the burden of more intensive pregnancy care will remain a reality posing psychological burden on these patients.

Key message

While systemic lupus erythematosus group's composite fetal risk surpasses the general population, it is notably lower than high-risk pregnant women. Maternal obstetric risk aligns with mixed high-risk cohorts. Prepregnancy counseling for women with systemic lupus erythematosus must contextualize both fetal and maternal risks appropriately.

For this reason, it is of utmost importance to understand the meaning of elevated obstetric risk and put it in perspective, not only in relation to healthy, low risk cohorts but also compared to mixed HR populations. In our study, we wish to compare obstetric risk of pregnancies with SLE to that of a mixed, HR population from a tertiary progressive obstetric center and of a standard-risk (SR) cohort from the Austrian Birth Registry.

2 | MATERIAL AND METHODS

This observational study was carried out according to the STROBE guidelines. The patients in the case group (SLE group) and the high-risk group (HR group) were selected with the help of a data query

from the Obstetric Documentation System of the Medical University of Vienna (ViewPoint®. Version 5.6.16.917).

The SLE group was selected through data query for pregnancies with the following key words: "SLE," "lupus,", "lupus erythematosus," "rheuma," "hydroxychloroquine, etc. (full list displayed in Table S1)." The SLE group was individually checked for the plausibility of diagnosis of SLE. Only women who had a record of diagnosis by a specialist in our documentation system were included in the study group.

The high-risk (HR) group was selected from the deliveries at the Department of Obstetrics and Feto-Maternal Medicine of the Medical University of Vienna in the period from 01.01.2004 to 30.06.2020 with the diagnosis code "high-risk pregnancies" based on the ICD 10 code (z35.8). High-risk pregnancies have a broad definition and include women with underlying chronic diseases, such as diabetes or preexistent high blood pressure; infections during pregnancy; history of complications in a previous pregnancy; or pathologies in the current pregnancy. The most frequent diagnoses in the high-risk group of the present study included the history of preterm birth (13.6%), maternal comorbidity (24.7%), and maternal obesity (body mass index [BMI] >30 kg/m^2) with 17%. Among the current risk factors, 16.3% of women had a preterm birth, 10% suffered from gestational diabetes mellitus, 17% were diagnosed with maternal obesity, and 7% of women had preeclampsia or HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelets). The main diagnostic features of the high-risk group are shown in the Table S4. We were able to match HR patients from 2004 to 2020 to our SLE patients.

In a further step, the following exclusion criteria were applied to both the SLE and the HR group: patients under the age of 18, deliveries where documentation of the delivery was missing, pregnancies that ended in early abortions <20 gestational weeks, pregnancies where the first hospital visit took place after the 20th gestational week. Women with autoimmune conditions were excluded from the HR group.

Patients of the SLE group were matched 1:3 with patients of the mixed HR group according to CaseControl Matching with SPSS version 26 (IBM Corp., USA) based on the following criteria: prepregnancy BMI, maternal age at delivery, and year of delivery. A maximum deviation factor of +/− 2.5 was applied in order to perform 1:3 matching for all patients in the SLE group.

The third group in the present study mirrors the risk of the general population (standard-risk). Data from all pregnancies in the Austrian Birth Registry between 01.01.2018 and 30.06.2020 were retrospectively analyzed. The Austrian Birth Registry is a nationwide, prospective registry that collects both maternal and fetal data on all live and stillbirths in all Austrian obstetric units, which was established in 2004. In 2018, the registry was expanded allowing for more detailed analysis of obstetric risks and outcomes. Therefore, we decided to use data from the Austrian birth Registry from 1.1.2018 to 30.6.2020 not to underestimate the adverse events.

As a second step, the same SLE cohort was compared to all deliveries between 01.01.2018 and 30.06.2020 from the Austrian birth registry (SR). Maternal and fetal/neonatal outcome were compared between the SLE and high-risk group and between the SLE and standard-risk group from the Austrian Birth Registry.

The serological activity of the SLE was determined by antibodies against double-stranded DNA (dsDNA) and complement component 3 (C3c) levels at the three timepoints of pregnancies. We then dichotomized the parameters based on the cut-off provided by the Department of Laboratory Medicine of the Medical University of Vienna and grouped the patients into dsDNA-negative and dsDNA-positive patients and those with normal or decreased C3c levels.

Composite maternal risk was defined as preeclampsia or eclampsia or HELLP syndrome (Hemolysis, Elevated Liver enzymes, and Low Platelets) or pregnancy-induced hypertension during pregnancy or in early puerperium (1–4 days after delivery), thromboembolic events, gestational diabetes mellitus, postpartum infections, sepsis, re-operation, or death of the mother. Preeclampsia, HELLP syndrome, and lupus nephritis have very similar symptoms. For that reason, before utilizing the sFLT-1/PlGF ratio as an additional factor for diagnosis of preeclampsia/HELLP syndrome, the entities have been differentiable by using serum complement and dsDNA concentrations, the amount of proteinuria and urine sedimentation, liver function and hemolysis parameters, and therapy response on cortisol administration. After the introduction of the sFLT-1/PlGF ratio, a pathognomonic factor for preeclampsia and HELLP syndrome, the differentiation between lupus exacerbation and preeclampsia or HELLP syndrome was possible. Elevated sFLT-1/PlGF ratio helps to establish the diagnosing of preeclampsia and HELLP syndrome and differentiate from lupus nephritis in SLE patients.[8]

In patients suffering from gestational diabetes mellitus (GDM), GDM was diagnosed with a 75-g oral glucose tolerance yest (OGTT) at three time points (fasting, 1 and 2 h) between the 24th and 28th gestational weeks (gws) for women without glucocorticoid therapy. Glucose monitoring was initiated for women under glucocorticoid therapy to assess hyperglycemia/GDM in pregnancy from the 24th gw in cases of higher than 5-mg corticosteroid dosage daily and signs of GDM, such as macrosomia, increased fetal abdominal circumference in biweekly fetal ultrasound.

Composite fetal risk was defined as the presence of any one of the following criteria: small for gestational age <10th percentile; large for gestational age >90th percentile; weight of the newborn <2500 gr; fetal growth restriction—defined according to the ISUOG criteria[9]; arterial cord blood pH <7.10; Apgar score at 5 min <7; admission to the neonatal intensive care unit (NICU); neonatal lupus; congenital malformation; preterm birth <37 gestational week; stillbirth; neonatal death postpartum.

Categorical variables are reported as absolute (*n*) and relative frequencies (%) and were compared using the Chi-square test and Fisher's exact test, respectively. Continuous data are reported as median and interquartile range and were analyzed using the Wilcoxon rank sum test. The significance level was set at $p < 0.05$.

Statistical analysis was conducted in STATA (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

3 | RESULTS

After applying the exclusion criteria, exactly 100 pregnancies with SLE remained (Figure 1), which were then matched 1:3 to 300 HR pregnancies and also compared to 207039 women with SR pregnancies. Maternal demographic characteristics, such as prepregnancy BMI and age at delivery, did not differ significantly between the three groups. More women smoked in the standard population during pregnancy as compared to the SLE or HR groups (22% vs. 52.3%; $p<0.001$; SLE vs. SR group). The number of spontaneous conceptions was significantly higher in the SR group than in the SLE group (87% vs. 99.57%; $p<0.001$; SLE vs. SR group). The number of nulliparas did not differ between the groups (Table 1).

3.1 | Characteristics of the SLE group

Table S2 provides an overview of the therapy of the women with SLE during pregnancy. Eighty-three percent of them took medication at some point during their pregnancies, with exception of vitamins and mineral substitution. Low-dose acetylsalicylic acid was taken by 41.0%, low-dose molecular heparin by 22%, hydroxychloroquine or chloroquine by 45.0%, glucocorticoids by 50.0% (glucocorticoids >5 mg by 21%), azathioprine by 21.0%. 22.0% of women with SLE were receiving antihypertensive therapy. Apheresis was performed in 6.0% of the patients.

Laboratory parameters, which might suggest SLE disease activity, were also collected from these patients. Table S3 provides an overview of all laboratory parameters collected in the SLE group. Low blood count with a Hb value below 10.0 mg/dL occurred in 26.5% of SLE pregnancies. Pathological platelet count (defined as thrombocytes <150.000/µL) occurred in 23.5% (thrombocytopenia) and 9.2% (thrombocytosis) of SLE pregnancies. 26.5% of the women experienced at least one prolongation of the activated partial thromboplastin time, aPTT to more than 41.0 s. Elevated creatinine (>1.2 mg/dL) occurred in 13.3%, elevated liver function parameters (glutamic-oxaloacetic transaminase, GOT >31 U/L and/or glutamate pyruvate transaminase, GPT >34 U/L) occurred in 36.1% of SLE pregnancies. 42.1% of pregnant women had proteinuria in the urine dipstick test (combur test), while 12% of the patients hat proteiuria > 500 mg/g. Immunological parameters were also assessed. Most of the patients (87%) had positive (>1:80) antinuclear antibody (ANA) titers while complement deficiency occurred in 34.8% (C3) and 25.8% (C4) of cases. In the majority of women, antibodies (AB) against double-stranded DNA (52.7%) and anti-Ro (50.5%) could be detected. Other antinuclear antibodies were also frequently positive in women with SLE during pregnancy (see Table S3).

The SLE group was further divided into four groups: patients with low-risk profiles ($n=62$), patients with kidney involvement ($n=20$), patients with antiphospholipid syndrome ($n=13$), patients with both lupus nephritis and APL ($n=3$) and not specified ($n=2$). Of the 22 patients, 5 had active nephritis with proteinuria during pregnancy; however, no patient had nephrotic range proteinuria. Two patients had a history of kidney transplantation, 4 patients had impaired kidney function, and none of the patients underwent dialysis during pregnancy.

3.2 | Maternal complications

The incidence of composite maternal complications was significantly higher in the SLE group than in the SR group (28.0% vs. 6.28%; SLE vs. SR; $p=0.001$) and did not differ between the SLE and the HR groups (28.0% vs. 29.6%; SLE vs. HR group; $p=0.80$). The SLE and the HR groups had similarly high incidence of hypertension-related pregnancy complications such as pregnancy-induced hypertension, preeclampsia, HELLP syndrome, or eclampsia (21% vs. 20.33%; $p=0.33$; SLE vs. HR), while in the SR group, the incidence was significantly

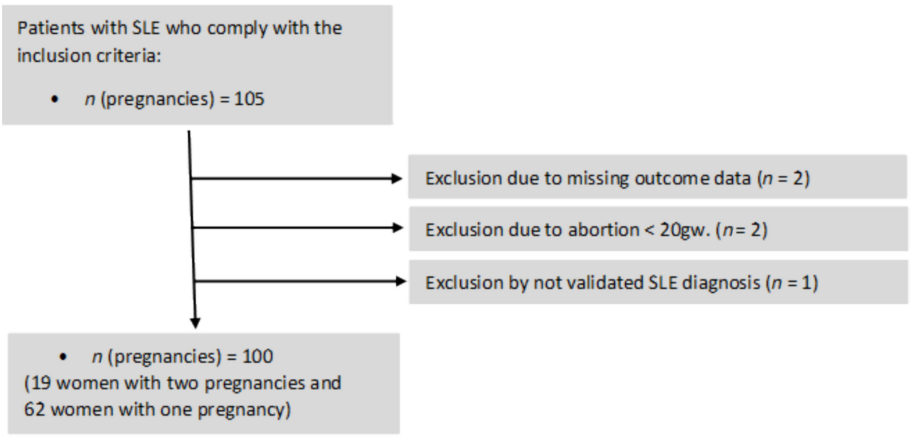

FIGURE 1 Flowchart of pregnancies in the systemic lupus erythematosus (SLE) group.

TABLE 1 Maternal characteristics among the three groups.

	SLE $N=100$	High-risk $N=300$	Standard-risk $N=207039$	p-value[1]	p-value[2]
Prepregnancy BMI kg/m^2, median (IQR)	23.3 (20–27)	23.34 (21–28)	22.94 (20.66–26.3)	0.62	0.77
Age at delivery median (IQR)	31 (27–35)	31 (27–35)	31 (27–34)	0.96	0.15
Spontaneous conception *N* (%)	87 (87)	297 (99)	206144 (99.57)	0.12	0.001*
Primiparity *N* (%)	29 (29)	71 (23.7)	68794 (33.23)	0.051	0.85
Smoking *N* (%)	22 (22)	57 (19.5)	108316 (52.32)	0.53	0.001*

Note: p-value[1]: SLE versus high-risk group; p-value[2]: SLE versus standard-risk group; *$p<0.05$.

Abbreviations: BMI, body mass index (kg/m^2); IQR, interquartile range; SLE, systemic lupus erythematosus.

TABLE 2 Maternal complications in systemic lupus erythematosus, high-risk, and standard risk groups.

	SLE $N=100$	High-risk $N=300$	Standard risk $N=207039$	p-value[1]	p-value[2]
Maternal complication as composite outcome (%)	28 (28.0)	89 (29.6)	12998 (6.28)	0.80	0.001*
Preeclampsia/eclampsia/HELLP/pregnancy-induced hypertension (%)	21 (21.0)	61 (20.33)	1576 (0.76)	0.33	0.001*
GDM/IGDM (%)	11 (11.0)	60 (20.0)	11230 (5.42)	0.054	0.004*
Maternal death (%)	1 (1.0)	0 (0.0)	24 (0.01)	0.563	0.001*
C-section (%)	59 (59)	209 (70.1)	61421 (29.67)	0.0005*	0.001*
Thromboembolic events (%)	1 (1.0)	3 (1.0)	264 (0.13)	1	0.001*
Postpartal maternal infection	4 (4%)	3 (1.0)	n.a	0.123	

Note: p-value[1]: SLE versus HR group; p-value[2]: SLE versus standard-risk group; *$p<0.05$.

Abbreviations: C-section, caesarean section; GDM, gestational diabetes mellitus; HELLP, Hemolysis, Elevated Liver enzymes and Low Platelets; IGDM, insulin-dependent gestational diabetes mellitus; n.a, not available data.

lower (21% vs. 0.76%; $p<0.001$). The differential diagnosis for preeclampsia in women with preconceptional hypertension and proteinuria was based on the amount of proteinuria, the decrease in the level of complement factors (C3, C4), the increase of the anti-ds-DNA titer and additional organ manifestations, suggesting a lupus flair. On the other hand, moderate proteinuria, normal complement, thrombocytopenia, elevated liver enzymes, and stabile anti-ds-DNA levels with elevated sFLT-1/PlGF suggested preeclampsia/HELLP.[8,10]

Four women (1.0%) experienced a thromboembolic event, of which one was from the SLE group (equivalent to 1.0% within the SLE group) and three were from the HR group (equivalent to 1.0% within the HR group); there was no thromboembolic event reported in the SR group. One pregnant woman died during pregnancy and suffered from SLE. She had a therapy-resistant low platelet count during pregnancy and suffered from a lethal intracranial bleeding during a hypertensive crisis. Lupus activity was not associated with adverse maternal outcome.

The incidences of gestational diabetes mellitus (GDM; 11% vs. 5.42%; $p=0.004$) and C-section (59% vs. 29.67%; $p<0.001$) were significantly increased in the SLE group compared to the standard-risk group and did not differ between the SLE and the HR groups (Table 2).

Postpartum maternal infections occurred in 4% of the SLE group and 1% of the high-risk group ($p>0.05$). No information was available from the SR group. All of the SLE patients with maternal postpartum infections were treated with more than 5-mg glucocorticoid daily and received HCQ as well.

3.3 | Fetal/neonatal complications

The incidence of composite fetal complications was higher in the SLE group than in the SR group (55.0% vs. 25.54%; SLE vs. SR; $p<0.001$). Interestingly, composite fetal complications were significantly more frequent in the HR group compared to the SLE group (55.0% vs. 75.0%; SLE vs. HR; $p=0.0005$). Table 3 provides an overview of the frequencies of fetal or neonatal complications in the groups. Composite adverse fetal outcome was not associated with lupus activity. Preterm birth before the 37th gestational week occurred in 27.0% in the SLE group; this is significantly lower than in the HR group (39.7%; $p=0.032$) and significantly higher than in the SR population (7.68%; $p<0.001$). Fetal birth weight differed significantly between the SLE and the SR groups (SLE vs. SR; 2970 g (2360–3330 g) vs. 3350 (3025–3670 g); $p<0.001$), as well as between the SLE and the HR group (SLE vs. HR; 2970 g (2360–3330 g) vs. 2660 g (2055–3050 g); $p=0.001$)—in this case in favor of the SLE group. Fetal growth restriction occurred in 11.0% of the SLE group and 7.6% of the HR group ($p=0.44$) and significantly more frequently than in the standard-risk group (SLE vs. SR; 11% vs. 0.33; $p=0.002$). Transfer of the newborn to the neonatal intensive care unit was required in

TABLE 3 Fetal and neonatal complications in the systemic lupus erythematosus, high-risk and standard-risk groups.

	SLE $N=100$	High-risk $N=300$	Standard risk $N=210262$	p-value[1]	p-value[2]
Fetal complication as composite outcome (%)	55 (55.0)	227 (75.0)	52878 (25.54)	0.0005*	0.001*
Preterm birth <37th gw	27 (27.0)	119 (39.7)	16148 (7.68)	0.032*	<0.001*
Preterm birth <28th gw	7 (7.0)	13 (4.3)	1098 (0.52)	0.44	0.01*
Fetal birth weight (g)	2970 (2350–3330)	2660 (2055–3050)	3350 (3025–3670)	0.001*	0.001*
Fetal growth restriction (%)	11 (11)	23 (7.60)	697 (0.33)	0.45	0.002*
Birth weight under 2500 g (%)	30 (30.0)	118 (40.0)	13508 (6.42)	0.10	0.001*
Admission to neonatal intensive unit (%)	23 (23.0)	80 (26.7)	15751 (7.49)	0.51	0.001*
Perinatal mortality (%) in 7 days after birth	2 (2.0)	5 (1.7)	410 (0.19)	1	0.017*
Stillbirth (%)	3 (3.0)	10 (3.3)	700 (0.33)	1	0.005*
5-min Apgar Score under 7 (%)	4 (4.0)	22 (7.3)	8772 (4.17)	0.35	0.05
Postnatal infection	5 (5.0)	n.a	89 (0.04)		0.001*

Note: p-value[1]: SLE versus HR group; p-value[2]: SLE versus standard-risk group; *$p<0.05$; Fetal growth restriction was defined according to the ISUOG guidelines.

Abbreviations: g, gram; gw, gestational week; HR, high-risk group; N, number; n.a, not available data; SR, standard-risk group.

23.0% of the SLE group and 26.7% of the HR group and significantly rarer in the SR group (SLE vs. SR; 23% vs. 7.49%; $p<0.001$). Stillbirth was detected in three cases in the SLE and thirteen cases (3.3%) in the HR group, while this complication happened in 0.33% in the SR group. Another two infants died perinatally or postpartum within 7 days after birth in the SLE group (2%) and five (1.7%) in the HR group, and 410 (0.19%) in the SR group (SLE vs. SR; $p=0.017$). Five-minute Apgar score <7 was noted in 8.2% of the SLE group, 11.7% in the HR group, and 4.17% in the SR group (SLE vs. HR, $p=0.355$; SLE vs. SR, $p=0.05$). Postnatal neonatal infections occurred in 5% of the SLE group and 0.04% of the SR group ($p<0.001$).

3.4 | Impact of disease on maternal and fetal outcomes

Out of 100 pregnancies, 53 patients had elevated dsDNA and/or reduced C3c levels during pregnancy. SLEDAI scores were not possible to assess in this retrospective study. The analysis revealed no correlation between serological lupus activity, as measured by immunological parameters, and maternal and fetal complications. To investigate if the long timespan of our retrospective study or the SLE subgroups (SLE subgroups: patients with low-risk profiles ($n=64$), patients with kidney involvement ($n=20$), patients with antiphospholipid syndrome ($n=13$), patients with both ($n=3$)) influenced our results, we conducted logistic regressions with regard to maternal as well as fetal complications. The timepoint of the pregnancy and kidney involvement did not influence obstetric outcome. Secondary APL syndrome, when compared to the baseline of solely SLE, was the only factor, which significantly and negatively influenced maternal and fetal outcome with a p-value of 0.01 (OR 4.7 and 6.9), respectively. Yet SLE with APL only occurred in 15 cases in total so that further statistical analysis had to be neglected (Data not shown). Additionally, we observed almost no change in either Brier score or AIC when comparing the regression models above to null models.

4 | DISCUSSION

In line with both prospective and retrospective studies,[11–13] our study demonstrates worse fetal/neonatal and maternal outcomes in SLE patients compared to a control cohort with low or SR pregnancies This is in accordance with a 2017 meta-analysis by Bundhun et al., comprising 10 studies with 529778 subjects, pregnancy complications in SLE patients were compared to healthy women.[14] Similarly, Smyth et al.'s 2010 meta-analysis, focusing on lupus nephritis patients, also found significantly higher complication rates during pregnancy.[15] Having a history of lupus nephritis serves as a negative predictive factor for pregnancy complications. The prospective PROMISSE study by Buyon et al. showed that 81% of SLE patients with low or no disease activity had favorable pregnancy outcome and that 19% of pregnant women with SLE experienced complications. This study excluded patients with severe courses of SLE and showed that even well-controlled SLE causes relevant risk concerning the pregnancy.[16] In our retrospective study, no correlation could be detected between serologic disease activity or kidney involvement and obstetric outcome; however, secondary APL syndrome correlated with a poorer obstetric outcome. Due to the retrospective nature of our research, we could not differentiate between high, low, or moderate disease activity in SLE, which might be the reason for the lack of correlation.

The prevalence of maternal complications due to hypertension-related diseases was similarly high in the SLE and the HR groups and significantly lower in the SR group. In the general population, preeclampsia occurs approximately in 1.2% to 4.2% of all pregnancies.[17] The lower prevalence in our SR group might show that preeclampsia is still underreported in the documentation systems of

the Austrian Birth Registry. The high prevalence of preeclampsia found in the SLE group is supported by a study from Chakravarty et al., in which 63 pregnancies of 48 mothers with SLE were retrospectively examined and 22.0% developed preeclampsia.[18] On the other hand, lower occurrence of preeclampsia was reported in a prospective study with 12.0% of 132 SLE pregnancies examined.[19] A meta-analysis by Dong et al. from 2020 showed that the relative risk of developing preeclampsia is 2.99 times higher for SLE patients,[20] while Bundhun et al.[14] found that the relative risk of preeclampsia for mothers with SLE was 1.91. Known risk factors for preeclampsia include the history of preeclampsia in the previous pregnancy, pre-existing hypertension, positive anti-phospholipid antibodies, active SLE, impaired renal function and the presence of lupus nephritis, the use of corticosteroids, obesity, and diabetes.[8,10] The majority of these risk factors affect women with SLE, which explains the increased preeclampsia rates in this group.[19]

Previous studies estimated the prevalence of premature births of children born to mothers with SLE at 17.9% to 34.7% of all pregnancies.[21–23] These studies also show a significantly higher preterm birth rate in the SLE group compared to a healthy control group. In the present study, 27.0% of all newborns born to SLE mothers were born before the 37th gestational week. This is consistent with the findings of previous studies. Delivery before the 37th gestational week occurred more often in the HR group (39.7%), which mirrors the composition of high-risk obstetric situations, which predispose to preterm delivery, such as history of preterm birth or cervical insufficiency, preeclampsia, fetal growth restriction, and placental insufficiency (also see Table S4).

It has been reported that 20.0% to 35.8% of all infants born to mothers with SLE require care in a NICU after birth,[22,23] which aligns with our findings, as 23% of newborns born to SLE mothers were admitted to the NICU in our study.

Over time, management of SLE pregnancies has improved, partly due to widespread hydroxychloroquine (HCQ) use for preventing disease flares and enhancing pregnancy outcomes.[24–28] Despite recommendations supporting HCQ treatment throughout pregnancy, only 45% of SLE patients in our study utilized HCQ, contrasting with the 74% usage reported in the Norwegian RevNatus multicenter registry study.[29] Additionally, 21% of our patients used glucocorticoid doses exceeding 5 mg/day during pregnancy, elevating risks of preterm birth and gestational diabetes mellitus.[30] This underscores the necessity for better preconception counseling and interdisciplinary care to ensure optimal treatment initiation before and during pregnancy. Low-dose aspirin (LDA) usage surged post the ASPRE trial in 2017 due to increased awareness of preeclampsia risks in SLE pregnancies.[31] However, in our study, only 41% of SLE women used LDA, possibly due to the longer inclusion period predating its standardization for preeclampsia prophylaxis between 2004 and 2018.

An important limitation of our study is the long observational period during which changes in clinical practice in both rheumatology and obstetrics were supplemented. According to a logistic regression analysis applied, the time period observed did not influence our outcome.

Furthermore, the small sample size of the SLE cohort and the monocentric character of the study, as well as the lack of data on sociodemographic parameters and educational status, limit the diversity of the patient population, thus potentially introducing biases and hindering a comprehensive understanding of potential influencing factors.

With an incidence of 0–241 per 100 000 (depending on the geographic region), SLE is a rare disease.[32] To avoid lower power due to multiple test corrections, individual fetal/neonatal and maternal complications were combined into combined/composite endpoint variables.

To our knowledge, our study is the first to compare SLE pregnancies to a mixed HR cohort without autoimmune disease in addition to a group with SR pregnancies. We could show that adverse maternal composite outcome was 4.5 times more frequent in the SLE and in the HR cohort compared to the SR group and did not differ between the SLE and HR groups. This is an important finding as population trends show that women tend to postpone their family planning[7] and more pregnant women have comorbidities, such as SLE and other risk factors, which may cause adverse pregnancy outcomes. Maternal obstetric risk seems to be similar to that observed in a mixed high-risk cohort in a progressive tertiary center, where a significant proportion of women facing elevated obstetric risks due to factors such as age, overweight, poor obstetric history, GDM, pregnancy-induced hypertension, and other complications (see Table S4). High-risk obstetrics has an important role in the care of women with comorbidities and poor obstetric history. For that reason, our results might bring reassurance to those colleagues who work in high-risk settings and face the challenges of pregnancy counseling of women with SLE. In addition, our findings are reassuring for pregnant women with SLE attending a tertiary setting with the observations here of pregnancy outcomes comparable to a mixed population of high-risk pregnancies. Prepregnancy care and multidisciplinary efforts may be ways of assuring the most optimal pregnancy outcomes.

5 | CONCLUSION

Drawing conclusions from a tertiary obstetric center, the composite fetal risk is higher in the SLE group than the general population and is significantly lower than that of high-risk pregnant individuals. Prepregnancy counseling for women with SLE should emphasize the context of fetal and maternal risks, comparing not only to healthy, low-risk cohorts but also to various high-risk populations.

AUTHOR CONTRIBUTIONS

The study was designed and conceptualized by Klara Rosta, Antonia Mazzucato-Puchner and Stefanie Schindler. Data collection was performed by Stefanie Schindler, Veronica Falcone, Marina Riedmann, Hermann Leitner, Elisabeth Simader, Valentin Ritschl and Valerie Kuczwara. Klara Rosta, Antonia Mazzucato-Puchner and Anja Catic wrote the manuscript, performed data interpretation, and designed

data tables. Florian Heinzl, Marina Riedmann, Hermann Leitner, Valentin Ritschl and Tanja Stamm performed statistical analysis and helped with data interpretation. Valerie Kuczwara, Elisabeth Simader, Anja Catic, Peter Mandl, Valentin Ritschl, Tanja Stamm and Alexandra Szlatinay critically reviewed helped to draft the manuscript. All authors have read and agreed to the published version of the manuscript.

ACKNOWLEDGMENTS

We wish to thank Renata Nagy, who concluded her medical studies with a thesis on pregnancy outcomes in women affected with rheumatic diseases.

FUNDING INFORMATION

This educational project was funded by the Erasmus plus COHRICE (2021-1-HU01-KA220-HED-000027613) grant. The establishment of the RhePro (Rheuma and Rheproduction) registry was supported by a grant from UCB, Gilead Sciences GesmbH and Pfizer.

CONFLICT OF INTEREST STATEMENT

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

DATA AVAILABILITY STATEMENT

The data from the Medical University of Vienna that support the results of this study are available from the corresponding author upon reasonable request. Austrian Birth registry data management policy does not allow data sharing.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki and good clinical practice and was approved by the Ethics Committee of the Medical University of Vienna (reference number 1866/2018) on December 14, 2018. Due to the retrospective character of the study, patients' informed consent was waived.

ORCID

Klara Rosta https://orcid.org/0000-0002-3502-3734
Valerie Kuczwara https://orcid.org/0009-0008-1633-1767
Anja Catic https://orcid.org/0000-0002-1065-5313
Valentin Ritschl https://orcid.org/0000-0001-8763-8215

REFERENCES

1. Hettenkofer H-J, Acar H. Teil III: Entzündlich-rheumatische Erkrankungen, Kollagenosen. In: Hettenkofer H-J, ed., Hrsg*Rheumatologie: Diagnostik-Klinik-Therapie*. 6. Auflage. Thieme; 2015:215-266.
2. 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.
3. Barber MRW, Drenkard C, Falasinnu T, et al. Global epidemiology of systemic lupus erythematosus. *Nat Rev Rheumatol*. 2021;17:515-532. Erratum in: Nat Rev Rheumatol. 2021 Sep 1.
4. Tan Y, Yang S, Liu Q, et al. Pregnancy-related complications in systemic lupus erythematosus. *J Autoimmun*. 2022;132:102864.
5. SMFM, High risk pregnancy. Available from: http://www.highriskpregnancyinfo.org/whats-a-high-risk-pregnancy. (Accessed on 20 March 2024).
6. NICE guideline. Intrapartum care for high risk women. Available from: https://www.nice.org.uk/guidance/ng121/documents/final-scope-2#:~:text=A%20pregnancy%20is%20'high%20risk,arise%20in%20association%20with%20labour.&text=by%20physiological%20changes%20that%20occur%20in%20labour. (Accessed on 20 March 2024)
7. Eurostat, Fertility Statistics. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Fertility_statistics#Total_fertility_rate_and_age_of_women_at_birth_of_first_child. (Accessed on 20 March 2024).
8. NICE guideline [NG133]. Hypertension in pregnancy: diagnosis and management. 2019. Last updated: 17 April 2023. Available from: www.nice.org.uk/guidance/ng133. (Accessed 20 March 2024)
9. Gordijn SJ, Beune IM, Thilaganathan B, et al. Consensus definition of fetal growth restriction: a Delphi procedure. *Ultrasound Obstet Gynecol*. 2016;48:333-339.
10. AWMF Leitlinie. 2019 Available from: https://register.awmf.org/assets/guidelines/015-018l_S2k_Diagnostik_Therapie_hypertensiver_Schwangerschaftserkrankungen_2019-07.pdf. (Accessed on 13 March 2024)
11. Clowse MEB, Jamison M, Myers E, James AH. A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol*. 2008;199(127):e1-e6.
12. Chakravarty EF, Nelson L, Krishnan E. Obstetric hospitalizations in the United States for women with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum*. 2006;54:899-907.
13. Chen Y-J, Chang J-C, Lai E-L, et al. Maternal and perinatal outcomes of pregnancies in systemic lupus erythematosus: a nationwide population-based study. *Semin Arthritis Rheum*. 2020;50:451-457.
14. Bundhun PK, Soogund MZ, Huang F. Impact of systemic lupus erythematosus on maternal and fetal outcomes following pregnancy: a meta-analysis of studies published between years 2001-2016. *J Autoimmun*. 2017;79:17-27.
15. Smyth A, Oliveira GH, Lahr BD, Bailey KR, Norby SM, Garovic VD. 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.
16. 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.
17. Abalos E, Cuesta C, Grosso AL, Chou D, Say L. Global and regional estimates of preeclampsia and eclampsia: a systematic review. *Eur J Obstet Gynecol Reprod Biol*. 2013;170:1-7.
18. Chakravarty EF, Colon I, Langen ES, et al. Factors that predict prematurity and preeclampsia in pregnancies that are complicated by systemic lupus erythematosus. *Am J Obstet Gynecol*. 2005;192:1897-1904.
19. Borella E, Lojacono A, Gatto M, et al. Predictors of maternal and fetal complications in SLE patients: a prospective study. *Immunol Res*. 2014;60:170-176.
20. Dong Y, Yuan F, Dai Z, Wang Z, Zhu Y, Wang B. Preeclampsia in systemic lupus erythematosus pregnancy: a systematic review and meta-analysis. *Clin Rheumatol*. 2020;39:319-325.
21. Jakobsen IM, Helmig RB, Stengaard-Pedersen K. Maternal and foetal outcomes in pregnant systemic lupus erythematosus patients: an incident cohort from a stable referral population followed during 1990-2010. *Scand J Rheumatol*. 2015;44:377-384.
22. Wallenius M, Salvesen K, Daltveit AK, Skomsvoll JF. Systemic lupus erythematosus and outcomes in first and subsequent births based on data from a national birth registry. *Arthritis Care Res (Hoboken)*. 2014;66:1718-1724.

23. Barnabe C, Faris PD, Quan H. Canadian pregnancy outcomes in rheumatoid arthritis and systemic lupus erythematosus. *Int J Rheumatol*. 2011;2011:345727.
24. Ruiz-Irastorza G, Khamashta MA. Hydroxychloroquine: the cornerstone of lupus therapy. *Lupus*. 2008;17:271-273.
25. Alijotas-Reig J, Esteve-Valverde E, Anunciación-Llunell A, Marques-Soares J, Pardos-Gea J, Miró-Mur F. Pathogenesis, diagnosis and management of obstetric antiphospholipid syndrome: a comprehensive review. *J Clin Med*. 2022;11:675.
26. Tektonidou MG, Laskari K, Panagiotakos DB, Moutsopoulos HM. Risk factors for thrombosis and primary thrombosis prevention in patients with systemic lupus erythematosus with or without antiphospholipid antibodies. *Arthritis Rheum*. 2009;61:29-36.
27. Sciascia S, Hunt BJ, Talavera-Garcia E, Lliso G, Khamashta MA, Cuadrado MJ. The impact of hydroxychloroquine treatment on pregnancy outcome in women with antiphospholipid antibodies. *Am J Obstet Gynecol*. 2016;214:273.e1-273.e8.
28. Andreoli L, Bertsias GK, Agmon-Levin N, et al. EULAR recommendations for women's health and the management of family planning, assisted reproduction, pregnancy and menopause in patients with systemic lupus erythematosus and/or antiphospholipid syndrome. *Ann Rheum Dis*. 2017;76:476-485.
29. Skorpen CG, Lydersen S, Gilboe IM, et al. Influence of disease activity and medications on offspring birth weight, pre-eclampsia and preterm birth in systemic lupus erythematosus: a population-based study. *Ann Rheum Dis*. 2018;77:264-269.
30. Palmsten K, Bandoli G, Vazquez-Benitez G, et al. Oral corticosteroid use during pregnancy and risk of preterm birth. *Rheumatology (Oxford)*. 2020;59:1262-1271.
31. Rolnik DL, Wright D, Poon LC, et al. Aspirin versus placebo in pregnancies at high risk for preterm preeclampsia. *N Engl J Med*. 2017;377:613-622.
32. Rees F, Doherty M, Grainge MJ, Lanyon P, Zhang W. The worldwide incidence and prevalence of systemic lupus erythematosus: a systematic review of epidemiological studies. *Rheumatology (Oxford)*. 2017;56:1945-1961.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Rosta K, Heinzl F, Kuczwara V, et al. Pregnancy outcomes in patients with systemic lupus erythematosus compared to a high-risk tertiary cohort and to standard population from the Austrian birth registry. *Acta Obstet Gynecol Scand*. 2024;00:1-9. doi:10.1111/aogs.14880