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The conditions that patients with systemic lupus erythematosus should fulfill before pregnancy to optimize outcomes: a large-scale multicenter cohort study from China

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Abstract

Background Systemic lupus erythematosus (SLE) is frequently associated with a lower rate of live birth and a higher incidence of adverse pregnancy outcomes (APOs), and pregnancy can also increase the risk of SLE flares. Comprehensive preconception assessment is critical for improved pregnancy outcomes in patients with SLE. Unfortunately, no global consensus on the conditions that patients with SLE should fulfill prior to pregnancy has yet been formed.

Objective This study aimed to investigate the conditions that patients with SLE should fulfill before pregnancy to optimize outcomes.

Study design This was a retrospective study utilizing data from a multicenter Chinese SLE cohort. Information on demographics, obstetric history, SLE activity, clinical manifestations, autoantibody profiles, laboratory parameters, therapeutics, and pregnancy outcomes was collected. Logistic regression was used to explore the optimal conditions.

Results The study comprised 347 singleton pregnancies from 332 patients with SLE in total, with a mean maternal age at conception of 30.3 (SD 4.0) years. The analysis revealed that patients who were stable for at least 6 months, had no active vital organ involvement, were on nonfluorinated corticosteroids no more than the dose equivalent to prednisone 7.5 mg per day, and were on hydroxychloroquine displayed a significantly higher incidence of live birth

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(86.1% vs. 73.7%, $p=0.004$) and a markedly decreased risk of APOs (29.4% vs. 52.1%, $p<0.001$). Additionally, flares occurred less frequently during pregnancy (14.7% vs. 27.3%, $p=0.009$), particularly for severe flares (5.8% vs. 14.8%, $p=0.011$).

Conclusion This study delineated the conditions that patients with SLE should fulfill before pregnancy, which provides better instructions for clinical practice.

Keywords Systemic lupus erythematosus, Pregnancy, Obstetrics

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that primarily affects women of childbearing age. Studies have proven that compared with the general population, women with SLE are more susceptible to adverse pregnancy outcomes (APOs), such as gestational hypertension, preterm delivery, small for gestational age, and neonatal death [1–3]. Unfortunately, pregnancy outcomes have not improved over the last three decades [4]. Meanwhile, during pregnancy and the postpartum period, patients with SLE experience more flares than during the non-pregnancy period [5, 6]. Researchers have identified several risk factors for APOs among patients with SLE, which include but are not limited to thrombocytopenia, hypocomplementemia, proteinuria, antiphospholipid antibodies (APLs) positivity, high corticosteroid dose, and failure to meet the criteria for remission or low disease activity [7–12]. As for disease flares, older age, disease remission, and hydroxychloroquine (HCQ) use have been recognized as protective factors [5, 13, 14]. Despite the aforementioned findings, high-quality evidence regarding the optimal pre-pregnancy conditions for patients with SLE to be satisfied is deficient, resulting in a lack of global consensus. Related recommendations in current guidelines, such as those developed by the European League Against Rheumatism (EULAR) in 2017, the American College of Rheumatology (ACR) in 2020, and China in 2022, are predominantly based on clinical observational studies and expert consensuses [15–17].

The guidelines primarily addressed six aspects of the conditions that should be met before pregnancy as summarized in Table 1. The three guidelines were generally consistent in requiring patients to be stable for a specified duration, have no active vital organ involvement, receive low-dose corticosteroid treatment, be administered HCQ, use pregnancy-compatible immunosuppressants to control disease, and discontinue teratogenic drugs for a required duration. However, the guidelines failed to reach a consensus on some issues, such as the necessary duration of stability, the requirement for serological activity, and the maximum corticosteroid dosage, thereby precluding the provision of optimal practice instructions. This study, which used data from the Chinese SLE Treatment and Research Group (CSTAR) registry, a multicenter Chinese SLE cohort, aimed to investigate the optimal conditions for patients with SLE to be satisfied before pregnancy, to reveal the current status of meeting the conditions among patients with SLE in China, and to compare pregnancy outcomes and disease flares between patients whether fulfilling the conditions.

Materials and methods

Data source and study population

This was a retrospective study using data from the CSTAR registry, a multicenter Chinese SLE cohort that includes patients fulfilling the revised 1997 ACR criteria, 2012 Systemic Lupus International Collaborating Clinics (SLICC) criteria, or 2019 EULAR/ACR criteria. Data from July 2009 to June 2023 were retrieved. The inclusion criteria were: (1) have singleton intrauterine pregnancy; (2) have follow-ups from three months before conception to the first trimester of pregnancy; (3) have information on disease activity and treatment from six months preceding conception to the first trimester of pregnancy; and (4) have recorded pregnancy outcomes. The exclusion criteria were: (1) meet the diagnostic criteria of other connective tissue diseases, such as systemic sclerosis, rheumatoid arthritis, and idiopathic inflammatory myopathy; (2) use potentially teratogenic drugs; (3) have an anembryonic pregnancy or elective termination of pregnancy.

Data collection

All participating centers of CSTAR followed a uniform protocol for data acquisition and recording. This study examined demographics, obstetric history, SLE activity, clinical manifestations, autoantibody profiles, laboratory parameters, therapeutics, and pregnancy outcomes. Demographic information included age at conception, body mass index (BMI), comorbidities, age at SLE onset, and duration of SLE. The obstetric history, comprising gravidity and previous APOs, was collected. APOs were defined as having at least one of the following manifestations: (1) miscarriage; (2) intrauterine fetal demise; (3) therapeutic abortion; (4) preterm delivery due to maternal or fetal complications not explained by anatomical or chromosomal abnormalities; (5) neonatal death not caused by anatomical or chromosomal abnormalities; and (6) gestational hypertension. The activity of SLE was assessed using systemic lupus erythematosus disease

Table 1 Statements on baseline conditions to be considered for SLE patients before pregnancy from current guidelines

Characteristics	EULAR 2017	ACR 2020	China 2022
SLE activity	SLE activity in the last 6–12 months or at conception increases risks of APOs.	Only consider pregnancy when SLE is quiescent or at low disease activity.	Consider pregnancy when SLE is stale for at least 6 months.
Active vital organ involvement	Active lupus nephritis at conception increases risks of APOs.	Not mentioned.	Consider pregnancy when 24-hour urine protein is less than 0.5 g and no vital organ damage is present.
Serological activity	Serological activity increases risks of SLE flares during pregnancy and pregnancy loss.	Not mentioned.	Not mentioned.
Corticosteroids	Limit corticosteroid exposure.	Continue low-dose corticosteroid treatment (≤ 10 mg daily of prednisone or nonfluorinated equivalent).	Consider pregnancy when corticosteroid dose is ≤ 15 mg daily of prednisone or nonfluorinated equivalent.
Hydroxychloroquine	Recommended preconceptionally and throughout pregnancy.	Recommended during pregnancy.	Recommended throughout pregnancy.
Other immunosuppressants	Use safe medications to control disease activity. Avoid drugs with teratogenicity.	Use compatible medications. Discontinue drugs with teratogenicity for a required period of time.	Discontinue drugs with teratogenicity for a required period of time.

activity index 2000 (SLEDAI-2K) and physician global assessment (PGA). Partly referring to the definition of lupus low disease activity state (LLDAS), patients were considered stable if they: (1) had an SLEDAI-2K score of no more than four; (2) had no new lupus disease activity compared to the previous assessment; and (3) had a PGA score of no more than one. Active vital organ involvement encompassed renal, central nervous system, cardiopulmonary, vasculitis, and gastrointestinal activity. Clinical manifestations such as mucocutaneous lesions, arthritis, serositis, lupus nephritis, neuropsychiatric lupus, and hematological involvement were defined as positive if they had ever been present before conception. The autoantibodies recorded in this study were anti-dsDNA antibodies, anti-Smith (Sm) antibodies, anti-Sjögren's syndrome-related antigen A (SSA) antibodies, anti-Sjögren's syndrome-related antigen B (SSB) antibodies, anti-ribonucleoprotein (RNP) antibodies, anti-ribosomal P protein (rRNP) antibodies, and antiphospholipid antibodies (APLs). Then, baseline data on hemoglobin levels, white blood cell (WBC) counts, platelet (PLT) counts, 24-hour urine protein quantification (24hUPro), complement levels, and therapeutics were retrieved. The baseline period was defined as the three months preceding conception to the first trimester of pregnancy.

This study examined pregnancy outcomes including live birth, gestational week at delivery, birthweight, delivery method, and APOs. Clinical manifestations, laboratory examinations, disease activity, and therapeutics were all recorded during follow-ups spanning from the second trimester to one year postpartum. Disease flares during follow-ups were defined and classified as mild/moderate or severe according to the SELENA-SLEDAI Flare Index (SSFI) [18].

Statistical analysis

Data were presented as mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables when appropriate, while presented as absolute value with percentage for categorical variables. To identify factors associated with live birth, APOs, and flares during pregnancy in patients with SLE, univariate logistic regression analysis was used. The preconception conditions that patients with SLE should fulfill was proposed based on the results of logistic regression analysis. The patients would be classified into group A if they fulfilled the conditions proposed in this study, while classified into group B if they did not fulfill the conditions. The Chi-square test, Fisher's exact test, unpaired t-test, or Mann-Whitney U test were employed to compare data between groups whether fulfilling the pregnancy conditions when appropriate. The time to flare or severe flare was compared between the two groups with the Kaplan-Meier method. The hazard ratio with a 95% confidence interval (CI) was calculated through Cox regression analysis. All significance tests were two-sided, with a p-value of less than 0.050 denoting statistical significance unless stated otherwise. The above statistical analyses were performed with SPSS 22.0 and R (version 4.3.1).

Ethics

This study was approved by the institutional review board (IRB) of Peking Union Medical College Hospital (Approval number I-23PJ1007). Other centers had received ethical approval from their respective local institutional review boards. Informed consent from all participants has been obtained.

Results

Exploring the optimal conditions that patients with SLE should fulfill before pregnancy

A total of 347 singleton pregnancies from 332 patients were analyzed. Patients were recruited from 26 medical centers throughout China. According to current guidelines, six major aspects should be evaluated before pregnancy among patients with SLE (Table 1). However, certain details remained ambiguous and some recommendations were inconsistent, such as the maximum dose of corticosteroids and serological activity. To investigate the optimal conditions, univariate logistic regression analysis was performed to examine the impacts of the six aspects on the incidences of live birth (Fig. 1A), APOs (Fig. 1B), and flares during pregnancy (Fig. 1C). Stable SLE for at least 6 months could significantly increase the incidence of live birth (OR 3.40, 95% CI 1.89–6.11, $p < 0.001$), as well as decrease the risks of APOs (OR 0.39, 95% CI 0.23–0.67, $p = 0.001$) and flares during pregnancy (OR 0.33, 95% CI 0.17–0.65, $p = 0.001$). Similar results were observed for no active vital organ involvement, with OR values of 4.11 (95% CI 1.67–10.14, $p = 0.002$), 0.25 (95% CI 0.09–0.66, $p = 0.005$), and 0.32 (95% CI 0.11–0.96, $p = 0.041$), respectively. Then, hypocomplementemia had a significant impact on the incidence of flares during pregnancy (OR 0.40, 95% CI 0.22–0.74, $p = 0.003$), but not on live birth or APOs. The anti-dsDNA antibody positivity showed a numerical impact on all three outcomes. Next, no consensus has been reached on the maximum dose of corticosteroids. The analysis demonstrated that patients administered prednisone more than 7.5 mg daily or its nonfluorinated equivalent were at a significantly higher risk of APOs. When the patients were administered prednisone no more than 7.5 mg daily or its nonfluorinated equivalent, the incidences of the three outcomes were typically comparable. Then, HCQ was found to substantially benefit patients with SLE in terms of live birth (OR 2.74, 95% CI 1.23–6.11, $p = 0.014$), APOs (OR 0.45, 95% CI 0.21–0.96, $p = 0.040$), and flares during pregnancy (OR 0.30, 95% CI 0.11–0.80, $p = 0.013$). Additionally, the guidelines recommended to use compatible immunosuppressants to control disease activity. As it was difficult to distinguish between patients who did not require immunosuppressants to control disease activity and those who declined the medications based on the cohort data, we did not conduct an analysis on this aspect.

For sensitivity analysis, only the first pregnancy recorded for each subject in the database was incorporated into the univariate logistic regression analysis (Figure S1). The results were similar to those obtained when taking all pregnancies into consideration regarding live birth (Figure S1A), APOs (Figure S1B), and flares during pregnancy (Figure S1C).

Based on the analysis above, we proposed the following conditions for patients with SLE to fulfill before pregnancy: (1) disease stability for at least 6 months; (2) no active vital organ involvement; (3) on nonfluorinated corticosteroids no more than the equivalent of prednisone 7.5 mg per day; and (4) on HCQ. In our cohort, 180 (51.9%) pregnancies met the conditions (Group A), whereas 167 (48.1%) did not (Group B).

Baseline characteristics of SLE patients divided by whether fulfilling the conditions for pregnancy

Table 2 summarizes the baseline characteristics of patients categorized based on the fulfillment of aforementioned conditions. Overall, the average maternal age at conception was 30.3 (SD = 4.0) years. 151 pregnancies (43.5%) were primigravida, and 196 pregnancies (56.5%) were multigravida. Among patients who were multigravida, 85 (43.4%) had experienced APOs before. The two groups displayed generally similar profiles in terms of age at conception, BMI, comorbidities, gravidity, and history of APOs. SLE disease activity was significantly higher in group B, regardless of whether assessed by SLEDAI-2K ($p < 0.001$) or PGA ($p < 0.001$). Consistent with disease activity, group A exhibited a lower prevalence of anemia (5.6% vs. 13.2%, $p = 0.016$), thrombocytopenia (2.2% vs. 6.6%, $p = 0.048$), proteinuria (0.0% vs. 14.9%, $p = 0.001$), and hypocomplementemia (22.8% vs. 37.1%, $p = 0.003$). The two groups had similar clinical manifestations and autoantibody profiles. When it comes to therapeutics, patients from Group A were less likely to be taking cyclosporine A and tacrolimus, potentially attributed to lower disease activity.

Pregnancy outcomes and disease flares in SLE patients divided by whether fulfilling the conditions for pregnancy

As displayed in Table 3, Group A had a significantly greater percentage of live birth than the other group (86.1% vs. 73.7%, $p = 0.004$). Furthermore, the gestational week at delivery (median 38.4 vs. 37.6 weeks, $p < 0.001$) and birthweight (mean 2956.7 vs. 2810.2 gram, $p = 0.004$) were significantly higher in the previous group, while the rate of cesarean section was numerically lower (65.5% vs. 73.0%, $p = 0.193$). Then, APOs were less frequent in group A (29.4% vs. 52.1%, $p < 0.001$). For each type of APOs, the incidences of therapeutic abortion (5.0% vs. 12.0%, $p = 0.019$), preterm delivery (14.2% vs. 33.3%, $p < 0.001$), and preeclampsia (1.1% vs. 5.4%, $p = 0.023$) were remarkably lower in group A, while the others showed numerically differences between the two groups. Additionally, the proportion of live birth increased, while the risk of APOs decreased as patients met more conditions at baseline (Table S1).

When it comes to disease flares, patients in group A experienced flares less frequently during pregnancy and

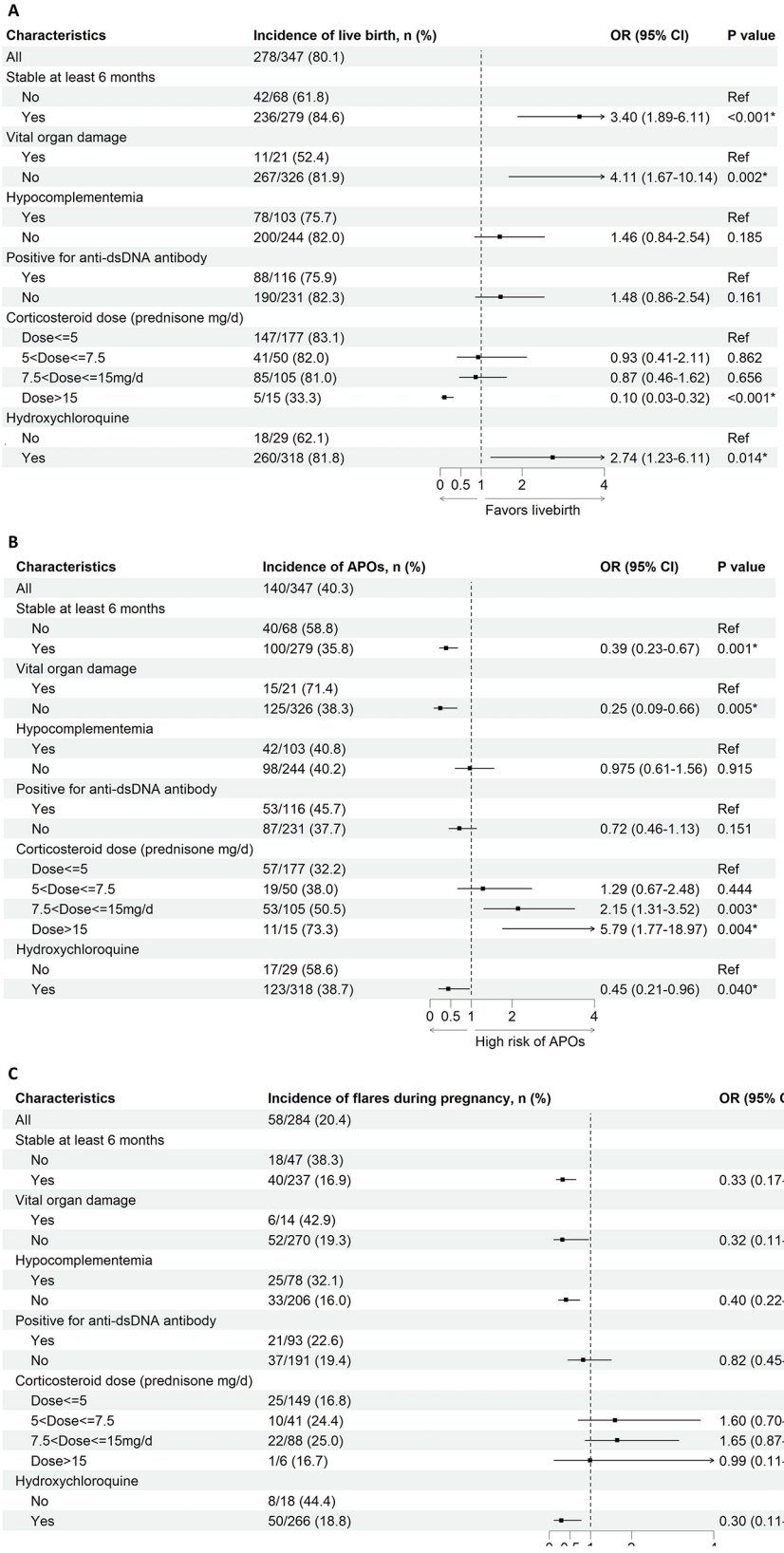

Fig. 1 Forest plots showing the impacts of baseline conditions on live birth (**A**), adverse pregnancy outcomes (**B**), and flares during pregnancy **(C)** among SLE patients

Table 2 Baseline characteristics of SLE patients divided by whether fulfilling the conditions for pregnancy

	All (*n* = 347)	Group A: Fulfilling the conditions (*n* = 180)	Group B: Not fulfilling the conditions (*n* = 167)	*P* value
Age at conception (years), mean (SD)	30.3 (4.0)	30.8 (4.1)	29.8 (3.8)	0.111
BMI (kg/m^2), median (IQR)	21.0 (19.4–23.8)	21.2 (19.6–23.9)	20.8 (19.2–23.5)	0.277
Comorbidities, n (%)				
Chronic hypertension	9 (2.7)	4 (2.3)	5 (3.1)	0.942
Diabetes mellitus	1 (0.3)	0 (0.0)	1 (0.6)	0.490
Primigravida, n (%)	151 (43.5)	79 (43.9)	72 (43.1)	0.884
Previous adverse pregnancy outcomes, n (%)	85 (43.4) (*n* = 196)	43 (42.6) (*n* = 101)	42 (44.2) (*n* = 95)	0.817
Age at SLE diagnosis (years), mean (SD)	24.6 (5.3)	25.2 (5.6)	24.1 (4.9)	0.015*
Duration of SLE (years), median (IQR)	5.0 (2.4-8.0)	5.0 (2.6–7.6)	4.9 (2.2–8.7)	0.893
SLEDAI-2K score, median (IQR)	2 (0–3)	0 (0–2)	2 (0–4)	< 0.001*
PGA score, median (IQR)	0.4 (0.1–0.7)	0.2 (0.0-0.5)	0.3 (0.6-1)	< 0.001*
Manifestations (ever present), n (%)				
Mucocutaneous lesions	268 (77.2)	135 (75.0)	133 (79.6)	0.303
Arthritis	186 (53.6)	91 (50.6)	95 (56.9)	0.237
Serositis	28 (8.1)	15 (8.3)	13 (7.8)	0.851
Lupus nephritis	128 (36.9)	65 (36.1)	63 (37.7)	0.756
Neuropsychiatric lupus	16 (4.6)	7 (3.9)	9 (5.4)	0.506
Hematological involvement	209 (60.2)	108 (60.0)	101 (60.5)	0.927
Autoantibodies, n (%)				
Anti-dsDNA antibodies	116 (33.4)	53 (29.4)	63 (37.7)	0.102
Anti-Sm antibodies	92 (29.5)	51 (31.9)	41 (27.0)	0.343
Anti-RNP antibodies	119 (39.8)	66 (43.1)	53 (36.3)	0.227
Anti-SSA antibodies	196 (64.3)	105 (67.7)	91 (60.7)	0.197
Anti-SSB antibodies	64 (21.0)	33 (21.2)	31 (20.8)	0.940
Anti-rRNP antibodies	64 (21.8)	31 (20.3)	33 (23.4)	0.514
Antiphospholipid antibodies	97 (33.0)	50 (32.3)	47 (33.8)	0.777
Triple antiphospholipid antibody positivity	19 (7.2)	10 (7.1)	9 (7.2)	0.986
Laboratory parameters, n (%)				
Anemia	32 (9.3)	10 (5.6)	22 (13.2)	0.016*
Leukocytopenia	8 (2.3)	4 (2.3)	4 (2.4)	1.000
Thrombocytopenia	15 (4.3)	4 (2.2)	11 (6.6)	0.048*
24hUPro > 0.5 g	11 (7.9)	0 (0.0)	11 (14.9)	0.001*
Hypocomplementemia	103 (29.7)	41 (22.8)	62 (37.1)	0.003*
Treatment at baseline, n (%)				
Glucocorticoid dose (equivalent to prednisone mg per day)				< 0.001*
≤5	177 (51.0)	141 (78.3)	36 (21.6)	
>5 and ≤ 7.5	50 (14.4)	39 (21.7)	11 (6.6)	
>7.5 and ≤ 15	105 (30.3)	0 (0.0)	105 (62.9)	
>15	15 (4.3)	0 (0.0)	15 (9.0)	
Hydroxychloroquine	318 (91.6)	180 (100.0)	138 (82.6)	< 0.001*
Azathioprine	37 (10.7)	20 (11.1)	17 (10.2)	0.779
Cyclosporine A	22 (6.3)	5 (2.8)	17 (10.2)	0.005*
Tacrolimus	59 (17.0)	22 (12.2)	37 (22.2)	0.014*

Note The conditions were defined as: (1) disease stable for at least 6 months; (2) no active vital organ involvement; (3) on nonfluorinated corticosteroids no more than the dose equivalent to prednisone 7.5 mg per day; (4) on HCQ

one year postpartum (32.4% vs. 46.1%, $p = 0.013$), with an HR of 0.61 (95% CI 0.43–0.87, $p = 0.006$; Fig. 2A) when analyzed by Cox regression, as well as for severe flares (16.2% vs. 26.2%, $p = 0.029$; HR 0.57, 95% CI 0.35–0.93, $p = 0.022$; Fig. 2B). When considering only the gestation period, Group A had a markedly reduced rate of flares (14.7% vs. 27.3%, $p = 0.009$; HR 0.48, 95% CI 0.28–0.81, $p = 0.005$; Fig. 2C), particularly severe flares (5.8% vs. 14.8%, $p = 0.011$; HR 0.36, 95% CI 0.16–0.80, $p = 0.009$; Fig. 2D). When only the first year postpartum was considered, group A also had a lower incidence of flares (25.2% vs. 36.1%, $p = 0.041$). Furthermore, the risk of

Table 3 Pregnancy outcomes and disease flares in SLE patients divided by whether fulfilling the conditions for pregnancy

	All (*n* = 347)	Group A: Fulfilling the conditions (*n* = 180)	Group B: Not fulfilling the conditions (*n* = 167)	*P* value
Live birth, n (%)	278 (80.1)	155 (86.1)	123 (73.7)	0.004*
Gestational week at delivery, median (IQR)	38.1 (37.1–38.9)	38.4 (37.7–39.0)	37.6 (36.4–38.6)	< 0.001*
Birthweight (gram), mean (SD)	2891.3 (497.5) (*n* = 150)	2956.7 (397.8) (*n* = 83)	2810.2 (591.7) (*n* = 67)	0.004*
Cesarean section, n (%)	178 (68.7)	97 (65.5)	81 (73.0)	0.254
Adverse pregnancy outcomes, n (%)	140 (40.3)	53 (29.4)	87 (52.1)	< 0.001*
Neonatal death	1 (0.3)	1 (0.6)	0 (0.0)	1.000
Miscarriage	17 (4.9)	7 (3.9)	10 (6.0)	0.365
Intrauterine fetal demise	23 (6.6)	9 (5.0)	14 (8.4)	0.206
Therapeutic abortion	29 (8.4)	9 (5.0)	20 (12.0)	0.019*
Preterm delivery	63 (22.7)	22 (14.2)	41 (33.3)	< 0.001*
Gestational hypertension	17 (4.9)	6 (3.3)	11 (6.6)	0.161
Preeclampsia	11 (3.2)	2 (1.1)	9 (5.4)	0.023*
Flares during pregnancy and one year postpartum	121 (38.5) (*n* = 314)	56 (32.4) (*n* = 173)	65 (46.1) (*n* = 141)	0.013*
Mild or moderate	56 (17.8)	28 (16.2)	28 (19.9)	0.398
Severe	65 (20.7)	28 (16.2)	37 (26.2)	0.029*
Flares during pregnancy	58 (20.4) (*n* = 284)	23 (14.7) (*n* = 156)	35 (27.3) (*n* = 128)	0.009*
Mild or moderate	30 (10.6)	14 (9.0)	16 (12.5)	0.336
Severe	28 (9.9)	9 (5.8)	19 (14.8)	0.011*
Flares during one year postpartum	89 (30.1) (*n* = 296)	41 (25.2) (*n* = 163)	48 (36.1) (*n* = 133)	0.041*
Mild or moderate	44 (14.9)	20 (12.3)	24 (18.0)	0.165
Severe	45 (15.2)	21 (12.9)	24 (18.0)	0.219

Note The conditions were defined as: (1) disease stable for at least 6 months; (2) no active vital organ involvement; (3) on nonfluorinated corticosteroids no more than the dose equivalent to prednisone 7.5 mg per day; (4) on HCQ

disease flares decreased as patients met more conditions at baseline generally (Table S1).

For sensitivity analysis, only the first pregnancy recorded for each subject in the database was included in the analysis. The findings were similar, demonstrating a benefit in live birth, APOs, and flares during pregnancy when the conditions proposed above were satisfied (Table S2).

Discussion

Due to the risks of APOs and disease flares, patients with SLE should undergo a comprehensive assessment before pregnancy [15–17]. Though previous studies have identified certain risk factors for APOs and disease flares, there has yet to be a global consensus on the optimal pre-pregnancy conditions for patients with SLE. In this multicenter Chinese SLE cohort, based on data from 347 singleton pregnancies observed in 332 patients collected between July 2009 and June 2023, we proposed the conditions that should be fulfilled before pregnancy. Further analysis confirmed the benefits of fulfilling the conditions, as it augmented the incidence of live birth, while decreased the risks of APOs and disease flares, particularly severe flares.

For the proposed conditions, the disease-stable duration before pregnancy was set as six months, as recommended by both EULAR and China guidelines. Due to data limitations, we were unable to compare different cut-off time points. It is worthwhile to explore whether an extended duration would bring more benefits and whether a shorter duration would not alter the outcomes, potentially allowing patients to conceive at a younger age. Unfortunately, limited studies focused on this topic. Data from Korea suggested that a four-month period might be an appropriate threshold for reduced rates of pregnancy loss and premature birth [19]. Generally, data is limited up to now, necessitating further investigation for this term.

The findings were inconsistent regarding the effects of serological activity on pregnancy outcomes and disease flares [7, 20], and our analysis revealed that it was not a significant factor in terms of live birth and APOs. Such inconsistency might be caused by different populations and varied definitions of baseline. One study found that the lack of an increase in complement levels during the first trimester compared to conception had the greatest clinical significance in predicting disease flares [21]. This suggested that monitoring the changes in complement levels was more important than focusing solely on the baseline level when managing SLE patients with pregnancy.

As for the baseline therapeutics, previous studies indicated that corticosteroid use was associated with preterm delivery [22, 23]. The recommended dose of corticosteroids in the guidelines were either inconsistent or unspecified. Analysis of this study suggested that a dose

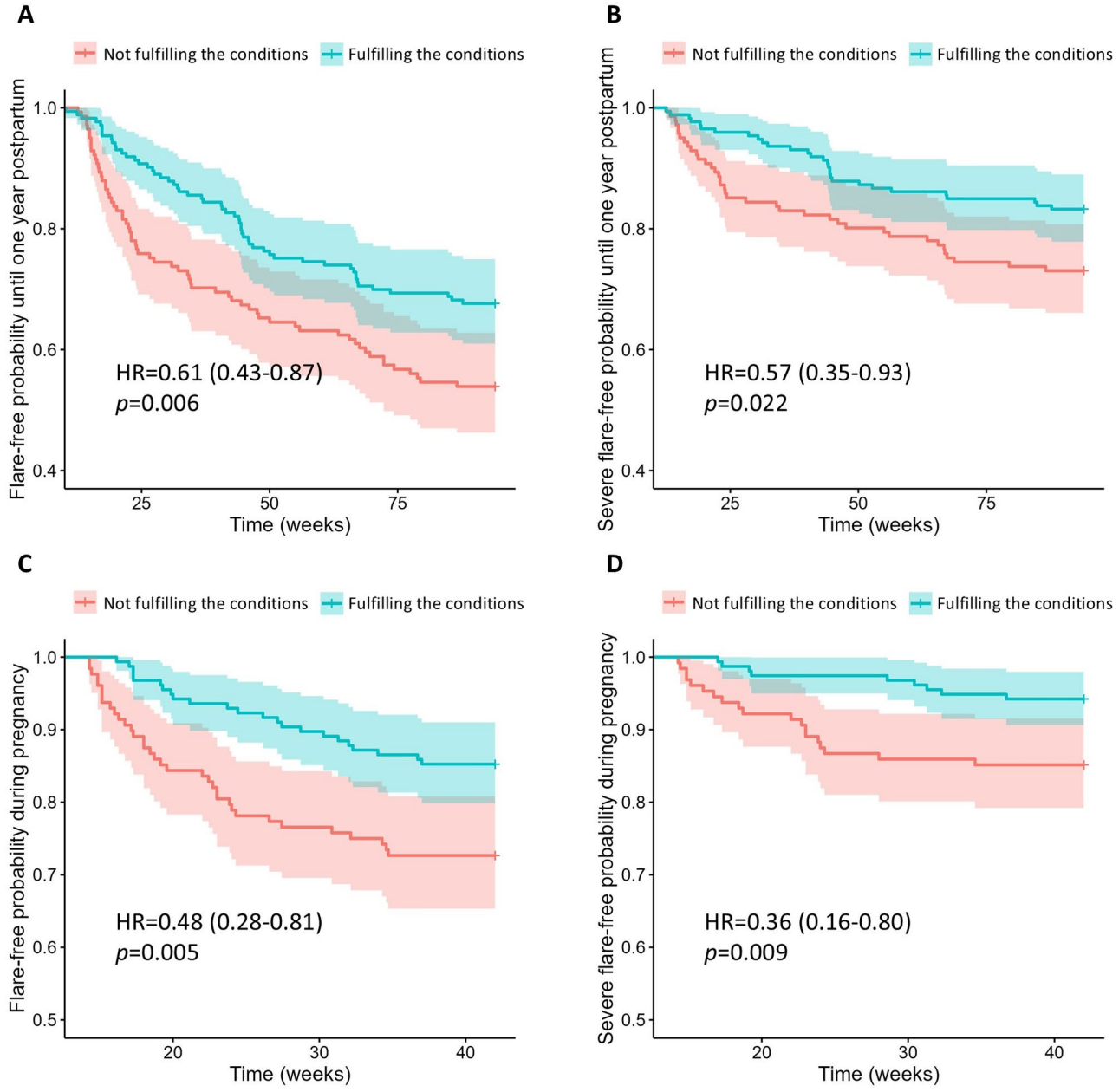

Fig. 2 Kaplan-Meier plots of the free of SLE flares or severe flares probability divided by whether fulfilling the conditions for pregnancy. (**A**) Free of flares probability from gestation period to one year postpartum. (**B**) Free of severe flares probability from gestation period to one year postpartum. (**C**) Free of flares probability during pregnancy. (**D**) Free of severe flares probability during pregnancy

equivalent to 7.5 mg of prednisone per day might be a suitable cut-off. Then, HCQ was found to protect SLE patients from preeclampsia and preterm delivery [24]. Investigation into mechanisms revealed that HCQ may have an anti-inflammatory effect on the placenta by promoting interleukin-10 (IL-10) secretion and syncytiotrophoblast regeneration [25]. As HCQ generally caused few pregnancy safety concerns [26–28], it appeared beneficial for SLE patients to use this medication during pregnancy for better outcomes if without contraindications. Additionally, all guidelines recommended the use of pregnancy-compatible immunosuppressants to control disease activity. However, as previously stated, distinguishing between patients who did not require immunosuppressants and patients who refused to take the medications was unfeasible using the cohort data, therefore we were unable to perform the analysis on this aspect.

Generally, pregnancies that fulfilled the proposed conditions ended in APOs and flares less frequently. Nevertheless, APOs and flares did occur in these patients, necessitating an investigation into the underlying

mechanisms. For the complement system, Matrai et al. displayed that, when compared to women without SLE, the placenta from women with SLE was more likely to be positive in C4d staining, which co-existed with a variety of histologic abnormalities such as infarction, intervillous thrombi, and malperfusion [29]. The high intensity of C4d staining correlated with reduced placental weight and birthweight [30]. Next, immune cell dysregulation participated in the development of APOs. Compared with healthy controls, women with SLE had significantly elevated levels of low-density granulocytes and $CD8^+$ regulatory T cells accompanied by a decreased level of $CD4^+$ regulatory T cells [31, 32]. Meanwhile, decidual natural killer cells and neutrophil extracellular traps were found to accumulate in the placentas of women with SLE [33]. The changes described above resulted in more placental injuries. Then, the altered profiles of long noncoding RNAs in the placenta have been revealed in several studies, possibly leading to a disturbed type I interferon response along with the release of anti-dsDNA antibodies [34, 35]. The aforementioned findings provided potential therapeutic targets for improved pregnancy outcomes, but they were far from sufficient. We advocated for a more thorough investigation into the mechanisms underlying poor pregnancy outcomes in patients with SLE.

According to our data, approximately 50% of pregnancies did not fulfill the conditions proposed in this study, highlighting current gaps in patient education. In general, when managing patients with SLE, physicians should discuss pregnancy intention with women of reproductive age at initial or early visits, making them aware of the importance of planned pregnancy and better prepared for a safe pregnancy [36].

This study has some limitations. This cohort did not collect data on certain APOs, such as fetal growth restriction, thromboembolic events, and preterm premature rupture of membranes [37]. Also, detailed information on disease flares, particularly the affected organs, was not collected. This might restrict the analysis of the outcomes. Finally, this study exclusively included Chinese participants, so the generalizability of the conditions beyond the Chinese population requires further validation.

Conclusion

Our study proposed the conditions that patients with SLE should fulfill before pregnancy and illustrated the benefits of satisfying the conditions in terms of live birth, APOs, and disease flares. The findings of this study highlight the importance of comprehensive preconception assessment and warrant the implementation of such criteria among patients with SLE in clinical practice.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13075-025-03497-9 .

Supplementary Material 1

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Author contributions

Jiuliang Zhao, Mengtao Li, and Xinping Tian conceived the study. Xueyang Zhang, Lingshan Liu, Shudian Lin, Xinwang Duan, Hui Luo, Yongfu Wang, Zhenbiao Wu, Can Huang, Yin Long, Yixin Cui, Xiaohua Shi, Yijun Song, Juntao Liu, Xiaofeng Zeng, Jiuliang Zhao, Mengtao Li, and Xinping Tian contributed to the data collection. Xueyang Zhang, Lingshan Liu, Shudian Lin, and Jiuliang Zhao designed the protocol and performed data analysis. Xueyang Zhang wrote the first manuscript draft. All authors provide revisions to the manuscript and approved the final version.

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Data availability

Data supporting this study are not publicly available due to that the data are under analysis for an ongoing study. Please contact corresponding authors for data if have requests due to ethical, legal or commercial reasons.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board (IRB) of Peking Union Medical College Hospital (Approval number, I-23PJ1007). Other centers had received ethical approval by the local institutional review board. Informed consents from all participants have been obtained.

Consent for publication

Consent to Publish declaration: not applicable.

Competing interests

The authors declare no competing interests.

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