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High-risk factors for adverse pregnancy outcomes in systemic lupus erythaematosus: a retrospective study of a Chinese population

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ABSTRACT

Objective To clarify high-risk factors for adverse pregnancy outcomes (APOs) in systemic lupus erythaematosus (SLE).

Design A retrospective chart review study.

Setting Data were collected in a tertiary medical centre, Shanghai, China, from November 2010 to December 2018.

Participants A total of 513 pregnancies with SLE were retrospectively analysed. Twenty-seven patients who underwent artificial abortions due to personal reasons were excluded.

Primary outcome measures APOs were primary outcomes, including foetal loss, premature birth, small for gestational age (SGA), asphyxia neonatorum, composite foetal APOs and hypertensive disorders of pregnancy (HDP). Multivariable logistic regression and Spearman correlation analysis were performed to determine the risk factors for APOs in SLE.

Results Risk factors for foetal loss included prepregnancy hypertension, hypocomplementaemia-C3, anticardiolipin antibodies-IgM positivity and disease flares during pregnancy. Risk factors for premature birth included disease flares, use of immunosuppressive agents and HDP. Moreover, twin pregnancy, disease flares and HDP were risk factors for SGA, and prepregnancy hypertension was an independent risk factor for asphyxia neonatorum. Independent risk factors for composite foetal APOs included twin pregnancy, prepregnancy hypertension, disease flares during pregnancy, HDP, hypocomplementaemia-C3 and the use of immunosuppressive agents. Risk factors for SLE complicated with HDP included prepregnancy hypertension, renal disorders and thrombocytopaenia. Conversely, the use of aspirin was a protective factor against foetal loss and premature birth. The ds-DNA value had a low diagnostic value for APOs, whereas the extent of complement reduction may predict the incidence of composite foetal APOs and foetal loss. Proteinuria occurring in the first 20 gestational weeks may lead to APOs.

Conclusion Established risk factors for each APO were identified in this study. Indicators with more predictive significance have been screened out from conventional indicators, which may help clinicians predict the pregnancy outcome of patients with SLE more accurately and minimise the incidence of APOs.

Strengths and limitations of this study

- A comprehensive analysis was performed of the most important risk factors for the main maternal and foetal adverse pregnancy outcomes (APOs) caused by placental dysfunction in systemic lupus erythaematosus (SLE) pregnancy with a large sample size.
- The study demonstrated that the ds-DNA value had a low diagnostic value for APOs, whereas the extent of complement decrease, especially C3, may predict the incidence of composite foetal APOs, especially foetal loss.
- The study contributes to a better counselling of obstetric surveillance in SLE pregnancy.
- As a retrospective study, inherent information bias was present.

INTRODUCTION

Systemic lupus erythaematosus (SLE) is an autoimmune disease involving multiple organs and autoantibodies. Nearly 90% of females with SLE are of reproductive age.[1] Previous epidemiological studies have demonstrated that the prevalence and incidence rates of patients with SLE among Asians are approximately 2–3 times higher than those among Caucasians. China has a higher prevalence of SLE than many other countries, especially among women (estimated to be more than 100 per 100 000 persons). Based on an estimated Chinese population of 1.3 billion published in 2009, the number of lupus patients in China could reach 520 000–910 000, which would be the largest cluster of cases in the world.[2] To tolerate the paternal antigens expressed in foetal cells or tissues, the maternal immune system may undergo adaptive changes during pregnancy, which can stimulate the autoimmune response and lead to SLE flares. The flare rate in pregnancy has been reported

to range from 13% to 68%, accompanied by irreversible organ damage and adverse pregnancy outcomes (APOs).[3] Although diagnostic and therapeutic strategies for SLE have greatly improved, SLE in pregnancy is still a high risk factor due to frequent complications, including preeclampsia (PE), small for gestational age (SGA), foetal loss and premature birth.[4 5]

Prepregnancy counselling and perinatal care are essential for the prevention of APOs in the SLE population. Indeed, potential clinical risk factors and serological predictors of adverse outcomes in SLE pregnancies have been widely studied in recent decades.[6–13] Nevertheless, there is no consensus regarding predictors for each APO, and most risk factors are presented as categorical variables. Given the different incidences of SLE in various countries and the limitation of methodology consistency, there is a need for a concise and evidence-based list of indicators to estimate SLE pregnancy risk. In addition, it remains unknown whether the extent of the abnormality of disease activity indexes for SLE, such as ds-DNA, complement and proteinuria, can accurately predict pregnancy outcomes. Furthermore, there are few studies involving large samples. Ren Ji Hospital has treated a leading number of SLE pregnancies in China, which provided our study with a rare large single-centre sample. Here, we evaluated 513 pregnant women and analysed high-risk factors for adverse SLE maternal and foetal outcomes to strengthen management and improve SLE pregnancy outcomes.

METHODS

Patient population

This was a retrospective study performed at Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. The medical records of all pregnant patients with SLE (meeting ≥4 of the revised American College of Rheumatology criteria[14]) between November 2010 and December 2018 were reviewed. The total number of deliveries in our hospital during the study period reached 24 859, with SLE pregnancies accounted for 2.2%. Twenty-seven patients who underwent artificial abortions due to personal reasons rather than therapeutic reasons were excluded. Rheumatologists diagnosed and obstetricians jointly managed SLE pregnant women.

Variables of interest

Clinical and laboratory information was recorded from the first antenatal care records (16–20 gestational weeks). Baseline maternal information included age, obstetric history, duration of SLE, previous manifestations of SLE (including renal disorders, mucocutaneous disorders, haematological disorders, neurological disorders, arthritis and serositis) and medication use. Comorbidities included prepregnancy hypertension and diabetes. Laboratory data collected included 24-hour urinary protein, antinuclear antibodies, complement 3 (C3), complement 4 (C4), ds-DNA and antiphospholipid antibody (aPL) results. aPL included IgG/IgM anticardiolipin antibodies (aCLs) and anti-2-glycoprotein I antibodies (anti-β2GPI); only titres of aCLs, β2GPI IgG, IgM ≥40 GPL or MPL units were considered positive. All laboratory tests were performed using standardised methods. Each pregnancy was recorded as a separate observation. Pregnancy outcomes were also evaluated, including delivery mode, foetal survival, Apgar score and foetal birth weight.

Patient and public involvement

Patients and the public were not involved in the design and conception of the study and there are no plans to disseminate the results to patients.

Definitions

Foetal APOs included one or more of the following: (1) foetal loss—spontaneous abortion (referring to termination before 28 weeks of pregnancy with foetal weight less than 1000 g), therapeutic abortion (iatrogenic abortion caused by a lupus flare or obstetric complications threatening the life of the mother), stillbirth (any baby born without signs of life at ≥28 completed weeks of gestation), and neonatal death (death of a liveborn baby within 28 days after birth)[15]; (2) premature birth—delivery prior to 37 weeks of gestation[16]; (3) SGA—birth weight below the 10th percentile according to gestational week at delivery and foetal sex[17]; and (4) asphyxia neonatorum—Apgar score of <7 at 1 and/or 5 min after birth.[18] Composite foetal APOs were defined as the occurrence of any adverse outcomes, including foetal loss, premature birth, SGA and asphyxia neonatorum.

Hypertensive disorders of pregnancy (HDPs) were categorised into three types in this study. (1) Gestational hypertension (GH): new-onset blood pressure ≥140/90 mm Hg without proteinuria after 20 weeks of gestation. (2) PE: the first incidence of systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg after 20 weeks of gestation plus one of the following criteria, protein loss of 300 mg or more in a 24-hour urine specimen or maternal organic dysfunction, such as loss of renal function, hepatic dysfunction, neurological complications (altered mental state, blindness, scotomas, visual blurring), haematological complications (thrombocytopaenia, haemolysis) or intrauterine growth restriction; PE can also overlap with other hypertensive states, such as prepregnancy hypertension preceding pregnancy or identified before 20 weeks. (3) Eclampsia: new-onset generalised seizures in a woman with PE.[19]

A disease flare during pregnancy was defined as a new or worsened presence of arthritis, malar rash, vasculitis, oral or nasal ulcers, serositis, neurological manifestations, haematological disorders, fever attributable to SLE, the addition of immunosuppressive medications or hydroxychloroquine, or an increase in prednisone ≥0.5 mg/kg/day. Additionally, new-onset SLE during pregnancy was included.[20]

Statistical analyses

Continuous variables were analysed using analysis of variance tests when the distributions were normal or Kruskal-Wallis H tests when the distributions were not normal, and the results are presented as the mean±SD or as the frequency. Categorical variables were analysed using χ^2 or Fisher's exact probability tests as appropriate. Multivariable and stepwise regression ($p<0.05$ for forward steps and $p<0.10$ for backward steps) was performed by selecting variables with a p value<0.05 in the univariate analysis. For categorical variables, univariate ORs and corresponding 95% CIs were computed. Spearman tests were employed to determine correlations between variables. The area under the receiver operating characteristic (ROC) curve (AUC) was used to assess discrimination of continuous variables with a p value<0.05 in the Spearman test and to obtain the critical cut-off value. All tests were two-tailed, and $p<0.05$ was considered statistically significant. All analyses were performed using SPSS V.25.0.

RESULTS

Population characteristics

A total of 513 pregnancies in 484 patients with SLE were recorded at Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, between November 2010 and December 2018. Of these patients, 456 (94.2%) had 1 pregnancy within the study period, 27 (5.6%) had 2 pregnancies and 1 (0.2%) had three pregnancies. Through retrieval by case diagnosis, 41 cases of antiphospholipid antibody syndrome were identified among patients with SLE. The mean age at conception was 29.7±4.0 years (range, 20–40 years). The average duration of SLE before pregnancy was 6.6±4.3 years (range, 1–18 years). There were 238 cases (46.4%) of primipara, 505 cases (98.4%) of singleton pregnancy and 8 cases (1.6%) of twin pregnancy. Twenty-one patients (4.1%) had prepregnancy hypertension. Almost 96% of the patients (495 cases) were in the SLE remission stage for more than 6 months prior to conception. Eighty-two of the patients (16%) had a disease flare before 20 weeks of gestation. A total of 501 patients (97.7%) used prednisone, 405 (78.9%) took hydroxychloroquine and 45 (8.8%) received immunosuppressive medications (such as azathioprine, tacrolimus and cyclosporine A). Of the patients, 398 (77.6%) used aspirin, and 138 (26.9%) received low-molecular-weight heparin.

Foetal outcomes

A total of 444 pregnancies (86.5%) resulted in live births. The average gestation days for the live births were 260.10±15.06 days (range, 201–282 days), and the average foetal weight was 2797.96±563.951 g (range, 940–4370 g). In total, 128 (24.9%) premature births were recorded, and there was no significant difference in the premature birth rate between twins and singletons (χ^2=115.28, p=0.09).

There were 11 cases (2.1%) with an Apgar score <7 at 1 min after birth. Only one newborn had Apgar scores<7 at 5 and 10 min after rescue and ultimately died due to oedema. In all cases of asphyxia neonatorum, there was no evidence of cardiac malformations based on B-ultrasound during pregnancy. The overall foetal loss rate was 13.6% (70 cases), and the SGA rate was 23.4% (120 cases). There were 236 cases (46.0%) with composite foetal APOs.

Maternal outcomes

In this study, 145 patients (28.3%) experienced disease flares during pregnancy. Among 513 pregnancies, 90 patients (17.5%) eventually developed HDP, 16 patients (3.1%) had GH, 74 patients (14.4%) had PE and 2 developed eclampsia (0.4%). All patients with disease flares and HDPs received timely diagnosis and treatment. One maternal death occurred in a patient with lupus that remained active without evaluation by the rheumatologist or obstetrician after conception. This patient was 30 years old and dramatically deteriorated with pulmonary haemorrhage, and multiple organ failure developed 15 days after iatrogenic abortion.

Predictors of adverse foetal and maternal outcomes

Table 1 provides a comparison of clinical events as well as laboratory parameters in patients with or without composite foetal APOs. Multivariable analysis revealed that multiple pregnancies, prepregnancy hypertension, disease flares during pregnancy, HDP, hypocomplementaemia-C3 and the use of immunosuppressive agents were independent predictors of composite foetal APOs (table 2).

Univariate analysis of foetal APOs is shown in online supplemental table 1. Multivariable analysis revealed that prepregnancy hypertension, hypocomplementaemia-C3, aCL-IgM positivity and disease flares during pregnancy were risk factors for foetal loss. Disease flares during pregnancy, HDPs and the use of immunosuppressive agents were responsible for premature birth, and multiple pregnancies, disease flares during pregnancy and HDPs were independent predictors of SGA. Moreover, the occurrence of asphyxia neonatorum correlated significantly only with prepregnancy hypertension (table 3).

The maternal characteristics significantly associated with HDPs in the univariate analysis are shown in table 4. In the multivariable analysis, prepregnancy hypertension (OR=9.03), renal disorders (OR=2.71) and thrombocytopaenia (OR=3.24) were independent risk factors for HDP (online supplemental table 2).

The influence of anti-dsDNA, complements and proteinuria on APOs in SLE pregnancies

The results showed that anti-dsDNA correlated slightly positively with the occurrence of foetal loss (ρ=0.147, $p<0.01$). The value of ds-DNA was converted into a categorical variable according to the critical cut-off value obtained with the ROC curve. Ds-DNA ≥14.41 IU/

Table 1 Maternal characteristics according to composite foetal adverse pregnancy outcomes (APOs)

Characteristics	Total	Composite foetal APOs		P value
		Yes (%, n=236)	No (%, n=277)	
Age≥35 years old	71	38 (16.1)	33 (11.9)	0.17
Primipara	238	102 (43.2)	136 (49.1)	0.18
Multiple pregnancy	8	7 (2.9)	1 (0.3)	0.03*
Prepregnancy hypertension	21	19 (8.1)	2 (0.7)	<0.01*
Diabetes	2	1 (0.4)	1 (0.3)	0.91
Remission <6 months prior to conception	18	17 (7.2)	1 (0.3)	<0.01*
Duration of SLE				
≤5 years	273	128 (54.2)	145 (52.3)	0.62
6–10 years	162	76 (32.2)	86 (31.0)	
>10 years	78	32 (13.6)	46 (16.6)	
Disease flares during pregnancy	145	110 (46.6)	35 (12.6)	<0.01*
APS	41	26 (11.0)	15 (5.4)	0.02*
HDP	90	69 (29.2)	21 (7.6)	<0.01*
Lupus characteristics				
Mucocutaneous	151	65 (27.5)	86 (31.0)	0.39
Neurological disorders	7	6 (2.5)	1 (0.3)	0.03*
Arthritis	116	53 (22.5)	63 (22.7)	0.94
Serositis	26	20 (8.5)	6 (2.2)	<0.01*
Leukopaenia	48	25 (10.6)	23 (8.3)	0.37
Thrombocytopaenia	42	28 (11.8)	14 (5.1)	<0.01*
Renal disorders	89	56 (23.7)	33 (11.9)	<0.01*
Laboratory parameters				
Anti-dsDNA	400	185 (78.4)	215 (77.6)	0.83
Hypocomplementaemia-C3	156	96 (40.7)	60 (21.7)	<0.01*
Hypocomplementaemia-C4	83	48 (20.3)	35 (12.6)	0.02*
SSA/Ro	276	129 (54.7)	147 (53.1)	0.72
SSB/La	70	40 (16.9)	30 (10.8)	0.04*
U1RNP	123	67 (28.4)	56 (20.2)	0.03*
Sm	35	22 (9.3)	13 (4.7)	0.04*
Nucleosome	131	73 (30.9)	58 (20.9)	0.01*
aCL-IgG	40	24 (10.1)	16 (5.8)	0.06
aCL-IgM	22	17 (7.2)	5 (1.8)	<0.01*
β2GP1-IgG	22	13 (5.5)	9 (3.2)	0.21
β2GP1-IgM	43	22 (9.3)	21 (7.6)	0.48
Medication				
Glucocorticoid	501	234 (99.2)	267 (96.4)	0.04*
Hydroxychloroquine	405	181 (76.7)	224 (80.9)	0.24
Immunosuppressive agent	45	30 (12.7)	15 (5.4)	<0.01*
Aspirin	398	159 (67.4)	239 (86.3)	<0.01*
LMWH	138	61 (25.8)	77 (27.8)	0.62

*P < 0.05.
APS, antiphospholipid antibody syndrome; HDP, hypertensive disorders of pregnancy; LMWH, low-molecular-weight heparin.

mL (AUC=0.624, YI=0.201, sensitivity=0.686, specificity=0.515) was found to be a risk factor for foetal loss among pregnant women with SLE. An AUC of less than 0.7 indicates a low diagnostic value of the optimal cut-off value. There was no significant correlation between anti-dsDNA and other APOs (p>0.05).

To clarify the impact of the degree of decrease in C3 on composite foetal APOs, foetal loss and HDP, the

Table 2 Predictors of composite foetal adverse pregnancy outcomes (APOs): results of multivariable analysis

Characteristics	B	P value	OR	95% CIs
Multiple pregnancy	2.368	0.03	10.67	1.22 to 93.31
Prepregnancy hypertension	2.143	<0.01	8.52	1.81 to 40.21
Disease flares during pregnancy	1.395	<0.01	4.03	2.51 to 6.50
HDP	1.114	<0.01	3.05	1.69 to 5.47
Hypocomplementaemia-C3	0.543	0.02	1.72	1.11 to 2.67
Use of immunosuppressive agent	0.856	0.02	2.35	1.15 to 4.82

*P < 0.05.
HDP, hypertensive disorders of pregnancy.

values of C3 were set according to the interval of every 0.1 g/L decrease below the lower normal limit. Following the same method, the values of C4 were set according to the interval of every 0.01 g/L decrease below the lower normal limit (online supplemental tables 3 and 4). In addition to HDPs, we found that in both C3 and C4, the incidences of composite foetal APOs and foetal loss in any interval below the lower normal limit increased with the decrease in complement (figure 1).

A total of 140 patients (27.3%) had proteinuria before 20 weeks of gestation. The diagnostic criterion for a renal disorder in SLE is 24-hour urinary protein of >0.5 g, and proteinuria during pregnancy is defined as 24-hour urinary protein of ≥0.3 g[21]. Therefore, all cases were divided into four groups regardless of the diagnosis: N group (n=373, without proteinuria), P1 group (n=60, 0.3 g≤24 hour urinary protein ≤0.5 g), P2 group (n=46, 0.5 g<24 hour urinary protein ≤1 g), and P3 group (n=34, 24-hour urinary protein >1 g).

As shown in table 5, foetal birth weights and the duration of pregnancy were highest in the N-group and lowest in the P3 group, both of which showed significant differences from each other group. Overall, the incidences of most APOs were lowest in the N group. The highest incidences of composite foetal APOs, SGA, HDP and premature birth were detected in the P3 group compared with the other three groups (p<0.05). Overall, foetal loss rates were similar in the P1, P2 and P3 groups and were higher than those in the N group (p<0.05), and premature birth rates differed significantly between each group, except for the N and P1 groups. There were no significant differences in the incidence of asphyxia neonatorum among the four groups.

Table 3 Multivariable analysis of different foetal adverse pregnancy outcomes

Characteristics	B	P value	OR	95% CI
Foetal loss				
Prepregnancy hypertension	1.739	<0.01	5.69	1.58 to 20.52
Disease flares during pregnancy	1.054	<0.01	2.87	1.45 to 5.69
Hypocomplementaemia-C3	1.552	<0.01	4.72	2.47 to 9.02
aCL-IgM positivity	1.421	0.02	4.14	1.24 to 13.84
Use of aspirin	−1.94	<0.01	0.14	0.07 to 0.29
Premature birth				
Disease flares during pregnancy	0.872	<0.01	2.39	1.48 to 3.84
HDP	0.585	0.02	1.79	1.07 to 3.00
Use of Immunosuppressive agent	0.694	0.03	2.00	1.04 to 3.86
Use of aspirin	−0.561	0.04	0.57	0.33 to 0.99
SGA				
Multiple pregnancy	2.085	<0.01	8.04	1.81 to 35.71
Disease flare during pregnancy	0.612	0.01	1.84	1.15 to 2.95
HDP	0.914	<0.01	2.49	1.49 to 4.15
Asphyxia neonatorum				
Prepregnancy hypertension	0.914	<0.01	2.49	1.49 to 0.91

HDP, hypertensive disorders of pregnancy; SGA, small for gestational age.

Table 4 Maternal characteristics according to hypertensive disorder of pregnancy (HDP)

Characteristics	Total	HDP		P value
		Yes (%, n=90)	No (%, n=423)	
Age≥35 years old	71	17 (18.9)	54 (12.8)	0.12
Primipara	238	39 (43.3)	199 (47.0)	0.52
Multiple pregnancy	8	0 (0)	8 (1.9)	0.36
History of PE	20	8 (8.9)	12 (2.8)	0.01*
Prepregnancy hypertension	21	14 (15.6)	7 (1.7)	<0.01*
Diabetes	2	0 (0)	2 (0.5)	0.51
Remission <6 months prior to conception	18	8 (8.9)	10 (2.4)	<0.01*
Duration of SLE				
≤5 years	273	48 (53.3)	225 (53.2)	0.99
6–10 years	162	28 (31.1)	134 (31.7)	
>10 years	78	14 (15.6)	64 (15.1)	
Disease flares during pregnancy	145	46 (51.1)	99 (23.4)	<0.01*
APS	41	8 (8.9)	33 (7.8)	0.73
Lupus characteristics				
Mucocutaneous	151	26 (28.9)	125 (29.6)	0.90
Neurological disorders	7	1 (1.1)	6 (1.4)	0.63
Arthritis	116	20 (22.2)	96 (22.7)	0.92
Serositis	26	10 (11.1)	16 (3.8)	<0.01*
Leukopaenia	48	10 (11.1)	38 (8.9)	0.52
Thrombocytopaenia	42	17 (18.9)	25 (5.9)	<0.01*
Renal disorders	89	32 (35.6)	57 (13.5)	<0.01*
Laboratory parameters				
Anti-dsDNA	400	73 (81.1)	327 (77.3)	0.42
Hypocomplementaemia-C3	156	42 (46.7)	114 (26.9)	<0.01*
Hypocomplementaemia-C4	83	24 (26.7)	59 (13.9)	<0.01*
SSA/Ro	276	42 (46.7)	234 (55.3)	0.13
SSB/La	70	15 (16.7)	55 (13.0)	0.35
U1RNP	123	24 (26.7)	99 (23.4)	0.51
Sm	35	6 (6.7)	29 (6.9)	0.94
Nucleosome	131	33 (36.7)	98 (23.2)	<0.01*
aCL-IgG	40	10 (11.1)	30 (7.1)	0.19
aCL-IgM	22	8 (8.9)	14 (3.3)	0.03*
β2GP1-IgG	22	2 (2.2)	20 (4.7)	0.39
β2GP1-IgM	43	7 (7.8)	36 (8.5)	0.82
Medication				
Glucocorticoid	501	90(100)	411 (97.2)	0.13
Hydroxychloroquine	405	67 (74.4)	338 (79.9)	0.24
Immunosuppressive agent	45	13 (14.4)	32 (7.6)	0.03*
Aspirin	398	56 (62.2)	342 (80.9)	<0.01*
LMWH	138	19 (21.1)	119 (28.1)	0.17

*P < 0.05.
APS, antiphospholipid antibody syndrome; HDP, hypertensive disorders of pregnancy; LMWH, low-molecular-weight heparin; PE, preeclampsia.

DISCUSSION

Our study presents a comprehensive analysis of the most important risk factors for each maternal and foetal APO in SLE pregnancy with a large sample size. We found that prepregnancy hypertension, HDP and flares during pregnancy were key risk factors for most APOs. The ds-DNA value had a low diagnostic value for APOs, whereas the extent of complement decrease, especially

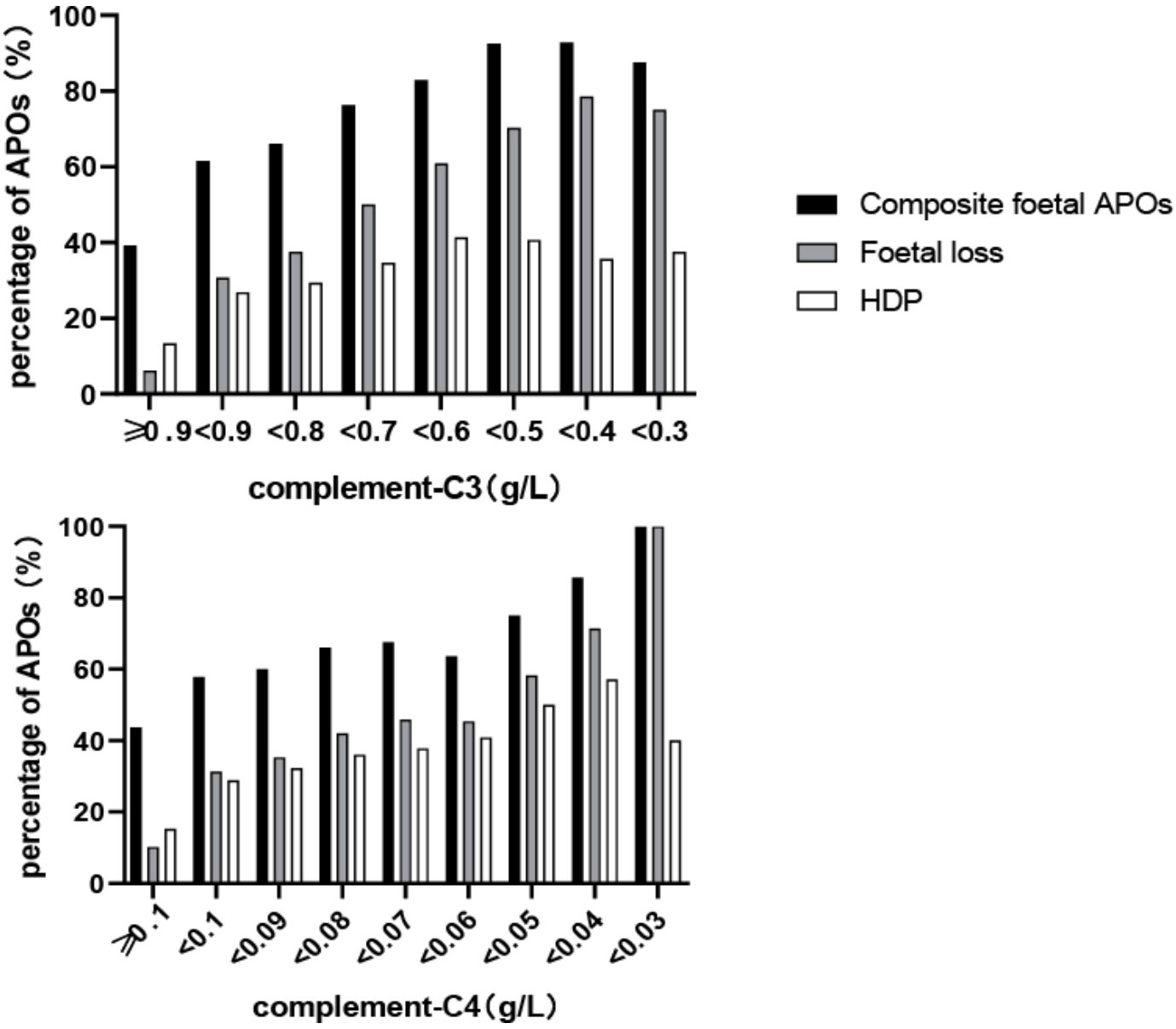

Figure 1 The incidences of adverse pregnancy outcomes (APOs) associated with the different intervals of complement C3 and C4. HDP, hypertensive disorders of pregnancy.

C3, may predict the incidence of composite foetal APOs, especially foetal loss. Proteinuria occurring in the first 20 gestational weeks may lead to APOs.

Patients with SLE have a higher incidence of APOs than the general population, including foetal loss, premature birth, SGA and HDP.[22–27] Overall, independent risk factors for composite foetal APOs included multiple pregnancies, prepregnancy hypertension, disease flares during pregnancy, HDP, hypocomplementaemia-C3 and the use of immunosuppressive agents, similar to the conclusions of other studies.[12 22 28] Predictors for each outcome are also proposed in this study. The main cause of foetal loss is generally recognised as aPL positivity.[29 30] Our results showed that aCL-IgM positivity has a greater impact on foetal loss than aCL-IgG or β2GPI positivity. In addition, hypocomplementemia-C3, prepregnancy hypertension, and disease flares during pregnancy were independent risk factors for foetal loss, consistent with previous findings.[9 15 24]

The main predictors of preterm birth and SGA in previous studies were lupus activity during pregnancy and HDP,[22 31–34] which was also confirmed in our study. In addition, immunosuppressant use and disease flares were jointly found to be independent risk factors for preterm birth in the present study, indicating that they may be caused by lupus flares rather than by adverse drug events.[35] We still felt that immunosuppressant use should be continued in patients who benefit from therapy. Data regarding foetal complications during therapy are scarce, but no evidence of teratogenesis has emerged. In addition, many studies have ruled out the effect of multiple pregnancies on SLE pregnancy. However, the dual factors of a twin pregnancy and an abnormal placenta induced by the disease may aggravate the risk of SGA in patients

Table 5 Pregnancy outcomes of systemic lupus erythaematosus (SLE) pregnancies with or without proteinuria

Characteristics	N-group (n=373, %)	P1-group (n=60, %)	P2-group (n=46, %)	P3-group (n=34, %)	P value
Live birth	348 (93.3)*	44 (73.3)	32 (69.5)	20 (58.8)	<0.01
Foetal birth weight (g, mean±SD)	2887.93±495.54*	2451.76±986.67†	2392.92±883.68†	1911.40±935.857*	<0.01
Duration of pregnancy (days, mean±SD)	254.62±34.56*	226.05±58.64†	221.87±52.84†	209.18±53.35*	<0.01
APOs					
Composite foetal APOs	134 (35.9)*	40 (66.7)†	33 (71.7)†	29 (85.3)*	<0.01
Foetal loss	26 (6.9)*	16 (26.7)	14 (30.4)	14 (41.2)	<0.01
Premature birth	83 (83/348, 23.8)‡	14 (14/44, 31.8)‡	16 (16/32, 50.0)*	15 (15/20, 75.0)*	<0.01
SGA	73 (73/348, 20.9)*	19 (19/44, 43.2)†	14 (14/32, 43.8)†	14 (14/20, 70.0)*	<0.01
Asphyxia neonatorum	6 (6/348, 1.7)	2 (2/44, 4.5)	1 (1/32, 3.1)	2 (2/20, 10.0)	0.17
HDP	31 (8.3)*	21 (35.0)†	17 (36.9)†	21 (61.7)*	<0.01

*Significantly different from each other group;
†Significantly different from the N and P3 groups;
‡Significantly different from the P2 and P3 groups;
HDP, hypertensive disorders of pregnancy; SGA, small for gestational age.

with SLE. It should be noted that for patients with SLE, multiple pregnancies caused by assisted reproductive technology should be avoided as much as possible.

In addition, our results showed that aspirin use is a protective factor for foetal loss and preterm birth, which is also consistent with other studies.[24 36] The improved pregnancy outcome in SLE pregnancies treated with aspirin appears to correlate with the mechanism of inhibiting platelet aggregation and anti-inflammatory activity, promoting normal uterine artery flow velocity.[37]

A total of eleven cases of asphyxia neonatorum (2.1%) were recorded in this study. In non-SLE pregnant women, hypertension increases the possibility of placental dysfunction, leading to foetal hypoxia and asphyxia after birth.[38] The same association for neonatal asphyxia in SLE pregnancy was found in our research.

Early studies have reported that specific predictors of HDP, especially PE complicated by SLE, include aPL positivity, thrombocytopaenia, hypocomplementaemia, disease flares and renal damage.[22 39–43] Although our results are basically consistent with those of previous studies, it is unexpected that aPL positivity and hypocomplementaemia are not independent risk factors for HDP with SLE. Our data indicate that prepregnancy hypertension, renal disorders and thrombocytopaenia are more significant in predicting HDP.

Many studies have only focused on whether ds-DNA or complements are abnormal as predictors of SLE pregnancy outcomes. To clarify the degree of abnormality of these indicators that threaten SLE pregnancy outcomes, we analysed the correlation between ds-DNA, complements and APOs. We found that the value of ds-DNA correlated slightly positively with the incidence of foetal loss. In addition, we found that the incidences of composite foetal APOs and foetal loss in any interval below the lower normal limit, whether complement C3 or C4, increased with the decrease in complements. These results may explain the clinical phenomenon that some patients with highly elevated ds-DNA did not have APOs, indicating that C3/C4 could be used as a disease severity scale rather than ds-DNA.

The diagnostic criterion for proteinuria in lupus-related renal damage is >0.5 g/d, while daily protein levels in pregnant women>0.3 g at any time during gestation is considered abnormal.[44] It was proposed that the rate of foetal loss in SLE pregnancy increases significantly when urine protein >0.5 g/day.[45 46] In addition, Moroni *et al* reported that the odds of preterm delivery increase by 15% for each quarterly increase in proteinuria by 1 g per day.[47] However, few studies have shown the effect of proteinuria with a quantity of less than 0.5 g/24 hours or higher on SLE pregnancy outcomes. In our study, loss of 24-hour urine protein influenced the incidence of APOs. SLE pregnancies without proteinuria before 20 weeks of gestation showed the lowest incidences of foetal APOs and HDPs. Our data indicate that proteinuria (≥0.3 g/day) in the first 20 weeks of pregnancy can significantly increase the risk of foetal loss, and the premature birth rate was significantly increased when 24-hour urine protein was >0.5 g. Furthermore, the probabilities of HDP and SGA increased significantly when 24-hour urine protein was greater than 1 g, suggesting that different degrees of urine protein loss correspond to rates of different adverse outcomes in SLE pregnancy. Thus, we found that proteinuria before the 20th gestational week may be more likely to progress to HDP, similar to previous studies not focusing on the SLE population.[48 49] Our data support the hypothesis that dividing 24-hour urine protein values during SLE pregnancy into 0.3 g, 0.5 g and 1 g can help to predict different APOs.

The findings in this study contribute to a better counselling and tailoring of obstetric surveillance in SLE pregnancy. Nevertheless, our study had some limitations. As a chart review study, inherent information bias was present. Meanwhile, there is a lack of information on uterine contraction inhibitors and follow-up frequency, which may also have an impact on pregnancy outcome. As a single-centre clinical study, it may lack external validity but also avoids the inconsistency and incomparability of data inherent in multi-centre research. Additionally, despite our large total sample size, larger sample sizes are needed to evaluate the identified predictors.

Overall, established risk factors for each APO were carefully assessed in this study. Indicators with more predictive significance have been screened out from conventional indicators, which may help clinicians predict the pregnancy outcome of patients with SLE more accurately and use more intensive monitoring approaches in SLE pregnancies to minimise the incidence of APOs.

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