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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 APOs in SLE.

Design: A retrospective cohort study.

Setting: Data was collected in a tertiary medical center, located in Shanghai, China, from November 2010 to December 2018.

Participants: 513 pregnancies with SLE were analyzed retrospectively. Patients who underwent artificial abortions due to personal reasons were excluded.

Primary outcome measures: APOs were primary outcomes. Multivariate logistic regression analysis was used to determine risk factors for APOs in SLE. Spearman correlation analysis was applied to investigate the influence of ds-DNA, complement and proteinuria values on pregnancy outcomes.

Results: Risk factors for foetal loss included pre-pregnancy hypertension (OR=5.37), hypocomplementaemia-C3 (OR=4.45), aCL-IgM positivity (OR=6.47) and disease flares during pregnancy (OR=2.89). Risk factors for premature birth included disease flares during pregnancy (OR=2.39), use of immunosuppressive agents (OR=2.00) and pregnancy-induced hypertension (PIH) (OR =1.79). Moreover, twin pregnancy (OR=8.04), disease flares during pregnancy (OR=1.84), and PIH (OR=2.49) were risk factors for small for gestational age (SGA), and pre-pregnancy hypertension (OR=5.65) was an independent risk factor for asphyxia neonatorum. Independent risk factors for composite foetal APOs included twin pregnancy (OR=10.67), pre-pregnancy hypertension (OR=8.52), disease flares during pregnancy (OR=4.03), PIH (OR=3.05), hypocomplementaemia-C3 (OR=1.72) and the use of

immunosuppressive agents (OR=2.35). Risk factors for SLE complicated with PIH included pre-pregnancy hypertension (OR=9.03), renal disorders (OR=2.71) and thrombocytopaenia (OR=3.24). Conversely, the use of aspirin was a protective factor against foetal loss and premature birth. The ds-DNA value correlated positively with the incidence of foetal loss, whereas complements correlated negatively with the incidence of composite foetal APOs, foetal loss and PIH. Proteinuria occurring in the first 20 gestational weeks might lead to APOs.

Conclusion: Knowledge of these risk factors is crucial for effective counselling and tailoring of foetal and maternal monitoring in SLE pregnancies to minimize the incidence of APOs.

Key words: Systemic lupus erythaematosus; Adverse pregnancy outcomes; Risk factors; ds-DNA; Complement

Strengths and limitations of this study

1. Present a comprehensive analysis of the most important risk factors for the main maternal and foetal APOs caused by placental dysfunction in SLE pregnancy with a large sample size.
2. Proposed the impact of ds-DNA, complements and urine protein as continuous variables or categorical variables on the prediction of SLE pregnancy outcome, which is often lacking in other studies.
3. The study contributed to a better tailoring of obstetric surveillance in SLE pregnancy.
4. As a retrospective observational study, inherent information bias was present.

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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 found that the prevalence and incidence rates of SLE patients in Asians are approximately 2 to 3 times higher than those of Caucasians. 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 13-68%, accompanied by irreversible organ damage and adverse pregnancy outcomes (APOs)[2]. Although diagnostic and therapeutic strategies for SLE have greatly improved, SLE in pregnancy is still a high risk due to frequent complications, including preeclampsia (PE), small for gestational age (SGA), foetal loss and premature birth[3, 4].

Pre-pregnancy 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[5-12]. Nevertheless, there is no consensus regarding predictors for each APO, and most risk factors are presented as categorical variables. Given the different incidence of SLE among countries and the limitation of method 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 continuous variables, such as ds-DNA or complements, can accurately predict pregnancy outcomes. Furthermore, there are

few studies involving large samples. Here, we evaluate 513 pregnant women and analyse 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, observational 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[13]) between November 2010 and December 2018 were reviewed. Patients who underwent artificial abortions due to personal reasons rather than therapeutic reasons were excluded.

Variables of interest

Clinical and laboratory information was recorded from the first antenatal care records (16-20 gestational weeks). Baseline maternal information included age, past 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 pre-pregnancy 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 or β2GPI IgG or IgM ≥40 GPL or MPL units were considered positive. All laboratory tests were performed using standardized 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.

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 lupus flare or obstetric complications threatening the life of the mother), stillbirth (any baby born without signs of life at greater than or equal to 28 completed weeks of gestation), and neonatal death (death of a live-born baby within 28 days after birth)[14]; 2) premature birth - delivery prior to 37 weeks of gestation[15]; 3) SGA - birth weight below the 10th percentile according to gestational week at delivery and foetal sex[16]; and 4) asphyxia neonatorum - Apgar score of < 7 at 1 and/or 5 minutes after birth[17]. Composite foetal APOs were defined as the occurrence of any adverse outcomes, including foetal loss, premature birth, SGA and asphyxia neonatorum.

Pregnancy-induced hypertension (PIH) was categorized into three types in this study. 1) Gestational hypertension (GH): new-onset blood pressure ≥140/90 mmHg without proteinuria after 20 weeks of gestation. 2) PE: the first incidence of SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg 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 (IUGR); PE can also overlap with other hypertensive states, such as pre-pregnancy hypertension preceding pregnancy or identified before 20 weeks. 3) Eclampsia: new-onset generalized seizures in a woman with PE[18].

Disease flare during pregnancy was defined by 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/d. Additionally, new-onset SLE during pregnancy was included[19].

Patient and public involvement

Since this is a retrospective study, patients were not involved in this research.

Statistical analyses

Continuous variables were analysed using ANOVA 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. A 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 univariate analysis. For categorical variables, univariate odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were computed. Spearman tests were employed to determine correlation between variables. All tests were two-tailed, and $P < 0.05$ was considered statistically significant. All analyses were performed using SPSS V.25.0.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki(as revised in 2013). The study was approved by the ethics committee of Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, [2017-113]. Due to the retrospective nature of the study, no informed consent was required to be taken from all the patients.

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, 456 patients (94.2%) had one pregnancy within the study period, 27 (5.6%) had two pregnancies, and one (0.2%) had three pregnancies. 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 pre-pregnancy 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. Of the patients, 398 (77.6%) used aspirin, and 138 (26.9%) received low-molecular-weight heparin (LMWH).

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). Int 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 eleven cases (2.1%) with an Apgar score < 7 at 1 minute after birth. Only one newborn had Apgar scores < 7 at 5 and 10 minutes 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 PIH, and 16 patients (3.1%) had GH; 74 patients (14.4%) had PE, with 2 developing eclampsia (0.4%). All patients with disease flares and PIH received timely diagnosis and treatment. Only one maternal death occurred in a patient with lupus active 15 days after iatrogenic abortion, with pulmonary haemorrhage and multiple organ failure.

Predictors of adverse foetal and maternal outcomes

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

Univariate analysis for foetal APOs is shown in **Supplementary Table 1**.

Multivariate analysis revealed that pre-pregnancy hypertension, hypocomplementaemia-C3, aCL-IgM positivity and disease flares during pregnancy were risk factors for foetal loss. Disease flares during pregnancy, PIH and use of immunosuppressive agents were responsible for premature birth, and multiple pregnancies, disease flares during pregnancy and PIH were independent predictors of

SGA. Moreover, the occurrence of asphyxia neonatorum correlated significantly only with pre-pregnancy hypertension (**Table 3**).

The maternal characteristics significantly associated with PIH in univariate analysis are shown in **Table 4**. In multivariate analysis, pre-pregnancy hypertension, renal disorders and thrombocytopaenia correlated positively with PIH (**Table 5**).

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

Few studies have analysed the pregnancy outcomes of SLE using anti-dsDNA and complements as continuous variables. SLE pregnancies in women with previous renal disorders may not be characterized by proteinuria during pregnancy, though disease flares may be accompanied by proteinuria. To clarify the relationship between ds-DNA, complements and proteinuria and adverse maternal-foetal outcomes, we conducted correlation analysis of these continuous variables.

The results showed that anti-dsDNA correlated slightly positively with the occurrence of foetal loss (ρ=0.147, $P < 0.01$). However, there was no significant correlation between anti-dsDNA and other APOs ($P > 0.05$). Moreover, C3 correlated negatively with composite foetal APOs (ρ=-0.215, $P < 0.01$), foetal loss (ρ=-0.357, $P < 0.01$), and PIH (ρ=-0.188, $P < 0.01$), and the same findings were observed between C4 and composite foetal APOs (ρ=-0.107, $P = 0.01$), foetal loss (ρ=-0.225, $P < 0.01$), and PIH (ρ=-0.166, $P < 0.01$). Neither C3 nor C4 exhibited a correlation with premature birth, SGA or asphyxia neonatorum ($P > 0.05$).

One hundred and forty patients (27.3%) had proteinuria before 20 weeks of gestation. The diagnostic criteria for renal disorder in SLE is 24-hour urinary protein of >0.5 g; proteinuria during pregnancy is defined as 24-hour urinary protein of ≥0.3 g[20]. 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), P -group (n=34, 24-hour urinary protein > 1 g).

As shown in **Table 6**, foetal birth weights and the duration of pregnancy were highest in the N-group and lowest in the P3 group, both of which showing 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, PIH 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, which 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.

DISCUSSION

Our study found that SLE had a higher incidence of APOs. The frequency of foetal loss has been reported to be 20-28.5% in previous studies of the SLE population[21-23]. Our rate of foetal loss, at 13.6%, is somewhat lower and may be explained by the lower frequency of disease flares prior to conception for at least 6 months. The main cause of foetal loss is generally recognized as aPL positivity[7, 8, 11, 24, 25]. In fact, Bundhun et al. reported that aPL-positive SLE was associated with significantly higher rates of foetal loss and stillbirth than aPL-negative SLE[26]. Our results showed that aCL-IgM positivity has a greater impact on foetal loss than does aCL-IgG or β_2GPI positivity. In addition, hypocomplementaemia-C3, pre-pregnancy hypertension, and disease flares during pregnancy were independent risk factors for foetal loss, consistent with previous findings[8, 14, 23].

Compared to the general population, neonates born to women with rheumatic disease are more likely to be preterm[27], and the incidence of premature birth in the Chinese general population is reported to be 6.2-7.2%[28]. However, in a study based on 555 cases of SLE pregnancies, the rate increases in women with SLE to as high as 21%[29], which was similar to our result. The main predictor for this outcome in previous studies was lupus activity during pregnancy, with the preterm birth rate increasing twofold in women with mild-to-severe disease activity during pregnancy[30]. PE also appears to be the key driver of the high rate of preterm birth and medically indicated delivery in SLE[31]. Chen et al. found that PIH (0R=6.0) and disease flares (0R=3.5) are the major causes of SLE preterm birth[21]. This conclusion 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 drug adverse events[32].

A case-control study reported a significantly higher frequency of SGA in SLE patients than in healthy subjects (25% vs 4.5%)[33], and Zhan et al. found that the incidence of this complication in neonates with SLE was 18.9%[34]. Moreover, a study on epidemiological investigations of SGA proposed that maternal risk factors include PIH, abnormal placenta and twins[35], and active status of SLE at conception (OR 3.23) and lupus flares during pregnancy (OR 2.44) were reported by Ko HS et al. to be predictors of IUGR[2]. It has been reported that the incidence of SGA increases significantly when disease flares are complicated by PIH, especially PE or eclampsia, which can be used as an independent predictor of adverse foetal outcomes[36]. Similar to previous studies, our study revealed an SGA rate in SLE pregnancies of 23.4%, with independent risk factors including multiple pregnancies, PIH and disease flares during pregnancy.

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[37]. The same association for neonatal asphyxia in SLE pregnancy was found in our research. Although the incidence of PIH in the non-SLE population is reportedly only 9%[38], it has been proposed that the probability of SLE complicated by PE is 2-35%[39, 40], which is approximately 3-7 times that in the general population[41]. According to our data, the

probability of SLE complicated by PIH was 17.5% and by PE was 14.4%, similar to the literature. Early studies have reported that specific predictors of PIH, especially PE complicated by SLE, include aPL positivity, thrombocytopaenia, hypocomplementaemia, disease flares and renal damage[11, 12, 21, 38-43]. SLE complicated by PE is not easy to distinguish clinically from lupus renal activity: both can manifest as proteinuria, deterioration of renal function, hypertension, thrombocytopaenia, or even coexistence. Additional clinical or analytical signs (extrarenal manifestations of lupus, active urinary sediment, hypocomplementaemia and anti-dsDNA antibodies) and normouricaemia in SLE patients may suggest a diagnosis of nephritis. Our data indicate that pre-pregnancy hypertension, renal disorders and thrombocytopaenia are independent risk factors predisposing patients towards PIH. This finding is comparable to that obtained in previous studies.

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 C3 and C4 correlated slightly negatively with the incidence of composite foetal APOs, foetal loss and PIH. Nevertheless, it is difficult to determine the extent to which C3 or C4 decrease when the incidence of APOs increases significantly. Thus, we suggest that ds-DNA and complements should be analysed as categorical variables for risk prediction in SLE pregnancy.

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 PIH. 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 greater than 0.5 g. Furthermore, the probabilities of PIH 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. Wagner et al. found that women with active lupus nephritis were more likely to deliver preterm than women without lupus nephritis (urinary protein <0.5 g/day)[44]. 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[45]. Another study proposed that SLE combined with proteinuria is a major predictor of foetal APOs and that the rate of foetal loss increases significantly when urine protein > 0.5 g/day[46]. Although other studies did not focus on the SLE population, it has been proposed that cases of new-onset proteinuria may be more likely to progress to PE[47, 48]. 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.

Overall, independent risk factors for composite foetal APOs included multiple pregnancies, pre-pregnancy hypertension, disease flares during pregnancy, PIH, hypocomplementaemia-C3, and use of immunosuppressive agents, similar to the

conclusions of other studies[11, 21, 49]. 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[23, 50]. 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[51].

Here, we present a comprehensive analysis of the most important risk factors for the main maternal and foetal APOs caused by placental dysfunction in SLE pregnancy with a large sample size. Predictors for each outcome are also proposed, especially the impact of ds-DNA, complements and urine protein as continuous variables or categorical variables on the prediction of SLE pregnancy outcome, which is often lacking in other studies. Nevertheless, our study had some limitations. As a retrospective observational study, inherent information bias was present. Additionally, despite our large total sample size, larger sample sizes are needed to evaluate the identified predictors.

In conclusion, despite pregnancy monitoring in a specialized centre, women with SLE are still at considerable risk for APOs. The study results indicate high predictive value and generalizability. The findings contribute to a better tailoring of obstetric surveillance in SLE pregnancy.

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Patient consent for publication: Not required.

Appendix. Supplement (Supplementary Table 1)

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Tables

Table 1. Maternal characteristics according to composite foetal 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*
Pre-pregnancy 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)	
6-10 years	162	76(32.2)	86(31.0)	0.62
>10 years	78	32(13.6)	46(16.6)	
Disease flares during pregnancy	145	110(46.6)	35(12.6)	<0.01*
PIH	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

PIH = pregnancy-induced hypertension; LMWH = low-molecular-weight heparin;

* $P < 0.05$

534 Table 2. Predictors for composite foetal APOs: results of multivariate analysis

Characteristics	B	*P* value	OR	95%CIs
Multiple pregnancy	2.368	0.03	10.67	1.22-90.91
Pre-pregnancy hypertension	2.143	<0.01	8.52	1.81-40.00
Disease flares during pregnancy	1.395	<0.01	4.03	2.51-6.49
PIH	1.114	<0.01	3.05	1.69-5.46
Hypocomplementaemia-C3	0.543	0.02	1.72	1.11-2.67
Use of immunosuppressive agent	0.856	0.02	2.35	1.15-4.83

535 PIH = pregnancy-induced hypertension; * $P < 0.05$

536

537 Table 3. Multivariate analysis of different foetal APOs

Characteristics	B	*P* value	OR	95%CI
Foetal loss				
Pre-pregnancy hypertension	1.682	0.02	5.37	1.46-19.74
Disease flares during pregnancy	1.063	<0.01	2.89	1.47-5.69
Hypocomplementaemia-C3	1.494	<0.01	4.45	2.34-8.46
aCL-IgM positivity	1.868	<0.01	6.47	2.08-20.15
Use of aspirin	-2.075	<0.01	0.12	0.06-0.25
Premature birth				
Disease flares during pregnancy	0.872	<0.01	2.39	1.48-3.84
PIH	0.585	0.02	1.79	1.07-3.00
Use of Immunosuppressive agent	0.694	0.03	2.00	1.04-3.86
Use of aspirin	-0.561	0.04	0.57	0.33-0.99
SGA				
Multiple pregnancy	2.085	<0.01	8.04	1.81-35.71
Disease flare during pregnancy	0.612	0.01	1.84	1.15-2.95
PIH	0.914	<0.01	2.49	1.49-4.15
Asphyxia neonatorum				
Pre-pregnancy hypertension	0.914	<0.01	2.49	1.49-0.91

538 PIH = pregnancy-induced hypertension; SGA = small for gestational age

539

Table 4. Maternal characteristics according to PIH

Characteristics	Total	PIH		*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*
Pre-pregnancy 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)	
6-10 years	162	28(31.1)	134(31.7)	0.99
>10 years	78	14(15.6)	64(15.1)	
Disease flares during pregnancy	145	46(51.1)	99(23.4)	<0.01*
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

PIH = pregnancy-induced hypertension; PE = preeclampsia; LMWH = low-molecular-weight heparin; * $P < 0.05$

Table 5. Multivariate analysis of PIH

Characteristics	B	*P* value	OR	95%CIs
Pre-pregnancy hypertension	2.200	<0.01	9.03	3.17-25.64
Renal disorders	0.997	<0.01	2.71	1.47-4.97
Thrombocytopaenia	1.175	<0.01	3.24	1.49-6.99

548 Table 6. Pregnancy outcomes of 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)Ł	14(14/44, 31.8)Ł	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
PIH	31(8.3)▲	21(35.0)◐	17(36.9)◐	21(61.7)▲	<0.01

549 ▲: Statistically different from each other group;

550 ◐: Statistically different from the N group and P3 group;

551 Ł: Statistically different from the P2 group and P3 group

552 SGA = small for gestational age; PIH = pregnancy-induced hypertension

Supplementary Table 1. Maternal characteristics according to different foetal APOs

Characteristics	Foetal loss		*P* value	Premature birth		*P* value	SGA		*P* value	Asphyxia neonatorum		*P* value
	Yes (n=70)	No (n=443)		Yes (n=128)	No (n=316)		Yes (n=120)	No (n=324)		Yes (n=11)	No (n=433)	
Primipara	30	208	0.6	55	153	0.5	54	154	0.72	5	203	0.86
Multiple pregnancy	7	1	0.93	4	3	0.24	5	2	0.02*	0	7	0.91
Diabetes	0	2	0.57	1	1	0.66	0	2	0.43	0	2	0.8
Pre-pregnancy hypertension	12	9	<0.01*	8	4	<0.01*	7	5	0.29	2	10	<0.01*
Remission < 6 months prior to conception	8	10	<0.01*	8	2	<0.01*	8	2	<0.01*	1	9	<0.01*
Duration of SLE												
≤5 years	45	228	0.15	67	162	0.43	55	174	0.04*	6	223	0.42
6-10 years	16	146		42	104		49	97		3	143	
>10 years	9	69		19	50		16	53		2	67	
Lupus characteristics												
Renal disorders	22	67	<0.01*	26	41	<0.01*	28	39	0.04*	3	64	<0.01*
Mucocutaneous	22	129	0.63	33	96	0.56	31	98	0.32	2	127	0.64
Neurological disorders	3	4	0.06	1	3	0.07	3	1	0.2	0	4	0.07
Leukopaenia	9	39	0.27	13	26	0.43	9	30	0.42	1	38	0.52
Thrombocytopaenia	8	34	0.28	17	17	0.02*	15	19	0.04*	2	32	0.23
Arthritis	14	102	0.62	30	72	0.87	22	80	0.2	3	99	0.83
Serositis	13	13	<0.01*	7	6	0.03*	6	7	0.96	0	13	<0.01*

PIH = pregnancy-induced hypertension; SGA = small for gestational age; * : P < 0.05

(Continued) Supplementary Table 1. Maternal characteristics according to different foetal APOs

Characteristics	Foetal loss		*P* value	Premature birth		*P* value	SGA		*P* value	Asphyxia neonatorum		*P* value
	Yes (n=70)	No (n=443)		Yes (n=128)	No (n=316)		Yes (n=120)	No (n=324)		Yes (n=11)	No (n=433)	
PIH	49	96	<0.01*	53	43	<0.01*	48	48	<0.01*	4	92	<0.01*
Disease flares during pregnancy	24	66	<0.01*	34	32	<0.01*	36	30	<0.01*	4	62	<0.01*
Laboratory parameters												
Anti-dsDNA	62	338	0.02*	93	246	0.05	88	251	0.16	8	331	0.07
Hypocomplemenatemia-C3	48	108	<0.01*	38	71	0.02*	39	70	0.56	3	106	0.26
Hypocomplementaemia-C4	26	57	<0.01*	18	39	0.11	19	38	0.9	1	56	0.36
SSA/Ro	40	236	0.45	70	166	0.69	66	170	0.76	2	234	0.04*
SSB/La	12	58	0.33	20	38	0.37	20	38	0.27	0	58	0.27
Sm	11	24	<0.01*	8	16	0.16	7	17	0.62	0	24	0.54
U1RNP	24	99	0.02*	33	66	0.05	34	65	0.2	1	98	0.2
Nucleosome	29	102	<0.01*	35	67	0.04*	31	71	0.93	2	100	0.28
aCL-IgG	12	28	<0.01*	10	18	0.12	10	18	0.8	0	28	0.48
aCL-IgM	9	13	<0.01*	7	6	0.03*	4	9	0.55	0	13	0.72
β2GP1-IgG	8	14	<0.01*	5	9	0.19	9	5	0.26	0	14	0.7
β2GP1-IgM	9	34	0.13	10	24	0.14	8	26	0.43	0	34	0.41
Medication												
Glucocorticoid	70	431	0.38	126	306	0.23	118	314	0.74	10	422	0.14
Hydroxychloroquine	41	364	<0.01*	108	257	0.08	99	266	0.27	9	356	0.29
Immunosuppressive agent	10	35	0.07	18	17	<0.01*	17	18	<0.01*	2	33	0.09
Aspirin	23	375	<0.01*	100	275	<0.01*	93	282	<0.01*	7	368	<0.01*
LMWH	10	128	<0.01*	39	89	0.08	35	93	0.09	0	128	0.02*

PIH = pregnancy-induced hypertension; SGA = small for gestational age; LMWH = low-molecular-weight heparin; *: $P < 0.05$

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	NA(no missing data)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	NA(no missing data)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
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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, aCL-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 SLE patients more accurately and minimize the incidence of APOs.

Key words: Systemic lupus erythaematosus; Adverse pregnancy outcomes; Risk factors; ds-DNA; Complement; Proteinuria

Strengths and limitations of this study

1. A comprehensive analysis was performed of the most important risk factors for the main maternal and foetal APOs caused by placental dysfunction in SLE pregnancy with a large sample size.
2. 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.
3. The study contributes to a better counselling of obstetric surveillance in SLE pregnancy.
4. As a retrospective study, inherent information bias was present.

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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 SLE patients among Asians are approximately 2 to 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 13–68%, 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, past 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 standardized 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 live-born 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 minutes 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 categorized into three types in this study. 1) Gestational hypertension (GH): new-onset blood pressure ≥140/90 mmHg without proteinuria after 20 weeks of gestation. 2) PE: the first incidence of SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg 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 (IUGR); PE can also overlap with other hypertensive states, such as prepregnancy hypertension preceding pregnancy or identified before 20 weeks. 3) Eclampsia: new-onset generalized 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/d. Additionally, new-onset SLE during pregnancy was included[20].

Statistical analyses

Continuous variables were analysed using ANOVA 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 odds ratios (ORs) and corresponding 95% confidence intervals (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.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as

revised in 2013). The study was approved by the ethics committee of Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine, [2017–113]. Due to the retrospective nature of the study, informed consent was not required.

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 one pregnancy within the study period, 27 (5.6%) had two pregnancies, and one (0.2%) had three pregnancies. Through retrieval by case diagnosis, 41 cases of antiphospholipid antibody syndrome (APS) were identified among SLE patients. 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 (LMWH).

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 eleven cases (2.1%) with an Apgar score < 7 at 1 minute after birth. Only one newborn had Apgar scores < 7 at 5 and 10 minutes 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 **Supplementary Table 1**.

Multivariable analysis revealed that pre-pregnancy 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 (**Supplementary 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/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 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 (**Supplementary Tables 3-4**). 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 (**Fig. 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.

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

SLE patients 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 recognized 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 SLE patients. It should be noted that for SLE patients, 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 adverse pregnancy outcomes, 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 h 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 SLE patients

more accurately and use more intensive monitoring approaches in SLE pregnancies to minimize the incidence of APOs.

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Appendix. Supplement (Supplementary Table 1-4)

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Tables

Table 1. Maternal characteristics according to composite foetal 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*
Pre-pregnancy 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)	
6–10 years	162	76(32.2)	86(31.0)	0.62
>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

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

Table 2. Predictors of composite foetal APOs: results of multivariable analysis

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

HDP = hypertensive disorders of pregnancy; * $P < 0.05$

Table 3. Multivariable analysis of different foetal APOs

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

HDP = hypertensive disorders of pregnancy; SGA = small for gestational age

Table 4. Maternal characteristics according to 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*
Pre-pregnancy 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)	
6–10 years	162	28(31.1)	134(31.7)	0.99
>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

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

Table 5. Pregnancy outcomes of 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)Ł	14(14/44, 31.8)Ł	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

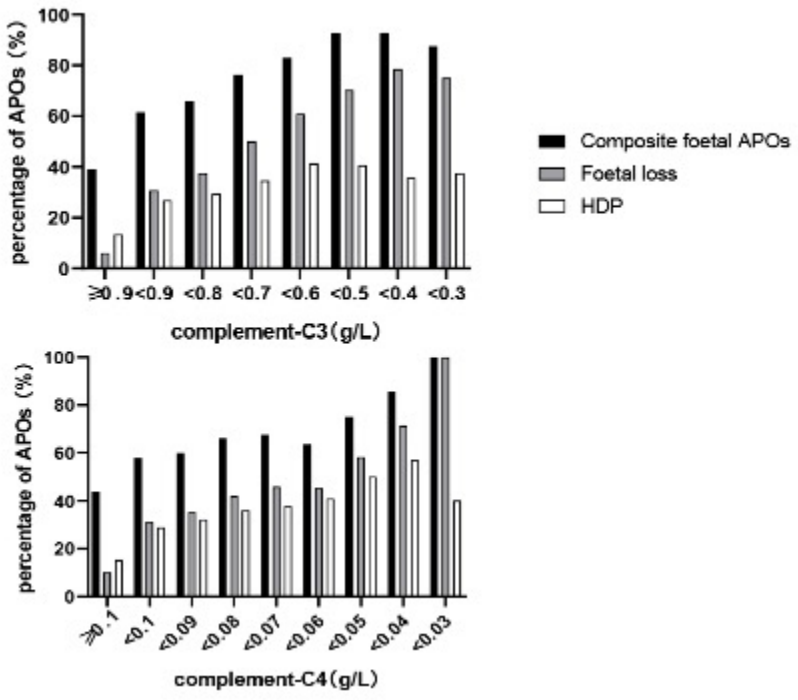
▲: Significantly different from each other group;

◐: Significantly different from the N and P3 groups;

Ł: Significantly different from the P2 and P3 groups;

SGA = small for gestational age; HDP = hypertensive disorders of pregnancy

Fig 1. The incidences of APOs associated with the different intervals of complement C3 and C4



The incidences of APOs associated with the different intervals of complement C3 and C4

146x128mm (72 x 72 DPI)

Supplementary Table 1. Maternal characteristics according to different foetal APOs

Characteristics	Foetal loss		*P* value	Premature birth		*P* value	SGA		*P* value	Asphyxia neonatorum		*P* value
	Yes (n=70)	No (n=443)		Yes (n=128)	No (n=316)		Yes (n=120)	No (n=324)		Yes (n=11)	No (n=433)	
Primipara	30	208	0.6	55	153	0.5	54	154	0.72	5	203	0.86
Multiple pregnancy	7	1	0.93	4	3	0.24	5	2	0.02*	0	7	0.91
Diabetes	0	2	0.57	1	1	0.66	0	2	0.43	0	2	0.8
Pre-pregnancy hypertension	12	9	<0.01*	8	4	<0.01*	7	5	0.29	2	10	<0.01*
Remission < 6 months prior to conception	8	10	<0.01*	8	2	<0.01*	8	2	<0.01*	1	9	<0.01*
Duration of SLE												
≤5 years	45	228	0.15	67	162	0.43	55	174	0.04*	6	223	0.42
6–10 years	16	146		42	104		49	97		3	143	
>10 years	9	69		19	50		16	53		2	67	
APS	10	31	0.04*	29	12	0.51	31	10	0.86	41	0	0.40
Lupus characteristics												
Renal disorders	22	67	<0.01*	26	41	<0.01*	28	39	0.04*	3	64	<0.01*
Mucocutaneous	22	129	0.63	33	96	0.56	31	98	0.32	2	127	0.64
Neurological disorders	3	4	0.06	1	3	0.07	3	1	0.2	0	4	0.07
Leukopaenia	9	39	0.27	13	26	0.43	9	30	0.42	1	38	0.52
Thrombocytopaenia	8	34	0.28	17	17	0.02*	15	19	0.04*	2	32	0.23
Arthritis	14	102	0.62	30	72	0.87	22	80	0.2	3	99	0.83
Serositis	13	13	<0.01*	7	6	0.03*	6	7	0.96	0	13	<0.01*

PIH = pregnancy-induced hypertension; SGA = small for gestational age; * P < 0.05

(Continued) Supplementary Table 1. Maternal characteristics according to different foetal APOs

Characteristics	Foetal loss		*P* value	Premature birth		*P* value	SGA		*P* value	Asphyxia neonatorum		*P* value
	Yes (n=70)	No (n=443)		Yes (n=128)	No (n=316)		Yes (n=120)	No (n=324)		Yes (n=11)	No (n=433)	
PIH	49	96	<0.01*	53	43	<0.01*	48	48	<0.01*	4	92	<0.01*
Disease flares during pregnancy	24	66	<0.01*	34	32	<0.01*	36	30	<0.01*	4	62	<0.01*
Laboratory parameters												
Anti-dsDNA	62	338	0.02*	93	246	0.05	88	251	0.16	8	331	0.07
Hypocomplemenatemia-C3	48	108	<0.01*	38	71	0.02*	39	70	0.56	3	106	0.26
Hypocomplementaemia-C4	26	57	<0.01*	18	39	0.11	19	38	0.9	1	56	0.36
SSA/Ro	40	236	0.45	70	166	0.69	66	170	0.76	2	234	0.04*
SSB/La	12	58	0.33	20	38	0.37	20	38	0.27	0	58	0.27
Sm	11	24	<0.01*	8	16	0.16	7	17	0.62	0	24	0.54
U1RNP	24	99	0.02*	33	66	0.05	34	65	0.2	1	98	0.2
Nucleosome	29	102	<0.01*	35	67	0.04*	31	71	0.93	2	100	0.28
aCL-IgG	12	28	<0.01*	10	18	0.12	10	18	0.8	0	28	0.48
aCL-IgM	9	13	<0.01*	7	6	0.03*	4	9	0.55	0	13	0.72
β2GP1-IgG	8	14	<0.01*	5	9	0.19	9	5	0.26	0	14	0.7
β2GP1-IgM	9	34	0.13	10	24	0.14	8	26	0.43	0	34	0.41
Medication												
Glucocorticoid	70	431	0.38	126	306	0.23	118	314	0.74	10	422	0.14
Hydroxychloroquine	41	364	<0.01*	108	257	0.08	99	266	0.27	9	356	0.29
Immunosuppressive agent	10	35	0.07	18	17	<0.01*	17	18	<0.01*	2	33	0.09
Aspirin	23	375	<0.01*	100	275	<0.01*	93	282	<0.01*	7	368	<0.01*
LMWH	10	128	<0.01*	39	89	0.08	35	93	0.09	0	128	0.02*

PIH = pregnancy-induced hypertension; SGA = small for gestational age; LMWH = low-molecular-weight heparin; *: P < 0.05

Supplementary Table 2. Multivariable analysis of HDP

Characteristics	B	P value	OR	95%CIs
Pre-pregnancy hypertension	2.200	<0.01	9.03	3.17–25.64
Renal disorders	0.997	<0.01	2.71	1.47–4.97
Thrombocytopaenia	1.175	<0.01	3.24	1.49–6.99

HDP = hypertensive disorders of pregnancy

Supplementary Table 3. The APOs associated with different intervals of complement-C3

Complement-C3 (g/L)	Total (N=513)	Composite foetal APOs (%)	Foetal loss (%)	HDP (%)
≥0.9	357	140（39.2）	22（6.1）	48（13.4）
<0.9	156	96（61.5）	48（30.7）	42（26.9）
<0.8	112	74（66.0）	42（37.5）	33（29.4）
<0.7	72	55（76.3）	36（50.0）	25（34.7）
<0.6	41	34（82.9）	25（60.9）	17（41.4）
<0.5	27	25（92.5）	19（70.3）	11（40.7）
<0.4	14	13（92.8）	11（78.5）	5（35.7）
<0.3	8	7（87.5）	6（75.0）	3（37.5）

Supplementary Table 4. The APOs associated with different intervals of complement-C4

Complement-C4 (g/L)	Total (N=513)	Composite foetal APOs (%)	Foetal loss (%)	HDP (%)
≥0.1	430	188（43.7）	44（10.2）	66（15.3）
<0.1	83	48（57.8）	26（31.3）	24（28.9）
<0.09	65	39（60.0）	23（35.3）	21（32.3）
<0.08	50	33（66.0）	21（42.0）	18（36.0）
<0.07	37	25（67.5）	17（45.9）	14（37.8）
<0.06	22	14（63.6）	10（45.4）	9（40.9）
<0.05	12	9（75.0）	7（58.2）	6（50.0）
<0.04	7	6（85.7）	5（71.4）	4（57.1）
<0.03	5	5（100.0）	5（100.0）	2（40.0）

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*
Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5-6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	8-9
		(*c*) Explain how missing data were addressed	NA(no missing data)
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10-11
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-10
		(b) Indicate number of participants with missing data for each variable of interest	NA(no missing data)
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	10-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	12-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	4

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.