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

3
4 Meng Jiang^{1,2}, MD; Yanling Chang^{1,2}, MM; You Wang^{1,2}, PhD; Qiong Fu^{4,5}, PhD;
5 Sihan Lin^{1,2}, BS; Jiayue WU^{1,2,4}, MD; Wen DI^{1,2,3,4}, MD, PhD
6

- 7 1. *Department of Obstetrics and Gynecology, Ren Ji Hospital, School of Medicine,*
8 *Shanghai Jiao Tong University, Shanghai 200127, China;*
9 2. *Shanghai Key Laboratory of Gynecologic Oncology, Shanghai 200127, China;*
10 3. *State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer*
11 *Institute, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University;*
12 4. *Department of Rheumatology, Ren Ji Hospital, School of Medicine, Shanghai*
13 *Jiao Tong University, Shanghai 200127, China;*
14 5. *Shanghai Institute of Rheumatology, Shanghai 200001, China.*

15 ⁴ **Correspondence to Jiayue Wu** Email: *janet_wu_jiayue@163.com* and **Wen Di**
16 Email: *diwen163@163.com*. *Department of Obstetrics and Gynecology, Ren Ji*
17 *Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, 200127,*
18 *China*

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4 **Abstract:**

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6 **Objective:** To clarify high-risk factors for APOs in SLE.

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9 **Design:** A retrospective cohort study.

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12 **Setting:** Data was collected in a tertiary medical center, located in Shanghai, China,
13
14 from November 2010 to December 2018.

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17 **Participants:** 513 pregnancies with SLE were analyzed retrospectively. Patients who
18
19 underwent artificial abortions due to personal reasons were excluded.

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22 **Primary outcome measures:** APOs were primary outcomes. Multivariate logistic
23
24 regression analysis was used to determine risk factors for APOs in SLE. Spearman
25
26 correlation analysis was applied to investigate the influence of ds-DNA, complement
27
28 and proteinuria values on pregnancy outcomes.

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30
31 **Results:** Risk factors for foetal loss included pre-pregnancy hypertension (OR=5.37),
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33 hypocomplementaemia-C3 (OR=4.45), aCL-IgM positivity (OR=6.47) and disease
34
35 flares during pregnancy (OR=2.89). Risk factors for premature birth included disease
36
37 flares during pregnancy (OR=2.39), use of immunosuppressive agents (OR=2.00) and
38
39 pregnancy-induced hypertension (PIH) (OR =1.79). Moreover, twin pregnancy
40
41 (OR=8.04), disease flares during pregnancy (OR=1.84), and PIH (OR=2.49) were risk
42
43 factors for small for gestational age (SGA), and pre-pregnancy hypertension
44
45 (OR=5.65) was an independent risk factor for asphyxia neonatorum. Independent risk
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47 factors for composite foetal APOs included twin pregnancy (OR=10.67),
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49 pre-pregnancy hypertension (OR=8.52), disease flares during pregnancy (OR=4.03),
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51 PIH (OR=3.05), hypocomplementaemia-C3 (OR=1.72) and the use of
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4 42 immunosuppressive agents (OR=2.35). Risk factors for SLE complicated with PIH
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6 43 included pre-pregnancy hypertension (OR=9.03), renal disorders (OR=2.71) and
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9 44 thrombocytopenia (OR=3.24). Conversely, the use of aspirin was a protective factor
10
11
12 45 against foetal loss and premature birth. The ds-DNA value correlated positively with
13
14 46 the incidence of foetal loss, whereas complements correlated negatively with the
15
16
17 47 incidence of composite foetal APOs, foetal loss and PIH. Proteinuria occurring in the
18
19 48 first 20 gestational weeks might lead to APOs.
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22 49 **Conclusion:** Knowledge of these risk factors is crucial for effective counselling and
23
24
25 50 tailoring of foetal and maternal monitoring in SLE pregnancies to minimize the
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28 51 incidence of APOs.
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32 53 **Key words:** Systemic lupus erythaematosus; Adverse pregnancy outcomes; Risk
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35 54 factors; ds-DNA; Complement
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4 57 **Strengths and limitations of this study**

58 1. Present a comprehensive analysis of the most important risk factors for the main
59 maternal and foetal APOs caused by placental dysfunction in SLE pregnancy with a
60 large sample size.

61 2. Proposed the impact of ds-DNA, complements and urine protein as continuous
62 variables or categorical variables on the prediction of SLE pregnancy outcome, which
63 is often lacking in other studies.

64 3. The study contributed to a better tailoring of obstetric surveillance in SLE
65 pregnancy.

66 4. As a retrospective observational study, inherent information bias was present.

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68 **Word Count: Abstract: 294 Main text: 3194**

69 INTRODUCTION

70 Systemic lupus erythaematosus (SLE) is an autoimmune disease involving multiple
71 organs and autoantibodies. Nearly 90% of females with SLE are of reproductive age¹.
72 Previous epidemiological studies have found that the prevalence and incidence rates
73 of SLE patients in Asians are approximately 2 to 3 times higher than those of
74 Caucasians. To tolerate the paternal antigens expressed in foetal cells or tissues, the
75 maternal immune system may undergo adaptive changes during pregnancy, which can
76 stimulate the autoimmune response and lead to SLE flares. The flare rate in pregnancy
77 has been reported to range from 13-68%, accompanied by irreversible organ damage
78 and adverse pregnancy outcomes (APOs)². Although diagnostic and therapeutic
79 strategies for SLE have greatly improved, SLE in pregnancy is still a high risk due to
80 frequent complications, including preeclampsia (PE), small for gestational age (SGA),
81 foetal loss and premature birth^{3, 4}.

82 Pre-pregnancy counselling and perinatal care are essential for the prevention of APOs
83 in the SLE population. Indeed, potential clinical risk factors and serological predictors
84 of adverse outcomes in SLE pregnancies have been widely studied in recent
85 decades⁵⁻¹². Nevertheless, there is no consensus regarding predictors for each APO,
86 and most risk factors are presented as categorical variables. Given the different
87 incidence of SLE among countries and the limitation of method consistency, there is a
88 need for a concise and evidence-based list of indicators to estimate SLE pregnancy
89 risk. In addition, it remains unknown whether continuous variables, such as ds-DNA
90 or complements, can accurately predict pregnancy outcomes. Furthermore, there are

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4 91 few studies involving large samples. Here, we evaluate 513 pregnant women and
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6 92 analyse high-risk factors for adverse SLE maternal and foetal outcomes to strengthen
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9 93 management and improve SLE pregnancy outcomes.
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13 14 95 **METHODS**

15 16 17 18 96 **Patient population**

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20 97 This was a retrospective, observational study performed at Ren Ji Hospital, Shanghai
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23 98 Jiao Tong University School of Medicine, Shanghai, China. The medical records of
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26 99 all pregnant patients with SLE (meeting ≥ 4 of the revised American College of
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28 100 Rheumatology criteria¹³) between November 2010 and December 2018 were
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31 101 reviewed. Patients who underwent artificial abortions due to personal reasons rather
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33
34 102 than therapeutic reasons were excluded.
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37 38 39 104 **Variables of interest**

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41 105 Clinical and laboratory information was recorded from the first antenatal care records
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44 106 (16-20 gestational weeks). Baseline maternal information included age, past obstetric
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47 107 history, duration of SLE, previous manifestations of SLE (including renal disorders,
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49 108 mucocutaneous disorders, haematological disorders, neurological disorders, arthritis
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51
52 109 and serositis) and medication use. Comorbidities included pre-pregnancy
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55 110 hypertension and diabetes. Laboratory data collected included 24-hour urinary
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58 111 protein, antinuclear antibodies, complement 3 (C3), complement 4 (C4), ds-DNA and
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60 112 antiphospholipid antibody (aPL) results. aPL included IgG/IgM anticardiolipin

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4 113 antibodies (aCLs) and anti-2-glycoprotein I antibodies (anti- β 2GPI); only titres of
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6 114 aCLs or β 2GPI IgG or IgM \geq 40 GPL or MPL units were considered positive. All
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9 115 laboratory tests were performed using standardized methods. Each pregnancy was
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12 116 recorded as a separate observation. Pregnancy outcomes were also evaluated,
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14 117 including delivery mode, foetal survival, Apgar score, and foetal birth weight.
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119 **Definitions**

120 Foetal APOs included one or more of the following: 1) foetal loss - spontaneous
121 abortion (referring to termination before 28 weeks of pregnancy with foetal weight
122 less than 1000 g), therapeutic abortion (iatrogenic abortion caused by lupus flare or
123 obstetric complications threatening the life of the mother), stillbirth (any baby born
124 without signs of life at greater than or equal to 28 completed weeks of gestation), and
125 neonatal death (death of a live-born baby within 28 days after birth)¹⁴; 2) premature
126 birth - delivery prior to 37 weeks of gestation¹⁵; 3) SGA - birth weight below the 10th
127 percentile according to gestational week at delivery and foetal sex¹⁶; and 4) asphyxia
128 neonatorum - Apgar score of < 7 at 1 and/or 5 minutes after birth¹⁷. Composite foetal
129 APOs were defined as the occurrence of any adverse outcomes, including foetal loss,
130 premature birth, SGA and asphyxia neonatorum.

131 Pregnancy-induced hypertension (PIH) was categorized into three types in this study.
132 1) Gestational hypertension (GH): new-onset blood pressure \geq 140/90 mmHg without
133 proteinuria after 20 weeks of gestation. 2) PE: the first incidence of SBP \geq 140 mmHg
134 and/or DBP \geq 90 mmHg after 20 weeks of gestation plus one of the following criteria,

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4 135 protein loss of 300 mg or more in a 24-hour urine specimen or maternal organic
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6 136 dysfunction, such as loss of renal function, hepatic dysfunction, neurological
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9 137 complications (altered mental state, blindness, scotomas, visual blurring),
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12 138 haematological complications (thrombocytopaenia, haemolysis) or intrauterine
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15 139 growth restriction (IUGR); PE can also overlap with other hypertensive states, such as
16
17 140 pre-pregnancy hypertension preceding pregnancy or identified before 20 weeks. 3)
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19 141 Eclampsia: new-onset generalized seizures in a woman with PE¹⁸.
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22 142 Disease flare during pregnancy was defined by a new or worsened presence of
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24 143 arthritis, malar rash, vasculitis, oral or nasal ulcers, serositis, neurological
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27 144 manifestations, haematological disorders, fever attributable to SLE, the addition of
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30 145 immunosuppressive medications or hydroxychloroquine, or an increase in prednisone
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33 146 ≥ 0.5 mg/kg/d. Additionally, new-onset SLE during pregnancy was included¹⁹.
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148 **Patient and public involvement**

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

151 **Statistical analyses**

152 Continuous variables were analysed using ANOVA tests when the distributions were
153 normal or Kruskal-Wallis H tests when the distributions were not normal, and the
154 results are presented as the mean \pm SD or as the frequency. Categorical variables were
155 analysed using χ^2 or Fisher's exact probability tests as appropriate. A multivariable
156 and stepwise regression ($P < 0.05$ for forward steps and $P < 0.10$ for backward steps)

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4 157 was performed by selecting variables with a P value < 0.05 in univariate analysis. For
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6 158 categorical variables, univariate odds ratios (ORs) and corresponding 95% confidence
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9 159 intervals (95% CIs) were computed. Spearman tests were employed to determine
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11 160 correlation between variables. All tests were two-tailed, and $P < 0.05$ was considered
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13
14 161 statistically significant. All analyses were performed using SPSS V.25.0.
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19 163 **Ethical Statement**

22 164 The authors are accountable for all aspects of the work in ensuring that questions
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24 165 related to the accuracy or integrity of any part of the work are appropriately
25
26 166 investigated and resolved. The study was conducted in accordance with the
27
28 167 Declaration of Helsinki(as revised in 2013). The study was approved by the ethics
29
30 168 committee of Ren Ji Hospital, Shanghai Jiao Tong University School of Medicine,
31
32 169 [2017-113]. Due to the retrospective nature of the study, no informed consent was
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34 170 required to be taken from all the patients.
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43 172 **RESULTS**

46 173 **Population characteristics**

49 174 A total of 513 pregnancies in 484 patients with SLE were recorded at Ren Ji Hospital,
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51 175 Shanghai Jiao Tong University School of Medicine between November 2010 and
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53 176 December 2018. Of these, 456 patients (94.2%) had one pregnancy within the study
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55 177 period, 27 (5.6%) had two pregnancies, and one (0.2%) had three pregnancies. The
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57 178 mean age at conception was 29.7 ± 4.0 years (range, 20-40 years). The average
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4 179 duration of SLE before pregnancy was 6.6 ± 4.3 years (range, 1-18 years). There were
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6 180 238 cases (46.4%) of primipara, 505 cases (98.4%) of singleton pregnancy and 8
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9 181 cases (1.6%) of twin pregnancy. Twenty-one patients (4.1%) had pre-pregnancy
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11 182 hypertension. Almost 96% of the patients (495 cases) were in the SLE remission stage
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14 183 for more than 6 months prior to conception. Eighty-two of the patients (16%) had a
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17 184 disease flare before 20 weeks of gestation. A total of 501 patients (97.7%) used
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19 185 prednisone, 405 (78.9%) took hydroxychloroquine, and 45 (8.8%) received
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22 186 immunosuppressive medications. Of the patients, 398 (77.6%) used aspirin, and 138
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25 187 (26.9%) received low-molecular-weight heparin (LMWH).
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30 189 **Foetal outcomes**

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32 190 A total of 444 pregnancies (86.5%) resulted in live births. The average gestation days
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35 191 for the live births were 260.10 ± 15.06 days (range, 201-282 days), and the average
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38 192 foetal weight was 2797.96 ± 563.951 g (range, 940-4370 g). In total, 128 (24.9%)
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41 193 premature births were recorded, and there was no significant difference in the
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43 194 premature birth rate between twins and singletons ($\chi^2=115.28$, $P=0.09$).
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46 195 There were eleven cases (2.1%) with an Apgar score < 7 at 1 minute after birth. Only
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48 196 one newborn had Apgar scores < 7 at 5 and 10 minutes after rescue and ultimately
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51 197 died due to oedema. In all cases of asphyxia neonatorum, there was no evidence of
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54 198 cardiac malformations based on B-ultrasound during pregnancy. The overall foetal
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56 199 loss rate was 13.6% (70 cases), and the SGA rate was 23.4% (120 cases). There were
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59 200 236 cases (46.0%) with composite foetal APOs.
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6 202 **Maternal outcomes**

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9 203 In this study, 145 patients (28.3%) experienced disease flares during pregnancy.

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11 204 Among 513 pregnancies, 90 patients (17.5%) eventually developed PIH, and 16

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13 205 patients (3.1%) had GH; 74 patients (14.4%) had PE, with 2 developing eclampsia

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15 206 (0.4%). All patients with disease flares and PIH received timely diagnosis and

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17 207 treatment. Only one maternal death occurred in a patient with lupus active 15 days

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19 208 after iatrogenic abortion, with pulmonary haemorrhage and multiple organ failure.

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27 210 **Predictors of adverse foetal and maternal outcomes**

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29 211 **Table 1** reveals a comparison of clinical events as well as laboratory parameters in

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31 212 patients with or without composite foetal APOs. Multivariate analysis revealed that

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33 213 multiple pregnancy, pre-pregnancy hypertension, disease flares during pregnancy,

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35 214 PIH, hypocomplementaemia-C3 and the use of immunosuppressive agents were

36
37 215 independent predictors of composite foetal APOs (**Table 2**).

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39 216 Univariate analysis for foetal APOs is shown in **Supplementary Table 1**.

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41 217 Multivariate analysis revealed that pre-pregnancy hypertension,

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43 218 hypocomplementaemia-C3, aCL-IgM positivity and disease flares during pregnancy

44
45 219 were risk factors for foetal loss. Disease flares during pregnancy, PIH and use of

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47 220 immunosuppressive agents were responsible for premature birth, and multiple

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49 221 pregnancies, disease flares during pregnancy and PIH were independent predictors of

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

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

227

228 **The influence of anti-dsDNA, complements and proteinuria on APOs in SLE** 229 **pregnancies**

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

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

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4 244 One hundred and forty patients (27.3%) had proteinuria before 20 weeks of gestation.
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6 245 The diagnostic criteria for renal disorder in SLE is 24-hour urinary protein of >0.5 g;
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9 246 proteinuria during pregnancy is defined as 24-hour urinary protein of ≥ 0.3 g²⁰.
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11 247 Therefore, all cases were divided into four groups regardless of the diagnosis: N
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14 248 group (n=373, without proteinuria), P1 group (n=60, 0.3 g \leq 24-hour urinary protein \leq
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17 249 0.5 g), P2 group (n=46, 0.5 g $<$ 24-hour urinary protein ≤ 1 g), P -group (n=34,
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20 250 24-hour urinary protein > 1 g).
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22 251 As shown in **Table 6**, foetal birth weights and the duration of pregnancy were highest
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25 252 in the N-group and lowest in the P3 group, both of which showing significant
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28 253 differences from each other group. Overall, the incidences of most APOs were lowest
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31 254 in the N group. The highest incidences of composite foetal APOs, SGA, PIH and
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34 255 premature birth were detected in the P3 group compared with the other three groups
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37 256 ($P < 0.05$). Overall, foetal loss rates were similar in the P1, P2 and P3 groups, which
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40 257 were higher than those in the N group ($P < 0.05$), and premature birth rates differed
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43 258 significantly between each group, except for the N and P1 groups. There were no
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46 259 significant differences in the incidence of asphyxia neonatorum among the four
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60 260 groups.

261 **DISCUSSION**

262 Our study found that SLE had a higher incidence of APOs. The frequency of foetal
263 loss has been reported to be 20-28.5% in previous studies of the SLE population²¹⁻²³.

264 Our rate of foetal loss, at 13.6%, is somewhat lower and may be explained by the
265 lower frequency of disease flares prior to conception for at least 6 months. The main
266 cause of foetal loss is generally recognized as aPL positivity^{7, 8, 11, 24, 25}. In fact,
267 Bundhun et al. reported that aPL-positive SLE was associated with significantly
268 higher rates of foetal loss and stillbirth than aPL-negative SLE²⁶. Our results showed
269 that aCL-IgM positivity has a greater impact on foetal loss than does aCL-IgG or
270 β_2 GPI positivity. In addition, hypocomplementaemia-C3, pre-pregnancy
271 hypertension, and disease flares during pregnancy were independent risk factors for
272 foetal loss, consistent with previous findings^{8, 14, 23}.

273 Compared to the general population, neonates born to women with rheumatic disease
274 are more likely to be preterm²⁷, and the incidence of premature birth in the Chinese
275 general population is reported to be 6.2-7.2%²⁸. However, in a study based on 555
276 cases of SLE pregnancies, the rate increases in women with SLE to as high as 21%²⁹,
277 which was similar to our result. The main predictor for this outcome in previous
278 studies was lupus activity during pregnancy, with the preterm birth rate increasing
279 twofold in women with mild-to-severe disease activity during pregnancy³⁰. PE also
280 appears to be the key driver of the high rate of preterm birth and medically indicated
281 delivery in SLE³¹. Chen et al. found that PIH (OR=6.0) and disease flares (OR=3.5) are
282 the major causes of SLE preterm birth²¹. This conclusion was also confirmed in our

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4 283 study. In addition, immunosuppressant use and disease flares were jointly found to be
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6 284 independent risk factors for preterm birth in the present study, indicating that they
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9 285 may be caused by lupus flares rather than by drug adverse events³².

10
11 286 A case-control study reported a significantly higher frequency of SGA in SLE patients
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14 287 than in healthy subjects (25% vs 4.5%)³³, and Zhan et al. found that the incidence of
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17 288 this complication in neonates with SLE was 18.9%³⁴. Moreover, a study on
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20 289 epidemiological investigations of SGA proposed that maternal risk factors include
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22 290 PIH, abnormal placenta and twins³⁵, and active status of SLE at conception (OR 3.23)
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24
25 291 and lupus flares during pregnancy (OR 2.44) were reported by Ko HS et al. to be
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28 292 predictors of IUGR². It has been reported that the incidence of SGA increases
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31 293 significantly when disease flares are complicated by PIH, especially PE or eclampsia,
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34 294 which can be used as an independent predictor of adverse foetal outcomes³⁶. Similar
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37 295 to previous studies, our study revealed an SGA rate in SLE pregnancies of 23.4%,
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40 296 with independent risk factors including multiple pregnancies, PIH and disease flares
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42
43 297 during pregnancy.

44
45 298 A total of eleven cases of asphyxia neonatorum (2.1%) were recorded in this study. In
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48 299 non-SLE pregnant women, hypertension increases the possibility of placental
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51 300 dysfunction, leading to foetal hypoxia and asphyxia after birth³⁷. The same
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54 301 association for neonatal asphyxia in SLE pregnancy was found in our research.
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57 302 Although the incidence of PIH in the non-SLE population is reportedly only 9%³⁸, it
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60 303 has been proposed that the probability of SLE complicated by PE is 2-35%^{39, 40}, which
304 is approximately 3-7 times that in the general population⁴¹. According to our data, the

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4 305 probability of SLE complicated by PIH was 17.5% and by PE was 14.4%, similar to
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6 306 the literature. Early studies have reported that specific predictors of PIH, especially
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9 307 PE complicated by SLE, include aPL positivity, thrombocytopenia,
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12 308 hypocomplementaemia, disease flares and renal damage^{11, 12, 21, 38-43}. SLE complicated
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14 309 by PE is not easy to distinguish clinically from lupus renal activity: both can manifest
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17 310 as proteinuria, deterioration of renal function, hypertension, thrombocytopenia, or
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20 311 even coexistence. Additional clinical or analytical signs (extrarenal manifestations of
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22 312 lupus, active urinary sediment, hypocomplementaemia and anti-dsDNA antibodies)
23
24
25 313 and normouricaemia in SLE patients may suggest a diagnosis of nephritis. Our data
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27 314 indicate that pre-pregnancy hypertension, renal disorders and thrombocytopenia are
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30 315 independent risk factors predisposing patients towards PIH. This finding is
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32 316 comparable to that obtained in previous studies.

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35 317 Many studies have only focused on whether ds-DNA or complements are abnormal as
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37 318 predictors of SLE pregnancy outcomes. To clarify the degree of abnormality of these
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40 319 indicators that threaten SLE pregnancy outcomes, we analysed the correlation
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43 320 between ds-DNA, complements and APOs. We found that the value of ds-DNA
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46 321 correlated slightly positively with the incidence of foetal loss. In addition, we found
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48 322 that C3 and C4 correlated slightly negatively with the incidence of composite foetal
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51 323 APOs, foetal loss and PIH. Nevertheless, it is difficult to determine the extent to
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53 324 which C3 or C4 decrease when the incidence of APOs increases significantly. Thus,
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56 325 we suggest that ds-DNA and complements should be analysed as categorical variables
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58 326 for risk prediction in SLE pregnancy.

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4 327 In our study, loss of 24-hour urine protein influenced the incidence of APOs. SLE
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6 328 pregnancies without proteinuria before 20 weeks of gestation showed the lowest
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9 329 incidences of foetal APOs and PIH. Our data indicate that proteinuria (≥ 0.3 g/day) in
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11 330 the first 20 weeks of pregnancy can significantly increase the risk of foetal loss, and
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13 331 the premature birth rate was significantly increased when 24-hour urine protein was
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15 332 greater than 0.5 g. Furthermore, the probabilities of PIH and SGA increased
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17 333 significantly when 24-hour urine protein was greater than 1 g, suggesting that
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19 334 different degrees of urine protein loss correspond to rates of different adverse
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21 335 outcomes in SLE pregnancy. Wagner et al. found that women with active lupus
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23 336 nephritis were more likely to deliver preterm than women without lupus nephritis
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25 337 (urinary protein <0.5 g/day)⁴⁴. In addition, Moroni et al. reported that the odds of
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27 338 preterm delivery increase by 15% for each quarterly increase in proteinuria by 1 g per
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29 339 day⁴⁵. Another study proposed that SLE combined with proteinuria is a major
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31 340 predictor of foetal APOs and that the rate of foetal loss increases significantly when
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33 341 urine protein > 0.5 g/day⁴⁶. Although other studies did not focus on the SLE
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35 342 population, it has been proposed that cases of new-onset proteinuria may be more
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37 343 likely to progress to PE^{47, 48}. Our data support the hypothesis that dividing 24-hour
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39 344 urine protein values during SLE pregnancy into 0.3 g, 0.5 g and 1 g can help to
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41 345 predict different APOs.
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53 346 Overall, independent risk factors for composite foetal APOs included multiple
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55 347 pregnancies, pre-pregnancy hypertension, disease flares during pregnancy, PIH,
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57 348 hypocomplementaemia-C3, and use of immunosuppressive agents, similar to the
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4 349 conclusions of other studies^{11, 21, 49}. In addition, our results showed that aspirin use is a
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7 350 protective factor for foetal loss and preterm birth, which is also consistent with other
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10 351 studies^{23, 50}. The improved pregnancy outcome in SLE pregnancies treated with
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12 352 aspirin appears to correlate with the mechanism of inhibiting platelet aggregation and
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15 353 anti-inflammatory activity, promoting normal uterine artery flow velocity⁵¹.

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17 354 Here, we present a comprehensive analysis of the most important risk factors for the
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20 355 main maternal and foetal APOs caused by placental dysfunction in SLE pregnancy
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22 356 with a large sample size. Predictors for each outcome are also proposed, especially the
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25 357 impact of ds-DNA, complements and urine protein as continuous variables or
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28 358 categorical variables on the prediction of SLE pregnancy outcome, which is often
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31 359 lacking in other studies. Nevertheless, our study had some limitations. As a
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33 360 retrospective observational study, inherent information bias was present. Additionally,
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36 361 despite our large total sample size, larger sample sizes are needed to evaluate the
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38 362 identified predictors.

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40 363 In conclusion, despite pregnancy monitoring in a specialized centre, women with SLE
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43 364 are still at considerable risk for APOs. The study results indicate high predictive value
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46 365 and generalizability. The findings contribute to a better tailoring of obstetric
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48 366 surveillance in SLE pregnancy.

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6 372 YL.C, Y.W, Q.F, JY.W, W.D. Collection and assembly of data: M.J, YL.C, SH.L,
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9 373 JY.W, W.D. Data analysis and interpretation: M.J, YL.C, Y.W, SH.L, JY.W, W.D.
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12 374 Manuscript writing: All authors. Final approval of manuscript: All authors
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33 381 **Data sharing statement:** No additional data are available.
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36 382 **Patient consent for publication:** Not required.
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39 383 **Appendix. Supplement (Supplementary Table 1)**
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529 **Tables**

530 Table 1. Maternal characteristics according to composite foetal APOs

Characteristics	Total	Composite foetal APOs		P value
		Yes (%,n=236)	No (%,n=277)	
Age \geq 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				
\leq 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

	<i>Hypocomplementaemia-C3</i>	156	96(40.7)	60(21.7)	<0.01*
	<i>Hypocomplementaemia-C4</i>	83	48(20.3)	35(12.6)	0.02*
	<i>SSA/Ro</i>	276	129(54.7)	147(53.1)	0.72
	<i>SSB/La</i>	70	40(16.9)	30(10.8)	0.04*
	<i>UIRNP</i>	123	67(28.4)	56(20.2)	0.03*
	<i>Sm</i>	35	22(9.3)	13(4.7)	0.04*
	<i>Nucleosome</i>	131	73(30.9)	58(20.9)	0.01*
	<i>aCL-IgG</i>	40	24(10.1)	16(5.8)	0.06
	<i>aCL-IgM</i>	22	17(7.2)	5(1.8)	<0.01*
	<i>β2GPI-IgG</i>	22	13(5.5)	9(3.2)	0.21
	<i>β2GPI-IgM</i>	43	22(9.3)	21(7.6)	0.48
	Medication				
	<i>Glucocorticoid</i>	501	234(99.2)	267(96.4)	0.04*
	<i>Hydroxychloroquine</i>	405	181(76.7)	224(80.9)	0.24
	<i>Immunosuppressive agent</i>	45	30(12.7)	15(5.4)	<0.01*
	<i>Aspirin</i>	398	159(67.4)	239(86.3)	<0.01*
	<i>LMWH</i>	138	61(25.8)	77(27.8)	0.62

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

532 * $P < 0.05$

533

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

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

539

540 Table 4. Maternal characteristics according to PIH

Characteristics	Total	PIH		P value
		Yes (%,n=90)	No (%,n=423)	
Age \geq 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				
\leq 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				
<i>Mucocutaneous</i>	151	26(28.9)	125(29.6)	0.90
<i>Neurological disorders</i>	7	1(1.1)	6(1.4)	0.63
<i>Arthritis</i>	116	20(22.2)	96(22.7)	0.92
<i>Serositis</i>	26	10(11.1)	16(3.8)	<0.01*
<i>Leukopaenia</i>	48	10(11.1)	38(8.9)	0.52
<i>Thrombocytopaenia</i>	42	17(18.9)	25(5.9)	<0.01*
<i>Renal disorders</i>	89	32(35.6)	57(13.5)	<0.01*
Laboratory parameters				
<i>Anti-dsDNA</i>	400	73(81.1)	327(77.3)	0.42
<i>Hypocomplementaemia-C3</i>	156	42(46.7)	114(26.9)	<0.01*

	<i>Hypocomplementaemia-C4</i>	83	24(26.7)	59(13.9)	<0.01*
	<i>SSA/Ro</i>	276	42(46.7)	234(55.3)	0.13
	<i>SSB/La</i>	70	15(16.7)	55(13.0)	0.35
	<i>UIRNP</i>	123	24(26.7)	99(23.4)	0.51
	<i>Sm</i>	35	6(6.7)	29(6.9)	0.94
	<i>Nucleosome</i>	131	33(36.7)	98(23.2)	<0.01*
	<i>aCL-IgG</i>	40	10(11.1)	30(7.1)	0.19
	<i>aCL-IgM</i>	22	8(8.9)	14(3.3)	0.03*
	<i>β2GPI-IgG</i>	22	2(2.2)	20(4.7)	0.39
	<i>β2GPI-IgM</i>	43	7(7.8)	36(8.5)	0.82
	Medication				
	<i>Glucocorticoid</i>	501	90(100)	411(97.2)	0.13
	<i>Hydroxychloroquine</i>	405	67(74.4)	338(79.9)	0.24
	<i>Immunosuppressive agent</i>	45	13(14.4)	32(7.6)	0.03*
	<i>Aspirin</i>	398	56(62.2)	342(80.9)	<0.01*
	<i>LMWH</i>	138	19(21.1)	119(28.1)	0.17

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

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544

545 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
Thrombocytopenia	1.175	<0.01	3.24	1.49-6.99

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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
<i>Foetal birth weight</i> (g, mean ± SD)	2887.93±495.54 [▲]	2451.76±986.67 [°]	2392.92±883.68 [°]	1911.40±935.857 [▲]	<0.01
<i>Duration of pregnancy</i> (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
<i>Foetal loss</i>	26(6.9) [▲]	16(26.7)	14(30.4)	14(41.2)	<0.01
<i>Premature birth</i>	83(83/348, 23.8) [‡]	14(14/44, 31.8) [‡]	16(16/32, 50.0) [▲]	15(15/20, 75.0) [▲]	<0.01
<i>SGA</i>	73(73/348, 20.9) [▲]	19(19/44, 43.2) [°]	14(14/32, 43.8) [°]	14(14/20, 70.0) [▲]	<0.01
<i>Asphyxia neonatorum</i>	6(6/348, 1.7)	2(2/44, 4.5)	1(1/32, 3.1)	2(2/20, 10.0)	0.17
<i>PIH</i>	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 ‡: 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			Premature birth			SGA			Asphyxia neonatorum		
	Yes	No	P value	Yes	No	P value	Yes	No	P value	Yes	No	P value
	(n=70)	(n=443)		(n=128)	(n=316)		(n=120)	(n=324)		(n=11)	(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			Premature birth			SGA			Asphyxia neonatorum		
	Yes	No	P value	Yes	No	P value	Yes	No	P value	Yes	No	P value
	(n=70)	(n=443)		(n=128)	(n=316)		(n=120)	(n=324)		(n=11)	(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												
<i>Anti-dsDNA</i>	62	338	0.02*	93	246	0.05	88	251	0.16	8	331	0.07
<i>Hypocomplementemia-C3</i>	48	108	<0.01*	38	71	0.02*	39	70	0.56	3	106	0.26
<i>Hypocomplementaemia-C4</i>	26	57	<0.01*	18	39	0.11	19	38	0.9	1	56	0.36
<i>SSA/Ro</i>	40	236	0.45	70	166	0.69	66	170	0.76	2	234	0.04*
<i>SSB/La</i>	12	58	0.33	20	38	0.37	20	38	0.27	0	58	0.27
<i>Sm</i>	11	24	<0.01*	8	16	0.16	7	17	0.62	0	24	0.54
<i>UIRNP</i>	24	99	0.02*	33	66	0.05	34	65	0.2	1	98	0.2
<i>Nucleosome</i>	29	102	<0.01*	35	67	0.04*	31	71	0.93	2	100	0.28
<i>aCL-IgG</i>	12	28	<0.01*	10	18	0.12	10	18	0.8	0	28	0.48
<i>aCL-IgM</i>	9	13	<0.01*	7	6	0.03*	4	9	0.55	0	13	0.72
<i>β2GPI-IgG</i>	8	14	<0.01*	5	9	0.19	9	5	0.26	0	14	0.7
<i>β2GPI-IgM</i>	9	34	0.13	10	24	0.14	8	26	0.43	0	34	0.41
Medication												
<i>Glucocorticoid</i>	70	431	0.38	126	306	0.23	118	314	0.74	10	422	0.14
<i>Hydroxychloroquine</i>	41	364	<0.01*	108	257	0.08	99	266	0.27	9	356	0.29
<i>Immunosuppressive agent</i>	10	35	0.07	18	17	<0.01*	17	18	<0.01*	2	33	0.09
<i>Aspirin</i>	23	375	<0.01*	100	275	<0.01*	93	282	<0.01*	7	368	<0.01*
<i>LMWH</i>	10	128	<0.01*	39	89	0.08	35	93	0.09	0	128	0.02*

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

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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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	NA

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10-11
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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.

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

3
4 Meng Jiang^{1,2,*}, MD; Yanling Chang^{1,2,*}, MM; You Wang^{1,2}, PhD; Qiong Fu^{4,5}, PhD;
5 Sihao Lin^{1,2}, MD; Jiayue WU^{1,2,4}, MD; Wen DI^{1,2,3,4}, MD, PhD

- 6
7 1. *Department of Obstetrics and Gynecology, Ren Ji Hospital, School of Medicine,*
8 *Shanghai Jiao Tong University, Shanghai 200127, China;*
9 2. *Shanghai Key Laboratory of Gynecologic Oncology, Shanghai 200127, China;*
10 3. *State Key Laboratory of Oncogenes and Related Genes, Shanghai Cancer Institute,*
11 *Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University;*
12 4. *Department of Rheumatology, Ren Ji Hospital, School of Medicine, Shanghai Jiao*
13 *Tong University, Shanghai 200127, China;*
14 5. *Shanghai Institute of Rheumatology, Shanghai 200001, China.*

15 **These authors contributed equally to this article.*

16 ⁴ **Correspondence to Jiayue Wu** Email: *janet_wu_jiayue@163.com* and **Wen Di**
17 Email: *diwen163@163.com*. *Department of Obstetrics and Gynecology, Ren Ji*
18 *Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, 200127,*
19 *China*

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4 21 **Abstract:**

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6 22 **Objective:** To clarify high-risk factors for adverse pregnancy outcomes (APOs) in
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9 23 systemic lupus erythaematosus (SLE).

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11 24 **Design:** A retrospective chart review study.

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14 25 **Setting:** Data were collected in a tertiary medical centre, Shanghai, China, from
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17 26 November 2010 to December 2018.

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19 27 **Participants:** A total of 513 pregnancies with SLE were retrospectively analysed.
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22 28 Twenty-seven patients who underwent artificial abortions due to personal reasons were
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25 29 excluded.

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27 30 **Primary outcome measures:** APOs were primary outcomes, including foetal loss,
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30 31 premature birth, small for gestational age (SGA), asphyxia neonatorum, composite
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32 32 foetal APOs and hypertensive disorders of pregnancy (HDP). Multivariable logistic
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34 33 regression and Spearman correlation analysis were performed to determine the risk
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37 34 factors for APOs in SLE.

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39 40 **Results:** Risk factors for foetal loss included prepregnancy hypertension,
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42 43 hypocomplementaemia-C3, aCL-IgM positivity and disease flares during pregnancy.
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45 46 Risk factors for premature birth included disease flares, use of immunosuppressive
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48 48 agents and HDP. Moreover, twin pregnancy, disease flares, and HDP were risk factors
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50 51 for SGA, and prepregnancy hypertension was an independent risk factor for asphyxia
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53 40 neonatorum. Independent risk factors for composite foetal APOs included twin
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55 56 pregnancy, prepregnancy hypertension, disease flares during pregnancy, HDP,
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58 42 hypocomplementaemia-C3 and the use of immunosuppressive agents. Risk factors for
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4 43 SLE complicated with HDP included prepregnancy hypertension, renal disorders and
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7 44 thrombocytopaenia. Conversely, the use of aspirin was a protective factor against foetal
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10 45 loss and premature birth. The ds-DNA value had a low diagnostic value for APOs,
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12 46 whereas the extent of complement reduction may predict the incidence of composite
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14 47 foetal APOs and foetal loss. Proteinuria occurring in the first 20 gestational weeks may
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17 48 lead to APOs.

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19 49 **Conclusion:** Established risk factors for each APO were identified in this study.
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22 50 Indicators with more predictive significance have been screened out from conventional
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24 51 indicators, which may help clinicians predict the pregnancy outcome of SLE patients
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27 52 more accurately and minimize the incidence of APOs.
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32 54 **Key words:** Systemic lupus erythaematosus; Adverse pregnancy outcomes; Risk
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35 55 factors; ds-DNA; Complement; Proteinuria
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4 **58 Strengths and limitations of this study**

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7 59 1. A comprehensive analysis was performed of the most important risk factors for the
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9 60 main maternal and foetal APOs caused by placental dysfunction in SLE pregnancy with
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11 61 a large sample size.
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14 62 2. The study demonstrated that the ds-DNA value had a low diagnostic value for
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17 63 APOs, whereas the extent of complement decrease, especially C3, may predict the
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19 64 incidence of composite foetal APOs, especially foetal loss.
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22 65 3. The study contributes to a better counselling of obstetric surveillance in SLE
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25 66 pregnancy.
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27 67 4. As a retrospective study, inherent information bias was present.
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33 69 **Word Count: Abstract: 296 Main text: 3267**
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70 INTRODUCTION

71 Systemic lupus erythaematosus (SLE) is an autoimmune disease involving multiple
72 organs and autoantibodies. Nearly 90% of females with SLE are of reproductive age¹.
73 Previous epidemiological studies have demonstrated that the prevalence and incidence
74 rates of SLE patients among Asians are approximately 2 to 3 times higher than those
75 among Caucasians. China has a higher prevalence of SLE than many other countries,
76 especially among women (estimated to be more than 100 per 100,000 persons). Based
77 on an estimated Chinese population of 1.3 billion published in 2009, the number of
78 lupus patients in China could reach 520,000–910,000, which would be the largest
79 cluster of cases in the world². To tolerate the paternal antigens expressed in foetal cells
80 or tissues, the maternal immune system may undergo adaptive changes during
81 pregnancy, which can stimulate the autoimmune response and lead to SLE flares. The
82 flare rate in pregnancy has been reported to range from 13–68%, accompanied by
83 irreversible organ damage and adverse pregnancy outcomes (APOs)³. Although
84 diagnostic and therapeutic strategies for SLE have greatly improved, SLE in pregnancy
85 is still a high risk factor due to frequent complications, including preeclampsia (PE),
86 small for gestational age (SGA), foetal loss and premature birth^{4, 5}.
87 Prepregnancy counselling and perinatal care are essential for the prevention of APOs
88 in the SLE population. Indeed, potential clinical risk factors and serological predictors
89 of adverse outcomes in SLE pregnancies have been widely studied in recent decades^{6–}
90 ¹³. Nevertheless, there is no consensus regarding predictors for each APO, and most
91 risk factors are presented as categorical variables. Given the different incidences of SLE

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4 92 in various countries and the limitation of methodology consistency, there is a need for
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6 93 a concise and evidence-based list of indicators to estimate SLE pregnancy risk. In
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9 94 addition, it remains unknown whether the extent of the abnormality of disease activity
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11 95 indexes for SLE, such as ds-DNA, complement and proteinuria, can accurately predict
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14 96 pregnancy outcomes. Furthermore, there are few studies involving large samples. Ren
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17 97 Ji Hospital has treated a leading number of SLE pregnancies in China, which provided
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19 98 our study with a rare large single-centre sample. Here, we evaluated 513 pregnant
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22 99 women and analysed high-risk factors for adverse SLE maternal and foetal outcomes
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25 100 to strengthen management and improve SLE pregnancy outcomes.
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30 102 **METHODS**

33 103 **Patient population**

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36 104 This was a retrospective study performed at Ren Ji Hospital, Shanghai Jiao Tong
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38 105 University School of Medicine, Shanghai, China. The medical records of all pregnant
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41 106 patients with SLE (meeting ≥ 4 of the revised American College of Rheumatology
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44 107 criteria¹⁴) between November 2010 and December 2018 were reviewed. The total
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47 108 number of deliveries in our hospital during the study period reached 24,859, with SLE
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49 109 pregnancies accounted for 2.2%. Twenty-seven patients who underwent artificial
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52 110 abortions due to personal reasons rather than therapeutic reasons were excluded.
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55 111 Rheumatologists diagnosed and obstetricians jointly managed SLE pregnant women.
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57 112 58 59 113 **Variables of interest**

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4 114 Clinical and laboratory information was recorded from the first antenatal care records
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6 115 (16–20 gestational weeks). Baseline maternal information included age, past obstetric
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9 116 history, duration of SLE, previous manifestations of SLE (including renal disorders,
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11 117 mucocutaneous disorders, haematological disorders, neurological disorders, arthritis
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14 118 and serositis) and medication use. Comorbidities included prepregnancy hypertension
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17 119 and diabetes. Laboratory data collected included 24-hour urinary protein, antinuclear
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19 120 antibodies, complement 3 (C3), complement 4 (C4), ds-DNA and antiphospholipid
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22 121 antibody (aPL) results. aPL included IgG/IgM anticardiolipin antibodies (aCLs) and
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24 122 anti-2-glycoprotein I antibodies (anti- β 2GPI); only titres of aCLs, β 2GPI IgG, IgM
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27 123 ≥ 40 GPL or MPL units were considered positive. All laboratory tests were performed
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30 124 using standardized methods. Each pregnancy was recorded as a separate observation.
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33 125 Pregnancy outcomes were also evaluated, including delivery mode, foetal survival,
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35 126 Apgar score, and foetal birth weight.
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40 128 **Patient and Public Involvement**

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43 129 Patients and the public were not involved in the design and conception of the study and
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45 130 there are no plans to disseminate the results to patients.
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50 132 **Definitions**

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53 133 Foetal APOs included one or more of the following: 1) foetal loss - spontaneous
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55 134 abortion (referring to termination before 28 weeks of pregnancy with foetal weight less
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58 135 than 1000 g), therapeutic abortion (iatrogenic abortion caused by a lupus flare or
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4 136 obstetric complications threatening the life of the mother), stillbirth (any baby born
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6 137 without signs of life at ≥ 28 completed weeks of gestation), and neonatal death (death
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9 138 of a live-born baby within 28 days after birth)¹⁵; 2) premature birth - delivery prior to
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11 139 37 weeks of gestation¹⁶; 3) SGA - birth weight below the 10th percentile according to
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13 140 gestational week at delivery and foetal sex¹⁷; and 4) asphyxia neonatorum - Apgar score
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15 141 of < 7 at 1 and/or 5 minutes after birth¹⁸. Composite foetal APOs were defined as the
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17 142 occurrence of any adverse outcomes, including foetal loss, premature birth, SGA and
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19 143 asphyxia neonatorum.

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24 144 Hypertensive disorders of pregnancy (HDPs) were categorized into three types in this
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26 145 study. 1) Gestational hypertension (GH): new-onset blood pressure $\geq 140/90$ mmHg
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28 146 without proteinuria after 20 weeks of gestation. 2) PE: the first incidence of SBP ≥ 140
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30 147 mmHg and/or DBP ≥ 90 mmHg after 20 weeks of gestation plus one of the following
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32 148 criteria, protein loss of 300 mg or more in a 24-hour urine specimen or maternal organic
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34 149 dysfunction, such as loss of renal function, hepatic dysfunction, neurological
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36 150 complications (altered mental state, blindness, scotomas, visual blurring),
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38 151 haematological complications (thrombocytopenia, haemolysis) or intrauterine growth
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40 152 restriction (IUGR); PE can also overlap with other hypertensive states, such as
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42 153 prepregnancy hypertension preceding pregnancy or identified before 20 weeks. 3)
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44 154 Eclampsia: new-onset generalized seizures in a woman with PE¹⁹.

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46 155 A disease flare during pregnancy was defined as a new or worsened presence of arthritis,
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48 156 malar rash, vasculitis, oral or nasal ulcers, serositis, neurological manifestations,
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50 157 haematological disorders, fever attributable to SLE, the addition of immunosuppressive
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4 158 medications or hydroxychloroquine, or an increase in prednisone ≥ 0.5 mg/kg/d.

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6 159 Additionally, new-onset SLE during pregnancy was included²⁰.

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10 11 161 **Statistical analyses**

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14 162 Continuous variables were analysed using ANOVA tests when the distributions were

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16 163 normal or Kruskal-Wallis H tests when the distributions were not normal, and the

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18 164 results are presented as the mean \pm SD or as the frequency. Categorical variables were

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20 165 analysed using χ^2 or Fisher's exact probability tests as appropriate. Multivariable and

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22 166 stepwise regression ($P < 0.05$ for forward steps and $P < 0.10$ for backward steps) was

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24 167 performed by selecting variables with a P value < 0.05 in the univariate analysis. For

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26 168 categorical variables, univariate odds ratios (ORs) and corresponding 95% confidence

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28 169 intervals (95% CIs) were computed. Spearman tests were employed to determine

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30 170 correlations between variables. The area under the receiver operating characteristic

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32 171 (ROC) curve (AUC) was used to assess discrimination of continuous variables with a

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34 172 p value < 0.05 in the Spearman test and to obtain the critical cut-off value. All tests

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36 173 were two-tailed, and $P < 0.05$ was considered statistically significant. All analyses

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38 174 were performed using SPSS V.25.0.

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49 176 **Ethical Statement**

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52 177 The authors are accountable for all aspects of the work in ensuring that questions related

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54 178 to the accuracy or integrity of any part of the work are appropriately investigated and

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56 179 resolved. The study was conducted in accordance with the Declaration of Helsinki (as

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4 180 revised in 2013). The study was approved by the ethics committee of Ren Ji Hospital,
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6 181 Shanghai Jiao Tong University School of Medicine, [2017–113]. Due to the
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9 182 retrospective nature of the study, informed consent was not required.
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14 184 **RESULTS**

18 185 **Population characteristics**

20 186 A total of 513 pregnancies in 484 patients with SLE were recorded at Ren Ji Hospital,
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23 187 Shanghai Jiao Tong University School of Medicine, between November 2010 and
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26 188 December 2018. Of these patients, 456 (94.2%) had one pregnancy within the study
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28 189 period, 27 (5.6%) had two pregnancies, and one (0.2%) had three pregnancies. Through
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31 190 retrieval by case diagnosis, 41 cases of antiphospholipid antibody syndrome (APS)
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33 191 were identified among SLE patients. The mean age at conception was 29.7 ± 4.0 years
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36 192 (range, 20–40 years). The average duration of SLE before pregnancy was 6.6 ± 4.3 years
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39 193 (range, 1–18 years). There were 238 cases (46.4%) of primipara, 505 cases (98.4%) of
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41 194 singleton pregnancy and 8 cases (1.6%) of twin pregnancy. Twenty-one patients (4.1%)
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44 195 had prepregnancy hypertension. Almost 96% of the patients (495 cases) were in the
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47 196 SLE remission stage for more than 6 months prior to conception. Eighty-two of the
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49 197 patients (16%) had a disease flare before 20 weeks of gestation. A total of 501 patients
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52 198 (97.7%) used prednisone, 405 (78.9%) took hydroxychloroquine, and 45 (8.8%)
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55 199 received immunosuppressive medications (such as azathioprine, tacrolimus and
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57 200 cyclosporine A). Of the patients, 398 (77.6%) used aspirin, and 138 (26.9%) received
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60 201 low-molecular-weight heparin (LMWH).

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6 203 **Foetal outcomes**

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9 204 A total of 444 pregnancies (86.5%) resulted in live births. The average gestation days
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11 205 for the live births were 260.10 ± 15.06 days (range, 201–282 days), and the average
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13 206 foetal weight was 2797.96 ± 563.951 g (range, 940–4370 g). In total, 128 (24.9%)
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15 207 premature births were recorded, and there was no significant difference in the premature
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17 208 birth rate between twins and singletons ($\chi^2=115.28$, $P = 0.09$).

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19 209 There were eleven cases (2.1%) with an Apgar score < 7 at 1 minute after birth. Only
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21 210 one newborn had Apgar scores < 7 at 5 and 10 minutes after rescue and ultimately died
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23 211 due to oedema. In all cases of asphyxia neonatorum, there was no evidence of cardiac
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25 212 malformations based on B-ultrasound during pregnancy. The overall foetal loss rate
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27 213 was 13.6% (70 cases), and the SGA rate was 23.4% (120 cases). There were 236 cases
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29 214 (46.0%) with composite foetal APOs.

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40 216 **Maternal outcomes**

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43 217 In this study, 145 patients (28.3%) experienced disease flares during pregnancy. Among
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45 218 513 pregnancies, 90 patients (17.5%) eventually developed HDP, 16 patients (3.1%)
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47 219 had GH, 74 patients (14.4%) had PE, and 2 developed eclampsia (0.4%). All patients
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49 220 with disease flares and HDPs received timely diagnosis and treatment. One maternal
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51 221 death occurred in a patient with lupus that remained active without evaluation by the
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53 222 rheumatologist or obstetrician after conception. This patient was 30 years old and
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55 223 dramatically deteriorated with pulmonary haemorrhage, and multiple organ failure
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4 224 developed 15 days after iatrogenic abortion.
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9 226 **Predictors of adverse foetal and maternal outcomes**

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11 227 **Table 1** provides a comparison of clinical events as well as laboratory parameters in
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14 228 patients with or without composite foetal APOs. Multivariable analysis revealed that
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17 229 multiple pregnancies, prepregnancy hypertension, disease flares during pregnancy,
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20 230 HDP, hypocomplementaemia-C3 and the use of immunosuppressive agents were
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22 231 independent predictors of composite foetal APOs (**Table 2**).
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25 232 Univariate analysis of foetal APOs is shown in **Supplementary Table 1**.
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27 233 Multivariable analysis revealed that pre-pregnancy hypertension,
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30 234 hypocomplementaemia-C3, aCL-IgM positivity and disease flares during pregnancy
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33 235 were risk factors for foetal loss. Disease flares during pregnancy, HDPs and the use of
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35 236 immunosuppressive agents were responsible for premature birth, and multiple
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38 237 pregnancies, disease flares during pregnancy and HDPs were independent predictors
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40 238 of SGA. Moreover, the occurrence of asphyxia neonatorum correlated significantly
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43 239 only with prepregnancy hypertension (**Table 3**).
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45 240 The maternal characteristics significantly associated with HDPs in the univariate
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48 241 analysis are shown in **Table 4**. In the multivariable analysis, prepregnancy hypertension
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50 242 (OR=9.03), renal disorders (OR=2.71) and thrombocytopaenia (OR=3.24) were
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53 243 independent risk factors for HDP (**Supplementary Table 2**).
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58 245 **The influence of anti-dsDNA, complements and proteinuria on APOs in SLE**
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4 246 **pregnancies**

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6 247 The results showed that anti-dsDNA correlated slightly positively with the occurrence
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9 248 of foetal loss ($\rho=0.147$, $P < 0.01$). The value of ds-DNA was converted into a
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11 249 categorical variable according to the critical cut-off value obtained with the ROC curve.
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14 250 Ds-DNA \geq 14.41 IU/ml (AUC=0.624, YI=0.201, sensitivity=0.686, specificity=0.515)
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17 251 was found to be a risk factor for foetal loss among pregnant women with SLE. An AUC
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19 252 of less than 0.7 indicates a low diagnostic value of the optimal cut-off value. There was
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22 253 no significant correlation between anti-dsDNA and other APOs ($P > 0.05$).

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24 254 To clarify the impact of the degree of decrease in C3 on composite foetal APOs, foetal
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27 255 loss and HDP, the values of C3 were set according to the interval of every 0.1 g/L
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30 256 decrease below the lower normal limit. Following the same method, the values of C4
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33 257 were set according to the interval of every 0.01 g/L decrease below the lower normal
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36 258 limit (**Supplementary Tables 3-4**). In addition to HDPs, we found that in both C3 and
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38 259 C4, the incidences of composite foetal APOs and foetal loss in any interval below the
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41 260 lower normal limit increased with the decrease in complement (**Fig. 1**).

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43 261 A total of 140 patients (27.3%) had proteinuria before 20 weeks of gestation. The
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46 262 diagnostic criterion for a renal disorder in SLE is 24-hour urinary protein of >0.5 g, and
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49 263 proteinuria during pregnancy is defined as 24-hour urinary protein of ≥ 0.3 g²¹.

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51 264 Therefore, all cases were divided into four groups regardless of the diagnosis: N group
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54 265 (n=373, without proteinuria), P1 group (n=60, $0.3 \text{ g} \leq 24\text{-hour urinary protein} \leq 0.5 \text{ g}$),
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57 266 P2 group (n=46, $0.5 \text{ g} < 24\text{-hour urinary protein} \leq 1 \text{ g}$), and P3 group (n=34, 24-hour
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60 267 urinary protein $> 1 \text{ g}$).

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4 268 As shown in **Table 5**, foetal birth weights and the duration of pregnancy were highest
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6 269 in the N-group and lowest in the P3 group, both of which showed significant differences
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9 270 from each other group. Overall, the incidences of most APOs were lowest in the N
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11 271 group. The highest incidences of composite foetal APOs, SGA, HDP and premature
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14 272 birth were detected in the P3 group compared with the other three groups ($P < 0.05$).
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17 273 Overall, foetal loss rates were similar in the P1, P2 and P3 groups and were higher than
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19 274 those in the N group ($P < 0.05$), and premature birth rates differed significantly between
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21
22 275 each group, except for the N and P1 groups. There were no significant differences in
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25 276 the incidence of asphyxia neonatorum among the four groups.
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4 277 **DISCUSSION**
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8 278 Our study presents a comprehensive analysis of the most important risk factors for each
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10 279 maternal and foetal APO in SLE pregnancy with a large sample size. We found that
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12 280 prepregnancy hypertension, HDP and flares during pregnancy were key risk factors for
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14 281 most APOs. The ds-DNA value had a low diagnostic value for APOs, whereas the
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16 282 extent of complement decrease, especially C3, may predict the incidence of composite
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18 283 foetal APOs, especially foetal loss. Proteinuria occurring in the first 20 gestational
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20 284 weeks may lead to APOs.
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26 285 SLE patients have a higher incidence of APOs than the general population, including
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28 286 foetal loss, premature birth, SGA and HDP²²⁻²⁷. Overall, independent risk factors for
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30 287 composite foetal APOs included multiple pregnancies, prepregnancy hypertension,
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32 288 disease flares during pregnancy, HDP, hypocomplementaemia-C3, and the use of
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34 289 immunosuppressive agents, similar to the conclusions of other studies^{12, 22, 28}. Predictors
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36 290 for each outcome are also proposed in this study. The main cause of foetal loss is
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38 291 generally recognized as aPL positivity^{29, 30}. Our results showed that aCL-IgM positivity
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40 292 has a greater impact on foetal loss than aCL-IgG or β 2GPI positivity. In addition,
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42 293 hypocomplementemia-C3, prepregnancy hypertension, and disease flares during
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44 294 pregnancy were independent risk factors for foetal loss, consistent with previous
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46 295 findings^{9, 15, 24}.
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52 296 The main predictors of preterm birth and SGA in previous studies were lupus activity
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54 297 during pregnancy and HDP^{22, 31-34}, which was also confirmed in our study. In addition,
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56 298 immunosuppressant use and disease flares were jointly found to be independent risk
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4 299 factors for preterm birth in the present study, indicating that they may be caused by
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6 300 lupus flares rather than by adverse drug events³⁵. We still felt that immunosuppressant
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9 301 use should be continued in patients who benefit from therapy. Data regarding foetal
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11 302 complications during therapy are scarce, but no evidence of teratogenesis has emerged.
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14 303 In addition, many studies have ruled out the effect of multiple pregnancies on SLE
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16 304 pregnancy. However, the dual factors of a twin pregnancy and an abnormal placenta
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18 305 induced by the disease may aggravate the risk of SGA in SLE patients. It should be
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20 306 noted that for SLE patients, multiple pregnancies caused by assisted reproductive
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22 307 technology should be avoided as much as possible.
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27 308 In addition, our results showed that aspirin use is a protective factor for foetal loss and
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29 309 preterm birth, which is also consistent with other studies^{24, 36}. The improved pregnancy
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31 310 outcome in SLE pregnancies treated with aspirin appears to correlate with the
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33 311 mechanism of inhibiting platelet aggregation and anti-inflammatory activity, promoting
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35 312 normal uterine artery flow velocity³⁷.
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40 313 A total of eleven cases of asphyxia neonatorum (2.1%) were recorded in this study. In
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42 314 non-SLE pregnant women, hypertension increases the possibility of placental
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44 315 dysfunction, leading to foetal hypoxia and asphyxia after birth³⁸. The same association
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46 316 for neonatal asphyxia in SLE pregnancy was found in our research.
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50 317 Early studies have reported that specific predictors of HDP, especially PE complicated
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52 318 by SLE, include aPL positivity, thrombocytopaenia, hypocomplementaemia, disease
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54 319 flares and renal damage^{22, 39-43}. Although our results are basically consistent with those
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56 320 of previous studies, it is unexpected that aPL positivity and hypocomplementaemia are
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4 321 not independent risk factors for HDP with SLE. Our data indicate that prepregnancy
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6 322 hypertension, renal disorders and thrombocytopaenia are more significant in predicting
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9 323 HDP.

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11 324 Many studies have only focused on whether ds-DNA or complements are abnormal as
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14 325 predictors of SLE pregnancy outcomes. To clarify the degree of abnormality of these
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17 326 indicators that threaten SLE pregnancy outcomes, we analysed the correlation between
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19 327 ds-DNA, complements and APOs. We found that the value of ds-DNA correlated
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22 328 slightly positively with the incidence of foetal loss. In addition, we found that the
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25 329 incidences of composite foetal APOs and foetal loss in any interval below the lower
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28 330 normal limit, whether complement C3 or C4, increased with the decrease in
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31 331 complements. These results may explain the clinical phenomenon that some patients
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33 332 with highly elevated ds-DNA did not have adverse pregnancy outcomes, indicating that
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35 333 C3/C4 could be used as a disease severity scale rather than ds-DNA.

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38 334 The diagnostic criterion for proteinuria in lupus-related renal damage is >0.5 g/d, while
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41 335 daily protein levels in pregnant women >0.3 g at any time during gestation is considered
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43 336 abnormal⁴⁴. It was proposed that the rate of foetal loss in SLE pregnancy increases
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46 337 significantly when urine protein > 0.5 g/day^{45,46}. In addition, Moroni *et al.* reported that
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49 338 the odds of preterm delivery increase by 15% for each quarterly increase in proteinuria
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51 339 by 1 g per day⁴⁷. However, few studies have shown the effect of proteinuria with a
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54 340 quantity of less than 0.5 g/24 h or higher on SLE pregnancy outcomes. In our study,
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57 341 loss of 24-hour urine protein influenced the incidence of APOs. SLE pregnancies
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59 342 without proteinuria before 20 weeks of gestation showed the lowest incidences of foetal
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4 343 APOs and HDPs. Our data indicate that proteinuria (≥ 0.3 g/day) in the first 20 weeks
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6 344 of pregnancy can significantly increase the risk of foetal loss, and the premature birth
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9 345 rate was significantly increased when 24-hour urine protein was >0.5 g. Furthermore,
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11 346 the probabilities of HDP and SGA increased significantly when 24-hour urine protein
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14 347 was greater than 1 g, suggesting that different degrees of urine protein loss correspond
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17 348 to rates of different adverse outcomes in SLE pregnancy. Thus, we found that
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19 349 proteinuria before the 20th gestational week may be more likely to progress to HDP,
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22 350 similar to previous studies not focusing on the SLE population^{48, 49}. Our data support
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24
25 351 the hypothesis that dividing 24-hour urine protein values during SLE pregnancy into
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27 352 0.3 g, 0.5 g and 1 g can help to predict different APOs.

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30 353 The findings in this study contribute to a better counselling and tailoring of obstetric
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32 354 surveillance in SLE pregnancy. Nevertheless, our study had some limitations. As a chart
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35 355 review study, inherent information bias was present. Meanwhile, there is a lack of
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38 356 information on uterine contraction inhibitors and follow-up frequency, which may also
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41 357 have an impact on pregnancy outcome. As a single-centre clinical study, it may lack
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43 358 external validity but also avoids the inconsistency and incomparability of data inherent
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46 359 in multi-centre research. Additionally, despite our large total sample size, larger sample
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48 360 sizes are needed to evaluate the identified predictors.

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53 362 Overall, established risk factors for each APO were carefully assessed in this study.
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56 363 Indicators with more predictive significance have been screened out from conventional
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58 364 indicators, which may help clinicians predict the pregnancy outcome of SLE patients
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4 365 more accurately and use more intensive monitoring approaches in SLE pregnancies to

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6 366 minimize the incidence of APOs.

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For peer review only

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4 369 **Contributorship statement:** Conception and design: M. J, JY. W, W. D;
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6 370 Administrative support: JY. W, W.D; Provision of study materials or patients: M. J,
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9 371 YL. C, Y. W, Q. F, JY. W, W.D; Collection and assembly of data: M. J, YL. C, SH.
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11 372 L, JY. W, W.D; Data analysis and interpretation: M. J, YL. C, Y. W, SH. L, JY. W,
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14 373 W.D; Manuscript writing: All authors; Final approval of manuscript: All authors.

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16
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33 380 **Data sharing statement:** No additional data are available

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37 381 **Patient consent for publication:** Not required.

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40 382 **Provenance and peer review:** Not commissioned; externally peer reviewed

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43 383 **Appendix. Supplement (Supplementary Table 1-4)**

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496 **Tables**497 **Table 1. Maternal characteristics according to composite foetal APOs**

Characteristics	Total	Composite foetal APOs		P value
		Yes (%,n=236)	No (%,n=277)	
Age \geq 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				
\leq 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
Thrombocytopenia	42	28(11.8)	14(5.1)	<0.01*
Renal disorders	89	56(23.7)	33(11.9)	<0.01*

Laboratory parameters

<i>Anti-dsDNA</i>	400	185(78.4)	215(77.6)	0.83
<i>Hypocomplementaemia-C3</i>	156	96(40.7)	60(21.7)	<0.01*
<i>Hypocomplementaemia-C4</i>	83	48(20.3)	35(12.6)	0.02*
<i>SSA/Ro</i>	276	129(54.7)	147(53.1)	0.72
<i>SSB/La</i>	70	40(16.9)	30(10.8)	0.04*
<i>UIRNP</i>	123	67(28.4)	56(20.2)	0.03*
<i>Sm</i>	35	22(9.3)	13(4.7)	0.04*
<i>Nucleosome</i>	131	73(30.9)	58(20.9)	0.01*
<i>aCL-IgG</i>	40	24(10.1)	16(5.8)	0.06
<i>aCL-IgM</i>	22	17(7.2)	5(1.8)	<0.01*
<i>β2GPI-IgG</i>	22	13(5.5)	9(3.2)	0.21
<i>β2GPI-IgM</i>	43	22(9.3)	21(7.6)	0.48
Medication				
<i>Glucocorticoid</i>	501	234(99.2)	267(96.4)	0.04*
<i>Hydroxychloroquine</i>	405	181(76.7)	224(80.9)	0.24
<i>Immunosuppressive agent</i>	45	30(12.7)	15(5.4)	<0.01*
<i>Aspirin</i>	398	159(67.4)	239(86.3)	<0.01*
<i>LMWH</i>	138	61(25.8)	77(27.8)	0.62

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

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501 **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

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

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504 **Table 3. Multivariable analysis of different foetal APOs**

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

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

506

507 **Table 4. Maternal characteristics according to HDP**

Characteristics	Total	HDP		P value
		Yes (% <i>,n=90</i>)	No (% <i>,n=423</i>)	
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				
<i>Mucocutaneous</i>	151	26(28.9)	125(29.6)	0.90
<i>Neurological disorders</i>	7	1(1.1)	6(1.4)	0.63
<i>Arthritis</i>	116	20(22.2)	96(22.7)	0.92
<i>Serositis</i>	26	10(11.1)	16(3.8)	<0.01*
<i>Leukopaenia</i>	48	10(11.1)	38(8.9)	0.52
<i>Thrombocytopaenia</i>	42	17(18.9)	25(5.9)	<0.01*
<i>Renal disorders</i>	89	32(35.6)	57(13.5)	<0.01*
Laboratory parameters				
<i>Anti-dsDNA</i>	400	73(81.1)	327(77.3)	0.42

	<i>Hypocomplementaemia-C3</i>	156	42(46.7)	114(26.9)	<0.01*
	<i>Hypocomplementaemia-C4</i>	83	24(26.7)	59(13.9)	<0.01*
	<i>SSA/Ro</i>	276	42(46.7)	234(55.3)	0.13
	<i>SSB/La</i>	70	15(16.7)	55(13.0)	0.35
	<i>UIRNP</i>	123	24(26.7)	99(23.4)	0.51
	<i>Sm</i>	35	6(6.7)	29(6.9)	0.94
	<i>Nucleosome</i>	131	33(36.7)	98(23.2)	<0.01*
	<i>aCL-IgG</i>	40	10(11.1)	30(7.1)	0.19
	<i>aCL-IgM</i>	22	8(8.9)	14(3.3)	0.03*
	<i>β2GPI-IgG</i>	22	2(2.2)	20(4.7)	0.39
	<i>β2GPI-IgM</i>	43	7(7.8)	36(8.5)	0.82
	Medication				
	<i>Glucocorticoid</i>	501	90(100)	411(97.2)	0.13
	<i>Hydroxychloroquine</i>	405	67(74.4)	338(79.9)	0.24
	<i>Immunosuppressive agent</i>	45	13(14.4)	32(7.6)	0.03*
	<i>Aspirin</i>	398	56(62.2)	342(80.9)	<0.01*
	<i>LMWH</i>	138	19(21.1)	119(28.1)	0.17

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

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512 **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
<i>Foetal birth weight</i> (g, mean ± SD)	2887.93±495.54 [▲]	2451.76±986.67 [°]	2392.92±883.68 [°]	1911.40±935.857 [▲]	<0.01
<i>Duration of pregnancy</i> (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
<i>Foetal loss</i>	26(6.9) [▲]	16(26.7)	14(30.4)	14(41.2)	<0.01
<i>Premature birth</i>	83(83/348, 23.8) [‡]	14(14/44, 31.8) [‡]	16(16/32, 50.0) [▲]	15(15/20, 75.0) [▲]	<0.01
<i>SGA</i>	73(73/348, 20.9) [▲]	19(19/44, 43.2) [°]	14(14/32, 43.8) [°]	14(14/20, 70.0) [▲]	<0.01
<i>Asphyxia neonatorum</i>	6(6/348, 1.7)	2(2/44, 4.5)	1(1/32, 3.1)	2(2/20, 10.0)	0.17
<i>HDP</i>	31(8.3) [▲]	21(35.0) [°]	17(36.9) [°]	21(61.7) [▲]	<0.01

513 **▲**: Significantly different from each other group;514 **°**: Significantly different from the N and P3 groups;515 **‡**: Significantly different from the P2 and P3 groups;

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

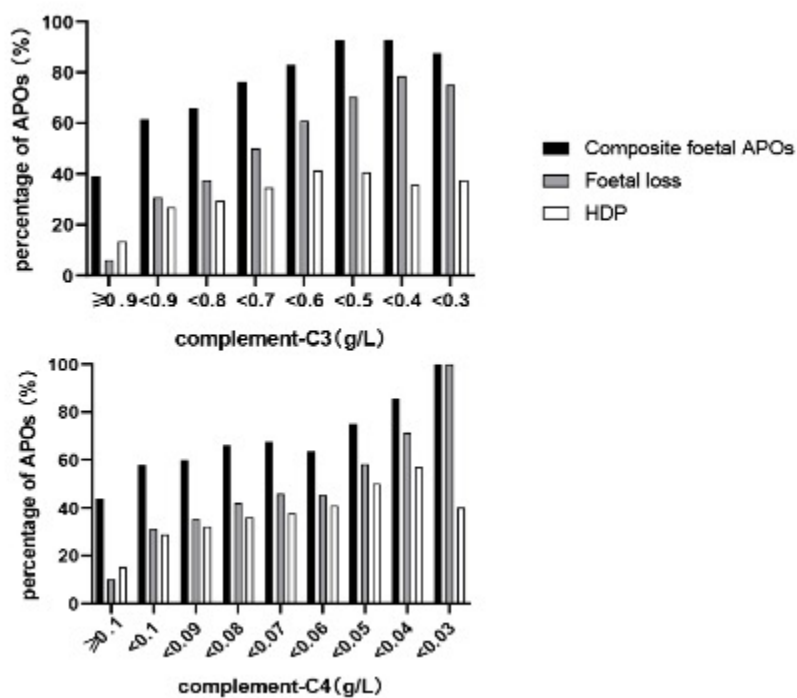
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518 **Fig 1. The incidences of APOs associated with the different intervals of**
519 **complement C3 and C4**

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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			Premature birth			SGA			Asphyxia neonatorum		
	Yes	No	P value	Yes	No	P value	Yes	No	P value	Yes	No	P value
	(n=70)	(n=443)		(n=128)	(n=316)		(n=120)	(n=324)		(n=11)	(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			Premature birth			SGA			Asphyxia neonatorum		
	Yes	No	P value	Yes	No	P value	Yes	No	P value	Yes	No	P value
	(n=70)	(n=443)		(n=128)	(n=316)		(n=120)	(n=324)		(n=11)	(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												
<i>Anti-dsDNA</i>	62	338	0.02*	93	246	0.05	88	251	0.16	8	331	0.07
<i>Hypocomplementemia-C3</i>	48	108	<0.01*	38	71	0.02*	39	70	0.56	3	106	0.26
<i>Hypocomplementaemia-C4</i>	26	57	<0.01*	18	39	0.11	19	38	0.9	1	56	0.36
<i>SSA/Ro</i>	40	236	0.45	70	166	0.69	66	170	0.76	2	234	0.04*
<i>SSB/La</i>	12	58	0.33	20	38	0.37	20	38	0.27	0	58	0.27
<i>Sm</i>	11	24	<0.01*	8	16	0.16	7	17	0.62	0	24	0.54
<i>UIRNP</i>	24	99	0.02*	33	66	0.05	34	65	0.2	1	98	0.2
<i>Nucleosome</i>	29	102	<0.01*	35	67	0.04*	31	71	0.93	2	100	0.28
<i>aCL-IgG</i>	12	28	<0.01*	10	18	0.12	10	18	0.8	0	28	0.48
<i>aCL-IgM</i>	9	13	<0.01*	7	6	0.03*	4	9	0.55	0	13	0.72
<i>β2GPI-IgG</i>	8	14	<0.01*	5	9	0.19	9	5	0.26	0	14	0.7
<i>β2GPI-IgM</i>	9	34	0.13	10	24	0.14	8	26	0.43	0	34	0.41
Medication												
<i>Glucocorticoid</i>	70	431	0.38	126	306	0.23	118	314	0.74	10	422	0.14
<i>Hydroxychloroquine</i>	41	364	<0.01*	108	257	0.08	99	266	0.27	9	356	0.29
<i>Immunosuppressive agent</i>	10	35	0.07	18	17	<0.01*	17	18	<0.01*	2	33	0.09
<i>Aspirin</i>	23	375	<0.01*	100	275	<0.01*	93	282	<0.01*	7	368	<0.01*
<i>LMWH</i>	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) <i>Cohort study</i> —Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up <i>Case-control study</i> —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 <i>Cross-sectional study</i> —Give the eligibility criteria, and the sources and methods of selection of participants	6
		(b) <i>Cohort study</i> —For matched studies, give matching criteria and number of exposed and unexposed <i>Case-control study</i> —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) <i>Cohort study</i> —If applicable, explain how loss to follow-up was addressed <i>Case-control study</i> —If applicable, explain how matching of cases and controls was addressed	NA

		<i>Cross-sectional study</i> —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) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	10-11
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	
		<i>Cross-sectional study</i> —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.