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ORIGINAL RESEARCH

Systemic Lupus Erythematosus and Pregnancy Complications and Outcomes: A Mendelian Randomization Study and Retrospective Validation

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Introduction: Previous studies have shown that pregnant women with systemic lupus erythematosus (SLE) tend to have a higher risk of adverse pregnancy outcomes, but the potential causal role remained unclear. In this study, we aimed to investigate the causal relationship between SLE and some common pregnancy complications and outcomes using two-sample Mendelian randomization (MR).

Methods: The genetic tools were derived from genome-wide association studies of SLE and pregnancy complications and outcomes. MR analysis was performed using inverse variance weighting as primary method. Sensitivity analyses were performed to evaluate the robustness of the results. A retrospective analysis was conducted on 200 pregnant women with SLE and a control group of pregnant women delivering at Tongji Hospital.

Results: In the results, we found that genetic susceptibility to SLE was associated with a higher risk of gestational diabetes mellitus (OR = 1.028, 95% CI: 1.006–1.050), premature delivery (OR = 1.039, 95% CI: 1.013–1.066), polyhydramnios (OR = 1.075, 95% CI: 1.004–1.151) and premature rupture of membranes (OR = 1.030, 95% CI: 1.001–1.060). Some of the retrospective analysis results align with the findings from the MR analysis, indicating that pregnant women with SLE have a higher risk of developing gestational diabetes mellitus and preterm birth. Additionally, although MR analysis did not reveal a causal relationship between SLE and preeclampsia/eclampsia, retrospective analysis discovered that SLE pregnant women are more susceptible to developing preeclampsia/eclampsia (OR = 2.935, 95% CI: 1.118–7.620).

Conclusion: Our study findings suggest a potential causal relationship between SLE and increased risks of gestational diabetes and preterm delivery. Clinical data indicate that pregnant women with SLE are more prone to developing preeclampsia/eclampsia. Clinicians need to be vigilant about the occurrence of these conditions when managing pregnant women with SLE.

Keywords: systemic lupus erythematosus, pregnancy complications, Mendelian randomization, gestational diabetes mellitus, preeclampsia, retrospective analysis

Introduction

Systemic lupus erythematosus (SLE) is a disease characterized by the immune system attacking healthy cells and tissues throughout the body.[1] The global prevalence of SLE is highly variable, ranging from 13 to 7713.5 cases per 100,000 individuals, with significant variations across different populations and regions. The mortality associated with SLE is two to three times higher than that of the general population.[2] Despite its prevalence, the pathogenesis of SLE remains unclear, and a complex interplay of genetic, epigenetic, immunomodulatory, ethnic, hormonal, and environmental factors has been suggested as the primary contributing factors.[3]

Women constitute the main affected population by SLE, with the incidence in females approximately 5 times higher than that in males (representing 85–93% of individuals with SLE). The peak incidence occurs earlier, mainly around the age of 30 compared to the age of 50,[4,5] making SLE one of the leading causes of death in young women.[6] Although it is

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generally believed that fertility in women with SLE is unaffected, disease-related factors, the psychosocial impact of chronic illness, and medication exposure may impair gonadal function.[7]

In the context of the ongoing second demographic transition globally, characterized by long-term sub-replacement fertility,[8] the implications of the low fertility rate are crucial for the rapid aging of populations worldwide.[9] The age range of high incidence for female SLE coincides with the reproductive age range, potentially impacting women's reproductive behavior.[10] While pregnancy in women with SLE was historically discouraged due to increased thrombotic risk, multi-organ damage, and consequences of immunosuppressive therapy, advancements in preconception counseling, rigorous monitoring, and improved treatment have enabled most SLE patients to have successful pregnancies.[11] Currently, women with SLE can conceive under the guidance and care of specialized medical professionals. However, these pregnancies still pose a higher susceptibility to certain complications, such as hypertensive disorders of pregnancy[12] and fetal growth restriction,[13] compounded by the abnormal immune environment in SLE patients and the use of corresponding medications. This often leads to severe adverse pregnancy outcomes, such as stillbirths and miscarriages.[14] Therefore, close attention to the progress of SLE in pregnant women and timely prevention or treatment of pregnancy complications is crucial for reducing adverse pregnancy outcomes, contributing to the well-being of SLE patients, and influencing social birth rates positively.

Despite the numerous observational studies on SLE and pregnancy,[12,15,16] the conclusions drawn are often confounded by causality. Mendelian Randomization (MR) analysis, an emerging epidemiological method, utilizes genetic variants as instrumental variables (IVs) to assess the causal effects of exposure factors on outcomes.[17] With genotype established at conception, minimizing the possibility of reverse causation, MR analysis, using robust instrumental variables from genome-wide association studies (GWAS), aligns with the normal causal order.

While MR analysis has been widely applied in studying various diseases, its use in obstetrics is still limited. There is a lack of MR analyses exploring the association between SLE and pregnancy complications or outcomes. Therefore, excluding diseases with a clear association with SLE, such as hypertensive disorders of pregnancy,[12] fetal growth restriction,[13] spontaneous abortion,[18] we selected six pregnancy complications or outcomes (gestational diabetes mellitus, pre-eclampsia/eclampsia, premature rupture of membranes, polyhydramnios, premature delivery, and prolonged pregnancy) to investigate the potential causal relationship between genetic susceptibility to SLE and the risk of these conditions. Among these, gestational diabetes is the most common pregnancy complication,[19] and preeclampsia/eclampsia is a dangerous condition.[20] Premature rupture of membranes and preterm birth can lead to the birth of premature infants, and the incidence of polyhydramnios and prolonged pregnancy has increased in recent years due to improved living standards.[21] Additionally, we conducted a retrospective analysis of the pregnancy outcomes in 200 pregnant women with SLE to validate the results obtained from the MR analysis. Through this study, clinicians can focus specifically on certain pregnancy complications when treating pregnant women with SLE, enhancing prenatal care and developing personalized management plans. This can ultimately improve the delivery outcomes for pregnant women with SLE.

Materials and Methods

Study Design and Data Sources

In this study, the two sample MR analysis[22] was used to explore the relationship between SLE and pregnancy complications or outcomes and the single nucleotide polymorphisms (SNPs) were used as IVs.[23] The overview of this study design is presented in Figure 1. Our analysis satisfies three principal hypotheses of classical MR analysis: (1) IVs should be closely related to the exposure. (2) IVs should be independent of confounders. (3) IVs can only influence the risk of outcomes through this exposure. This study was conducted based on the STROBE-MR guidelines.[24]

Summary data of SLE were derived from a large meta-analysis of GWAS by Bentham et al[25] including 23,210 European participants with 7219 cases and 15,991 controls. All outcome data were derived from FinnGen (https://www.finngen.fi/en).[26] Among them, GWAS data for gestational diabetes mellitus (GDM) included 11,279 cases and 179,600 controls, GWAS data for preeclampsia-eclampsia included 6436 cases and 176,113 controls, GWAS data for premature rupture of membranes included 6129 cases and 154,102 controls, GWAS data for polyhydramnios included 1049 cases

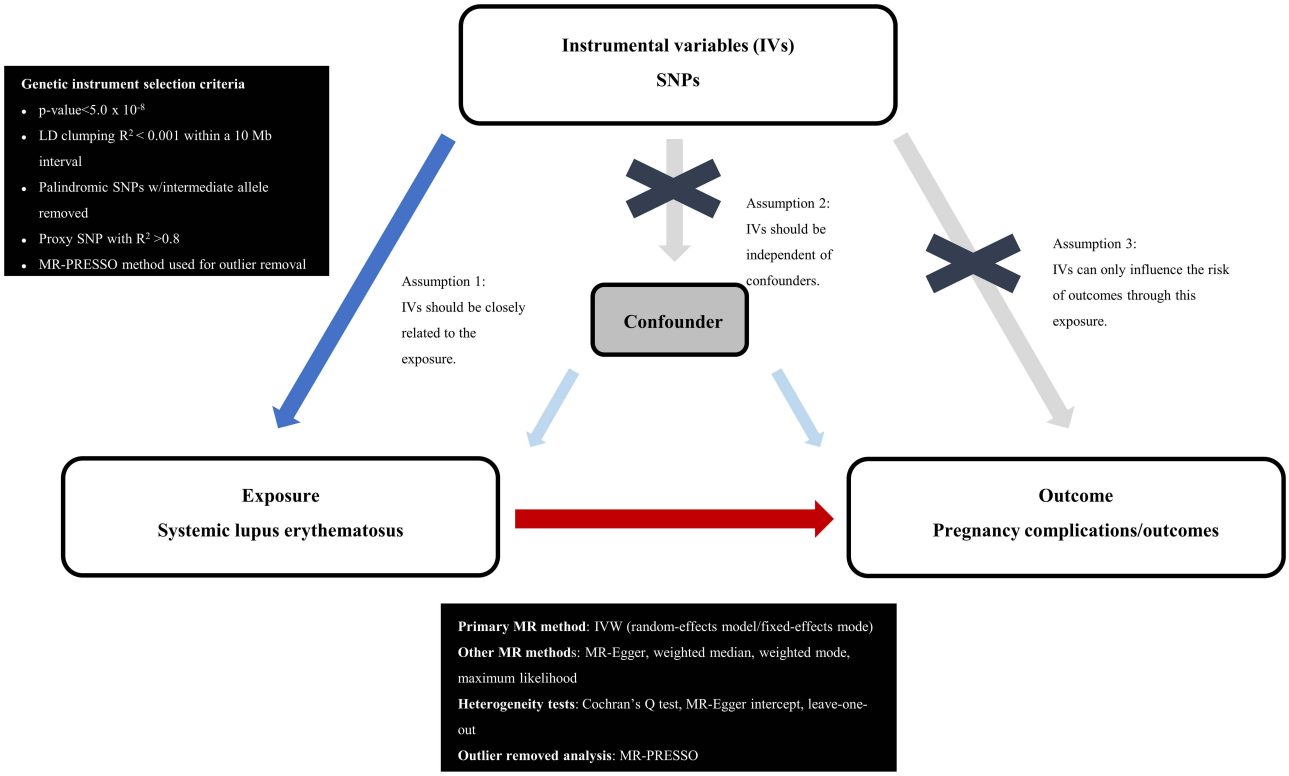

Figure 1 Study design flowchart of the Mendelian randomization study.

and 154,102 controls, GWAS data for premature delivery included 7678 cases and 148,153 controls, and prolonged pregnancy included 3896 cases and 154,102 controls. Table 1 shows the data sources and the sample size of each GWAS.

Selection of IVs

As Figure 1 shows, all SNPs significantly associated with SLE ($p < 5\times10^{-8}$) were considered as IVs, and LD-pruned was used to ensure the independence of selected SNPs within a 10 Mb window with an $r^2 < 0.001$. We also searched for secondary phenotypes of these SNPs in GWAS Catalog[27] to rule out the influence of potential confounders and SNPs corresponding to the phenotype related to the outcomes were excluded and Supporting Information Table S1 provides the SNPs that were excluded and the reasons for exclusion. Furthermore, we used variance (R^2) and F-statistics to assess the extent of weak instrument bias.[28] R^2 was evaluated by the formula of 2 x MAF x (1-MAF) x β^2, and F was calculated by

Table 1 Data Sources of This Study

Traits	Data Sources	Ancestry	Cases	Controls	Case (%)	Lambda
Exposure						
Systemic lupus erythematosus	Bentham et al[25]	European	7219	15,991	31.10	0.992
Outcomes						
Gestational diabetes mellitus	FinnGen[26]	European	11,279	179,600	5.91	1.084
Preeclampsia/eclampsia		European	6436	176,113	3.53	1.068
Premature rupture of membranes		European	6129	154,102	3.83	1.053
Polyhydramnios		European	1049	154,102	0.68	1.001
Premature delivery		European	7678	148,153	4.94	1.039
Prolonged pregnancy		European	3896	154,102	2.47	1.060

Notes: Lambda: Calculating the value of the Genomic Inflation Factor for GWAS data.

the formula of R^2 x (N-K-1)/(1-R^2). If F > 10, the correlation between IVs and exposure was considered strong enough that the MR analysis results could be avoided from being affected by weak-tool bias.

Study Population

A retrospective analysis was conducted on pregnant women delivering at Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, from January 2017 to November 2023. The study randomly enrolled 200 pregnant women diagnosed with SLE. Exclusion criteria were as follows: 1) the diagnosis of SLE occurred after pregnancy; 2) a history of hypertension, diabetes, kidney disease, thyroid dysfunction, or other related conditions; 3) age ≤18 or ≥35 years. A control group of 200 women was randomly selected during the same period. The control group women were not diagnosed with SLE, and no cardiovascular or endocrine diseases were detected before pregnancy.

Statistical Analyses

In our study, the inverse-variance weighted (IVW) method was used as the primary MR analysis. As a classic approach to MR analysis, the IVW meta-analysis Wald ratio estimates the effect of each SNP on the outcome and provides an accurate estimate of the causal effect when all SNPs are valid IVs.[29] In addition, MR Egger,[30] weighted median,[31] weighted mode,[32] Maximum likelihood[33] and MR-pleiotropy residual sum and outlier (MR-PRESSO)[34] were used to infer the causal relationship. Supporting Information Table S2 provides the main characteristics of each model.

Next, we used various methods for sensitivity analysis. Cochran's Q test was used to assess the heterogeneity of IVs, and with p-value <0.05 indicating heterogeneity,[35] the random-effects IVW method was used as the main method; otherwise, the fixed-effects model was considered. MR-PRESSO was used to find outliers with NbDistribution = 10,000 and provided analysis after exclusion of outliers. Then, MR-Egger intercept method was used to test the horizontal pleiotropic of IVs and if p-value <0.05, the IVW estimate might be biased.[30] In addition, we conducted a leave-one-out sensitivity test to examine whether the causal effect was disturbed by a single SNP. Besides, funnel and forest plots were generated to detect the existence of pleiotropy.

All MR-related analyses were performed by TwoSampleMR[36] packages using the R software (4.2.2), and all p-values were two-sided. The analysis of clinical data utilized the chi-square test. A value of $p < 0.05$ was considered statistically significant.

Results

Selected Genetic Variants of SLE and Pregnancy Complications and Outcomes

As previously mentioned, we selected SNPs that were strongly associated with SLE ($p<5 \times 10^{-8}$) as instrumental variable candidates and removed LD ($r^2 < 0.001$, window=10Mb). Forty-two SNPs were obtained, and all of them were searched in the GWAS catalog database to determine whether they were associated with an outcome phenotype. Five SNPs associated with pregnancy (rs597808, rs6679677, rs389884, rs58721818, rs7097397) were excluded and the reasons were presented in Supporting Information Table S1, and some other SNPs were also excluded in subsequent analyses according to different outcomes. The F-statistic of SLE ranged from 296 to 1742, showing a strong instrument strength. In further analyses, we deleted palindromic SNPs with a moderate allele frequency.

Information on SNPs used for each outcome is provided in Supporting Information Tables S3–S8.

MR Analysis

The results of MR analysis are shown in Figure 2 and Table 2. For gestational diabetes mellitus, the IVW method suggested that SLE was a risk factor with OR = 1.028 (95% CI: 1.006–1.050). Maximum likelihood method also indicated a positive conclusion, and the MR-PRESSO found no outliers. Although significant association was not obtained with MR Egger, weighted median and weighted mode, the direction of the ORs were consistent with OR of IVW. IVW method also suggested that SLE is associated with a higher risk of premature rupture of membranes (OR = 1.030, 95% CI: 1.001–1.060), which was consistent with the result obtained by maximum likelihood method. No outlier has been found and other methods got the same direction of OR. Besides, compared with the control group, the SLE

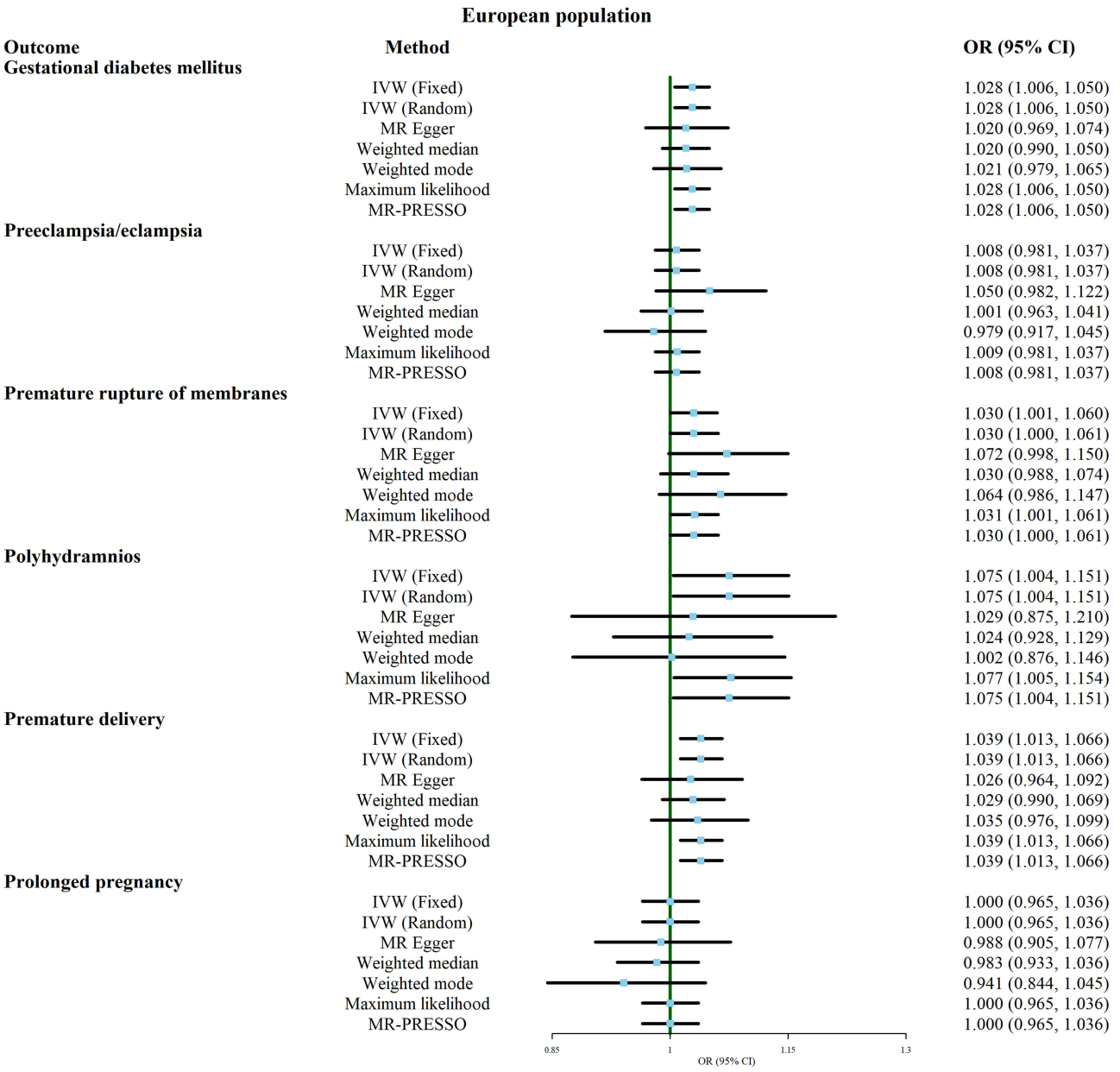

Figure 2 Mendelian randomization estimates of SLE on the risk for pregnancy complications and outcomes. OR, Odds ratio; CI, Confidence interval; IVW, inverse-variance weighted; IVW (fixed), fixed-effects inverse-variance weighted; MR-PRESSO, MR-pleiotropy residual sum and outlier.

patients had a 1.075-fold risk of polyhydramnios (95% CI: 1.004–1.151) and a 1.039-fold risk of premature delivery (95% CI: 1.013–1.066). The results of the maximum likelihood and MR-PRESSO were consistent with IVW method. In addition, no significant association was found between SLE and preeclampsia-eclampsia (OR = 1.008, 95% CI: 0.981–1.037) or prolonged pregnancy (OR = 1.000, 95% CI: 0.965–1.036).

Sensitivity Analyses of MR

Cochran's Q test showed that no significant heterogeneity existed for SLE and those pregnancy complications and outcomes (all $p > 0.05$), as shown in Table 2. MR Egger intercept and the MR-PRESSO test suggested no evidence of directional pleiotropy for all SNPs. Supporting Information Figures S1 and S2 provide the scatter plots and funnel plots, which could more intuitively show heterogeneity. However, positive results for associations between SLE and PRM, and

Table 2 Two-Sample Mendelian Randomization Estimations Showing the Effects, Heterogeneity and Horizontal Pleiotropy of SLE on the Risk of Pregnancy Complications or Outcomes

	Gestational Diabetes Mellitus	Preeclampsia/ Eclampsia	Premature Rupture of Membranes	Polyhydramnios	Premature delivery	Prolonged pregnancy
Main analysis						
IVW (Fixed)						
OR (95% CI)	1.028 (1.006–1.050)	1.008 (0.981–1.037)	1.030 (1.001–1.060)	1.075 (1.004–1.151)	1.039 (1.013–1.066)	1.000 (0.965–1.036)
P value	0.011	0.555	0.040	0.038	0.003	0.993
IVW (Random)						
OR (95% CI)	1.028 (1.006–1.050)	1.008 (0.981–1.037)	1.030 (1.000–1.061)	1.075 (1.004–1.151)	1.039 (1.013–1.066)	1.000 (0.965–1.036)
P value	0.011	0.555	0.047	0.038	0.003	0.993
MR Egger						
OR (95% CI)	1.020 (0.969–1.074)	1.050 (0.982–1.122)	1.072 (0.998–1.150)	1.029 (0.875–1.210)	1.026 (0.964–1.092)	0.988 (0.905–1.077)
P value	0.460	0.162	0.066	0.735	0.424	0.782
Weighted median						
OR (95% CI)	1.020 (0.990–1.050)	1.001 (0.963–1.041)	1.030 (0.988–1.074)	1.024 (0.928–1.129)	1.029 (0.990–1.069)	0.983 (0.933–1.036)
P value	0.188	0.949	0.165	0.638	0.143	0.516
Weighted mode						
OR (95% CI)	1.021 (0.979–1.065)	0.979 (0.917–1.045)	1.064 (0.986–1.147)	1.002 (0.876–1.146)	1.035 (0.976–1.099)	0.941 (0.844–1.045)
P value	0.334	0.524	0.119	0.982	0.262	0.278
Maximum likelihood						
OR (95% CI)	1.028 (1.006–1.050)	1.009 (0.981–1.038)	1.031 (1.001–1.061)	1.077 (1.005–1.154)	1.039 (1.013–1.066)	1.000 (0.965–1.036)
P value	0.012	0.549	0.040	0.036	0.003	0.993
MR-PRESSO						
OR (95% CI)	1.028 (1.006–1.050)	1.008 (0.981–1.037)	1.030 (1.000–1.061)	1.075 (1.004–1.151)	1.039 (1.013–1.066)	1.000 (0.965–1.036)

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P value	0.011	0.555	0.047	0.038	0.003	0.993
Sensitivity analysis						
Cochran's Q						
Q-statistics	22.097	20.074	32.152	26.037	27.987	25.280
Q_df	30	28	30	29	30	30
P value	0.851	0.862	0.361	0.624	0.571	0.711
MR-Egger						
Q-statistics	21.993	18.352	30.643	25.694	27.790	25.188
Q_df	29	27	29	28	29	29
P value	0.820	0.892	0.382	0.590	0.529	0.668
Egger intercept						
Intercept	2.66E-3	−1.40E-2	1.36E-2	1.53E-2	4.50E-3	4.30E-3
P value	0.750	0.200	0.242	0.563	0.660	0.764
MR-PRESSO						
P value	0.863	0.863	0.346	0.635	0.578	0.686

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Table 3 Clinical Data on the Correlation Between SLE and Six Pregnancy Complications or Outcomes

	SLE n=200	Control n=200	OR	P
GDM	42	25	1.861 (1.074–3.142)	0.023
Preeclampsia/eclampsia	14	5	2.935 (1.118–7.620)	0.034
Premature rupture of membranes	12	6	2.064 (0.790–5.479)	0.148
Polyhydramnios	3	4	0.746 (0.186–2.812)	0.746
Premature delivery	28	12	2.550 (1.251–5.005)	0.007
Prolonged pregnancy	1	3	0.330 (0.023–2.233)	0.315

SLE and preterm birth, may not be robust because they were influenced by individual SNP elimination (Supporting Information Figure S3).

Retrospective Clinical Data Analysis

A total of 200 pregnant women with SLE and 200 pregnant women with normal pregnancies were included in the analysis, as shown in Table 3. Consistent with the MR analysis results, pregnant women with SLE had a significantly higher risk of developing GDM (OR = 1.861, 95% CI: 1.074–3.142) and preterm delivery (OR = 2.550, 95% CI: 1.251–5.005) compared to the control group. However, no significant differences were observed between the two groups regarding premature rupture of membranes (OR = 2.064, 95% CI: 0.790–5.479), polyhydramnios (OR = 0.746, 95% CI: 0.186–2.812), and prolonged pregnancy (OR = 0.330, 95% CI: 0.023–2.233). Additionally, while the MR analysis did not reveal a significant correlation between SLE and preeclampsia/eclampsia, the retrospective analysis results indicated a higher risk of preeclampsia/eclampsia in pregnant women with SLE (OR = 2.935, 95% CI: 1.118–7.620).

Discussion

For the first time, we employed MR analysis to systematically investigate the causal relationship between SLE and prevalent pregnancy complications and outcomes. Our findings indicate that a genetic predisposition to SLE is linked to a heightened risk of gestational diabetes mellitus, premature rupture of membranes, polyhydramnios, and preterm delivery. Additionally, our clinical evidence supports that SLE serves as a risk factor for gestational diabetes mellitus, preterm delivery, and preeclampsia/eclampsia.

As a complex autoimmune disease, SLE can cause multiple-organ damage. During pregnancy, the various systems of a woman are also different from the normal state,[37] which makes the diagnosis and treatment of pregnancy with SLE more complicated. In a healthy pregnancy, increased intravascular volume leads to a hypercoagulable state, thromboembolism formation, and secretion of inflammatory cytokines and fibrinogen.[38] However, these manifestations contribute to the occurrence of adverse pregnancy outcomes.[39] Although the current medical technology allows most patients with SLE to have successful pregnancies, all SLE pregnancies should be considered "high risk" due to potential maternal and fetal complications.[40] Previous studies showed pregnancy with SLE was associated with an increased incidence of adverse outcomes, such as preeclampsia,[41] fetal growth restriction,[13] preterm delivery,[42] stillbirth and miscarriage,[14] some of which were also confirmed in our study.

The impact of SLE on GDM has been controversial. A retrospective cohort study suggested that gestational diabetes was negatively associated with SLE in pregnant women,[43] while another study showed SLE was associated with a 2-fold higher risk of GDM.[44] Although our result suggested that SLE may be a risk factor for GDM, this conclusion should be taken with caution, as it may be biased by drug used to treat SLE. Previous studies indicated treatment with high-dose glucocorticoids (prednisolone use ≥1 mg/kg/day) causes 12% of pregnant SLE women to develop GDM.[45,46] A meta-analysis showed use of glucocorticoids during pregnancy in SLE patients is positively correlated with the risk of GDM, and steroid exposure should be limited to a minimum during pregnancy,[47,48] and use of hydroxychloroquine, which was safe enough for continued use throughout pregnancy in all pregnant women with SLE, may reduce the dose of glucocorticoids during pregnancy, thereby reducing the risk of GDM development.[38,49] Future studies should focus

more on the role of drug use in the association between SLE and GDM and provide appropriate medication guidance for pregnant women with SLE.

Preterm delivery is another adverse pregnancy outcome that has been identified as a consequence of SLE.[40,50] Our study also suggested an association between SLE and preterm delivery. Contributing factors include disease activity and preeclampsia, but often no apparent causative factor is found.[40] However, in terms of the relationship between SLE and the risk of preeclampsia and eclampsia, our results did not find a significant association, which is inconsistent with most previous studies. Actually, we also performed separate MR analyses for gestational hypertension, preeclampsia and eclampsia, none of which suggested significant association with SLE. Despite the lack of a significant association observed in the MR analysis, our retrospective analysis revealed that SLE is a high-risk factor for preeclampsia/eclampsia. The possible reason is that SLE is not an independent risk factor for hypertensive diseases. The risk of preeclampsia in pregnant women with SLE is related to prednisone, lupus nephritis and antiphospholipid antibodies,[40] but we excluded SNPs with phenotypes associated with nephritis, hypertension and immune antibodies, which might explain the discrepancy between our conclusion and previous studies. Therefore, clinicians still need to be alert to the occurrence of preeclampsia and eclampsia in SLE pregnancy, and pay close attention to urinary protein.

Furthermore, although our study suggested that SLE increased the risk of polyhydramnios and premature rupture of membranes, the results were disturbed by a single SNP. The unstable results might be due to the low proportion of cases in the data for these two outcomes (3.83% in premature rupture of membranes and 0.68% in polyhydramnios). We reviewed previous studies of SLE and these two outcomes and found that preterm premature rupture of membranes was common in SLE in a single center case series.[51] Surprisingly, it was not associated with disease activity, or with prednisone dose. Combining with our results, SLE might be an independent risk factor of premature rupture of membranes. The association between SLE and polyhydramnios has only been identified in one retrospective study.[52] However, no correlation between SLE and these two diseases was observed in our clinical data. More studies are expected to explore the association between SLE and polyhydramnios and premature rupture of membranes in the future.

Nowadays, the global fertility rate is low, and some countries even have negative population growth, accompanied by population aging and other problems, which cause serious social and economic burden.[53] SLE, as an autoimmune disease mostly affects women of childbearing age, has a great impact on female fertility, asking for reasonable monitoring and management of SLE pregnant women during perinatal period to achieve a smooth pregnancy process. Our study explored the correlation between SLE and pregnancy complications and outcomes by MR analysis for the first time, which provided reference for clinical pregnancy management of pregnant women with SLE. Our study also has some limitations. First, our study was primarily limited to European population, so its generalizability needs to be questioned. However, it is noteworthy that our validation cohort consisted of an Asian population, and partial validation results confirmed the universality of the findings. Second, we did not restrict the subjects to females in the acquisition of exposure strongly associated SNPs, which may have led to the selection of instrumental variables being biased by gender. Third, not all analytic models yielded significant results, and retrospective studies may face limitations in terms of statistical power due to smaller sample sizes, particularly for less common outcomes. Fortunately, the direction of exposure effects on outcomes was consistent across all models, and no evidence of horizontal pleiotropy or heterogeneity was found, confirming this study's findings. In addition, the OR value was relatively low and should be interpreted carefully.

Conclusion

In summary, our findings indicate a potential causal relationship between SLE and an increased risk of gestational diabetes mellitus and preterm delivery. While SLE may also elevate the risk of premature rupture of membranes and polyhydramnios, this conclusion lacks robustness. The retrospective analysis revealed an association between SLE and preeclampsia/eclampsia. However, further cohort studies are warranted to strengthen the clinical implications of these results. Additionally, there is a need for research to investigate potential mechanisms and elucidate the roles of SLE in pregnancy complications and outcomes.

Abbreviations

SLE, Systemic lupus erythematosus; MR, Mendelian randomization; GWAS, genome-wide association studies; SNPs, single nucleotide polymorphisms; IVs, instrumental variables; GDM, gestational diabetes mellitus; IVW, inverse-variance weighted.

Data Sharing Statement

All data generated or analysed during this study are included in this published article and its Supplementary Information Files.

Ethics Approval and Consent to Participate

This study adhered to the principles outlined in the Helsinki Declaration. Verbal consent was obtained from all patients included in the retrospective analysis, as well as from healthy pregnant women. This consent method was deemed acceptable and received approval from the Ethics Committee of Tongji Hospital, Huazhong University of Science and Technology.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests in this work.

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