Increased risk of congenital malformations in offspring born to women with systemic lupus erythematosus in South Korea: a nationwide population-based study

Young Mi Jung,1,2 Jin Kyun Park,3 Min-Jeong Oh,2 Chan-Wook Park,1 Joong Shin Park,1 Jong Kwan Jun,1 Seung Mi Lee1,4,5 Geum Joon Cho1,2

ABSTRACT

Objectives The aim of this study was to determine the risk of congenital malformations in offspring born to women with systemic lupus erythematosus (SLE).

Methods This nationwide population-based study included Korean women who had a singleton pregnancy. The risk of congenital malformations in women with SLE was compared with those without SLE. Multivariable analyses were performed to estimate the OR of congenital malformations. In a sensitivity analysis, the risk of malformation was compared between the offspring of women with SLE and those of propensity-matched women without SLE.

Results Of a total of 3279204 pregnant women, 0.1% had SLE and their offspring had a higher frequency of congenital malformations (17.13% vs 11.99%, p<0.0001). After adjustment for age, parity, hypertension, diabetes, and fetal sex, the SLE group was found to be associated with an increased risk of congenital malformations in the nervous system (adjusted OR (aOR), 1.90; 95% CI, 1.20 to 3.03), eye, ear, face, and neck (aOR, 1.37; 95% CI, 1.09 to 1.71), circulatory system (aOR, 1.91; 95% CI, 1.67 to 2.20), and musculoskeletal system (aOR, 1.26; 95% CI, 1.05 to 1.52). Even after propensity matching, some of the tendencies were maintained.

Conclusions This nationwide population-based study in South Korea indicates that compared with the general population, neonates born to SLE mothers have a slightly increased risk of congenital malformations affecting the nervous system, head and neck, cardiovascular system, and musculoskeletal system. When a woman with lupus becomes pregnant, careful fetal ultrasound and newborn screening can be helpful in identifying the risk of potential malformations.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that often affects women of reproductive age. Compared with healthy women, women with SLE were at an increased risk of having unfavourable maternal and fetal pregnancy outcomes.1-8 Maternal complications include pre-eclampsia, lupus flare and increased mortality, while fetal complications involve abortion, preterm birth, intrauterine growth restriction, fetal death and congenital heart block. However, little is known about the risk of congenital malformations in the offspring of women with SLE.9

Pregnancy outcomes have improved dramatically in recent decades.10 Since SLE is no longer a contraindication to pregnancy, it is important to attend prepregnancy counselling and peripartum and postpartum risk management to mitigate the possibility of immediate and long-term adverse maternal and fetal outcomes.11 12 While transient growth restriction, heart block or neonatal lupus in offspring resolves with time without...
long-term consequences, severe congenital malformations contain information on demographics, socioeconomic status and lifestyle.

Study population
As patients with rare diseases are covered under the Individual Copayment Beneficiaries Program, which subsidises medical expenses for patients with a definitive diagnosis of SLE according to 1997 American College of Rheumatology criteria or 2012 Systemic Lupus International Collaborating Clinics criteria, International Classification of Diseases, 10th edition (ICD-10) is reliable to identify SLE. This population-based cohort study included pregnant Korean women who met the following criteria: (1) singleton pregnancy with live born delivery; (2) delivery between 2007 and 2015; and (3) participation in the NHSE within 4 years before pregnancy. Women with incomplete information on pregnancy and the neonatal outcome and those with multifeetal gestation were excluded. Medical information before pregnancy was collected from the NHSE database. Women without SLE were chosen for propensity matching after matching for age, parity, baseline (ie, before pregnancy) hypertension, diabetes mellitus and year of delivery at a ratio of 1:5 and nearest neighbour matching.

Outcome measures
The diagnosis of congenital malformations was ascertained by the ICD-10. Women with SLE were identified by a diagnostic code (ICD-10 diagnostic code of M32)
recorded within 4 years prior to pregnancy. The primary outcome was defined as the presence of a congenital malformation in the offspring. Congenital malformations were defined using ICD-10 codes during the first 12 months of life, indicating an organ-specific class of malformations, such as nervous system; eye, ear, face and neck; circulatory system; respiratory system; cleft lip and cleft palate; digestive system; genital organs; urinary system; musculoskeletal system; and other malformations. The secondary outcome included each of the organ-specific malformations.

**Covariables**

We selected four groups of variables that might be associated with congenital malformations in the cohort: maternal demographics such as age and parity; maternal comorbidities before pregnancy (such as pre-existing diabetes, pre-existing hypertension) and during pregnancy (gestational diabetes, and pre-eclampsia); and neonatal characteristics (sex and birth weight). Comorbidities before and during pregnancy were identified by ICD-10 codes.

**Patient and public involvement**

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

**Statistical analysis**

Continuous variables are described as mean and SD and compared using Student’s t-test. Categorical variables are given as numbers and percentages and compared using the $\chi^2$ test. Multivariable logistic regression analysis was used to estimate the adjusted ORs (aOR) and 95% CIs for the calculation of the risk of malformation in neonates born to women with SLE in comparison to women without SLE. A generalised estimating equation was used to account for the familial correlation between offspring from a single mother. Additionally, propensity score matching analysis was conducted to address selection bias. Multivariable logistic regression was performed to derive propensity score with covariates such as maternal age, parity, hypertension, diabetes before pregnancy and year of delivery. A 1:5 matching algorithm was applied to minimise the potential confounding effects of variables on the incidence of congenital malformations. Analyses were performed using IBM SPSS Statistics for Windows, V.23. The level of statistical significance was set at $p<0.05$.

**RESULTS**

**Characteristics of the study population**

A total of 3,778,561 women who delivered between 2007 and 2015 underwent NHSE within 4 years before pregnancy. After excluding women with multifetal pregnancies and women with incomplete clinical data, a total of 3,279,204 women were included in the final analysis. Among them, 3,953 (0.1%) had SLE (figure 1). Baseline characteristics are summarised in table 1. Women with SLE were older (31.8 vs 30.9 years, $p<0.001$) and more often primiparous (56.4% vs 52.7%, $p<0.001$) than those without SLE. More women with SLE had hypertension and diabetes mellitus than those without SLE.

### Table 1: Characteristics and pregnancy outcomes of the study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-maternal SLE (N=3,275,251)</th>
<th>Maternal SLE (N=3,953)</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.87±3.87</td>
<td>31.82±3.70</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Nulliparity</td>
<td>1,727,073 (52.73)</td>
<td>2,229 (56.39)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Comorbidities before pregnancy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>106,313 (3.25)</td>
<td>745 (18.85)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>157,014 (4.79)</td>
<td>577 (14.60)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pregnancy outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>136,314 (4.16)</td>
<td>193 (4.88)</td>
<td>0.0234</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>60,855 (1.86)</td>
<td>139 (3.52)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>85,095 (2.60)</td>
<td>268 (6.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Caesarean section</td>
<td>11,820,25 (36.09)</td>
<td>1,691 (42.78)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>11,572 (0.35)</td>
<td>28 (0.71)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Placenta previa</td>
<td>35,646 (1.09)</td>
<td>80 (2.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Neonatal outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neonatal sex, male</td>
<td>1,687,580 (51.53)</td>
<td>2,076 (52.52)</td>
<td>0.2124</td>
</tr>
<tr>
<td>Mean birth weight (kg)</td>
<td>3.21±0.46</td>
<td>3.06±0.55</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>1,156,666 (3.53)</td>
<td>396 (10.02)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Large for gestational age</td>
<td>124,614 (3.80)</td>
<td>89 (2.25)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are presented as number (%) or mean±SD. SLE, systemic lupus erythematosus.
Pregnancy complications
More women with SLE developed obstetric complications that included gestational diabetes, pre-eclampsia, preterm birth, caesarean delivery, placental abruption and placenta previa. Newborns of SLE mothers had lower birth weights than those of mothers without SLE (table 1).

Congenital malformations
Congenital malformations were more frequent in the neonates born to women with SLE than in those born to women without SLE (17.13% vs 11.99%, p<0.0001). The circulatory system was the most common malformation in neonates born to SLE mothers, followed by the digestive system, musculoskeletal system and genital organs (table 2). Women with malformed offspring were more likely to be primiparous than women with healthy offspring. Further, they were more likely to have hypertension, diabetes before and during pregnancy and pre-eclampsia (online supplemental table 1).

More offspring of women with SLE had congenital malformations of the nervous system, eye, ear, face and neck, circulatory system, and musculoskeletal system than those of women without SLE (table 2). In a logistic regression analysis adjusting for age, parity, hypertension, diabetes and fetal sex, SLE was significantly associated with an increased risk for congenital malformations affecting the nervous system (aOR, 1.90; 95% CI, 1.20 to 3.03), the circulatory system (aOR, 1.91; 95% CI, 1.67 to 2.20), eye, ear, face and neck (aOR, 1.37; 95% CI, 1.09 to 1.71) and musculoskeletal system (aOR, 1.26; 95% CI, 1.05 to 1.52). Maternal SLE, on the other hand, was not associated with an increased risk of malformation of the respiratory system, cleft lip and palate, digestive system, genital organs or urinary system.

Organ system-specific malformations
Table 2 and online supplemental table 2 show the association between SLE and types of congenital malformations within the organ system. In the nervous system, the frequency of congenital hydrocephalus was particularly increased (aOR, 3.18; 95% CI, 1.01 to 10.05) and the frequency of other congenital malformations of the brain also increased (aOR, 2.53; 95% CI, 1.13 to 5.66). Among head and neck abnormalities, malformations of eyelids, lacrimal apparatus and orbit (aOR, 1.35; 95% CI, 1.04 to 1.76) and hearing impairment (aOR, 1.84; 95% CI, 1.13 to 2.97) were more common in the newborns of patients with SLE. With respect to the circulatory system, congenital malformations of the cardiac septa (aOR, 2.29; 95% CI, 1.37 to 3.87) and great arteries (aOR, 1.84; 95% CI, 1.04 to 2.76) were particularly increased. In the musculoskeletal system, the risk of other congenital musculoskeletal deformities (aOR, 1.48; 95% CI, 1.01 to 2.10) and polydactyly (aOR, 1.97; 95% CI, 1.06 to 3.67) were particularly increased.

Sensitivity analysis
A sensitivity analysis was performed using propensity score matching to adjust for unbalanced baseline characteristics. After matching, there were no significant differences in major comorbidities before pregnancy between 3953 women with SLE and 19765 matched controls (online supplemental table 3). Overall, congenital malformations were more frequent in neonates born to women with SLE than in those without SLE (17.3% vs...

Table 3  Risk of organ system-specific congenital malformations in the propensity-score matched cohorts

<table>
<thead>
<tr>
<th>Any congenital malformation (Q00–Q89)</th>
<th>Unadjusted OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q00–07 (congenital malformations of the nervous system)</td>
<td>1.70 (0.99 to 2.91)</td>
<td>1.71 (0.99 to 2.91)</td>
</tr>
<tr>
<td>Q10–Q18 (congenital malformations of the eye, ear, face and neck)</td>
<td>1.38 (1.07 to 1.78)</td>
<td>1.38 (1.07 to 1.78)</td>
</tr>
<tr>
<td>Q20–Q28 (congenital malformations of the circulatory system)</td>
<td>1.72 (1.47 to 2.01)</td>
<td>1.72 (1.47 to 2.02)</td>
</tr>
<tr>
<td>Q30–Q34 (congenital malformations of the respiratory system)</td>
<td>1.10 (0.57 to 2.12)</td>
<td>1.10 (0.57 to 2.11)</td>
</tr>
<tr>
<td>Q35–Q37 (cleft lip and cleft palate)</td>
<td>0.97 (0.40 to 2.32)</td>
<td>0.97 (0.40 to 2.32)</td>
</tr>
<tr>
<td>Q38–Q45 (other congenital malformations of the digestive system)</td>
<td>0.90 (0.76 to 1.07)</td>
<td>0.90 (0.76 to 1.07)</td>
</tr>
<tr>
<td>Q50–Q56 (congenital malformations of the genital organs)</td>
<td>0.93 (0.63 to 1.39)</td>
<td>0.93 (0.63 to 1.38)</td>
</tr>
<tr>
<td>Q60–Q64 (congenital malformations of the urinary system)</td>
<td>1.08 (0.72 to 1.62)</td>
<td>1.07 (0.71 to 1.62)</td>
</tr>
<tr>
<td>Q65–Q79 (congenital malformations and deformations of the musculoskeletal system)</td>
<td>1.17 (0.95 to 1.43)</td>
<td>1.17 (0.95 to 1.43)</td>
</tr>
<tr>
<td>Q80–Q89 (other congenital malformations)</td>
<td>1.04 (0.62 to 1.72)</td>
<td>1.04 (0.62 to 1.72)</td>
</tr>
</tbody>
</table>

ORs and 95% CIs are shown. The control group was selected after matching for age, parity, hypertension, diabetes before pregnancy and year of delivery.
*Adjusted for age, parity, hypertension, diabetes and neonatal sex.
CI, confidence interval; OR, odds ratio.

13.2%, p<0.0001). SLE remained significantly associated with an increased risk of congenital malformations of the cardiovascular system (aOR, 1.72; 95% CI, 1.47 to 2.02), eye/ear/face and neck (aOR, 1.38; 95% CI, 1.07 to 1.78) (table 3).

DISCUSSION

Main findings

The major findings of this study are as follows: (1) the risk of congenital malformations in neonates born to mothers with SLE was significantly increased compared with those born to mothers without SLE and (2) these congenital malformations preferentially involved the nervous system, eye/ear/face and neck, circulatory system and musculoskeletal system.

Comparison with findings from previous studies

The current study is the largest to demonstrate the increased risk of congenital malformations in offspring born to mothers with SLE. This is consistent with previous studies showing that children born to women with SLE are at an increased risk of adverse health outcomes such as neurodevelopmental disorders, congenital heart defects, haematologic malignancies and autoimmune disease.9 Another study using the national birth registry showed that congenital malformations were more prevalent among children born to SLE mothers than among those born to women without SLE (7.4% vs 2.8%).25 In this study, the frequency of congenital malformation in the offspring of SLE mothers and those of mothers without SLE was estimated at 17.13% and 11.99%, respectively, confirming that maternal SLE was associated with an increased risk of congenital malformation. The higher frequency of congenital malformations in the general population in this study could be explained by better diagnosing24 and/or reporting less severe congenital malformations using the ICD. In fact, the prevalence of anomalies have been increasing compared with that in the past, which is consistent with the major role of improved postnatal detection of less severe malformations.25

In this study, the frequency of congenital malformation in the cardiovascular system was higher (5.5% vs 2.6%, p<0.0001), which was comparable to the findings by Vinet et al9 who reported increased risk of the circulatory system in 719 SLE offspring compared with 8493 controls (5.1% vs 1.9%, p<0.0001). In addition, we also showed that pregnancies with SLE were also at increased risk for other organ system abnormalities such as nervous system, eye, ear, face and neck abnormalities as well as musculoskeletal system abnormalities (table 4).

We also evaluated each type of malformation within organ systems. Some congenital malformations were particularly increased. In the cardiovascular system, congenital malformations of the cardiac septa and great arteries were particularly increased, consistent with results from prior studies that showed children born to women with SLE had an increased risk of congenital heart defects, including a specifically increased risk of atrial septal defect (ASD), ventricular septal defect (VSD) and valve anomalies.7 The increased risk of ASD and VSD were similar to that observed in our study. Here, we show that the risk of congenital malformation of the great arteries (coarctation of the aorta, atresia of the aorta, etc) was increased. While several studies have compared the risk of congenital malformations between SLE and non-SLE groups in a few organ systems, this study is one of the first to systematically evaluate all the organ systems. Interestingly, SLE in the mother did not affect the risk of malformation in all organ systems equally.
Clinical and research implications

SLE itself might cause some congenital malformations through the mechanism of autoantibodies, cytokines or treatment-associated side effects. Maternal anti-Ro/SS-A and anti-La/SS-B were associated with congenital heart block in newborns and neonatal lupus. Little is known about anti-Ro/SS-A and anti-La/SS-B and the development of other congenital malformations. Cardiac septation occurs early in embryogenesis and is usually completed around four to 7 weeks of gestation. It may be difficult to explain that the septal defect is caused by the antibody because the passage of maternal autoantibodies through the placenta usually occurs after 20 weeks. However, since most VSDs are thought to arise from foci of apoptosis within an already formed ventricular septum, the maternal anti-Ro/SS-A and anti-La/SS-B may prevent spontaneous closure of defects. Increased cytokines in patients with SLE might also contribute to cardiac malformation. Cytokines, such as Transforming growth factor-β (TGF-β), play an important role in the normal development of the heart. Multiple signalling pathways, including notch, Fibroblast growth factor (FGF) and TGF-β, have been implicated in outflow tract (aorta or pulmonary artery) development. Edwards et al found that transplacental acquisition of anti-Ro/SS-A antibodies has been associated with external hydrocephalus. It is possible that autoantibody-mediated inflammation is implicated in its pathogenesis. It may be quite possible that the observed risk of congenital malformation in pregnant women with SLE may be attributable to the medications prescribed to these women. Unfortunately, information on medication exposures was not available in the current study. Patients with SLE usually continue some medications such as corticosteroids, antimalarials and pregnancy-compatible immunosuppressants during pregnancy to control disease activity and major organ involvement. Corticosteroids are commonly used to treat SLE during pregnancy. Several studies have shown an association between in utero exposure and an increased risk of oral cleft. In a nationwide cohort study, no association was found between maternal use of oral corticosteroids and congenital heart defects. Another study found no evidence of an association between the use of corticosteroids and a risk of congenital malformations in offspring. Antimalarial drugs are commonly used in pregnant women with SLE to reduce disease activity and the risk of congenital heart block and neonatal lupus syndrome. Some investigators concluded that hydroxychloroquine is a safe drug in the treatment of SLE during pregnancy. There was no increased risk of congenital malformations in newborns. Recently, some studies suggest a small increased risk of malformations associated with the use of hydroxychloroquine in early pregnancy. However, the observed birth defects among hydroxychloroquine-exposed women did not present a clear pattern. Rather, discontinuing a drug during pregnancy increased the risk of flare and worsened pregnancy outcomes. Immunosuppressive drugs such as azathioprine are sometimes used, too. Several studies have found that azathioprine is relatively safe in pregnancy. The drug has not been associated with congenital defects in these studies. Mycophenolate mofetil is another widely used drug for the treatment of SLE. It is known to be teratogenic based on observational studies of pregnancies exposed to mycophenolate mofetil. Unintended pregnancies while on teratogenic drugs such as mycophenolate mofetil contribute to facial malformation observed in this study. Taken together, it is difficult to say that the effects of drugs on congenital malformations have been fully studied.

SLE is actually a disease with heterogeneous phenotypes. Therefore, it is hard to assume that specific disease phenotypes can be all responsible for the induction of certain malformations. However, the heterogeneous phenotypes of SLE can still share common biological mechanisms, such as interferon production, immune complex-mediated inflammation and vasculopathy. While the patients might be clinically in remission before conception, the serological activity might contribute to the proinflammatory milieu that drives the congenital malformations in various forms.

While increased relative risk of malformations in offspring born to mothers with SLE was observed, the absolute numbers of children with malformation are

<table>
<thead>
<tr>
<th>Pregnancy, n</th>
<th>Target malformation</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wallenius et al&lt;sup&gt;33&lt;/sup&gt; 95 women with SLE 257327 control</td>
<td>Major congenital malformations</td>
<td>Major congenital malformations were more frequent in children with SLE (OR, 2.71; 95% CI, 1.25 to 5.86).</td>
</tr>
<tr>
<td>Vinet et al&lt;sup&gt;34&lt;/sup&gt; 719 SLE offspring 8493 control children</td>
<td>Congenital heart defects</td>
<td>Children born to women with SLE had a substantially increased risk of CHD in comparison with controls (OR, 2.62; 95% CI, 1.77 to 3.88).</td>
</tr>
<tr>
<td>Current study (2023) 3953 women with SLE 3272521 control</td>
<td>All kinds of congenital malformations</td>
<td>After adjustment for age, parity, hypertension, diabetes, and fetal sex, the SLE group was found to be associated with an increased risk of congenital malformations in the nervous system (adjusted OR (aOR, 1.90; 95% CI, 1.20 to 3.03), eye, ear, face and neck (aOR, 1.37; 95% CI, 1.09 to 1.71), circulatory system (aOR, 1.91; 95% CI, 1.67 to 2.20) and musculoskeletal system (aOR, 1.26; 95% CI, 1.05 to 1.52).</td>
</tr>
</tbody>
</table>

CHD, congenital heart defect; SLE, systemic lupus erythematosus.
very small. Both relative risk and absolute numbers of malformation should be considered when counselling the patient. Calculated number needed to harm for any malformation is 19.45.

Strengths and limitations
This study was the first to determine the interaction of maternal SLE and neonatal congenital malformation in a large population-based study. The incidence of major congenital malformations in the general population is about 2.4%–6.9%.

Therefore, it is difficult to analyse the relationship between maternal SLE and the risk of congenital malformation using a small cohort. However, because it is a government paid, biannual health screening examination, we were able to acquire data on lupus before pregnancy and assess its correlation with congenital malformations systematically in a large cohort.

This study has several limitations. First, we identified congenital malformations using ICD-10 diagnostic codes, which were recorded for reimbursement purposes. It is possible that the diagnosis of malformations was not correctly recorded during the postpartum workup of all newborns. A closer monitoring of children born to SLE mothers that can lead to the increased identification of asymptomatic or non-clinically significant malformations. Clinically, it is thought that major structural anomalies are the conditions that account for most of the deaths, morbidity and disability related to congenital anomalies. In studying malformation, it is also important to consider the severity of malformation. However, there is no fully defined description of major malformation. Second, in our database, data on clinical and laboratory parameters such as antinuclear antibody, anti-Ro and anti-La autoantibodies, and antiphospholipid antibodies were not available. The effects of disease activity and autoantibody presence on congenital malformations would not be estimated. Anti-Ro and La antibodies, found in 40% of lupus women, cross the placenta and are associated with the development of neonatal lupus, with congenital heart block being the most characteristic cardiac manifestation.

Third, the analysis accounting for medication exposures could not be performed; hence, the association with the occurrence of drug-induced congenital malformations could not be established. Therefore, the current findings need to be confirmed in a larger prospective cohort study. Fourth, there is a slight increase in the adjusted OR for malformations in SLE. Therefore, further research is needed to determine whether warnings should be issued in terms of public health and precautions to be implemented.

In conclusion, this nationwide population study in South Korea indicates that neonates born to mothers with SLE have a slightly increased risk of congenital malformations affecting the nervous system, eye/ear/face and neck, circulatory system and musculoskeletal system. When a woman with lupus becomes pregnant, careful fetal ultrasound and newborn screening can be helpful in identifying the risk of potential malformations.

REFERENCES


