Editorial

Systemic Lupus Erythematosus Increases the Risk of Gestational Diabetes: Truth or Illusion?

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In this issue of *The Journal of Rheumatology*, Gernaat et al¹ conducted a population-based study to evaluate whether the risk of gestational diabetes mellitus (GDM) was associated with systemic lupus erythematosus (SLE) by comparing pregnancies in women with SLE to those in general population controls. The authors used a Swedish medical registry to collect data from 695 SLE pregnancies and 4644 non-SLE pregnancies in Sweden between November 2006 and 2016. They found a 2-fold increased risk of GDM in SLE, which did not differ by glucocorticoid (GC) or hydroxychloroquine (HCQ) medication. Pregnancy with SLE is considered a high-risk pregnancy. Studies have shown that patients with SLE are at increased risk of maternal death, preeclampsia, preterm delivery, and infection.² However, whether pregnancy with SLE is associated with an increased risk of GDM remains controversial. GDM, one of the most common metabolic disorders during pregnancy, is associated with adverse pregnancy outcomes.³ The prevalence of GDM in the study by Gernaat et al¹ (2.6%) was lower than that previously reported in pregnancy with SLE (5–28.3%).⁴ Maternal overweight and obesity, maternal age ≥ 35 years, previous history of GDM, and family history of type 2 DM are major GDM risk

factors.⁵ Previous studies have shown that patients with SLE have hyperinsulinemia, insulin resistance, and metabolic syndrome.⁶ In other words, GDM and pregnancy in patients with SLE have similar pathological features. When these confounders were adjusted for,⁶ the risk of GDM on pregnancy with SLE was eliminated. Additionally, although GC and HCQ are both widely used in the treatment of SLE,^{7,8} Gernaat et al¹ found that neither of these drugs increased the risk of GDM in patients with SLE. However, it has been reported that GDM develops in 12.6% of patients with SLE who receive high-dose GC (≥ 1 mg/kg/day).⁸ Therefore, the significant association between GDM and SLE should be interpreted carefully in the study by Gernaat et al.¹

Studies have shown that there are significant racial and regional differences in the risk of GDM, and the incidence is increasing annually. A study conducted in the United States showed that Native American, Hispanic, and Asian women were more likely to develop GDM than non-Hispanic White women, with Asian and Pacific Islander women having the highest incidence of GDM, and Asian women having a higher prevalence of GDM than women of European ancestry.^{9,10} Therefore, the risk of GDM in pregnancy in patients with SLE is also different. The prevalence of GDM in the study by Gernaat et al¹ (1.4%) was lower than that of a study in the same region, southern Sweden, which reported a 2.6% prevalence of GDM in the general population.¹¹ A study conducted in Oman involving 56 pregnant women with SLE and 91 pregnant women without SLE showed a significantly higher incidence of GDM in pregnant women with SLE than in controls (28.3% vs 10.2%).¹² However, a previous study in China reported different results, comparing the pregnancy outcomes of 338 SLE women and 1014 non-SLE women, in which the incidence of GDM in pregnancy with SLE was reduced compared with non-SLE women (5.6% vs 11.5%).¹³ A recent systematic review and metaanalysis was conducted with 3424 pregnant women, including 248 patients with GDM and showed no significant increase in the risk of GDM in preg-

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nancy with SLE compared with the control group.⁴ However, GC use was positively associated with the risk of GDM.⁴ The inconsistent results could be explained by several reasons. First, there are inconsistent diagnostic criteria for GDM globally. There are several different protocols in use internationally to diagnose GDM, and each protocol has its own recommendations regarding which pregnant women should be selected for biochemical testing, how and when the testing should be conducted, and glucose threshold standards.¹⁴ In most parts of Sweden, GDM is strictly defined, and there is a lack of universal screening for oral glucose tolerance tests.¹¹ Second, the dosage of GC or HCQ is inconsistent. GC, as one of the most commonly used medications in SLE treatment, may lead to different pregnancy outcomes due to different doses. The benefit–risk ratio of oral GC is acceptable.¹⁵ The use of HCQ can reduce the dosage of GC, which may reduce the occurrence of GDM, and the use of HCQ in patients with SLE throughout pregnancy is relatively safe.¹⁶ Further, as a retrospective study, Gernaat et al¹ had some missing data related to the risk of GDM, such as BMI, use of antiinflammatory and anticoagulant drugs (low-dose aspirin and low-molecular-weight heparin), dietary control, and SLE activity. In general, these factors will lead to a decline in the applicability of this study.

GDM has several distinct pathophysiological features, including maternal insulin resistance, excessive inflammatory response, and placental endothelial dysfunction.¹⁷ These mechanisms may partially explain the association between elevated GDM risk and SLE. GC and HCQ have constituted the cornerstone of SLE therapy.¹⁸ The adverse effects of GC observed in pregnancy include insulin resistance, infection, and premature membrane rupture.¹² GC may also be involved in the occurrence of type 2 DM by affecting the proliferation and development of islet β cells, secretion function, insulin signal transduction pathway, glucolipid metabolism, glucose transport, and absorption.¹⁹ Therefore, GCs may increase the risk of GDM in patients with SLE. In contrast, HCQ can improve hyperglycemia and hyperlipidemia and protect patients with autoimmune disease from infection, in addition to having direct immunomodulatory effects.²⁰

In summary, there remains much work to be done in the future regarding whether pregnancy complicated with SLE increases the risk of GDM. Detailed prepregnancy counseling and the correct timing of pregnancy are very important. In addition, for pregnancy in patients with SLE, uniform diagnostic criteria need to be developed for GDM. We also need to strengthen blood glucose monitoring, assess SLE disease activity, and control the doses of GC and HCQ. Therefore, it is necessary to further explore the relationship between GDM and SLE in different countries and populations through prospective multicenter cohort studies. Further study is also needed to explore the incidence of GDM in SLE and its potential molecular mechanism through different doses of GC or HCQ in pregnancy with SLE mice.

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