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# Gestational Diabetes Mellitus Risk in Pregnant Women With Systemic Lupus Erythematosus

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*ABSTRACT.* ***Objective.*** To investigate the risk of gestational diabetes mellitus (GDM) associated with systemic lupus erythematosus (SLE) by comparing pregnancies in women with SLE to general population controls.

***Methods.*** We identified singleton pregnancies among women with SLE and general population controls in the Swedish Medical Birth Register (MBR; 2006–2016), sampled from the population-based Swedish Lupus Linkage (SLINK) cohort (1987–2012). SLE was defined by ≥ 2 International Classification of Diseases (ICD)-coded visits in the National Patient Register (NPR) and MBR, with ≥ 1 visit before pregnancy. GDM was defined by ≥ 1 ICD-coded visit in the NPR or MBR. Glucocorticoid (GC) and hydroxychloroquine (HCQ) dispensations within 6 months before and during pregnancy were identified in the Prescribed Drug Register. Risk ratios (RRs) and 95% CIs of GDM associated with SLE were estimated using modified Poisson regression models, stratified by parity and adjusted for maternal age at delivery, year of birth, and obesity.

***Results.*** We identified 695 SLE pregnancies including 18 (2.6%) with GDM and 4644 non-SLE pregnancies including 65 (1.4%) with GDM. Adjusted RRs of GDM associated with SLE were 1.11 (95% CI 0.38–3.27) for first deliveries and 2.03 (95% CI 1.21–3.40) for all deliveries. Among SLE pregnancies, GDM occurred in 7/306 (2.3%) with ≥ 1 GC before and/or during pregnancy, 11/389 (2.8%) without GC, 7/287 (2.4%) with ≥ 1 HCQ before and/or during pregnancy, and in 11/408 (2.7%) without HCQ.

***Conclusion.*** When looking at all deliveries, SLE was associated with a 2-fold higher risk of GDM. GDM occurrence did not differ by GC or HCQ.

*Key Indexing Terms*: gestational diabetes, glucocorticoids, pregnancy, systemic lupus erythematosus

Gestational diabetes mellitus (GDM) is an endocrine complication during pregnancy. GDM is associated with, among other adverse pregnancy complications, a higher risk of preeclampsia, preterm delivery, and cesarean delivery.[1] Globally, GDM prevalence is increasing, partly due to older maternal age at pregnancy and higher prevalence of obesity and diabetes.[1] Insulin resistance is an important risk factor for GDM and is more common in women with systemic lupus erythematosus (SLE) than in women from the general population.[1,2] Whether women with SLE have a higher risk of GDM than women from the general population remains unclear.

A metaanalysis of the SLE–GDM association reported a range of risk ratios (RRs) between 0.49 and 2.71, finding no increased risk of GDM in women with SLE, with a pooled RR of 1.08 (95% CI 0.49–2.41).[3] This metaanalysis included only 5 studies with unclear GDM identification criteria and largely missing medication use data. Glucocorticoids (GCs) are widely used to treat SLE and may increase the risk of GDM.[4] GCs promote gluconeogenesis in the liver and decrease glucose uptake and utilization in the skeletal muscle and white adipose tissue, which can cause hyperglycemia and insulin resistance.[4] Hydroxychloroquine (HCQ), another widely used treatment in SLE, has been shown to improve glycemia and reduce the risk of type 2 diabetes mellitus (DM).[5,6]

In this study, we investigated the risk of GDM in women with SLE compared to women from the general population in a Swedish population-based study.

## METHODS

*Study population and data sources.* This study included all singleton pregnancies among women with prevalent SLE and general population comparators without SLE who had a delivery registered between November 1,

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2006, and December 31, 2016, from the population-based Swedish Lupus Linkage (SLINK) cohort (1987–2012).[7] Briefly, SLINK included all individuals with ≥ 1 SLE International Classification of Diseases, 10th revision (ICD-10)-coded visit (M32, excluding M32.0, drug-induced SLE) in the National Patient Register (NPR). The NPR captures hospitalization information (national coverage from 1987 onward) and nonprimary care/outpatient visits in public and some private practices (nationwide since 2001 for specialized outpatient care). Five randomly sampled comparators from the general population without SLE, were identified in the Total Population Register, and matched with SLE cases on age, sex, calendar time, and county of residence.

Pregnancies were identified in the Swedish Medical Birth Register (MBR), which includes information on maternal health during pregnancy and delivery, and neonatal outcomes of over 98% of deliveries in Sweden since 1973. All live births are included in the MBR. Stillbirths occurring ≥ 28 weeks' gestation are included in the MBR before July 2008; starting in July 2008, those stillbirths occurring ≥ 22 weeks' gestation are also included. The nationwide Prescribed Drug Register (PDR) includes all pharmacy-dispensed prescription medications from July 2005 onward. To include medication dispensations at least 6 months before pregnancy, deliveries registered from November 1, 2006, were included.

In the current study, SLE was defined as ≥ 2 ICD-coded visits in the in- or outpatient records of the NPR and MBR, with ≥ 1 code from a specialist who typically treats or diagnoses SLE (ie, rheumatology, dermatology, nephrology, internal medicine, or pediatrics), occurring any time before pregnancy. General population comparators had no SLE codes before the date of first observed SLE ICD-coded visit of their matched case (original matching date in SLINK). The current study included pregnancies among general population comparators if they occurred after the SLINK matching date. Ethical approval was provided by the Regional Ethics Review Board in Stockholm (DNR 2011/920-31/1, 2017-2523-32). Informed consent was not required.

*Outcome.* GDM was identified using ≥ 1 ICD-coded visit (ICD-10: O24.4) in the in- or outpatient records of the NPR and MBR. In Sweden, the diagnostic criteria for GDM was relatively strict during the years of the study and selective oral glucose tolerance tests (OGTTs) were performed based on risk factors in most parts of the country.[8] The risk factors during pregnancy that indicate an OGTT are accelerating fetal growth, polyhydramnios, and elevated random capillary plasma glucose.[8] The diagnostic criteria were based on a 75-g OGTT with a fasting capillary whole blood glucose level of 6.1 mmol/L (plasma 7.0 mmol/L) and/or a 2-h blood glucose level of 9.0 mmol/L (plasma glucose 10.0 mmol/L).[9]

*Exclusion criteria.* We excluded women with pregestational DM as they should not receive a diagnosis of GDM, and therefore these women are not at risk of GDM. Women with an ICD-coded visit listing a DM diagnosis (ICD-10: E10, E11, O24.0-O24.3, O24.8, H36) in the NPR any time before pregnancy or during the first trimester were excluded. Pregnancies with any use of antidiabetic medication in the PDR using Anatomical Therapeutic Chemical (ATC) codes (ATC: A10A, A10B) prior to the second trimester, with the exception of use for a GDM in a prior pregnancy, were excluded.

*Covariates.* Maternal age at delivery, date of last menstrual period, delivery date, cesarean section, height, weight, and parity were collected from the MBR. Maternal BMI (kg/m$^2$) was calculated from height and weight from the first antenatal visit. Obesity was defined as BMI of ≥ 30. Among women with SLE, GCs (ATC codes: betamethasone H02AB01, dexamethasone H02AB02, methylprednisolone H02AB04, prednisolone H02AB06, and prednisone H02AB07) and HCQ (ATC: P01BA02) dispensations within 6 months before pregnancy and during pregnancy were collected from the PDR. The cumulative defined daily dose of GC and HCQ dispensations was calculated for each time period by multiplying the defined daily dose (number of days) for each dispensed package with the total number of packages dispensed. The defined daily dose is the average daily dose used by an adult for its primary indication when the drug is prescribed.

*Statistical analysis.* Continuous variables were described using means and SDs and categorical variables using frequencies and column percentages. To compare the risk of GDM between pregnancies of women with SLE and without SLE, we estimated RRs and corresponding 95% CI using modified Poisson regression models for first deliveries and all deliveries separately.[10] The models were adjusted for maternal age at delivery, year of delivery, and obesity as possible confounders. In a sensitivity analysis, we used a stricter definition for our study population and excluded those women who received a (nongestational) DM ICD code for the first time during the second or third trimester in the event that they had prevalent pregestational diabetes and were misclassified. We performed data management and analyses with SAS version 9.4 (SAS Institute).

## RESULTS

We identified 695 pregnancies in women with SLE and 4644 pregnancies in women without SLE between November 2006 and 2016. Maternal age at delivery, duration of pregnancy, BMI, and obesity at first prenatal visit were comparable between women with and without SLE (Table 1). Women with SLE were more likely to have a cesarean section than women without SLE (31.1% vs 18.1%), and women with SLE were more likely to have only 1 delivery compared to women without SLE (46.7% vs 39.9%; Table 1).

*GDM among women with and without SLE.* GDM was diagnosed in 18 SLE pregnancies (2.6%) and in 65 non-SLE pregnancies (1.4%; Table 2). Among those pregnancies with GDM, compared to women without SLE, women with SLE had a higher mean maternal age at delivery (35 vs 33 yrs) and were more often obese at first prenatal visit (38.9% vs 32.8%; Table 2).

The adjusted RR of GDM associated with SLE was 1.11 (95% CI 0.38–3.27) for first deliveries only and 2.03 (95% CI 1.21–3.40) for all deliveries (Table 3). In the sensitivity analysis excluding those with a diagnosis code for DM in the second or third trimester (n = 6, all in the non-SLE group), the RR of GDM associated with SLE was 1.17 (95% CI 0.40–3.44) for first deliveries only and 2.18 (95% CI 1.30–3.68) for all deliveries (Supplementary Table 1, available with the online version of this article).

*Medication use among women with SLE.* The risk of GDM was similar across medication groups. Among 306 SLE pregnancies receiving at least 1 GC dispensation within 6 months before or any time during pregnancy, 7 (2.3%) were diagnosed with GDM (Supplementary Table 2, available with the online version of this article). Similarly, 11 of the 389 (2.8%) SLE pregnancies that did not receive any GC dispensation before or during pregnancy were diagnosed with GDM. During pregnancy, fewer women with SLE were dispensed GCs and the cumulative defined daily dose was lower compared to the 6 months before pregnancy. The risk of GDM was also similar across medication groups with or without HCQ dispensations. There were 287 SLE pregnancies which received at least 1 HCQ dispensation during 6 months before or any time during pregnancy, and among these, 7 (2.4%) were diagnosed with GDM. Among 408 SLE pregnancies that did not receive any HCQ dispensation before or during pregnancy, 11 (2.7%) were diagnosed with GDM. There were more women with SLE with HCQ dispensations and the cumulative

*Table 1.* Characteristics of pregnancies among women with SLE and women from the general population.

| | Pregnancies in Women With SLE, n = 695 | Pregnancies in Women From the General Population, n = 4644 |
|---|---|---|
| Maternal age at delivery, yrs, mean ± SD | 31.6 (4.7) | 31.9 (5.0) |
| Maternal age at delivery in categories, yrs, n (%) | | |
| < 35 | 490 (70.5) | 3,211 (69.1) |
| ≥ 35 | 205 (29.5) | 1,433 (30.9) |
| Duration of pregnancy, weeks, mean ± SD | 38.1 (2.9) | 39.4 (1.8) |
| Cesarean section, n (%) | 216 (31.1) | 841 (18.1) |
| BMI[a], mean ± SD | 24.2 (4.2) | 24.6 (4.5) |
| Obesity at first prenatal visit[a], n (%) | 70 (11.2) | 491 (11.4) |
| Missing data on BMI, n (%) | 69 (9.9) | 317 (6.8) |
| Parity, n (%) | | |
| 1 | 325 (46.7) | 1855 (39.9) |
| 2 | 254 (36.6) | 1813 (39.1) |
| 3 | 79 (11.4) | 700 (15.1) |
| ≥ 4 | 37 (5.3) | 276 (5.9) |
| Year of delivery, n (%) | | |
| 2006–2008 | 96 (13.8) | 911 (19.6) |
| 2009–2011 | 219 (31.5) | 1,441 (31.0) |
| 2012–2014 | 216 (31.1) | 1,421 (30.6) |
| 2015–2016 | 164 (23.6) | 871 (18.8) |

[a] Mean or percentage excludes missing values. SLE: systematic lupus erythematosus.

*Table 2.* Characteristics of pregnancies with GDM among women with SLE and women from the general population.

| | GDM Among Women With SLE, n = 18 | GDM Among Women From the General Population, n = 65 |
|---|---|---|
| Maternal age at delivery, yrs, mean ± SD | 35.0 (3.9) | 33.1 (5.7) |
| Duration of pregnancy, weeks, mean ± SD | 37.0 (4.3) | 38.5 (2.2) |
| Cesarean section, n (%) | 4 (22.2) | 20 (30.8) |
| BMI, mean ± SD * | 28.6 (5.7) | 28.6 (6.4) |
| Obesity at first prenatal visit, n (%) * | 7 (38.9) | 21 (32.8) |
| Missing data on BMI, n (%) | 0 (0.0) | 1 (1.5) |
| Parity, n (%) | | |
| 1 | 4 (22.2) | 22 (33.8) |
| 2 | 8 (44.5) | 20 (30.8) |
| 3 | 4 (22.2) | 14 (21.5) |
| ≥ 4 | 2 (11.1) | 9 (13.9) |
| Year of delivery, n (%) | | |
| 2006–2008 | 5 (27.8) | 17 (26.2) |
| 2009–2011 | 6 (33.3) | 20 (30.8) |
| 2012–2014 | 6 (33.3) | 17 (26.2) |
| 2015–2016 | 1 (5.6) | 11 (16.9) |

[a] Mean or percentage excludes missing values. GDM: gestational diabetes mellitus; SLE: systematic lupus erythematosus.

defined daily dose was higher in the 6 months before pregnancy than during pregnancy.

## DISCUSSION

This population-based study showed that GDM was not associated with SLE in first deliveries only, but when including all deliveries, SLE was associated with a 2-fold higher risk of GDM. The absolute risk of GDM was low, with a prevalence of 2.6% in women with SLE and 1.4% in women without SLE. We did not find a difference in GDM occurrence by exposure to GC or HCQ dispensations. GDM occurred among 2.3% and 2.4% of those with GC and HCQ dispensations respectively before and/or during pregnancy, and among 2.8% and 2.7% of those without GC and HCQ dispensations, respectively.

Pregnant women with SLE are recommended to follow the local protocols based on the European Alliance of Associations for Rheumatology guidelines applied to high-risk pregnancies.[11]

*Table 3.* The risk of GDM among pregnant women with SLE compared to pregnant women from the general population.

| | No. of Pregnancies With GDM, n (%) | Unadjusted | | Adjusted[a] | |
|---|---|---|---|---|---|
| | | RR | 95% CI | RR | 95% CI |
| First pregnancies only | | | | | |
| SLE | 4/325 (1.2) | 1.04 | 0.36–2.99 | 1.11 | 0.38–3.27 |
| General population | 22/1855 (1.2) | 1.00 | – | 1.00 | – |
| All pregnancies | | | | | |
| SLE | 18/695 (2.6) | 1.85 | 1.10–3.10 | 2.03 | 1.21–3.40 |
| General population | 65/4644 (1.4) | 1.00 | – | 1.00 | – |

[a] Adjusted for maternal age at delivery, year of birth, and obesity. GDM: gestational diabetes mellitus; RR: risk ratio; SLE: systemic lupus erythematosus.

Presently, these guidelines do not include extra screening for GDM as part of antenatal care. Women with SLE may receive more antenatal care than women from the general population because their pregnancies are considered high risk, potentially leading to detection bias.

Limited power to study the association between SLE and GDM in first deliveries, with only 4 women with SLE diagnosed with GDM in this study, may explain the lack of association between SLE and GDM in the first delivery analysis. On the other hand, it can be hypothesized that parity (ie, the number of pregnancies) may be an important factor in the association between SLE and GDM. Women with SLE may have a higher risk of insulin resistance with more pregnancies, as they may be less likely to manage the change in insulin levels during pregnancy compared to women from the general population. These hypothetical mechanisms should be further investigated in future studies.

The results of our study are different from those previously reported by a study from China comparing pregnancy outcomes, including GDM, among 338 women with SLE and 1014 women without SLE.[12] This study found a prevalence of GDM of 5.6% in women with SLE and 11.5% in women without SLE, with an adjusted odds ratio of 0.49 (95% CI 0.28–0.85). Women with DM or those on antidiabetic medication before pregnancy and/or during the first trimester were not excluded, and GDM was defined as any degree of glucose intolerance with onset during pregnancy; however, it was not explained how women with or without SLE were screened for GDM or diagnosed with GDM.

The prevalence of GDM in the current study (2.6%) is lower than previously published by other studies reporting a GDM prevalence between 4.5% and 28.3% in women with SLE.[3] The lower prevalence of GDM in Sweden is likely the result of a strict definition of GDM, and most parts of Sweden lack universal screening with an OGTT. Also, the prevalence of GDM may be overestimated in previously reported studies due to misclassification of previously unknown or known DM, as women with DM or on antidiabetic medication before pregnancy or during the first trimester were not excluded.[3] A study from Southern Sweden reported a prevalence of GDM in the general population in Southern Sweden of 2.4% compared to 1.2% in the current study.[13] This can be mainly explained by the universal OGTT screening performed in Southern Sweden. Also, Ignell and colleagues[13] did not exclude women with DM nor those who received antidiabetic medication any time before pregnancy or during the first trimester as the current study did.

The diagnostic criteria and screening practices of GDM vary widely across and within countries, as is the case in Sweden, which makes the prevalence of GDM difficult to compare.[1] Selective screening based on risk factors before and during pregnancy is most commonly used in Sweden.[8] Risk factors include family history of type 2 DM, previous GDM, maternal age > 35 years, fetal macrosomia (≥ 4500 g) or stillbirth in previous pregnancy, BMI of 30 kg/m$^2$, and non-European nationality.[8] The risk factors during pregnancy that indicate an OGTT are accelerating fetal growth, polyhydramnios, and elevated random capillary plasma glucose.[8]

To our knowledge, this is the first population-based study investigating the risk of GDM in women with SLE. The population-based design using registry data limited selection bias, and all healthcare data were registered prospectively. Women with SLE were identified before pregnancy using an established register-based case definition.[14] The identification of SLE before pregnancy reduces misclassification and selection bias compared to definitions requiring that SLE is recorded as a diagnosis at delivery.[15] We were unable to investigate the association between GC and HCQ dispensations with GDM in the current study. There were only 11 SLE pregnancies with GDM dispensed with at least one of these medications. Further, despite dispensation data, adherence to these medications was unknown.

Misclassification of undiagnosed DM as GDM may have occurred and may have happened more often among pregnancies from the general population as they were under less surveillance; this would bias the measure of effect downward. In Sweden, diabetes is diagnosed and cared for mostly in primary care, the data for which were unavailable for this study. We may not have been able to identify all women with DM before pregnancy or during the first trimester solely based on ICD codes in the NPR or MBR. Therefore, we included dispensed antidiabetic medications to cover potential missed DM diagnoses in primary care, but we may still have missed those women who control their DM with lifestyle adjustments.

To conclude, women with SLE are at an almost 2-fold higher risk of GDM compared to women from the general population when looking at all deliveries. Early and proper screening for GDM, including SLE as a risk factor for GDM, may be a way to manage women with SLE and reduce associated maternal and

fetal complications. Future studies should investigate the risks of diseases later in life associated with GDM in women with SLE, such as the risk of type 2 DM and cardiovascular disease. Also, the long-term effects in the children born to mothers with GDM associated with SLE are unclear.

## ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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