Fetal Sex and the Natural History of Maternal Risk of Diabetes During and After Pregnancy

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Context: It has recently emerged that carrying a male fetus is associated with poorer maternal β-cell function in pregnancy and an increased risk of gestational diabetes mellitus (GDM). β-cell dysfunction is the central pathophysiologic defect underlying both GDM and subsequent postpartum progression to type 2 diabetes mellitus (T2DM).

Objective: This was a retrospective cohort study that aimed to determine whether fetal sex influences the natural history of maternal risk of diabetes after delivery and in a subsequent pregnancy.

Setting: Population-based administrative databases in Ontario, Canada.

Patients: All women with a singleton live-birth first pregnancy between April 2000 and March 2010 (n = 642,987).

Exposure: Fetal sex (313,280 delivered a girl; 329,707 delivered a boy).

Main Outcome Measure: Development of T2DM or a second pregnancy. Glucose tolerance in each pregnancy was classified as either GDM or non-GDM.

Results: The population was followed for a median of 3.8 years. Carrying a boy yielded a higher risk of GDM in both the first pregnancy (odds ratio [OR] = 1.03; 95% confidence interval [CI], 1.0002–1.054) and second pregnancy (OR = 1.04, 95% CI, 1.01–1.08). For women with GDM in the first pregnancy, the likelihood of developing T2DM before a second pregnancy was higher if they delivered a girl (OR = 1.07; 95% CI, 1.01–1.12). Recurrence of GDM was not affected by fetal sex (P = .7). However, among women with a non-GDM first pregnancy while carrying a girl, having a boy in their second pregnancy predicted an increased risk of GDM (OR = 1.07, 95% CI, 1.01–1.14).

Conclusions: Fetal sex is a previously unrecognized factor that is associated with maternal diabetic risk both after delivery and in a subsequent pregnancy.

Gestational diabetes mellitus (GDM) arises in women who have a defect in pancreatic β-cell function such that they are unable to secrete sufficient insulin to fully compensate for the insulin resistance of the latter half of pregnancy, resulting in antepartum hyperglycemia (1, 2). Although blood glucose levels in women with GDM typically normalize immediately after delivery owing to abatement of the insulin resistance of pregnancy, this β-cell defect nevertheless persists (3–6). Furthermore, in many women with GDM, β-cell function begins to decline within the first year postpartum (4) and continues to do so in the years thereafter (5, 6), thereby ultimately driving the high risk of progression to type 2 diabetes mellitus (T2DM) seen in this patient population (7, 8).
Thus, although its mechanistic basis is not fully understood, β-cell dysfunction plays a central role in the pathophysiology of both GDM and the subsequent development of T2DM (1, 2).

Interestingly, it has recently emerged that the presence of a male fetus is associated with poorer maternal β-cell function in pregnancy (9), thereby providing a pathophysiologic basis for previous studies showing that women who are carrying a boy have a higher risk of GDM (9–13). Given the central role of β-cell dysfunction in determining a woman’s risk of GDM and T2DM, we hypothesized that this previously unsuspected effect of the fetus on maternal β-cell function potentially could hold implications for the natural history of maternal diabetic risk after delivery and in a subsequent pregnancy. Specifically, whether it affects β-cell function only during the pregnancy or its natural history after delivery as well, the sex of the fetus could be associated with the risk of postpartum progression to T2DM and with the likelihood of having GDM in a second pregnancy. Thus, in this study, we sought to address the following three research questions: 1) the effect of fetal sex in a first pregnancy on the likelihood that a woman will develop diabetes before her next pregnancy; 2) the effect of fetal sex in a second pregnancy on the risk of recurrence of GDM; and 3) whether the relationship between fetal sex and glucose tolerance status in her first pregnancy holds implications for their relationship in a woman’s second pregnancy.

Materials and Methods

We conducted a population-based retrospective cohort study using population-level healthcare databases from the Ministry of Health and Long-Term Care of Ontario (Canada). These databases track hospital discharge abstracts, physician service claims, and demographic data for all residents of Ontario, which is the most populous province of Canada. Because Ontario has a single-payer universal healthcare system, these data capture virtually all healthcare received by residents of the province. Individuals are linked between all data sources through a unique, virtually all healthcare received by residents of the province. Individuals are linked between all data sources through a unique and reproducibly-encrypted health card number. The Ontario Diabetes Database is a validated registry of physician-diagnosed nongestational diabetes that is identified using these administrative data (14). The study was approved by the Institutional Review Board of Sunnybrook Health Sciences Centre.

The study population consisted of all women age 15–49 years inclusive, who had a singleton first pregnancy with live-birth delivery between April 2000 and March 2010 and did not have pregravid diabetes. First pregnancies were identified using an 8-year look-back window. GDM was identified if a woman without pregestational diabetes had diabetes coded on the delivery record. All women were followed until March 2013 for 1) a subsequent singleton pregnancy and its corresponding glucose tolerance status (GDM or non-GDM), 2) the development of diabetes outside of pregnancy (identified using a validated algorithm based on hospitalization and physician service claims (14), or 3) another censoring event (death or multiple gestation pregnancy).

Statistical analyses were performed using SAS version 9.3. To determine the effect of fetal sex in the first pregnancy on the likelihood of developing diabetes, a Cox proportional hazards regression model was used with censoring at second pregnancy, death, or the end of followup. The model was adjusted for maternal age, socioeconomic status (measured ecologically as the neighborhood household income, divided into province-wide quintiles), and region of residence (urban/rural). This model was applied in both the entire cohort and after stratification based on GDM status. Among those women who had a second singleton pregnancy, logistic regression was used to determine the effect of fetal sex in the second pregnancy on GDM status in that pregnancy, adjusting for maternal age, socioeconomic status, and region of residence. This model was applied 1) in the entire cohort, 2) when stratifying on GDM status of the first pregnancy, and 3) when stratifying on GDM status and fetal sex of the first pregnancy.

Results

Table 1 shows the demographic and clinical characteristics of the 642,987 women composing the study population. There were 313,280 women who delivered a boy and 329,707 who delivered a girl. Women who delivered a boy had a higher risk of GDM (OR = 1.03; 95% confidence interval [CI], 1.0002–1.054). Figure 1 shows the temporal sequence of subsequent second pregnancies and the development of diabetes in the study population over median followup of 3.8 years. During this time, there were 16,272 women who were diagnosed with diabetes before any subsequent pregnancy.

Research question 1: Effect of fetal sex in first pregnancy on the likelihood that a woman will develop diabetes before her next pregnancy

Table 2 shows the relationship between the sex of the baby in her first pregnancy and the likelihood that a
woman would develop diabetes before any further pregnancy. The sex of the baby in the first pregnancy was not associated with the risk of developing diabetes before a subsequent pregnancy in the entire study population (P = .3) or in the women who did not have GDM (P = .6). However, in the 23,302 women who had GDM in their first pregnancy, the likelihood of developing diabetes before a second pregnancy was higher if they had a girl (OR = 1.07; 95% CI, 1.01–1.12; P = .02). This relationship was unchanged upon adjustment for maternal age, income, and region of residence (OR = 1.07; 95% CI, 1.01–1.13; P = .02).

**Research question 2: Effect of fetal sex in second pregnancy on recurrence of GDM**

There were 366,419 women who had a second pregnancy without developing known diabetes in the interim. As shown in Table 3, the presence of a male fetus in the

### Table 2. Hazard Ratios for the Development of Diabetes before a Second Pregnancy for (Exposure) Delivery of a Girl in First Pregnancy

<table>
<thead>
<tr>
<th>First Pregnancy</th>
<th>Unadjusted</th>
<th></th>
<th></th>
<th>Adjusted</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR(^a)</td>
<td>95% CI</td>
<td>P</td>
<td>HR(^a)</td>
<td>95% CI</td>
<td>P</td>
</tr>
<tr>
<td>All</td>
<td>1.02</td>
<td>0.98–1.05</td>
<td>.3</td>
<td>1.02</td>
<td>0.99–1.05</td>
<td>.3</td>
</tr>
<tr>
<td>Non-GDM</td>
<td>1.01</td>
<td>0.97–1.05</td>
<td>.6</td>
<td>1.01</td>
<td>0.97–1.05</td>
<td>.6</td>
</tr>
<tr>
<td>GDM</td>
<td>1.07</td>
<td>1.01–1.12</td>
<td>.02</td>
<td>1.07</td>
<td>1.01–1.13</td>
<td>.01</td>
</tr>
</tbody>
</table>

Abbreviation: HR, hazard ratio.

\(^a\) Reference: delivery of boy in first pregnancy.
second pregnancy was associated with an increased likelihood of GDM in the entire study population (OR = 1.04; 95% CI, 1.01–1.08) and in the women who did not have GDM in their first pregnancy (OR = 1.07; 95% CI, 1.02–1.11). These findings were unchanged with adjustment for age, income, and region of residence (Table 3). In contrast, however, in women who had GDM in their first pregnancy, having a boy in the second pregnancy was not associated with the likelihood of recurrence of GDM (OR = 1.02; 95% CI, 0.93–1.11; P = .7).

Research question 3: Effect of the relationship between fetal sex and glucose tolerance status in her first pregnancy on their relationship in a woman’s second pregnancy

Having established that both fetal sex and GDM are relevant to diabetic risk, we postulated that combined consideration of both the sex of the baby and glucose tolerance status (GDM/non-GDM) in her first pregnancy may provide enhanced insight into a woman’s underlying β-cell function and thereby hold implications for the relationship between fetal sex and risk of GDM in her second pregnancy. Table 4 shows the effect of fetal sex on the risk of GDM in the second pregnancy, after stratifying women according to the sex of the baby and glucose tolerance status in the first pregnancy. Among women whose first pregnancy was complicated by GDM, fetal sex in the second pregnancy was not associated with the recurrence of GDM whether the mother had delivered a boy in her first pregnancy (P = .9) or a girl (P = .5). In women who had a non-GDM first pregnancy with a male baby, having a boy in the second pregnancy was associated with the risk of GDM at only borderline significance (OR = 1.06; 95% CI, 1.00–1.12; P = .06). In contrast, among women with a non-GDM first gestation while carrying a girl, having a boy in their next pregnancy predicted an increased risk of GDM in that pregnancy (OR = 1.07; 95% CI, 1.01–1.14; P = .02). These findings were unchanged upon covariate adjustment (Table 4). Thus, the sex of the baby in a non-GDM first pregnancy can hold implications for the association between fetal sex and risk of GDM in the second pregnancy.

Discussion

In this study, we demonstrate that the sex of the baby and her glucose tolerance status in pregnancy can together provide insight into a woman’s diabetic risk after delivery and in a subsequent pregnancy. Specifically, in women with GDM, the delivery of a girl is associated with a higher risk of early progression to T2DM, compared with having a boy. Although carrying a male fetus is associated with an elevated risk of GDM overall, it does not increase the likelihood of recurrence of GDM. Instead, in women with a non-GDM first pregnancy, the increased risk of GDM conferred by a male fetus in a subsequent pregnancy is particularly evident in those who previously delivered a girl. Taken together, these data show that fetal sex is a factor that is associated with the natural history of maternal diabetic risk both after delivery and in a subsequent pregnancy.

Although several previous studies have reported an increased risk of GDM in pregnant women who are carrying

![Table 3. Odds Ratios for GDM in the Second Pregnancy Associated With (Exposure) Carrying a Boy, in Relation to Glucose Tolerance Status in the First Pregnancy](image)

![Table 4. Odds Ratios for GDM in the Second Pregnancy Associated With (Exposure) Carrying a Boy, in Relation to Both Glucose Tolerance and Sex of the Baby in the First Pregnancy](image)

\( ^a \) Reference: carrying a girl in second pregnancy.
a boy (8–12), the current study in over 600,000 women is, to our knowledge, the largest such demonstration to date. Importantly, it has recently been shown that the pathophysiologic basis for the effect of fetal sex on the risk of GDM is an adverse effect of a male fetus (compared with female) on maternal β-cell function in pregnancy (8). This pivotal observation may reconcile the findings of the current study as well.

Figure 2 is a schematic showing how the effect of a male fetus on maternal β-cell function may relate to the current findings. Notably, the development of GDM while carrying a girl while carrying a boy. Because of the negative effect of the male fetus on maternal β-cell function in pregnancy, the woman who delivered the girl would be expected to have the comparatively lower level of β-cell function outside of pregnancy, which would then manifest in her observed higher risk of early progression to type 2 diabetes. B, Schematic comparing β-cell function between the first and second pregnancies in a woman who had a non-GDM first pregnancy while carrying a girl and a GDM second pregnancy while carrying a boy. In her second pregnancy, the adverse effect of the male fetus lowers her β-cell function below an arbitrary threshold such that she will now develop GDM (a threshold that she surpasses in her previous non-GDM pregnancy while carrying a girl).

Several previous studies have reported that GDM recurs in ~40% of affected women (15–21), consistent with the recurrence rate of 39.5% observed in the current study. As such, there has been considerable interest in the identification of predictors of recurrence in this patient population, with previous studies suggesting a variety of potential factors including maternal ethnicity, age, obesity, hypertension, infant birth weight, postpartum maternal dysglycemia, parity, interpregnancy interval, and dietary fat intake (15–20, 22). Of note, a systematic review reported that only nonwhite ethnicity has been consistently predictive of recurrence across studies (23). In this context, the current study extends this literature by evaluating fetal sex as a potential determinant that has not who develop GDM while carrying a girl to have the higher risk of early progression to T2DM before a subsequent pregnancy, as observed in Research Question 1. With this model, the development of GDM in the presence of a female fetus (as compared with a male) would represent a marker of comparatively poorer maternal β-cell function, which then drives an enhanced risk of subsequent early progression to T2DM.

The same model may apply to the effect of fetal sex on the risk of GDM in a subsequent pregnancy. Specifically, among women with a non-GDM first pregnancy while carrying a girl, one would expect there to be a subset in which the potential adverse effect of a male fetus on their β-cell function would have otherwise been sufficient to cause GDM (had they been carrying a boy). In that patient population, carrying a male fetus in a subsequent pregnancy would be expected to yield an increased risk of GDM, as observed in Research Question 3 (Figure 2B). Although this model cannot be confirmed with the current data (owing to the absence of measurement of β-cell function within the provincial administrative data sources that track clinical care), it nevertheless provides a unifying pathophysiologic basis for the findings of this study and warrants direct evaluation with assessment of β-cell function in future research studies.
been previously considered. We show that, whereas carrying a male baby was associated with an increased risk of GDM in women who did not have GDM in their first pregnancy, it was not predictive of recurrence in women with a history of GDM in this cohort (Research Question 2). It is possible that, following the early postpartum deterioration of β-cell function that takes place after an initial GDM pregnancy (4, 6, 24), maternal insulin secretory capacity is generally reduced to an extent where the modest effect of a male fetus is no longer relevant to the recurrence of GDM, although this basis remains speculative at this time.

As noted earlier, the absence of measurement of β-cell function is a limitation of this study that otherwise may have provided relevant insight into the mechanistic basis of our findings. Another limitation also associated with the nature of the administrative data sources is the absence of information on maternal obesity and ethnicity, as factors that may be relevant to both the fetus and diabetic risk. Conversely, however, a strength of this study is its population-based design (consisting of the entire maternal population of Canada’s largest province) and longitudinal followup over time, which has enabled this comprehensive evaluation of the effect of fetal sex on maternal diabetic risk both during pregnancies and between them. Indeed, in implicating fetal sex in this context, our findings pertaining to this novel research objective should lead to additional studies. Specifically, studies evaluating glucose tolerance and its determinants in women during and after pregnancy should consider the potential effect of fetal sex (particularly if not measuring β-cell function).

In summary, sex of the baby and maternal GDM status can together provide insight into a woman’s risk of diabetes after delivery and in a subsequent pregnancy. First, in women with GDM, delivery of a girl is associated with a higher risk of early progression to T2DM, compared with having a boy. Second, carrying a male fetus is associated with an increased risk of GDM overall but does not increase the likelihood of its recurrence in a second pregnancy. Third, in women with a non-GDM first pregnancy, the increased risk of GDM associated with a male fetus in a subsequent pregnancy is particularly evident in those who previously delivered a girl. Fetal sex thus emerges as a previously unrecognized factor associated with the natural history of maternal diabetic risk both after delivery and in a subsequent pregnancy.

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