Fetal Sex and Maternal Risk of Gestational Diabetes Mellitus: The Impact of Having a Boy

DOI: 10.2337/dc14-2551

OBJECTIVE

Retrospective analyses of perinatal databases have raised the intriguing possibility of an increased risk of gestational diabetes mellitus (GDM) in women carrying a male fetus, but it has been unclear if this was a spurious association. We thus sought to evaluate the relationship between fetal sex and maternal glucose metabolism in a well-characterized cohort of women reflecting the full spectrum of gestational glucose tolerance from normal to mildly abnormal to GDM.

RESEARCH DESIGN AND METHODS

A total of 1,074 pregnant women underwent metabolic characterization, including oral glucose tolerance test (OGTT), at mean 29.5 weeks gestation. The prevalence of GDM, its pathophysiologic determinants (β-cell function and insulin sensitivity/resistance), and its clinical risk factors were compared between women carrying a female fetus (n = 534) and those carrying a male fetus (n = 540).

RESULTS

Women carrying a male fetus had lower mean adjusted β-cell function (insulinogenic index divided by HOMA of insulin resistance: 9.4 vs. 10.5, P = 0.007) and higher mean adjusted blood glucose at 30 min (P = 0.025), 1 h (P = 0.004) and 2 h (P = 0.02) during the OGTT, as compared with those carrying a female fetus. Furthermore, women carrying a male fetus had higher odds of developing GDM (odds ratio 1.39 [95% CI 1.01–1.90]). Indeed, male fetus further increased the relative risk of GDM conferred by the classical risk factors of maternal age >35 years and nonwhite ethnicity by 47 and 51%, respectively.

CONCLUSIONS

Male fetus is associated with poorer β-cell function, higher postprandial glycemia, and an increased risk of GDM in the mother. Thus, fetal sex potentially may influence maternal glucose metabolism in pregnancy.

Fetal sex has been associated with differential risks of perinatal outcomes. Specifically, it has long been recognized that the presence of a male fetus carries increased risks of adverse outcomes, including preterm delivery, premature rupture of membranes, umbilical cord prolapse, true umbilical cord knot, failure to progress in the first and second stages of labor, non reassuring fetal heart rate patterns, Cesarean delivery, and lower Apgar scores (1,2). Although the mechanisms by which male sex may contribute to these events are not clearly understood, it seems probable that these outcomes relate primarily to biological factors determined by the fetus. In contrast, however, different pathophysiologic effects would likely need to be

1Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, Ontario, Canada
2Division of Endocrinology, University of Toronto, Toronto, Ontario, Canada
3Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Ontario, Canada
4Department of Nutritional Sciences, University of Toronto, Toronto, Ontario, Canada
5Keenan Research Centre for Biomedical Science of St. Michael’s Hospital, Toronto, Ontario, Canada
6Division of Obstetrics and Gynecology, Mount Sinai Hospital, Toronto, Ontario, Canada

Corresponding author: Ravi Retnakaran, rretnakaran@mtsini.on.ca.

Received 27 October 2014 and accepted 14 January 2015.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-2551/-/DC1.

© 2015 by the American Diabetes Association.

Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.

Diabetes Care Publish Ahead of Print, published online February 18, 2015
invoked to explain intriguing observations from retrospective analyses of perinatal databases suggesting that the presence of a male fetus may be associated with an increased incidence of gestational diabetes mellitus (GDM) in the mother (1–5). Indeed, the pathophysiologic basis of GDM is maternal pancreatic β-cell dysfunction, which is defined as the inability of the β-cells to secrete enough insulin to fully compensate for the physiologic insulin resistance of late pregnancy, thereby resulting in the hyperglycemia by which GDM is diagnosed (6). Furthermore, as compared with their peers, women with GDM have chronic insulin resistance that is present both before and after the pregnancy (7,8). In this context, it is difficult to understand how the sex of the fetus could increase the risk of GDM, raising the possibility that the previous retrospective analyses may have noted a spurious association. Thus, our objective in this study was to systematically evaluate the relationship between fetal sex and maternal glucose metabolism in a well-characterized cohort of women reflecting the full spectrum of glucose tolerance in pregnancy.

RESEARCH DESIGN AND METHODS

The study population consisted of women participating in a prospective observational cohort at our institution, in which pregnant women are recruited at the time of antepartum screening for GDM and undergo metabolic characterization. The protocol for this cohort has been described in detail previously (9). At our institution, all pregnant women are screened for GDM by 50-g glucose challenge test (GCT) in late second trimester, followed by referral for diagnostic oral glucose tolerance test (OGTT) if the GCT is abnormal (blood glucose ≥7.8 mmol/L at 1-h postchallenge). For the cohort study, women are recruited either before or after the GCT, and all participants then undergo a 3-h 100-g OGTT for determination of GDM status (regardless of the GCT result). As previously described (9), the recruitment of women after an abnormal GCT serves to enrich the study population with those with varying degrees of glucose intolerance. The resultant cohort thus reflects the full spectrum of glucose tolerance in pregnancy from normal to mildly abnormal to GDM, as determined on the OGTT. Metabolic characterization is performed during this OGTT, including the assessment of insulin sensitivity/resistance and pancreatic β-cell function. The protocol has been approved by the Mount Sinai Hospital Research Ethics Board, and all women have provided written informed consent for their participation. The current analysis was restricted to women with singleton pregnancies who underwent their OGTT between 24 and 34 weeks gestation inclusive (n = 1,074).

Assessment of Participants

On the morning of the OGTT, interviewer-administered questionnaires were completed pertaining to medical, obstetrical, and family history. Pregravid physical activity in the year before pregnancy was assessed using the Baecke questionnaire, a validated instrument that measures total physical activity and its three component domains: occupation-associated activity (work index), sport-related physical activity (sport index), and nonsport leisure-time activity (leisure-time index) (10,11). This questionnaire was completed during the OGTT (prior to knowledge of gestational glucose tolerance status). The OGTT enabled classification of glucose tolerance status as follows:

1. GDM, defined by National Diabetes Data Group (NDDG) criteria (12), which require at least two of the following on the OGTT: fasting blood glucose ≥5.8 mmol/L, 1-h glucose ≥10.6 mmol/L, 2-h blood glucose ≥9.2 mmol/L, or 3-h blood glucose ≥8.1 mmol/L;
2. gestational impaired glucose tolerance, defined by meeting only one of the above NDDG criteria; or
3. normal glucose tolerance, defined by meeting none of the NDDG criteria.

Women diagnosed with GDM were referred to a specialized diabetes in pregnancy clinic, where they received glucose-lowering treatment consisting of dietary/lifestyle counseling ± antepartum insulin therapy.

Data at delivery were obtained from the labor and delivery database at our institution. These data included total length of gestation, infant birth weight, sex, mode of delivery, and Apgar scores.

Laboratory Measurements and Physiologic Indices

All OGTTs were performed in the morning after overnight fast, with venous blood samples drawn for the measurement of glucose and specific insulin at fasting and at 30, 60, 120, and 180 min following the ingestion of the 100-g glucose load. Specific insulin was measured with the Roche Elecsys 1010 Immunoassay analyzer and electrochemiluminescence immunoassay kit (Roche Diagnostics, Laval, Canada). In 742 women, lipids (cholesterol, triglycerides, apolipoprotein B [apoB], and apoA1), leptin, adiponectin, and C-reactive protein (CRP) were measured from fasting serum, as previously described (9).

Area under the glucose curve on the OGTT (AUCglyc) was calculated by trapezoidal rule. Insulin sensitivity was measured on the OGTT with the Matsuda index, an established measure of whole-body insulin sensitivity that has been validated against the euglycemic-hyperinsulinemic clamp (13). Insulin resistance was assessed with HOMA (HOMA-IR), as described by Matthews et al. (14). Pancreatic β-cell function was assessed with the insulinogenic index divided by HOMA-IR (insulinogenic index/HOMA-IR), a well-established measure that has been widely used in previous studies (15,16) and defined as the incremental change in insulin between 0 and 30 min divided by the incremental change in glucose over the same interval, divided by HOMA-IR. β-Cell function was also assessed with the Insulin Secretion Sensitivity Index 2 (ISSI-2), calculated as previously described (15–18).

Statistical Analyses

All analyses were conducted using SAS 9.2 (SAS Institute, Cary, NC). Continuous variables were tested for normality of distribution, and natural log transformations of skewed variables were used, where necessary, in subsequent analyses. Variables with approximately normal distributions are presented as mean ± SD, and those with skewed distributions are presented as median and interquartile range (25th–75th percentile). The characteristics of women carrying a female fetus were compared with those of women carrying a male fetus, using two-sample Student t test for continuous variables and either χ² test or Fisher exact test for categorical variables (Table 1). Mean
adjusted glucose levels at each time point of the OGTT, mean adjusted insulin sensitivity (Matsuda index), and mean adjusted β-cell function (insulinogenic index/HOMA-IR) were obtained from multiple linear regression models and compared between the women carrying girls and those carrying boys (Fig. 1A–C). After adjustment for the following covariates: weeks gestation at the OGTT, risk factors for GDM (age, ethnicity, family history of diabetes, prepregnancy BMI, and lipids, leptin, adiponectin, and CRP were measured in 742 women.

Table 1—Comparison of women carrying male fetus versus women carrying female fetus

<table>
<thead>
<tr>
<th>At OGTT in pregnancy</th>
<th>Women with female fetus (n = 534)</th>
<th>Women with male fetus (n = 540)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks gestation at OGTT (weeks) 29.6 ± 2.2</td>
<td>29.5 ± 2.1</td>
<td>0.652</td>
<td></td>
</tr>
<tr>
<td>Maternal age (years) 33.8 ± 4.5</td>
<td>33.6 ± 4.4</td>
<td>0.380</td>
<td></td>
</tr>
<tr>
<td>Ethnicity (%) 0.798</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>68.9</td>
<td>70.0</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>12.6</td>
<td>13.9</td>
<td></td>
</tr>
<tr>
<td>South Asian</td>
<td>5.2</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>5.2</td>
<td>5.2</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>8.1</td>
<td>6.7</td>
<td></td>
</tr>
<tr>
<td>Family history of type 2 diabetes (%) 49.9</td>
<td>51.3</td>
<td>0.649</td>
<td></td>
</tr>
<tr>
<td>Parity (%) 0.401</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>53.2</td>
<td>56.5</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>35.2</td>
<td>34.1</td>
<td></td>
</tr>
<tr>
<td>&gt;1</td>
<td>11.6</td>
<td>9.4</td>
<td></td>
</tr>
<tr>
<td>Pregravid physical activity 7.67 ± 1.29</td>
<td>7.66 ± 1.26</td>
<td>0.915</td>
<td></td>
</tr>
<tr>
<td>Work index 2.39 ± 0.61</td>
<td>2.44 ± 0.65</td>
<td>0.187</td>
<td></td>
</tr>
<tr>
<td>Sport index 2.27 ± 0.76</td>
<td>2.25 ± 0.72</td>
<td>0.542</td>
<td></td>
</tr>
<tr>
<td>Nonsport leisure-time index 3.01 ± 0.59</td>
<td>2.99 ± 0.61</td>
<td>0.587</td>
<td></td>
</tr>
<tr>
<td>Current smoking (%) 2.8 1.9 0.296</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prepregnancy BMI (kg/m2) 23.5 (21.3–27.5)</td>
<td>23.4 (21.0–27.3)</td>
<td>0.283</td>
<td></td>
</tr>
<tr>
<td>Pregnancy weight gain up to OGTT (kg) 10.5 ± 5.1</td>
<td>10.6 ± 5.5</td>
<td>0.889</td>
<td></td>
</tr>
<tr>
<td>GCT (mmol/L) 8.1 ± 1.3</td>
<td>8.3 ± 1.3</td>
<td><strong>0.001</strong></td>
<td></td>
</tr>
<tr>
<td>Glucose levels on OGTT Fasting glucose (mmol/L) 4.5 ± 0.5</td>
<td>4.6 ± 0.6</td>
<td>0.091</td>
<td></td>
</tr>
<tr>
<td>30-min glucose (mmol/L) 8.1 ± 1.3</td>
<td>8.2 ± 1.4</td>
<td><strong>0.047</strong></td>
<td></td>
</tr>
<tr>
<td>1-h glucose (mmol/L) 9.1 ± 1.8</td>
<td>9.4 ± 1.8</td>
<td><strong>0.016</strong></td>
<td></td>
</tr>
<tr>
<td>2-h glucose (mmol/L) 8.0 ± 1.6</td>
<td>8.2 ± 1.7</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>3-h glucose (mmol/L) 6.6 ± 1.6</td>
<td>6.6 ± 1.7</td>
<td>0.929</td>
<td></td>
</tr>
<tr>
<td>AUCglucose (mmol/L × h) 22.6 ± 3.6</td>
<td>23.1 ± 3.9</td>
<td><strong>0.034</strong></td>
<td></td>
</tr>
<tr>
<td>Glucose tolerance on OGTT Normal glucose tolerance (%) 63.9</td>
<td>58.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gestational impaired glucose tolerance (%) 17.4</td>
<td>18.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM (%) 18.7</td>
<td>22.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin sensitivity/resistance Matsuda index 4.4 (2.9–6.3)</td>
<td>4.4 (2.8–6.3)</td>
<td>0.685</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR 1.8 (1.2–2.7)</td>
<td>1.7 (1.1–2.8)</td>
<td>0.925</td>
<td></td>
</tr>
<tr>
<td>β-Cell function Insulinogenic index/HOMA-IR 10.3 (6.9–15.8)</td>
<td>10.0 (6.0–15.1)</td>
<td><strong>0.018</strong></td>
<td></td>
</tr>
<tr>
<td>ISSI-2 734.2 (577.1–913.8)</td>
<td>720.9 (559.7–908.5)</td>
<td>0.215</td>
<td></td>
</tr>
<tr>
<td>Lipids* Total cholesterol (mmol/L) 6.45 ± 1.20</td>
<td>6.33 ± 1.22</td>
<td>0.209</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L) 3.63 ± 1.13</td>
<td>3.56 ± 1.11</td>
<td>0.411</td>
<td></td>
</tr>
<tr>
<td>HDL cholesterol (mmol/L) 1.70 ± 0.36</td>
<td>1.70 ± 0.37</td>
<td>0.918</td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/L) 2.48 ± 0.73</td>
<td>2.43 ± 0.83</td>
<td>0.408</td>
<td></td>
</tr>
<tr>
<td>ApoB (g/L) 1.29 ± 0.30</td>
<td>1.26 ± 0.29</td>
<td>0.227</td>
<td></td>
</tr>
<tr>
<td>ApoA1 (mmol/L) 2.11 ± 0.30</td>
<td>2.09 ± 0.29</td>
<td>0.348</td>
<td></td>
</tr>
<tr>
<td>Leptin (ng/ml)* 35.6 (23.5–49.8)</td>
<td>34.6 (24.3–47.5)</td>
<td>0.804</td>
<td></td>
</tr>
<tr>
<td>Adiponectin (µg/mL)* 7.7 ± 2.7</td>
<td>7.9 ± 3.0</td>
<td>0.361</td>
<td></td>
</tr>
<tr>
<td>CRP (mg/L)* 4.4 (2.5–7.4)</td>
<td>4.5 (2.4–7.8)</td>
<td>0.844</td>
<td></td>
</tr>
</tbody>
</table>

At delivery Total length of gestation (weeks) 39.1 ± 1.6 | 39.0 ± 1.6 | 0.225 |
| Infant birth weight (g) 3,315.5 ± 519.4 | 3,400.5 ± 537.1 | **0.009** |
| Cesarean delivery (%) 37.8 | 37.0 | 0.779 |
| Apgar <7 at 1 min (%) 5.4 | 7.2 | 0.223 |
| Apgar <7 at 5 min (%) 0.8 | 0.6 | 0.724 |

Data for continuous variables are mean ± SD, except for prepregnancy BMI, Matsuda index, HOMA-IR, insulinogenic index/HOMA-IR, ISSI-2, leptin, and CRP, which are median (interquartile range). Categorical variables are presented as percentages. P values refer to the overall difference across groups as derived from two-sample Student t test for continuous variables and either χ² test or Fisher exact test for categorical variables. Bold font indicates P < 0.05. *Lipids, leptin, adiponectin, and CRP were measured in 742 women.
and weight gain in pregnancy), and infant birth weight (which provided a surrogate measure to account for the potential effect of fetal size). Logistic regression of dependent variable GDM was performed with the same covariates (Table 2). Post hoc power calculation showed that a sample size of 1,074 women yielded >95% power to detect an odds ratio (OR) of 1.39, in the setting of 18.7% prevalence of GDM in women carrying a female fetus, when adjusting for weeks gestation at OGTT, maternal age, ethnicity, family history of diabetes, prepregnancy BMI, weight gain in pregnancy up to the OGTT, and infant birth weight.

To test for biological interaction between fetal sex and the classical risk factors for GDM (maternal age >35 years, nonwhite ethnicity, family history of diabetes, and prepregnancy BMI >25 kg/m²), we used the equation described by Rothman (19) and others (20–22) to determine whether the combined impact of male fetus and each of these risk factors on the likelihood of GDM exceeded the sum of their individual effects alone (Table 3 and Fig. 2). With this approach (20–22), the following three measures of biological interaction are calculated to quantify the amount of interaction: the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (S). RERI can be interpreted as the risk that is additional to that which is to be expected on the basis of addition of the ORs under exposure,
calculated as the difference between the expected risk and the observed risk \((\text{RERI} = \text{OR}_{12} - \text{OR}_1 - \text{OR}_2 + 1)\). \(\text{AP}\) can be interpreted as the proportion of disease that is due to interaction among people with both exposures \((\text{AP} = \text{RERI}/\text{OR}_{12})\). \(S\) can be interpreted as the excess ease that is due to interaction among people without both exposures \((S = [\text{OR}_{12} - \text{OR}_1 - \text{OR}_2 + 1])\). As previously described \((19,20)\), \(\text{RERI} = 0\), \(\text{AP} = 0\), and \(S = 1\) indicate the absence of biological interaction.

**RESULTS**

**Comparison of Women Carrying Female Versus Male Fetus**

Table 1 shows the study population of 1,074 pregnant women, stratified into those carrying a female fetus \((n = 534)\) and those carrying a male fetus \((n = 540)\). There were no significant differences between the groups with respect to the major clinical risk factors for GDM: maternal age, ethnicity, family history of diabetes, and maternal weight (prepregnancy BMI and weight gain in pregnancy). There were also no significant differences in parity, smoking status, and pregravid physical activity in the year before the pregnancy. However, despite the absence of differences in clinical risk factors, the blood glucose response to the 50-g GCT was higher in women carrying a male fetus than in those carrying a girl (mean 8.3 vs. 8.1 mmol/L, \(P = 0.001\)). Furthermore, during the OGTT, women carrying boys had higher glucose levels than their peers at 30 min \((P = 0.047\), 1 h \((P = 0.016\), and 2 h \((P = 0.055)\) postchallenge, yielding an overall greater AUC_{glucose} \(P = 0.034\). Women carrying boys had a higher prevalence of GDM on the OGTT than those carrying girls \((22.2\% \text{ vs. } 18.7\%)\), but this difference in glucose tolerance status did not reach significance \((P = 0.22)\).

We next evaluated metabolic factors that may be relevant to glucose tolerance. Insulin sensitivity (Matsuda index) and insulin resistance (HOMA-IR) did not differ significantly between the groups. However, \(\beta\)-cell function, as measured by the insulinogenic index/HOMA-IR, was lower in women carrying a male fetus than in those with a girl \((P = 0.018)\). Other metabolic factors, including lipid profile, leptin, adiponectin, and CRP, did not differ significantly between the groups.

At delivery, birth weight was higher in boys than in girls, as expected \((P = 0.009)\). Otherwise, there were no significant differences between the groups in total length of gestation, rates of Caesarean delivery, and Apgar scores at 1 and 5 min.

**Adjusted Analyses**

To assess for an independent association between fetal sex and maternal glucose metabolism, we compared the two groups with respect to mean glucose levels at each time point of the OGTT, after adjustment for the following covariates: weeks gestation at the OGTT, risk factors for GDM (age, ethnicity, family history of diabetes, prepregnancy BMI, and weight gain in pregnancy up to the OGTT), and infant birth weight (i.e., to account for fetal size). As shown in Fig. 1A, women carrying a male fetus had a higher mean adjusted blood glucose than those carrying a female at each of 30 min \((P = 0.025)\), 1 h \((P = 0.004)\), and 2 h \((P = 0.02)\) during the OGTT. Mean adjusted insulin levels are shown in Supplementary Fig. 1. There was no significant difference between the groups in mean adjusted insulin sensitivity (Matsuda index \(P = 0.24\) (Fig. 1B) or insulin resistance (HOMA-IR \(P = 0.44\) (data not shown). However, \(\beta\)-cell function differed between the groups, as women carrying a boy had a lower mean adjusted insulinogenic index/HOMA-IR than their peers \((P = 0.007)\) (Fig. 1C). They also had lower mean adjusted ISSI-2, although this difference did not reach statistical significance \((698.7 \text{ vs. } 721.9, P = 0.10)\) (data not shown).

On logistic regression analysis (Table 2), the classical risk factors of higher maternal age, ethnicity (Asian and South Asian), family history of diabetes, and greater prepregnancy BMI were significant predictors of GDM. Infant birth weight was inversely associated with GDM, reflecting the impact of the clinical treatment of the women diagnosed with this condition, as previously described \((15)\). Importantly, male fetus also emerged as a significant independent predictor of GDM (OR 1.39 [95% CI 1.01–1.90]).

**Interaction Between Male Fetus and Classical GDM Risk Factors**

To test for biological interaction between male fetus and classical risk factors for GDM (maternal age >35 years,
nonwhite ethnicity, family history of diabetes, and prepregnancy overweight/obesity), we investigated whether the combined impact of male fetus and each of these risk factors on the likelihood of GDM exceeded the sum of their individual effects. Interaction was detected between sex of the fetus and maternal age (Table 3). Indeed, the presence of maternal age > 35 years and male fetus conferred increments in the risk of GDM of 31.8 and 15.4%, respectively, as compared with the reference group (maternal age ≤ 35 years and female fetus). However, when both conditions were present, there was a 47.3% relative excess risk of GDM above and beyond the sum of these individual risks (Fig. 2A). Similarly, male fetus showed significant interaction with nonwhite ethnicity (Table 3), such that the combined effect with this risk factor was again greater than the sum of their individual risks (51.1% relative excess risk) (Fig. 2B). The analysis was equivocal as to whether there was interaction between male sex and family history of diabetes (Table 3), with only a very modest relative excess risk (Fig. 2C). With prepregnancy BMI, there was no interaction with male sex (RERI ~ 0, AP ~ 0, and S ~ 1) (Table 3), yielding no increase in relative risk with both factors combined (Fig. 2D). In addition, the findings from the analyses in Fig. 2A–C were unchanged with further adjustment for prepregnancy BMI (data not shown).

CONCLUSIONS

In this study, we demonstrate that the presence of a male fetus is associated with higher postprandial glycemia and modestly increased odds of GDM above and beyond the sum of these individual risks (51.1% relative excess risk) (Fig. 2B). The analysis was equivocal as to whether there was interaction between male sex and family history of diabetes (Table 3), with only a very modest relative excess risk (Fig. 2C). With prepregnancy BMI, there was no interaction with male sex (RERI ~ 0, AP ~ 0, and S ~ 1) (Table 3), yielding no increase in relative risk with both factors combined (Fig. 2D). In addition, the findings from the analyses in Fig. 2A–C were unchanged with further adjustment for prepregnancy BMI (data not shown).

CONCLUSIONS

In this study, we demonstrate that the presence of a male fetus is associated with higher postprandial glycemia and modestly increased odds of GDM above and beyond the sum of these individual risks (51.1% relative excess risk) (Fig. 2B). The analysis was equivocal as to whether there was interaction between male sex and family history of diabetes (Table 3), with only a very modest relative excess risk (Fig. 2C). With prepregnancy BMI, there was no interaction with male sex (RERI ~ 0, AP ~ 0, and S ~ 1) (Table 3), yielding no increase in relative risk with both factors combined (Fig. 2D). In addition, the findings from the analyses in Fig. 2A–C were unchanged with further adjustment for prepregnancy BMI (data not shown).

CONCLUSIONS

In this study, we demonstrate that the presence of a male fetus is associated with higher postprandial glycemia and modestly increased odds of GDM above and beyond the sum of these individual risks (51.1% relative excess risk) (Fig. 2B). The analysis was equivocal as to whether there was interaction between male sex and family history of diabetes (Table 3), with only a very modest relative excess risk (Fig. 2C). With prepregnancy BMI, there was no interaction with male sex (RERI ~ 0, AP ~ 0, and S ~ 1) (Table 3), yielding no increase in relative risk with both factors combined (Fig. 2D). In addition, the findings from the analyses in Fig. 2A–C were unchanged with further adjustment for prepregnancy BMI (data not shown).

CONCLUSIONS

In this study, we demonstrate that the presence of a male fetus is associated with higher postprandial glycemia and modestly increased odds of GDM above and beyond the sum of these individual risks (51.1% relative excess risk) (Fig. 2B). The analysis was equivocal as to whether there was interaction between male sex and family history of diabetes (Table 3), with only a very modest relative excess risk (Fig. 2C). With prepregnancy BMI, there was no interaction with male sex (RERI ~ 0, AP ~ 0, and S ~ 1) (Table 3), yielding no increase in relative risk with both factors combined (Fig. 2D). In addition, the findings from the analyses in Fig. 2A–C were unchanged with further adjustment for prepregnancy BMI (data not shown).

CONCLUSIONS

In this study, we demonstrate that the presence of a male fetus is associated with higher postprandial glycemia and modestly increased odds of GDM above and beyond the sum of these individual risks (51.1% relative excess risk) (Fig. 2B). The analysis was equivocal as to whether there was interaction between male sex and family history of diabetes (Table 3), with only a very modest relative excess risk (Fig. 2C). With prepregnancy BMI, there was no interaction with male sex (RERI ~ 0, AP ~ 0, and S ~ 1) (Table 3), yielding no increase in relative risk with both factors combined (Fig. 2D). In addition, the findings from the analyses in Fig. 2A–C were unchanged with further adjustment for prepregnancy BMI (data not shown).

CONCLUSIONS

In this study, we demonstrate that the presence of a male fetus is associated with higher postprandial glycemia and modestly increased odds of GDM above and beyond the sum of these individual risks (51.1% relative excess risk) (Fig. 2B). The analysis was equivocal as to whether there was interaction between male sex and family history of diabetes (Table 3), with only a very modest relative excess risk (Fig. 2C). With prepregnancy BMI, there was no interaction with male sex (RERI ~ 0, AP ~ 0, and S ~ 1) (Table 3), yielding no increase in relative risk with both factors combined (Fig. 2D). In addition, the findings from the analyses in Fig. 2A–C were unchanged with further adjustment for prepregnancy BMI (data not shown).

CONCLUSIONS

In this study, we demonstrate that the presence of a male fetus is associated with higher postprandial glycemia and modestly increased odds of GDM above and beyond the sum of these individual risks (51.1% relative excess risk) (Fig. 2B). The analysis was equivocal as to whether there was interaction between male sex and family history of diabetes (Table 3), with only a very modest relative excess risk (Fig. 2C). With prepregnancy BMI, there was no interaction with male sex (RERI ~ 0, AP ~ 0, and S ~ 1) (Table 3), yielding no increase in relative risk with both factors combined (Fig. 2D). In addition, the findings from the analyses in Fig. 2A–C were unchanged with further adjustment for prepregnancy BMI (data not shown).

CONCLUSIONS

In this study, we demonstrate that the presence of a male fetus is associated with higher postprandial glycemia and modestly increased odds of GDM above and beyond the sum of these individual risks (51.1% relative excess risk) (Fig. 2B). The analysis was equivocal as to whether there was interaction between male sex and family history of diabetes (Table 3), with only a very modest relative excess risk (Fig. 2C). With prepregnancy BMI, there was no interaction with male sex (RERI ~ 0, AP ~ 0, and S ~ 1) (Table 3), yielding no increase in relative risk with both factors combined (Fig. 2D). In addition, the findings from the analyses in Fig. 2A–C were unchanged with further adjustment for prepregnancy BMI (data not shown).

CONCLUSIONS

In this study, we demonstrate that the presence of a male fetus is associated with higher postprandial glycemia and modestly increased odds of GDM above and beyond the sum of these individual risks (51.1% relative excess risk) (Fig. 2B). The analysis was equivocal as to whether there was interaction between male sex and family history of diabetes (Table 3), with only a very modest relative excess risk (Fig. 2C). With prepregnancy BMI, there was no interaction with male sex (RERI ~ 0, AP ~ 0, and S ~ 1) (Table 3), yielding no increase in relative risk with both factors combined (Fig. 2D). In addition, the findings from the analyses in Fig. 2A–C were unchanged with further adjustment for prepregnancy BMI (data not shown).
of investigation and no adjustment for covariates was undertaken. Similarly, an evaluation of fetal sex ratios in a database of 288,009 women in California found a preponderance of males in GDM pregnancies (5). Against this background, the current study was designed to definitively address this question through detailed prospective assessment of glucose metabolism, its physiologic determinants (insulin sensitivity and β-cell function), and associated risk factors in a cohort of pregnant women.

With this design, we demonstrate that male fetus is indeed independently associated with higher odds of GDM after adjustment for classical risk factors. This increased risk is modest in its overall magnitude, as is apparent in 1) the logistic regression analysis (Table 2), 2) its lack of detection in clinical care and smaller studies, and 3) its previous detection only in very large databases. Furthermore, this modest increment in risk is also consistent with our demonstration that women carrying a male fetus have a small but clear increase in postchallenge glycemia, as compared with their peers (Fig. 1A). Nevertheless, magnitude notwithstanding, this robust evidence of a relationship between fetal sex and maternal glucose homeostasis holds important implications for our understanding of maternal-fetal physiology.

Although it is possible that specific maternal features may predispose to both the viability of a male fetus and the development of GDM (akin to the observation that interpregnancy weight gain may favor birth of a male fetus [23]), it appears more likely that the fetus may influence maternal metabolism. Although the effect of maternal physiology on fetal metabolism is well recognized, the current study supports the emerging concept of a bidirectional relationship wherein the mother and the fetus can each affect the metabolism of the other (24). A growing body of evidence is supportive of the concept of fetal influence on maternal physiology. First, it has been reported that women carrying a fetus with Beckwith-Wiedemann syndrome had more than twice the risk of developing gestational hypertension than when the same mothers carried unaffected siblings (25). Recently, Hocher et al. (26–28) have noted that fetal sex can have variable effects on maternal total glycated hemoglobin at delivery, depending on polymorphisms in diverse maternal genes, including the peroxisome proliferator-activated receptor γ-2, progesterone receptor, and angiotensin-converting enzyme. Remarkably, Hinckers (29) suggested in 1977 that there may be sex-specific interrelationships between the fetoplacental unit and maternal glucose metabolism based on his evaluation of blood glucose patterns from >1,700 intravenous glucose tolerance tests, which revealed more abnormal responses in women carrying a male fetus than in their peers. The current study now extends these observations by specifically showing a mild impairment of the postchallenge glycemic response to a physiologic oral load and demonstrating a resultant increased incidence of GDM in the presence of a male fetus.

The pathophysiologic basis of this relationship may be an impairment of maternal β-cell function, given the observed independent association between male fetus and lower insulinogenic index/HOMA-IR (Fig. 1C). For the maintenance of normal glucose homeostasis in pregnancy, maternal β-cells must compensate for the severe acquired insulin resistance of late gestation by markedly increasing their secretion of insulin. Although the mechanism of this compensation has not been fully elucidated, it is known to involve placental lactogens and prolactin acting through a series of downstream mediators (including the transcription factor FoxMI, the serotonin synthetic enzyme Tph1, and the cell cycle regulator menin), ultimately leading to the expansion of β-cell mass and enhanced insulin secretion (30). In this context, the current findings suggest that male fetuses is a previously unrecognized factor that may adversely affect the maternal β-cell compensatory response. Although the mechanism through which it may do so is unclear, one possibility is that a feature of the male fetus (possibly involving the Y chromosome) may impact the placental secretion of hormones or proteins involved in β-cell compensation. Of note, there have been previous reports of differential levels of maternal circulating hormones and proteins (including human placental lactogen and prolactin) in relation to fetal sex (31,32). Further study is now needed to determine whether there exist fetal sex-specific differentials in circulating levels of maternal factors that are associated with β-cell function and postprandial glycemia.

Strengths of this study include the large study population spanning the full spectrum of glucose tolerance undergoing detailed assessment of glucose metabolism, insulin sensitivity/resistance, β-cell function, and associated risk factors. A limitation is the absence of an absolute measurement of fetal size at the time of the OGTT. In this regard, infant birth weight has been used as a proxy measure to account for sex-specific size differences, although direct measurement at the OGTT (such as with ultrasound-based fetal measurement) would be preferable. Of note, fetal size has not been previously recognized as a determinant of GDM risk. We also do not have measurements of placental size, which potentially could be relevant to placental secretion of other factors beyond those measured in this study (such as tumor necrosis factor-α [33]) that may be associated with the observed fetal sex differentials. Another possible limitation is that the testing protocol and diagnostic criteria for GDM in this study may not be the same as those used at other institutions, thereby affecting the generalizability of our findings. However, the application of different glycemic thresholds for diagnosing GDM would not obscure our key demonstration of associations between fetal sex and maternal glycemia and β-cell function. Another limitation is the use of surrogate measures of insulin sensitivity/resistance and β-cell function, rather than clamp studies. However, their invasive time-consuming nature would have made clamp studies difficult to complete in 1,074 pregnant women. Moreover, Matsuda index, HOMA-IR, insulinogenic index/HOMA-IR, and ISSI-2 are valid measures that have been widely used in previous studies (8,13–18).

The current findings hold several implications. First, the interaction analyzes show that classical risk factors may confer differential risks of GDM depending on fetal sex. Interestingly, the apparent absence of interaction between male fetus and prepregnancy BMI was also noted by Hinckers (29) in 1977 when studying glycemic patterns on intravenous glucose
tolerance test. Another implication pertainsto postpartum diabetic risk after GDM. Indeed, women with GDM have a chronic defect in \( \beta \)-cell function that persists after the pregnancy, leading to an increased risk of progression to T2DM in the years thereafter (8). The current data raise the intriguing question of whether fetal sex may impact the natural history of \( \beta \)-cell function after pregnancy and hence future risk of maternal T2DM. Future studies to address this question are needed. Finally, and most importantly, the emerging perspective that maternal-fetal metabolic interplay appears to be bidirectional has fundamental implications for our understanding of the maternal adaptations that take place during pregnancy and the direction/interpretation of future research into their mechanistic bases.

In summary, pregnant women carrying a male fetus have poorer \( \beta \)-cell function and greater postprandial glyceremia than women with a female fetus. Accordingly, male fetus is independently associated with higher odds of GDM in the mother. It thus emerges that fetal sex is a previously unrecognized factor that is relevant to maternal glucose homeostasis in pregnancy.

**References**