Pre-pregnancy diabetes mellitus and risk of placental vascular disease

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Maternal diabetes mellitus (DM) before pregnancy is associated with adverse maternal and perinatal outcomes, including acquired hypertension in pregnancy (1-3). The maternal placental syndromes -- preeclampsia and abruption (PA) or infarction (PI) of the placenta (4)-- are also more prevalent in women with insulin resistance, DM and the metabolic syndrome (3, 5-8). We evaluated the risk of placental vascular disease in association with pre-pregnancy DM.

Research Design and Methods:
We completed a retrospective population-based study of all women who underwent antenatal maternal serum screening (MSS) in Ontario between 1993 and 2000, as described elsewhere (9). Those with a multiple gestation pregnancy at the time of MSS were excluded.
Maternal characteristics (Table) were recorded on a standardized form and completed by her caregiver at the time of MSS. Data on obstetrical outcomes and the health status of each newborn were also linked to the Discharge Abstract Database of the Canadian Institute for Health Information (CIHI), providing up to eight International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes for each woman and for each newborn (Appendix [available online at http://care.diabetesjournals.org]).
The primary study outcome was a diagnosis of either PA or PI, according to the relevant ICD-9 codes recorded at the delivery hospitalization (Appendix). Secondary study outcomes included an individual diagnosis of PA, PI, maternal preeclampsia/eclampsia, as well as poor fetal growth or fetal growth restriction.

Statistical analysis
The association between pre-pregnancy DM and study outcomes was analyzed using logistic regression analysis, and expressed as a crude odds ratio (OR) and 95% confidence interval (CI). The OR were further adjusted for those variables listed in the footnotes of the Table. All statistical analyses were done using SAS version 9.1, and statistical significance was set at a 2-sided P-value less than 0.05.

The study research protocol was originally approved through the Ministry of Health and Longterm Care in Ontario, and by the Research Ethics Board of St. Michael's Hospital.

Results
There were 386,323 singleton pregnancies included during the period of study; 1,717 women (0.44%) had a diagnosis of pre-pregnancy DM. Most maternal characteristics were similar among women with and without pre-pregnancy DM (Table). Fewer women with pre-pregnancy DM were of non-white ethnicity (21.7% vs. 27.4%), but they weighed more at the time of MSS (74.6 kg vs. 66.9 kg).
The rate of preeclampsia was about 12% in women with pre-pregnancy DM and 3% in those without DM (adjusted OR 3.4, 95% CI 2.9-4.0) (Table).
PA or PI was diagnosed among 2.2% of women with pre-pregnancy DM and 1.8% of those without DM (adjusted OR 1.1, 95% CI 0.79-1.5) (Table).

Discussion
Despite having a more than a three times greater risk of preeclampsia, women with pre-pregnancy DM did not appear to be at elevated risk for PI or PA. A non-significantly higher risk of fetal growth restriction was seen among the women with pre-pregnancy DM.

How do we explain the higher observed risk of preeclampsia, but not PA or PI, in association with pre-pregnancy DM? The current study had more than 90% statistical power to detect at least a 1.5 times higher risk of PA or PI between groups, so a type 2 statistical error is unlikely. Poor coding and ascertainment of PA or PI in a database
There is a direct relationship between abnormal glucose metabolism prior to, or in early pregnancy, and the development of preeclampsia (1-3); the current study confirms this. Although the hypertensive disorders of pregnancy are a major risk factor for PA and PI (13,14), a link between pre-pregnancy DM and PA or PI was not found, an original observation. It has been postulated that longer duration of exposure of the placental vessels to a hyperglycemic and hypertensive environment is harmful (15,16). In one prospective study of 290 pregnant women with type 1 DM, an elevated HbA1c at 24 weeks’ gestation was associated with a significantly higher risk of preeclampsia (17). However, as in our study, there are no data on glycemic control in pregnancy and the risk of PA or PI.

A prospective study can address the issue of maternal glycemic control and the risk of preeclampsia, PA and PI. Both PA and PI might be captured not only at delivery, with a systematic examination of the placenta, but also prior to delivery, using ultrasonography. The gestational age at onset of the preeclampsia and PA or PI, as well as the mode of delivery, should also be documented.

**Acknowledgement**

We thank the Ontario provincial laboratories and genetics clinics for contributing data to the Ontario MSS Database, and the women of Ontario for supporting the maternal serum screening programme. Dr. Ray is supported by a Canadian Institutes of Health Research New Investigator Award.
References:
## Table: Characteristics of women with and without pre-pregnancy diabetes mellitus and risk of adverse placental and perinatal outcomes

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Pre-pregnancy diabetes mellitus</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Present (n = 1,717)</td>
<td>Absent (n = 384,606)</td>
</tr>
<tr>
<td><strong>Maternal characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD) age, years</td>
<td>30.0 (5.1)</td>
<td>29.7 (5.0)</td>
</tr>
<tr>
<td>Mean (SD) gestational age at the time of maternal serum screening, weeks</td>
<td>16.5 (1.1)</td>
<td>16.7 (1.1)</td>
</tr>
<tr>
<td>No. (%) non-white ethnicity</td>
<td>362 (21.7)</td>
<td>101,670 (27.4)</td>
</tr>
<tr>
<td>Median gravidity</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Median parity</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Mean (SD) weight at the time of maternal serum screening, kg</td>
<td>74.6 (17.6)</td>
<td>66.9 (14.4)</td>
</tr>
<tr>
<td>No. (%) with preeclampsia or eclampsia at delivery</td>
<td>205 (11.9)</td>
<td>11,410 (3.0)</td>
</tr>
<tr>
<td>No. (%) with gestational hypertension at delivery</td>
<td>117 (6.8)</td>
<td>7071 (1.8)</td>
</tr>
<tr>
<td>No. (%) with hypertension outside of pregnancy, coded at delivery</td>
<td>8 (0.47)</td>
<td>148 (0.040)</td>
</tr>
<tr>
<td>No. (%) with tobacco use at delivery</td>
<td>1 (0.060)</td>
<td>951 (0.25)</td>
</tr>
<tr>
<td>No. (%) with drug dependence at delivery</td>
<td>0 (0.00)</td>
<td>221 (0.060)</td>
</tr>
<tr>
<td><strong>Study outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. (%) placental abruption or infarction</td>
<td>38 (2.2)</td>
<td>7120 (1.8)</td>
</tr>
<tr>
<td>No. (%) placental infarction</td>
<td>19 (1.1)</td>
<td>3998 (1.0)</td>
</tr>
<tr>
<td>No. (%) placental abruption</td>
<td>20 (1.2)</td>
<td>3274 (0.85)</td>
</tr>
<tr>
<td>No. (%) poor fetal growth or fetal growth restriction</td>
<td>17 (0.99)</td>
<td>2000 (0.52)</td>
</tr>
<tr>
<td>No. (%) preeclampsia</td>
<td>205 (11.9)</td>
<td>11,410 (3.0)</td>
</tr>
</tbody>
</table>

* Adjusted for maternal age, non-white ethnicity, parity and body weight at the time of maternal serum screening, as well as preeclampsia/eclampsia, gestational hypertension, gestational diabetes mellitus, tobacco use and drug dependence at the time of delivery.

** Adjusted for maternal age, non-white ethnicity, parity and maternal body weight at the time of maternal serum screening, as well as gestational diabetes mellitus and tobacco use at the time of delivery.