Dysglycemia and a history of reproductive risk factors

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Running Title: Dysglycemia and reproductive risk factors

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**Objective** - To identify reproductive risk factors associated with dysglycemia (diabetes, impaired glucose tolerance, and impaired fasting glucose) in a contemporary, multiethnic population.

**Research Design and Methods Study Design** - We studied 14,661 women screened with an OGTT for the DREAM Trial. Reproductive risk factors were compared in normoglycemic and dysglycemic women.

**Results** - Dysglycemia was significantly associated with the number of children born (OR 1.03 per child, 95% CI 1.01-1.05), age (OR 1.05 per year, 1.04-1.05), non-European ancestry (OR 1.09, 1.01-1.17), pre-eclampsia/eclampsia (OR 1.14, 1.02-1.27), irregular periods (OR 1.21, 1.07-1.36), and GDM (OR 1.53, 1.35-1.74). The relationship between GDM and dysglycemia did not differ across BMI tertiles (p=0.84), nor did the relationships of other risk factors.

**Conclusions** - Reproductive factors, particularly GDM, are associated with dysglycemia in middle-aged women from many ethnicities. Reproductive factors can be used to counsel young women about their future risk of dysglycemia, while in middle age they may help screen for dysglycemia.
Gestational diabetes (GDM) is a well-known reproductive risk factor for subsequent type 2 diabetes. Other reproductive factors such as pre-eclampsia are associated with insulin resistance during pregnancy and may also increase the subsequent risk for diabetes. Furthermore, some (2-4) but not all (5) studies suggest that pregnancy itself is a risk factor for future type 2 diabetes. For example, a population-based study of 1186 elderly women found that even after accounting for age, obesity and family history of diabetes, parity was associated with an increased risk of type 2 diabetes, with an odds ratio (OR) of 1.16 per pregnancy (95% CI 1.04-1.20).[3] An even larger study comprising 2,310 women with type 2 diabetes reported that parity greater than 6 was associated with a relative risk (RR) of diabetes of 1.56 (95% CI 1.27-1.91); however, the estimate of the RR decreased to 1.19 (95% CI 0.97-1.48) after adjustment for current age.(2) The applicability of these results is limited by the homogeneity of the population (registered nurses with relatively high socioeconomic status and 98% Caucasian), and the use of the older fasting plasma glucose cut-off for diabetes of > 7.8 mmol/L (140 mg/dL) rather than the current, more sensitive value of 7.0 mmol/L (126mg/dL).[6]

The prevalence of dysglycemia (type 2 diabetes, impaired glucose tolerance [IGT], and impaired fasting glucose [IFG]) is increasing; however, reproductive risk factors are often under-recognized. In particular, their association with the more recently recognized forms of glucose dysregulation, IGT and IFG, have not yet been well studied. The detection of dysglycemia could be improved if risk factors were better known. Moreover, if reproductive factors such as parity and preeclampsia are risk factors for dysglycemia, they could be used to refine screening approaches. The goal of this research was to identify reproductive risk factors for dysglycemia in a contemporary, multiethnic group of women.

Research Design and Methods

Design, Setting: This is a study of 14,661 women screened as possible participants in the DREAM Trial (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) (7,8), a large, international, multi-centre, randomized double-blind controlled diabetes prevention trial.

Participants: Participants were volunteers recruited from 21 countries on 5 continents from a wide variety of sources including first degree relatives of diabetic people in diabetic clinics, ads in newspapers, pharmacies, national diabetes associations, newsletters, clinics, community announcements, screening programs and targeted mailings.

Assessment: After an overnight (8 - 18 hours) fast participants consumed 75 g anhydrous glucose and provided a fasting and 2 hour blood sample for local measurement of plasma glucose. At the same time they completed a 12-page questionnaire regarding baseline characteristics, medications and personal and family history, and women completed a one page reproductive questionnaire regarding regularity of menstrual cycles, fertility, how many children they had given birth to, and complications of pregnancy including GDM, pre-eclampsia or eclampsia.

Definitions: Type 2 diabetes was defined as a fasting plasma glucose ≥ 7.0 mmol/L (≥126 mg/dL) OR a plasma glucose ≥ 11.1 mmol/L (≥200 mg/dL) 2 hours after a 75 g oral glucose load. Impaired glucose tolerance (IGT) was defined as a plasma glucose 7.8-11.0 mmol/L (140-199 mg/dL) 2 hours after a 75 g oral glucose load. Impaired fasting glucose (IFG) was defined as fasting glucose of 6.1-6.9 mmol/L (110-124 mg/dL).
Dysglycemia was defined as IFG, IGT or Type 2 diabetes. Parity was defined as the number of infants a woman had borne. Irregular menses was defined as 6 or fewer menstrual cycles per year between the ages of 18-45 years not including pregnancy and was used as a surrogate for polycystic ovary syndrome. Early menopause was defined as the permanent cessation of menstrual periods before the age of 45. Income range tables with 5 strata were developed specific to each country in which recruitment occurred; low socioeconomic status was defined as the lowest strata for that country. In Canada, for example, that included a household income ≤ $29,999, and for the United States, ≤ $15,400. Non-European ancestry was defined as anyone indicating any ancestry other than European at the time of their clinic visit.

### Statistical Analysis

Women were classified into those with and without dysglycemia. Continuous variables were compared using a $t$ test and categorical variables with a Chi-square test. Logistic regression was used to calculate age-adjusted odds ratios and 95% confidence intervals for reproductive risk factors for dysglycemia. Factors which were statistically significant at $p<0.10$ in the age-adjusted analysis were included in the multivariate logistic regression to determine their independent relationship with prevalent dysglycemia. This model was rerun for each tertile of BMI (and $p$ values for heterogeneity were calculated) to determine if the risk of dysglycemia for each risk factor varied with BMI. All $p$ values are reported as two-tailed. All analyses were performed using SAS software, version 9.1 (SAS Institute, North Carolina, USA).

Institutional Research Ethics Boards at each site approved the DREAM trial. The funding organizations had no part in the design of the study, the collection, analysis or interpretation of the data or the decision to approve publication of the finished manuscript.

### RESULTS

Table 1 presents the baseline characteristics of the women with (n=6,298) and without (n=8,363) dysglycemia, whose 2 hour plasma glucose concentrations were $10.0 \pm 3.1$ mmol/L versus $5.7 \pm 1.1$ mmol/L, respectively ($p<0.0001$), with fasting values of $6.3 \pm 1.4$ mmol/L versus $5.0 \pm 1.1$ mmol/L ($p<0.0001$). Women with dysglycemia were significantly older than those without dysglycemia (55.1 years versus 50.0 years, respectively, $p<0.0001$). After adjustment for age, most of the reproductive factors remained significantly associated with dysglycemia, including the number of children a woman had (OR 1.05 per child, 95% CI 1.04-1.06), pre-eclampsia/eclampsia (OR 1.19, 95% CI 1.07-1.32), irregular menses (OR 1.22, 95% CI 1.09-1.38), GDM (OR 1.58, 95% CI 1.40-1.78), low socioeconomic status (OR 1.09, 95% CI 1.01-1.17) and non-European ancestry (OR 1.10, 95% CI 1.02-1.17). (Table 1)

In a multivariate model that included age, ancestry, and fertility-related factors, dysglycemia was significantly associated with the number of children a woman had (OR 1.03 per child, 95% Confidence Interval [CI] 1.01-1.05), age (OR 1.05 per year, 95% CI 1.04-1.05), non-European ancestry (OR 1.09, 95% CI 1.01-1.17), a history of pre-eclampsia/eclampsia (OR 1.14, 95% CI 1.02-1.27), irregular periods (OR 1.21, 95% CI 1.07-1.36), and GDM (OR 1.53, 95% CI 1.35-1.74). (Figure 1) Early menopause (OR 1.24, 95% CI 0.98-1.53), and low socioeconomic status (OR 0.95, 95% CI 0.88-1.02) were no longer significantly associated with dysglycemia.

In order to determine if there was an interaction between BMI and the reproductive risk factors, particularly GDM, we reran the multiple regression model for each tertile of BMI, with 27.1 and 32.2 defining lower, middle and upper levels. The relationships
between GDM and current dysglycemia did not differ significantly across tertiles of BMI, p for heterogeneity= 0.84, nor did they for any of the other risk factors, p for heterogeneity ≥ 0.10 for all. The OR for GDM and current dysglycemia for each tertile of BMI (<27.1, 27.1-32.2 and >32.2) was 1.81 (95% CI 1.42-2.30), 1.44 (95% CI 1.14-1.81) and 1.47 (95% CI 1.20-1.81), respectively.

This large, multiethnic study of middle-aged women found that a history of GDM is independently associated with prevalent dysglycemia, confirming that pregnancy is a “stress test for life”.(9,10) This observation may be understood in light of the fact that the occurrence of GDM is clear evidence of an impaired ability to maintain normoglycemia under the metabolic stress of pregnancy and is consistent with previous reports(11-14) from smaller studies. Hence, in young women of child-bearing age, reproductive factors, particularly GDM, can be used to counsel patients about their future risk of dysglycemia regardless of future BMI, while in middle aged women a history of reproductive risk factors may be useful as a screening tool for dysglycemia.

This study also found that a history of a variety of reproductive risk factors including irregular menses, parity, and preeclampsia were independently associated with dysglycemia, and were not explained by age, ethnicity or socioeconomic status. One potential explanation is the association of many of these factors with insulin resistance, including preeclampsia(15,16), pregnancy(17), and even in non-obese women, polycystic ovary syndrome (of which irregular menses is a key component)(18-21).

This is the only study to our knowledge examining reproductive risk factors for dysglycemia involving a broad population, allowing for wide applicability of results. Participation spanned all socioeconomic strata, and involved 21 countries on 5 continents. Another strength is the large sample size (14, 661 women), by far the largest study in the literature on reproductive risk factors and dysglycemia, which allowed for control of multiple confounding factors. Another strength is the fact that reproductive risk factors which identified women at increased risk of dysglycemia were elicited with simple screening questions which are part of a routine history, not requiring serology or imaging investigations such as pelvic ultrasounds. Participants were asked, for instance, about irregular menses as a surrogate for polycystic ovary syndrome, as many patients remain undiagnosed or unfamiliar with the medical term. Although this approach would potentially misclassify some patients who had had fertility-related risk factors as being unaffected, this suggests that the associations between fertility-related risk factors and dysglycemia are likely even stronger than those observed.

Limitations of the study include the fact that the participants were asked to recall events, such as pregnancies, which in many instances occurred several decades earlier. However, by gathering this baseline information prior to the administration of the OGTT, recall bias was limited. We did not have access to the participants’ medical charts and relied on patient history which may not always be reliable, and may underestimate some of the above associations.

CONCLUSIONS
In summary, in this large, multiethnic study of middle-aged women without a previous diagnosis of diabetes, prevalent dysglycemia was independently associated with a history of several reproductive risk factors, particularly GDM. Moreover, the relationship between prior GDM and current dysglycemia persisted across BMI strata.

ACKNOWLEDGMENTS
Dysglycemia and reproductive risk factors

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Reference List


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Table 1 Baseline characteristics of participants and age-adjusted univariate analyses of reproductive risk factors and the risk of dysglycemia

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dysglycemia (n=6,298)</th>
<th>No dysglycemia (n=8,363)</th>
<th>p value (unadjusted)</th>
<th>Age-adjusted OR (95%CI) of dysglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean years (SD)</td>
<td>55.1 (11.1)</td>
<td>50.0 (10.0)</td>
<td>&lt;0.0001</td>
<td>n/a</td>
</tr>
<tr>
<td>Number of children, mean (SD)</td>
<td>2.74 (1.6)</td>
<td>2.53 (1.3)</td>
<td>&lt;0.0001</td>
<td>1.05 (1.04-1.06)</td>
</tr>
<tr>
<td>Low SES, N (%)</td>
<td>2,243 (37.7)</td>
<td>2,636 (33.2)</td>
<td>&lt;0.0001</td>
<td>1.09 (1.01-1.17)</td>
</tr>
<tr>
<td>Non-European ancestry, N (%)</td>
<td>3,339 (53.0)</td>
<td>4,649 (55.6)</td>
<td>0.002</td>
<td>1.10 (1.02-1.17)</td>
</tr>
<tr>
<td>Pre-eclampsia/eclampsia</td>
<td>700 (11.0)</td>
<td>853 (10.1)</td>
<td>0.10</td>
<td>1.19 (1.07-1.32)</td>
</tr>
<tr>
<td>Irregular periods, N (%)</td>
<td>608 (9.6)</td>
<td>734 (8.8)</td>
<td>0.08</td>
<td>1.22 (1.09-1.38)</td>
</tr>
<tr>
<td>GDM, N (%)</td>
<td>588 (9.4)</td>
<td>673 (8.1)</td>
<td>0.01</td>
<td>1.58 (1.40-1.78)</td>
</tr>
<tr>
<td>Early menopause, N (%)</td>
<td>124 (2.0)</td>
<td>217 (2.6)</td>
<td>0.01</td>
<td>1.24 (0.99-1.56)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>31.6 (6.0)</td>
<td>29.4 (6.0)</td>
<td>&lt;0.0001</td>
<td>1.06 (1.06-1.07)</td>
</tr>
</tbody>
</table>

Dysglycemia= impaired fasting glucose or impaired glucose intolerance or type 2 diabetes mellitus, OR=Odds Ratio, Low SES=low socioeconomic status, irregular periods=6 or fewer menstrual cycles/year between the ages of 18 and 45 years not including pregnancy, early menopause= permanent cessation of menses <45 years of age, BMI=body mass index
Figure Legend
Figure 1: Graphic representation of the adjusted ORs for dysglycemia with reproductive risk factors
dysglycemia= impaired fasting glucose or impaired glucose intolerance or type 2 diabetes mellitus, CI=Wald confidence interval, Low SES=low socioeconomic status, irregular menses = 6 or fewer menstrual cycles/year between the ages of 18 and 45 years not including pregnancy, GDM=gestational diabetes mellitus, BMI=body mass index, OR = Odds Ratio, 95% CI=95% Confidence Interval

![Figure 1 Graphic representation of the adjusted ORs for dysglycemia with reproductive risk factors](image)