

## Review Article

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# Gestational prediabetes: a new term for early prevention?

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**Women with gestational diabetes mellitus (GDM) have higher rates of foetal macrosomia, shoulder dystocia and pregnancy-induced hypertension, and are at higher risk of developing type 2 diabetes. Herein, we introduce a new conceptual term, “gestational prediabetes”, which requires the absence of diabetes before pregnancy, and the presence of blood glucose levels (or a related marker) in early pregnancy that are higher than normal, but not yet high enough to meet the diagnostic criteria for GDM. Identifying women with gestational prediabetes might be done in early pregnancy (e.g., 12 weeks' gestation) using conventional glycaemic testing, assessment of visceral abdominal adiposity or hepatic fat by ultrasonography, or measuring serum sex hormone-binding globulin or adiponectin. However, none of these approaches has been systematically compared to conventional predictors, such as maternal body mass index or waist circumference. Any early-pregnancy predictor of gestational prediabetes risk needs to have low cost, ease of administration, and a short turnaround time. The theoretical advantage of identifying women with gestational prediabetes would be to “prevent” the onset of GDM (and its inherent risks to the pregnancy) in a timelier manner. One sensible starting point would be an intervention to prevent early excessive weight gain in pregnancy, which is currently being evaluated by two randomized clinical trials. In addition, early intervention could offset the need for resource-intense GDM management or insulin therapy.**

**Key words** Diabetes in pregnancy - gestational diabetes - gestational prediabetes - prediction - pregnancy - prevention - risk

### Prediabetes

The concept of prediabetes refers to blood glucose levels above normal, but not high enough to meet the diagnostic criteria for type 2 diabetes mellitus (DM), traditionally designated as “impaired glucose tolerance” (IGT) and “impaired fasting glucose” (IFG)<sup>1</sup>. About 6 to 10 per cent of patients with IGT go on to develop

DM annually, and among those with both IGT and IFG, 60 per cent will have DM within six years<sup>2</sup>. Thirteen-year trajectories of blood glucose, insulin sensitivity and insulin secretion show that those who develop type 2 DM not only have higher fasting and postload levels of glucose, but higher insulin secretion and lower insulin sensitivity as well<sup>3</sup>. The American Diabetes

Association recently declared that prediabetes, “IFG and IGT should not be viewed as clinical entities in their own right but rather risk factors for diabetes as well as cardiovascular disease”<sup>4</sup>.

Beyond the epidemiological evidence, the concept of prediabetes has potential relevance to clinical practice: at some early and reasonable point in the pathogenesis of type 2 DM, health care providers can prevent or postpone the development of this harmful condition. Fortunately, in the case of prediabetes, randomized clinical trials have demonstrated a sustained benefit of lifestyle interventions in the prevention of type 2 DM in selective groups of middle-aged adults<sup>5,6</sup>.

### Gestational diabetes

Gestational diabetes mellitus (GDM) - a condition in which women without previously diagnosed DM exhibit high blood glucose levels in later pregnancy - bears the same risk factors as type 2 DM: greater age, higher body mass index (BMI), a family history of type 2 DM and a sedentary lifestyle<sup>7,8</sup>. Like type 2 DM, GDM is more common among certain non-White ethnic groups<sup>9</sup>. In addition, the insulin-inhibiting hormones of pregnancy amplify a woman’s pre-existing tendency to insulin resistance, increasing her likelihood of hyperglycaemia<sup>10</sup>.

The main adverse impact of GDM on pregnancy is foetal macrosomia and the associated risk of shoulder dystocia<sup>11</sup>, which in turn can lead to neonatal musculoskeletal and brachial plexus injury<sup>12</sup>. Women with GDM have higher rates of pregnancy-induced hypertension<sup>13,14</sup>, and their offspring are potentially at higher risk of childhood obesity<sup>15</sup>. In terms of perinatal outcomes, one randomized clinical trial found that glycaemic control among women with GDM reduced the primary composite outcome of stillbirth, shoulder dystocia, bone fractures, nerve palsy, neonatal intensive care unit admission and jaundice<sup>16</sup>. However, this evidence was not strong, and in the latter study there was heterogeneity in the primary composite endpoint, along with selective recruitment of participants<sup>17</sup>.

Evidence also exists that women diagnosed with GDM in pregnancy are at higher risk of developing type 2 DM<sup>18</sup>. The risk of pre-diabetes after pregnancy largely reflects the degree of dysglycaemia in pregnancy. Retnakaran *et al*<sup>19</sup> included 93 women with normal glucose testing in pregnancy, 91 women with gestational IGT and 137 women with GDM, and evaluated them at three months postpartum by a fasting OGTT. The

respective risk for postpartum glucose intolerance was 3.2 per cent among unaffected women, 16.5 per cent among those with gestational IGT [odds ratio (OR) 5.7, 95% confidence interval (CI) 1.6 to 21.1] and 32.8 per cent (OR 14.3, 95% CI 4.2 to 49.1) in women with GDM. Moreover, postpartum insulin sensitivity and pancreatic beta-cell function was respectively worse across groups<sup>19</sup>.

Though controversial<sup>20</sup>, most recommend that all pregnant women be screened at 24 to 28 wk gestation with a 50 g glucose challenge test (GCT); those who screen positive are expected to undergo a confirmatory 2 h 75 g or 100 g oral glucose tolerance test (OGTT)<sup>4,21</sup>. While some strategies for selective screening of women at higher risk of developing GDM may improve the true-positive and false-positive detection rates of GDM, some women without the classical risk factors for GDM will be missed, accordingly<sup>22</sup>. A separate issue is whether starting dietary or pharmacological therapy after 24 wk is simply too late to favourably impact on foetal growth or the placental vasculature. Indeed, excessive weight gain and a high serum insulin concentration in the first half of pregnancy are associated with an increased risk of foetal macrosomia, independent of pre-pregnancy BMI<sup>23</sup>. Accordingly, we may need to re-think about the pathogenesis of GDM and the timeliness of interventions aimed at maternal metabolic control and the prevention of adverse pregnancy outcomes.

### Gestational prediabetes

It is at this juncture that we introduce a new conceptual term - “gestational prediabetes” - and make a case for its potential relevance. Gestational prediabetes requires the absence of diabetes before pregnancy, and the presence of blood glucose levels (or a related marker) in early pregnancy that are higher than normal, but not yet high enough to meet the diagnostic criteria for GDM. Some women with gestational prediabetes would be expected to go on to develop GDM by 24 to 28 wk gestation. The concept of gestational prediabetes would exclude women whose glucose concentration in early pregnancy is so high that they meet the criteria for “overt” type 2 DM, as defined by the American Diabetes Association<sup>4</sup>.

The theoretical advantage of identifying women with gestational prediabetes would be to “prevent” the onset of GDM (and its inherent risks to the pregnancy) in a timelier manner. In a recent nested case-control study of 345 women with GDM and 800

women without GDM, compared to the lowest tertile of gestational weight gain (< 0.27 kg/wk), the risk of GDM was higher in the second tertile of weight gain of 0.27 to 0.40 kg/wk (adjusted OR 1.43, 95% CI 0.96 to 2.14) and the highest tertile of  $\geq 0.41$  kg/wk (adjusted OR 1.74, 95% CI 1.16 to 2.60)<sup>24</sup>. This association was significant despite adjusting for pre-pregnancy BMI, and was most pronounced in overweight women and in relation to weight gain in the first trimester. Thus, one sensible starting point would be an intervention to prevent early excessive weight gain, such as better nutrition and greater low-impact physical activity. Excessive weight gain in pregnancy can be prevented by counseling, including patient-focused caloric intake as 40 per cent carbohydrates, 30 per cent protein and 30 per cent fat, along with moderate-intensity exercise at least three times per week<sup>25</sup>. Other randomized clinical trials are underway to determine whether an exercise programme twice a week impacts on plasma glucose levels, insulin resistance and newborn weight among women at risk of GDM<sup>26,27</sup>. If these prove to prevent the onset of GDM, then these approaches could be easily adopted, as these are the same as those currently used in women with recognized GDM, in whom dietary therapy is the cornerstone of treatment. In addition, early intervention could offset the need for resource-intensive GDM management or insulin therapy<sup>28</sup>.

### Identifying gestational prediabetes

What remains more problematic is developing a method that can practically identify women with gestational prediabetes. One way might be to perform conventional glycaemic testing in early pregnancy (*e.g.*, at 12 wk gestation). If one used the conventional 50 g GCT screening test for GDM, or the confirmatory 2 h 75 g OGTT, then thresholds to define abnormal would need to be carefully lowered to account for the relatively lesser presence in early pregnancy of human placental lactogen and other insulin-inhibitory hormones<sup>10</sup>, and the fact that one is not trying to identify GDM, *per se*, but a pre-GDM state. In one study of women at risk for GDM, all underwent a 2 h 75 g OGTT before 17 wk gestation<sup>29</sup>. At fasting and 2 h post-load glucose cut-off values of 5.3 and 6.8 mmol/l, the positive (PPV) and negative predictive values (NPV) of the early OGTT for subsequent GDM were 25 and 92 per cent, respectively<sup>29</sup>. More interestingly, an elevated fasting insulin level had a PPV of 90 per cent and a NPV of 87 per cent for subsequent GDM, while hyperinsulinaemia 2 h after the 75 g glucose load had PPV and NPV values of 75 and 96 per cent,

respectively<sup>30</sup>. Thus, even among women determined to be at high risk for GDM according to conventional risk factors, an early-pregnancy OGTT may not predict the onset of GDM; measuring insulin levels in early pregnancy might be a better choice. Regardless, these data were based on selective small-sample studies, and knowing how these apply to a general population of pregnant women would need to be determined.

Besides using conventional risk factors (*e.g.*, age, BMI, family history of type 2 DM, and excessive weight gain)<sup>7-9</sup>, or measuring blood glucose or insulin in early pregnancy, other novel methods may emerge to identify women with gestational prediabetes. Evidence shows that visceral (peritoneal cavity) adiposity is a strong predictor of type 2 DM and the metabolic syndrome<sup>31,32</sup>, and that centrally located visceral fat is more diabetogenic than subcutaneous adipose tissue<sup>33</sup>. We recently completed a small prospective cohort study using ultrasonography to measure subcutaneous and visceral adipose tissue depth at about 12 wk gestation (conveniently, at the same time as women undergo measurement of foetal nuchal translucency)<sup>34</sup>. The inter-observer reliability of ultrasound for measuring visceral fat depth was 0.87 (95% CI 0.82 to 0.93). An elevated visceral adipose tissue depth (above the upper quartile) was significantly associated with a positive GCT at about 27 wk, even upon adjusting for maternal age and pre-pregnancy BMI (OR 16.9, 95% CI 1.5 to 194.6). No association was however seen for subcutaneous fat<sup>34</sup>.

As a second novel method that might identify women with gestational prediabetes is the presence of a fatty liver in early pregnancy. Non alcoholic fatty liver disease (NAFLD), ranging from simple steatosis (fatty infiltration) to inflammatory steatohepatitis (NASH), to possible long-term injury (fibrosis), is a strong indicator of insulin resistance in non-pregnant adults<sup>35</sup>. Even among obese adolescents, hepatic fat content increases in parallel to insulin resistance and glucose dysregulation<sup>36</sup>. In young non-pregnant women with previous GDM, and who underwent MRI of the liver, those with high liver fat had elevated fasting serum triglyceride and insulin concentrations and lower whole body insulin sensitivity than those with low liver fat content<sup>37</sup>. Unfortunately, since little is known about the association between NAFLD in pregnancy and GDM risk, it is premature to consider using this to predict gestational prediabetes.

Several other early-pregnancy markers have been evaluated for identifying women at high risk for

GDM<sup>38,39</sup>. Low concentrations of serum sex hormone-binding globulin<sup>38</sup> and serum adiponectin<sup>39</sup> are the most promising biochemical markers, but neither has been systematically compared to conventional predictors, such as maternal BMI, waist circumference, age and ethnicity<sup>7-9</sup>, and both are quite expensive. Any early-pregnancy predictor of GDM risk - biochemical, sonographic, or otherwise - needs to be inexpensive, available in most prenatal care centres, have a short period of turnaround, and place a minimal burden on the time of patients and health care providers.

### Gestational prediabetes: a useful concept, but not yet ready

We have introduced the concept of “gestational prediabetes” because we believe that it may aid in identifying in a timely manner women at high risk of developing GDM. At the same time, we acknowledge that labelling a woman with gestational prediabetes may or may not produce excess anxiety, just as screening for, or labelling a woman with GDM may<sup>40</sup> or may not<sup>41</sup> be stressful.

While dietary interventions and increased physical activity in early pregnancy might effectively prevent the evolution from gestational prediabetes to GDM, an acceptable early indicator or marker needs to be developed first. We urge ourselves and others to make this a priority in researching GDM.

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