

ASK THE EXPERTS

Management of diabetes during pregnancy



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What is gestational diabetes & why does it occur?

■ Moshe Hod

Gestational diabetes (GDM) is defined as any degree of glucose intolerance that started or was first diagnosed during pregnancy. This does not rule out the possibility that glucose intolerance preceded pregnancy or that it will persist afterwards. Gestational diabetes occurs in up to 15% of all pregnancies and its prevalence is related to the prevalence of Type 2 diabetes and impaired glucose tolerance (IGT) in a given population. It is estimated that only 10% of diabetic pregnancies are due to pregestational diabetes, therefore GDM comprises the lion's share of pregnancies complicated by diabetes. Insulin resistance is a part of every normal pregnancy, especially during the third trimester.

The term diabetes mellitus encompasses a wide range of conditions characterized by hyperglycemia. This leads to a myriad of metabolic disturbances in carbohydrate, protein and fat metabolism. In one end of the spectrum are metabolic disturbances that arise during the postprandial state when insulin's effect fails to meet metabolic demands, as in patients with GDM and normal fasting glucose. At the extreme end of the spectrum, insulin is insufficient or absent and patients (mainly those with Type 1 diabetes) are totally dependent on exogenous insulin for metabolic control and mere survival. The presence of persistently high levels of glucose and its metabolic consequences cause damage to small and large blood vessels, which affects multiple organs such as eyes, kidneys, nervous system, heart and limbs of the mother and also has a detrimental effect on the fetus.

How prevalent is diabetes among pregnant women?

■ Donald R Coustan

The prevalence of diabetes in pregnant women varies with the overall population prevalence of diabetes. GDM is similar to Type 2 diabetes and its prevalence will track that of Type 2 diabetes. It is difficult to compare population-wide statistics for GDM because different diagnostic protocols are in use throughout the world. A survey of healthcare providers involved in GDM in 173

countries found estimates ranging from <1% of pregnant women to 28% [1]. An analysis of a nationwide US sample of hospital discharge data from 1994 to 2004 determined that deliveries in which diabetes of any type was recorded rose from 3.5 to 5.5% [2]. This was attributable to increases in both Type 2 diabetes (0.1–0.4%) and gestational diabetes (3–4.6%). These statistics are likely underestimates, since complicating conditions are notoriously under-reported on hospital discharge summaries. Because the prevalence of Type 2 diabetes has increased in recent years, presumably secondary to the obesity epidemic, both Type 2 diabetes and GDM have probably continued in this upward trend since 2004. When the International Association of Diabetes in Pregnancy Study Groups (IADPSG) recommendations for the diagnosis and classification of hyperglycemia in pregnancy (see fourth question) become universally adopted, comparative data will become more easily available. These new criteria should lead to an increase in the prevalence of gestational diabetes to the range of 15–20%.

How are women screened for GDM? Should all pregnant women be screened?

■ Moshe Hod

The detection of GDM is based upon selective screening that is based upon risk factors, which should be determined as early as the first prenatal visit. Screening for GDM is recommended for all pregnant patients unless they are considered at low risk for diabetes [3].

Women are to be considered at low risk for GDM if they meet all the following criteria (if so, no challenge test is required for the detection of gestational diabetes):

- Normal body weight;
- Age <25 years;
- No family history of diabetes;
- No personal history of abnormal glucose tests;
- No history of adverse pregnancy outcome;
- Not a member of a high prevalence ethnic group (Hispanic–American, Native

American, Asian–American, African–American, Pacific Islander populations).

Intermediate risk women are those not meeting the criteria for low or high risk. For this group, a challenge test is required. This should be made at 24–28 weeks of gestation either by performing a single step oral glucose tolerance test, or by a two step approach: first, performing a 1-h 50-g plasma glucose level screening test (glucose challenge test), performed without regard to the time of the last meal. Second, if plasma glucose level in the glucose challenge test is ≥ 140 mg/dl (7.8 mmol/l), a full oral glucose tolerance test (OGTT) should be performed to exclude or confirm the diagnosis of GDM – either by a 75- or a 100-g glucose load, with a fasting glucose level prior to the load and hourly glucose measurements thereafter, for 2 or 3 h, accordingly. Using the 140 mg/dl (7.8 mmol/l) threshold helps to identify approximately 80% of pregnant patients with GDM, and a threshold of 130 mg/dl (7.2 mmol/l) identifies 90% of patients.

Women at a high risk, according to the criteria below, should be tested in a single- or two-stage manner, as soon as possible during pregnancy (if diabetes is not diagnosed, testing should be repeated at 24–28 weeks or if clinical suspicion for diabetes arises):

- Obesity;
- Positive family history of Type 2 diabetes mellitus;
- Gestational diabetes in past pregnancy;
- Known prediabetic state;
- High urinary glucose.

Can you describe the recent IADPSG criteria for diagnosing GDM? How have they changed standard practice? What controversies surround these guidelines?

▪ Donald R Coustan

In 2010, the IADPSG published a set of consensus recommendations for the diagnosis and classification of hyperglycemia in pregnancy [4]. Data from the HAPO study (see seventh question), along with data from other studies of mild GDM, enabled a consensus to develop around

outcomes-based criteria for diagnosing GDM using a 75-g, 2-h OGTT.

In order to diagnose and treat overt diabetes as early in gestation as possible, patients with risk factors, or alternatively all patients, should undergo a standard test for diabetes at the first prenatal visit. Pre-existing diabetes may be diagnosed in any of the following ways:

- Fasting plasma glucose ≥ 126 mg/dl (7.0 mmol/l);
- A1c $\geq 6.5\%$;
- Random plasma glucose ≥ 200 mg/dl (11.1 mmol/l), to be confirmed by one of the other two tests.

If the fasting plasma glucose value at the first visit is ≥ 92 mg/dl (5.1 mmol/l), but < 126 mg/dl (7.0 mmol/l), the patient should be classified as having GDM.

Patients not already diagnosed with diabetes or GDM should undergo a 75-g, 2-h OGTT at 24–28 weeks. GDM is diagnosed if one or more of the following thresholds is satisfied:

- Fasting plasma glucose ≥ 92 mg/dl (5.1 mmol/l);
- 1-h plasma glucose ≥ 180 mg/dl (10.0 mmol/l);
- 2-h plasma glucose ≥ 153 mg/dl (8.5 mmol/l).

These guidelines have been adopted by the American Diabetes Association, and in Japan and Germany, and are under consideration in other parts of the world.

A number of controversies surround these guidelines. Primarily, they center on whether it is appropriate for $>15\%$ of the pregnant population to be diagnosed with gestational diabetes. In recent years, there has been a worldwide epidemic of obesity and Type 2 diabetes; the prevalence of diabetes and prediabetes in the USA, for example, exceeds a third of the adult population [10]. The proposed thresholds for diagnosing GDM are similar to the diagnostic criteria for prediabetes, so it should not be controversial that the prevalence of GDM in the childbearing population is almost half that of prediabetes in the overall adult population.

Another issue of controversy is whether the adverse outcomes identified can be prevented with interventions. That issue will be addressed in the answer to the sixth question.

While it is too early to precisely describe changes in standard practice that will occur, some predictions may be made:

- Laboratory confusion and error will be reduced with the movement from different glucose loads and time intervals for glucose tolerance tests (GTTs) in pregnant and nonpregnant testing to a single standard test load and interval (75 g, 2 h) for all situations;
- It will finally be possible to compare prevalences of GDM, effectiveness of treatment and temporal trends using common diagnostic criteria and a common language;
- On average, GDM will be diagnosed in over 15% of the pregnant population. This will engender the need for more efficient treatment paradigms. Fortunately, two recent randomized trials of identification and treatment of mild GDM found that between 80 and 92% of such patients may be successfully managed with medical nutrition therapy alone, without the need for insulin;
- An increased number of women with prediabetes will be identified by testing after GDM pregnancies, increasing the opportunity to prevent future Type 2 diabetes.

Can the three values on the 75-g, 2-h OGTT reliably predict the likelihood of pregnancy outcomes?

▪ Moshe Hod

The results of the HAPO study demonstrate an association between increasing levels of fasting, 1- and 2-h plasma glucose during a 75-g OGTT with the four primary end points of the study: birth weight above the 90th percentile, cord blood serum C-peptide level above the 90th percentile, primary cesarean delivery and clinical neonatal hypoglycemia. Although significant correlations exist, they are weaker for the two latter primary end points – primary cesarean delivery and

clinical neonatal hypoglycemia. Positive correlations were also found between increasing plasma glucose levels and the five secondary outcomes: premature delivery, shoulder dystocia or birth injury, intensive neonatal care admission, hyperbilirubinemia and preeclampsia. Adjustments were made for field center, maternal BMI, blood pressure, height, parity, baby gender and ethnic group – these reduced the observed associations, but they generally remained valid. This validates the results for all age groups, countries and ethnic origin, thus eliminating the proposed impacts of some speculated confounders. Additional analysis from the HAPO collaborative group examined the issue of neonatal adiposity. Out of the total HAPO participants, cord serum C-peptide results were available for 19,885 newborns and skinfold measurements were available for 19,389 of the HAPO newborns. These measurements were used to determine the relationship between neonatal adiposity (defined as the sum of skinfolds higher than the 90th percentile or body fat percentage over the 90th percentile) and maternal glucose levels. There is a statistically significant correlation between increasing values of maternal glycemia on all OGTT values, and cord serum C-peptide with neonatal adiposity. The pattern is similar to the correlation between maternal glucose values and birth weight above the 90th percentile, and also held true for fat free mass (derived by subtracting fat mass from total body weight). The results of these anthropometric measurements suggest a link between maternal glycemia and neonatal adiposity, which may be mediated by fetal insulin, thus validating the 50-year-old Pedersen hypothesis. Maternal glucose transported to the fetus across the placenta causes fetal hyperglycemia. Fetal glucose stimulates fetal insulin that acts as the messenger leading to fetal overgrowth. However, there may be a variety of other nutrients in addition to glucose and insulin that mediate fetal overgrowth and adiposity.

Other than the physiological aspects concerning the Pederson hypothesis, the HAPO study demonstrates that fasting glucose levels and 75-g OGTT values are correlated with maternal, perinatal and

neonatal outcomes. Glucose has an impact on pregnancy outcome, even if levels are below the current commonly accepted range for GDM. There seems to be no apparent threshold, but rather a continuum of glucose levels. These results may be the basis for developing risk-based standards to diagnose and classify GDM, with a world-wide consensus. The associations between adverse outcomes and ‘nondiabetic’ hyperglycemia mainly suggest the need to lower the diagnostic threshold for GDM.

How is GDM managed? Are current interventions effective?

■ Donald R Coustan

The management of GDM focuses on preventing adverse outcomes by prevention of maternal/fetal hyperglycemia, and identification of impending problems:

- Self-glucose monitoring is prescribed. Most paradigms involve testing glucose fasting, either 1 or 2 h after each meal, daily. When goals are consistently met with diet, it may be possible to decrease the frequency of testing. Goals we utilize are fasting values of <95 mg/dl, 1-h values of <130–140 mg/dl and 2-h values of <120 mg/dl;
- Medical nutrition therapy, aimed at maintaining euglycemia, is provided by an experienced dietitian;
- When glycemic goals are not accomplished with medical nutrition therapy, medication is prescribed. Little if any insulin crosses the placenta to the fetus. Oral agents such as glyburide and metformin are also used in some centers. While both have been demonstrated in fetal cord blood, neither has been shown to be directly harmful, or beneficial, to the fetus. When metformin was used in a randomized trial, nearly half of the patients needed the addition of insulin when therapeutic goals were not achieved at maximal metformin doses;
- Ultrasound examination may uncover developing macrosomia; in some centers insulin therapy is added when fetal abdominal circumference is excessive, even if blood glucose levels do not exceed targets. Ultrasound near term is also

useful in guiding the mode of delivery. When the estimated fetal weight by ultrasound is ≥ 4500 g, we offer cesarean section without a trial of labor in order to prevent shoulder dystocia;

- Fetal kick counting and/or antepartum fetal testing may be reassuring with regard to fetal wellbeing. In our center, patients with GDM whose control is less than adequate begin twice-weekly antepartum testing (modified biophysical profile) at 34–36 weeks. Those who are well controlled with insulin begin at 36 weeks. GDM patients who are well controlled with diet usually begin once-weekly testing at 36 weeks, but in some centers testing is not prescribed until term;
- In order to decrease the likelihood of stillbirth, we deliver well-controlled GDM patients by their due date, but not before 39 weeks. Women whose GDM is not well controlled are delivered sooner.

Interventions similar to those described above are effective, even when gestational diabetes is mild. Two randomized trials have been published recently. In the ACHOIS study, patients with GDM whose fasting value was <140 mg/dl (average 86 ± 12 mg/dl) and whose 2-h 75-g OGTT value was 140–199 mg/dl (7.8–11 mmol/l) were randomized; half were identified as having GDM and treated by their caregivers [5]. The other half were blinded to the diagnosis, as were their caregivers. The mild GDM patients who were identified and treated had 66% fewer ‘serious complications’ (death, shoulder dystocia, bone fracture and nerve palsy). Macrosomia was reduced by 50%, preeclampsia by 30% and the cesarean section rate was not changed. Only 20% of GDM patients required insulin treatment. In another randomized trial, mild GDM was defined as at least two abnormal values (1-h ≥ 180 mg/dl, 2-h ≥ 155 mg/dl or 3-h ≥ 140 mg/dl) on a 100-g, 3-h OGTT but normal fasting plasma glucose (<95 mg/dl) [6]. Those randomized to identification and treatment were compared with those whose GDM status was blinded to both patients and caregivers. Identification and treatment lowered rates

of macrosomia, primary cesarean section, shoulder dystocia and preeclampsia by half. In this trial, only 8% of GDM patients required insulin treatment.

What were the aims of the HAPO study?

■ Moshe Hod

The HAPO study was an investigator-initiated trial, meticulously planned as a prospective, observational, multicenter, blinded study. Special care was implemented in planning the study, with standardization applied for participant enrollment, data collection, laboratory analyses and interpretation of results. The study was held in a multinational, multicultural, ethnically diverse population from various countries. It was designed to find out whether there is a correlation between adverse pregnancy outcomes and maternal glucose intolerance that falls short of overt diabetes values and what it is. Also, it was meant to set the evidence-based criteria for diagnosis and classification of GDM, to be based upon the correlation between glycemic levels and perinatal outcome. The preliminary hypothesis of the study was that gestational hyperglycemia, even below the threshold for diabetes, is associated with increased maternal, fetal and neonatal morbidities.

Are women with GDM predisposed to post-partum diabetes mellitus? Which interventions are most successful in preventing this transition?

■ Donald R Coustan

The O'Sullivan and Mahan criteria for diagnosing GDM were validated by their predictive value for future Type 2 diabetes; approximately 50% of GDM patients developed Type 2 diabetes over the ensuing 20 years. A varying proportion of GDM patients will still have diabetes when tested 4–6 weeks post-partum, and probably had the condition prior to pregnancy. Another sizable proportion will have prediabetes, being either IGT, impaired fasting glucose or both; these women are at the highest risk for subsequent diabetes. A randomized trial compared >3000 individuals with prediabetes (both fasting and 2-h GTT values elevated but not diagnostic

of diabetes) randomized to metformin 850 mg twice daily, a lifestyle modification program or placebo followed for an average of 2.8 years [7]. Of subjects randomized to placebo, 11%/year developed Type 2 diabetes, versus 7.8% in the metformin group and 4.8% in the lifestyle intervention group. Lifestyle intervention (aimed at 7% weight loss using a healthy diet and at least 150 min of moderate physical activity per week) reduced the likelihood of diabetes by 58%; metformin reduced the likelihood by 31%. In order to prevent one case of diabetes over 3 years, 6.9 individuals would have to participate in the lifestyle intervention program or 13.9 would have to take metformin. In a subanalysis, subjects with previous GDM who were randomized to placebo in the aforementioned study were much more likely to develop Type 2 diabetes (15.2%/year) than those without a history of GDM (8.9%/year), even though their glucose values at enrollment were similar [8]. Metformin and lifestyle intervention had similar effects, each reducing the likelihood of diabetes by approximately 50%.

The identification of GDM offers an important opportunity to prevent diabetes in the future. Testing for diabetes or prediabetes after pregnancy and prescribing lifestyle modification (or alternatively metformin) is a highly effective intervention.

How successful are alternative therapies such as intensive lifestyle modification & glyburide treatment in this patient group?

■ Moshe Hod

Glucose metabolism usually returns to normal in women who were diagnosed with GDM unless they suffer from prediabetes (IGT or impaired fasting glycemia) or frank diabetes (including pre-existing Type 1 or 2 diabetes that was unrecognized before pregnancy). Women who were diagnosed with GDM are more likely to suffer from GDM in consecutive pregnancies. The recurrence rate may be as high as 75% if insulin treatment was required. Furthermore, they are at risk of developing Type 2 diabetes later in life. A review surveying 28 studies regarding risk factors associated with later diagnosis of Type 2 diabetes reported that the

rate of transformation to Type 2 diabetes was up to 70% over a long follow-up period (up to 28 years) and the incidence increased most rapidly during the first 5 years post-partum. This review also found that the factor most predictive of developing Type 2 diabetes was fasting glucose levels from OGTTs performed during pregnancy.

All women who were diagnosed with GDM should be re-evaluated during the post-partum period with a 75-g OGTT performed 3–6 weeks after delivery. This test may help to determine whether one of the three following conditions exists:

- Overt diabetes: if fasting blood glucose level is >126 mg/dl or the 2-h level is 200 mg/dl or above;
- Impaired glucose tolerance: fasting blood glucose level between 100 and 125 mg/dl or the 2-h level is 140–199 mg/dl;
- Normal: fasting plasma glucose below 100 mg/dl and 2-h value <140 mg/dl.

Women who are found to have prediabetes should be advised about lifestyle modification and the increased risk for GDM in future pregnancies. A yearly repeat of the GTT may also be prudent so that timely intervention could be offered to those who subsequently convert to diabetes (based on the National Service Framework for diabetes recommendations).

The study concluded that women with a history of GDM who currently have IGT remain at an increased risk of developing diabetes years after the index pregnancy and appear to benefit from either lifestyle or pharmacologic interventions.

In what ways are maternal GDM & obesity associated with adverse pregnancy outcomes?

▪ Donald R Coustan

HAPO data indicate that both maternal glucose and obesity are independently associated with adverse outcomes. The associations of each OGTT value with each primary outcome (birth weight >90th percentile, primary cesarean section, neonatal hypoglycemia and cord blood C-peptide >90th percentile), as well as with secondary outcomes such as neonatal adiposity, preeclampsia, shoulder dystocia and delivery

after <37 weeks gestation, were independent of BMI at the time of the GTT [9]. Conversely, when the associations of BMI with primary and secondary outcomes were adjusted for maternal fasting glucose, they were independently associated with birth weight >90th percentile, primary cesarean section, cord C-peptide >90th percentile (a marker for fetal hyperinsulinemia) and preeclampsia [10]. There was an independent negative association of BMI and pre-term delivery. Because subjects recruited for the HAPO study were unblinded for safety reasons when fasting plasma glucose >105 mg/dl (5.8 mmol/l) or 2-h OGTT >200 mg/dl (11.1 mmol/l), the 1.7% of subjects with the greatest hyperglycemia were excluded from analyses. These subjects would comprise the most severe 10% of GDM patients had they been included. Thus the range of glucose values in the analyses were truncated at the high end. There was no truncation of BMIs, so the influence of BMI (vs glucose) on outcomes is artificially strengthened. Nevertheless, glucose values were associated with outcomes independently of BMI.

When data were analyzed to compare the impact of obesity and of GDM, each was independently associated with adverse pregnancy outcomes, and when combined, they had a greater impact than either one alone [10].

From the perspective of maternal health, efforts to prevent and reverse obesity are appropriate at any time of life. Prevention of excessive weight gain during pregnancy is also a reasonable goal. It is also clear that treating GDM is practical and effective. There need not be a choice between preventing the adverse effects of maternal obesity and the adverse effects of GDM.

What challenges remain in this field? What will be the main research focus in the next 5 years?

▪ Donald R Coustan & Moshe Hod

Many challenges remain, and there will be plenty to keep basic scientists and clinical researchers busy. Potential issues include:

- As the IADPSG recommendations for the diagnosis of GDM are adopted, research into new strategies for delivering

care to patients with GDM will be of great importance;

- How can we deliver care more efficiently with limited resources? Can counseling and monitoring be carried out safely and effectively in a group setting and/or by healthcare professionals who are not physicians?
- Do all patients with GDM require the same treatment paradigm? Can some patients with milder GDM perform self-glucose monitoring less frequently than daily? Which patients require antepartum fetal testing, and how often? What is the most appropriate timing of delivery for mild GDM patients?
- What is the most effective dietary prescription for mild GDM?
- What are the most appropriate goals for glucose control in GDM pregnancy?
- What are the long-term effects of oral antidiabetic medications used during pregnancy? Metformin and glyburide both cross the placenta. Are the long-term fetal effects of these drugs beneficial or harmful? Are exposed fetuses more or

less likely to develop obesity, diabetes and/or metabolic syndrome as they mature? Because of the long follow-up period necessary to address these questions, animal models may be helpful;

- Do other newer antidiabetic medications such as α -glucosidase inhibitors, incretin-based therapy, dipeptidyl peptidase IV inhibitors and/or amylin analogs offer promise for treating GDM? Which ones do and do not cross the placenta?
- Are offspring of GDM pregnancies more likely to develop obesity and diabetes as they mature, as was previously shown in the Pima population?

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