EDITORIAL

Gestational diabetes mellitus: why screen and how to diagnose

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Abstract

Gestational diabetes mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy. Women with GDM and their offspring have an increased risk of developing type 2 diabetes mellitus in the future. The global incidence of GDM is difficult to estimate, due to lack of uniform diagnostic criteria. Various diagnostic criteria have been proposed. The benefit of treating GDM has also been controversial. The clinical significance of treating maternal hyperglycemia was made evident in the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study. The HAPO study demonstrated that there is a continuous association of maternal glucose levels with adverse pregnancy outcomes and served as the basis for a new set of diagnostic criteria, proposed in 2010 by the International Association of Diabetes and Pregnancy Groups (IADPSG). According to these criteria the diagnosis of GDM is made if there is at least one abnormal value (≥92, 180 and 153 mg/dl for fasting, one-hour and two-hour plasma glucose concentration respectively), after a 75 g oral glucose tolerance test (OGTT). Hippokratia 2010; 14 (3): 151-154

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For many years, gestational diabetes mellitus (GDM) has been defined as "any degree of glucose intolerance with onset or first recognition during pregnancy"[1]. According to the American Diabetes Association (ADA), it complicates approximately 7% of all pregnancies[1], whereas its total incidence is estimated up to 17.8%[2]. Women who have had GDM have at least a seven-fold increased risk of developing type 2 diabetes mellitus in the future[3]. Moreover, the presence of a hyperglycemic intrauterine enviroment due to GDM is associated with the development of type 2 diabetes in the offspring[4]. Additionally, there is evidence that women with GDM are less likely to breastfeed and that breastfeeding improves the subsequent glucose tolerance of the mother and may reduce the risk of type 2 diabetes in children[5]. Even though GDM is a common disorder in pregnancy, it has been difficult to compare its frequency among various populations and estimate its global incidence, due to the lack of uniform diagnostic criteria[6].

What are the existing diagnostic criteria?

O' Sullivan and Mahan in 1964 proposed the first diagnostic criteria for GDM, assaying whole blood glucose with the Somogyi-Nelson method, during a three-hour oral glucose tolerance test (OGTT)[7]. Glucose levels of 90, 165, 145 and 125 mg/dl (for fasting, one-hour, two-hour and three-hour postglucose load respectively) were proposed as diagnostic thresholds for GDM. More than a decade later, in 1979, the National Diabetes Data Group (NDDG) suggested measuring plasma instead of whole blood glucose and set new threshold values (105, 190, 165 and 145 mg/dl)[8]. In 1982, Carpenter and Coustan proposed changing the values to 95, 180, 155 and 140 mg/dl[9]. According to the NDDG and Carpenter and Coustan criteria, the diagnosis of GDM is established if two or more glucose values are higher than the defined cutoffs during a three-hour OGTT. In 1989, Sacks et al proposed the more inclusive criteria of 96, 172, 152 and 131 mg/dl, after calculating glucose concentrations in paired whole blood and plasma specimens of 995 consecutive pregnant women[10].

All the aforementioned diagnostic thresholds were based on data from women who were diagnosed with diabetes after gestation and not on any short-term adverse pregnancy outcomes. In 2010, the International Association of Diabetes and Pregnancy Groups (IADPSG) proposed a new set of criteria, based on the incidence of adverse perinatal outcomes, as assessed in the Hyperglycemia and Adverse Pregnancy Outcomes (HAPO) study[11,12]. According to these criteria, the diagnosis of GDM is made if at least one value of plasma glucose concentration is equal to or exceeds the thresholds of 92, 180 and 153 mg/dl (for fasting, one-hour and 2-hour postglucose load glucose values respectively), after performing a 75 g OGTT[2].

To treat or not to treat?

The rationale of screening for GDM is based on the assumption that treating the condition leads to a decrease in maternal or fetal complications. The effect of GDM treatment on fetal and maternal outcomes has long been

controversial. According to a 2003 Cochrane Collaboration systematic review "there are insufficient data for any reliable conclusions about the effects of treatments for impaired glucose tolerance on perinatal outcome"[13]. Data from two pilot randomized controlled trials suggested that intensive GDM treatment had no statistically significant effect on various perinatal outcomes[14,15]. The first study, by Garner et al[14], included 300 women between 24 and 32 weeks of gestation, who were diagnosed with GDM according to the Hatem et al criteria[16], following a 75 g OGTT. Women were randomized either to strict glycemic control and tertiary care, or to routine obstretic care. There were no statistically significant differences between the two groups in birth weight or in any of the secondary outcomes, including neonatal hypoglycemia, birth trauma, perinatal mortality and cesarean section rates. In a similar study by Bancroft et al, 68 pregnant women with impaired glucose tolerance (IGT) were randomly assigned[15] to either intensified or standard antenatal care. No statistically significant differences were found in any neonatal or maternal outcomes between the groups. However, both pilot trials lacked sufficient power to detect differences in the measured outcomes and they both suffered from ineffective blinding.

The clinical significance of treating GDM with respect to various adverse perinatal outcomes has been demonstrated by Langer et al in an observational case-control study of 2775 pregnant women[17]- 555 with untreated GDM, 1110 with treated GDM and 1110 non-diabetic controls. Diagnosis of GDM was based on the criteria by Carpenter-Coustan[9]. Rates of a composite adverse outcome (stillbirth, neonatal macrosomia/large-for-gestational-age (LGA), neonatal hypoglycemia, erythrocytosis and hyperbilirubinemia) in the three groups were 59%, 18% and 11%, respectively. More robust evidence concerning the reduction of risk of perinatal complications following treatment of GDM was provided by the Australian Carbohydrate Intolerance Study in Pregnant Women (ACHOIS)[18] and a trial conducted by Landon et al[19]. In each of these randomized controlled trials, approximately 1000 women with GDM were assigned either to prenatal dietary advice, blood glucose monitoring and insulin therapy (treatment group), or to routine care (control group). The incidence of various predefined perinatal outcomes, including LGA births and preeclampsia, was significantly reduced in the treatment group in both trials[18,19]. However, there were differences in the GDM diagnostic criteria used in each of the studies, hence the study population, was not identical in the two trials. The first study to provide solid evidence of a direct association between maternal glucose levels and pregnancy outcome, irrespective of the diagnosis of GDM, was the HAPO study[11,12].

The HAPO study

The HAPO study was a large multinational prospective study that included 25505 women in the third trimester of gestation[11]. The participants underwent a two-hour OGTT with 75 g of glucose between 24 and 32 weeks of gestation and their glycemic levels were investigated in relation to predefined adverse pregnancy outcomes. The four predifined primary outcomes were primary cesarean delivery, clinical neonatal hypoglycemia, and birth weight and cord serum C-peptide above the 90th percentile. Premature delivery, shoulder dystocia or birth injury, intensive neonatal care, hyperbilirubinemia, and preeclampsia were chosen as secondary outcomes. In respect to secondary outcomes, glucose levels were analyzed only as a continuous variable. For the primary outcomes, glucose concentration was also analyzed as a categorical variable, after stratifying the women into seven categories according to the glucose values obtained during the two-hour OGTT.

The frequency of the primary outcomes increased in parallel with increasing maternal glucose levels and odds ratios (ORs) were calculated for all seven glycemic categories, using as reference (OR=1) the category with the lowest glucose concentration ranges. The ORs increased across the categories of maternal glycemia and these results were statistically significant for all primary outcomes, with the exception of neonatal hypoglycemia. Similarly, when glucose concentration was analyzed as a continuous variable, a continuous association of maternal glucose with primary and secondary outcomes was observed. Notably, these associations were detected even for low glucose levels and did not differ among the 15 centers in nine countries that participated in the study[11].

Even though the HAPO study indicated the need to revise the diagnostic criteria of GDM, it did not deduce any threshold glucose values that can be used in clinical practice. Therefore, even after completion of the study, screening and diagnostic methods of GDM still differ among various associations and organizations.

ADA, ACOG, WHO and IDF recommendations

The American Diabetes Association (ADA) in its more recent position statement suggests that all pregnant women should be screened for GDM between the 24th and 28th week of gestation, unless they are of low risk status[1]. Women of low risk are defined as those that fulfill all of the following characteristics: age below 25 years, normal pregestational weight, member of an ethnic group with low prevalence of diabetes, no history of glucose intolerance and poor obstetrical outcome, and no known diabetes in first degree relatives. Two approaches are suggested for screening for GDM (at 24-28 weeks). In the two-step approach, women are initially screened by measuring plasma glucose 1 hour after a 50 g glucose load; women with glucose concentration $\geq$130 or $\geq$140 mg/dl (depending on the diagnostic sensitivity we wish to achieve) undergo an 100 g OGTT on a separate day. In the one-step approach, the 100 g OGTT is performed directly without any initial screening. In both occasions, the diagnosis of GDM is established by the Carpenter and Coustan criteria.

The American Council of Obstetricians and Gynecologists (ACOG) also suggests screening of all women

except for those of low risk status[20]. It supports the use of the 100 g OGTT and application of either NDDG or Carpenter and Coustan criteria. The World Health Organization (WHO) recommends using the 75 g two-hour OGTT and the diagnostic thresholds of 126 mg/dl and 140 mg/dl for fasting and 2-hour glucose concentrations, respectively[21]. Finally, according to the 2009 International Diabetes Federation (IDF) recommendations, women who are at high risk (history of previous GDM) should undergo an OGTT as soon as possible[22]. For all other women the OGTT should be performed between the 26th and 28th week of gestation. In both cases, a one-stage procedure with the 75 g OGTT is preferred.

Due to the lack of uniform diagnostic criteria for more than 40 years, there has been no global consensus about the appropriate screening/diagnostic test, whether it should be applied selectively or to all pregnant women and about the diagnostic thresholds of each test. ADA[1], IDF[22] and other organizations are expected to consider adopting the recently proposed IADPSG diagnostic criteria[2].

IADPSG recommendations

The IADPSG was formed "as an umbrella organization to facilitate collaboration between the various regional and national groups that have a primary or significant focus on diabetes and pregnancy"[2]. In 2010, the IADPSG proposed a new set of diagnostic criteria for GDM, based on the results of the HAPO study[11,12], thus association of maternal glucose concentration with the risks for birth weight, cord C-peptide and % neonatal body fat to be above the 90th percentile. Mean values for fasting, one-hour, and two-hour OGTT plasma glucose of the entire study population were used as reference for calculation of ORs. An OR of 1.75 was prespecified by the IADPSG consensus panel as a threshold to define the diagnostic criteria. The values that correspond to this OR are 92, 180, and 153 mg/dl for fasting, one-hour, and two-hour OGTT plasma glucose concentrations, respectively. These cutoff points represent the glucose concentrations at which odds for birth weight, cord C-peptide and % neonatal body fat to be above the 90th percentile are 1.75 times the odds of these outcomes at reference glucose values (mean glucose values)[2]. The diagnosis of GDM is made if one or more glucose values during a 75 g OGTT meet or exceed the above thresholds. According to these criteria, the incidence of GDM in the overall population in the HAPO study was 17.8%. When ORs of 1.5 and 2.0 were used as thresholds, the percentage of women that met the diagnostic criteria was 25% and 8.8%, respectively[2].

For the identification of overt diabetes during pregnancy and its distinction from GDM, the IADPSG recommends that fasting plasma glucose (FPG) or glycosylated hemoglobin (A1C) should be measured at the first prenatal visit on all or only high-risk women (depending on the frequency of diabetes in the background population and on local cicrumstances)[2]. Values equal to or above 126 mg/dl and 6.5% (for FPG and A1C, respectively) establish the diagnosis of overt diabetes. Women with 92≤ FPG <126 mg/dl are diagnosed with GDM, while those with FPG<92 mg/dl should undergo a 75 g OGTT at 24 to 28 weeks of gestation. Finally, the diagnosis of GDM by means of the 75 g OGTT is based on the aforementioned criteria (92, 180, and 153 mg/dl for fasting, one-hour, and two-hour OGTT glucose concentrations, respectively)[2].

Concluding remarks

Lack of uniform diagnostic criteria for gestational diabetes mellitus has often led to misconceptions and undertreatment of GDM. The diagnostic threshold values of various organizations are summarized in Table 1. The recently proposed IADPSG criteria are based on the results of the HAPO study, which demonstrated a continuous as-

Table 1: GDM diagnostic threshold values from various organizations.

		Plasma glucose concentration thresholds (mg/dl)			
Organization	**OGTT glucose load**	**Fasting**	**1-hour**	**2-hour**	**3-hour**
ADA*	100 g	95	180	155	140
ACOG*	100 g	105	190	165	145
WHO§	75 g	126	-	140	-
IADPSG§	75 g	92	180	153	-

*Diagnosis of GDM if two or more glucose values equal to or exceeding the threshold values
§Diagnosis of GDM if one or more glucose values equal to or exceeding the threshold values
GDM: Gestational Diabetes Mellitus, OGTT: Oral Glucose Tolerance Test, ADA: American Diabetes Association, ACOG: American Council of Obstetricians and Gynecologists, WHO: World Health Organization, IADPSG: International Association of Diabetes and Pregnancy Groups

sociation of maternal glycemia with adverse pregnancy outcomes. The IADPSG consensus panel consisted of leading experts in the field of GDM from a variety of countries, hence their recommendations are expected to "serve as the basis for internationally endorsed criteria for the diagnosis and classification of diabetes in pregnancy"[2], as stated in its 2010 report. The IADPSG suggests screening in all women at the first prenatal visit and a 75 g OGTT between the 24th and 28th week of gestation in those not already diagnosed with overt diabetes or GDM by early testing. One or more abnormal value (≥ 92, 180 or 153 mg/dl for fasting, 1-hour and 2-hour plasma glucose, respectively) after a 75 g OGTT is diagnostic of GDM. However, as a result of using these criteria, the total incidence of GDM, hence its total therapeutic costs will increase. Thus, additional randomized clinical trials are required in order to determine the cost-effectiveness of the IADPSG criteria and their association with long-term development of diabetes mellitus and metabolic disorders in the mother and the offspring[2].

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