REVIEW

SCREENING, DIAGNOSIS AND GLUCOSE MONITORING OF GESTATIONAL DIABETES – A BRIEF UPDATE

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ABSTRACT

Diabetes is most common metabolic and clinical condition in pregnancy. The diabetes complicating pregnancy may be either preexistent (type 1 diabetes, type 2 diabetes or other specific forms) or gestational diabetes. International Diabetes Federation estimates that 6% of live births had some form of hyperglycemia in pregnancy and approximately 84% of it was attributable to gestational diabetes. Pregnancies complicated by gestational diabetes are associated with adverse short-term and long-term maternal and fetal outcomes. In order to reduce adverse pregnancy outcomes a proper diagnosis of GDM is required and carefully monitoring and control of blood glucose levels is mandatory.

KEYWORDS: *gestational diabetes, diagnostic criteria, continuous glucose monitoring*

INTRODUCTION

Currently gestational diabetes mellitus (GMD) is defined as a form of diabetes which is first diagnosed in pregnancy during the second or third trimester and which was not clearly overt diabetes prior to gestation [1]. This definition imposed in the last decade in order to clearly underline the difference between a preexisting diabetes (usually a type 2 diabetes mellitus - T2DM), with hyperglycemia at the time of conception and during main organogenesis period, and associated with an increased risk of congenital malformations [2], and diabetes occurring later in pregnancy and indicating an underlying b-cell dysfunction that cannot compensate for the insulin resistance induced hormonal changes during pregnancy.

Depending on the general T2DM prevalence, on the utilized diagnostic cut off values and strategy, on the characteristics of the studied population, the prevalence of GDM is variable in different reports, but globally, the International Diabetes Federation appreciates that 1 in 6 births is affected by GDM (16.8%). [3]. The most affected countries are those with low- and middle-income, with limited access to maternal care. A recent exhaustive review of evidences from retrospective, prospective, and meta-analysis studies, identified as established risk factors for GDM ethnicity, obesity, and family history of diabetes [4]. Other risk factors, less clearly identified are represented by lifestyle, diet type, body composition, pregnancy weight gain, increasing age at conception, polycystic ovarian syndrome, multiple pregnancies, previous macrosomic baby, previous stillbirth or hypothyroidism [5]. The present paper is a short review that describes the screening and diagnostic procedure of GDM in relation to the latest medical trends.

MATERIALS AND METHOD

In order to conduct the research for this review a search on Web of Science database was conducted using gestational diabetes, screening and diagnosis as key words. The search was filtered to include only recent articles, published since 2008. However, 3 older papers were included because of the paramount importance of the data they presented. After the initial search 348 articles were listed, but only 22 were considered relevant enough to be included in our research. Their relevance was established using the PICO (population, intervention, control, and outcomes) format. The information was presented in two sections: one was centered on screening and the other one on diagnosis.

RESULTS AND DISCUSSION

Screening for GDM

Distinguishing between diabetes in pregnancy and GDM was first proposed by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) consensus [6] as a consequence of the data accumulated in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study. This was a large prospective, observational, multicenter, blinded trial that enrolled more than 25,000 nondiabetic pregnant women, from 9 different countries, in 15 field centers, and was designed in order to elaborate globally accepted cut-off glycemic values for GDM, based upon its predictive power for adverse pregnancy outcomes (short-term and perinatal) [7]. A 75-g, 2-hour OGTT was performed in each pregnant woman, between 24 and 32 weeks of gestation (mean gestational age, 27.8 weeks), and blood glucose samples were obtained in fasting state, at 1 and 2 hours during the test. Increases in each of the 3 values on the 75-g, 2-hour OGTT were associated with continuous, graded increases in the likelihood of adverse pregnancy outcomes such as large for gestational age, cesarean section, fetal insulin levels, and neonatal fat content [7,8]. There were not obvious inflection points in the associations with risk of poor pregnancy outcomes. At that time there was a stringent need for such a study, as GDM criteria were, even from the beginning subject of debate, with a multitude of international organizations giving various definitions. IADPSG [6] recommend screening of ‘all or high-risk women’ at the initial visit during pregnancy, using the standard diagnosis criteria for non-gestational diabetes, and if these criteria are met, the diagnosis should be overt (preexisting) diabetes which was not recognized before pregnancy. The following factors situate the women at high risk for diabetes: obesity, previous pregnancy complicated by GDM or having delivered a baby weighing more than 9

lb., strong family history for diabetes, high-risk race/ethnicity, previously diagnosis of altered glucose tolerance states, presence of hypertension, dyslipidemia or cardiovascular disease in overweight/obese subjects, detection of glycosuria. Universal screening is indicated in all women not yet diagnosed with diabetes at 24–28 weeks of gestation with the fasting 75-g OGTT [6].

Diagnosis criteria for GDM

The first case of hyperglycemia in pregnancy was described in 1824 in the doctoral thesis of Heinrich Bennewitz from Charite Hospital in Berlin [9], but it was not until 1940's when milder degrees of hyperglycemia in pregnancy were beginning to be recognized as associated to pregnancy outcomes. Then a term of 'prediabetes in pregnancy' and a concept of 'temporary' or 'latent' diabetes gains place into the history of medicine. O´Sullivan et al. designed first diagnostic test for GDM. The approach included two steps: an initial test consisting in a 50g oral glucose load with a single glycemic measurement at one hour, recommended at the first medical visit of the pregnant woman. If abnormal, this screening test was followed by a three-hour 100g oral glucose load with four blood glucose samples (fasting, at 1, 2 and 3 hours after the load) and the diagnosis of GDM established if two or more values were above the mean plus two standard deviations [10]. After some modifications made by Carpenter and Coustan, the test was the main screening and diagnostic tool for GDM in the USA [11].

After HAPO study, IADPSG recommended one step approach. At 24-28 weeks of gestation, according to IADPSG, the diagnosis of GDM is established if any of the following three 75-g, 2-hour oral glucose tolerance thresholds are met or exceeded: fasting 92 mg/dL, 1-hour 180 mg/dL, or 2 hours 153 mg/dL [6]. The oral glucose tolerance test should be performed after an overnight fasting at least 8 hours. Since publication of these criteria, many international, national or local professional associations adopted it. American Diabetes Association (ADA) endorsed the IADPSG recommendation in 2011, even if it recognized an expected increase in the prevalence of GDM because only one abnormal value was needed for diagnostic [12]. Women with less expressed hyperglycemia than identified using older GDM diagnostic criteria would benefit most. In 2013 National Institutes of Health (NIH) gathered a panel of representatives and reviewed once more the evidence. Although NIH consensus panel appreciated that there are clear benefits to international standardization with regard to the one-step approach, it found that at the moment there is insufficient evidence of maternal or perinatal benefit to adopt a one-step approach proposed by the IADPSG [6], and continued to recommend the 2 step strategy of screening with an initial 1-h 50-g glucose load test, followed by a 3-h 100-g oral glucose tolerance test (OGTT) for those women who screen positive [13]. As a consequence, since 2014 ADA appreciated that are insufficient data to strongly demonstrate the superiority of one strategy over the other and recommended that screening should be realized with either of two strategies. [14]. ADA also acknowledges that different magnitudes of maternal hyperglycemia and maternal/fetal risk will be identified with different strategies [14]. Current ADA recommendations for GDM diagnosis are presented in Table 1 [1]. ScreenR2GDM, a recent large randomized trial enrolled 23,792 women in order to compare the one-step strategy with the two-step strategy to screen and diagnose of GDM in relationship with maternal and neonatal outcomes. Despite more diagnoses of GDM with the one-step approach (16.5%) than with the two-step approach (8.5%), the study did not identify significant differences between the two strategies in the risks of the primary outcomes relating to perinatal and maternal complications. [15]. The study did not address the potential long-term benefits of increased diagnosis of GDM potentially resulting from identifying more women at high risk for subsequent diabetes in whom early intervention in order to reduce risk might be implemented.

Concerning HbA1c, there is no cutoff point to establish the diagnosis of GDM and it is not used to diagnose GDM.

Diagnostic strategy		Fasting plasma glucose (mg/dL)	Glucose challenge test			
			OGTT type	1-h plasma glucose (mg/dL)	2-h plasma glucose	3-h plasma glucose (mg/dL)
One-step	One value is sufficient for diagnosis	≥92	75 g	≥180	≥153	Not required
Two-step	Step 1	Not required	50 g	If ≥130, 135 or 140 proceed to step 2	Not required	Not required
	Step 2 (two values are needed for diagnosis) Carpenter–Coustan criteria [11]	≥95	100 g	≥180	≥155	≥140

Table 1 – Diagnosis of GDM [1]

Glycemic targets and glucose monitoring in GDM

Even if in most cases of GDM the glucose metabolism normalizes soon after delivery, GDM is associated with short- and long-term risks both for mother and fetus. Fetal risks associated with GDM are especially macrosomia, shoulder dystocia. The neonate has increased risk for respiratory distress syndrome and neonatal metabolic complications such as neonatal hypoglycemia, hyperbilirubinemia, polycythemia. Long-term risks for the offspring are obesity, T2dm, and metabolic syndrome in adolescence or at the adult age. Short-term maternal risks include preeclampsia, polyhydramnios, pre-term delivery, caesarian delivery. On long-term GDM is an independent risk factor for T2DM, metabolic syndrome, hypertension, and cardiovascular disease [16].

After GDM diagnosis, pregnant women need individualized medical care that includes medical nutritional therapy, physical activity counseling, self-monitoring of blood glucose, and obstetric care. Self-monitoring of blood glucose levels (SMBG) is the preferred measure of glycemic control during pregnancy. In order to reduce adverse pregnancy outcomes, blood glucose values should be as close as possible to the normal pregnancy glucose values. Therapeutic targets are mainly based on diagnostic thresholds. ADA [17] recommends the following targets for maternal capillary glucose concentrations: pre-prandial: ≤95 mg/dL, and postprandial either: 1-h post-meal: ≤140 mg/dL or 2-h post-meal: ≤120 mg/dL.

Due to the modified red blood cell turnover and physiological changes in glycemic parameters, glycated hemoglobin (HcA1c) is considered useful, but it must be regarded as a complementary measure for blood glucose control, and may need to be monitored more frequently than usual (e.g., monthly) [17]. Also, HbA1c may not capture very well the postprandial glycemic load. ADA appreciates a target value for HbA1c of less than 6% to be optimal if it can be achieved without significant hypoglycemia [17].

The new technologies of continuous glucose monitoring (CGM) may bring additional information about glucose control, glycemic profiles and their relationship with pregnancy outcomes. Among benefits of CGM we may notice better identification of highest postprandial glycemic excursions and of glycemic variability. Several studies are addressing the potential benefits of CGM systems in GDM, but the available data are scarce; many of these studies having a small number of patients and a short period of glucose monitoring period (e.g. 72 hours). The obtained results are not always consistent.

Some studies have compared the CGM usage vs. SMBG usage in GDM and occurrence of adverse maternal and neonatal outcomes. A study enrolling 340 women with GDM, compared 150 women which utilized retrospective intermittent CGM (every 2–4 weeks) to the rest which utilized the routine SMBG, and showed lower risk of preeclampsia, caesarian section and lower infant birth weight in the CGM group [18]. The GlucoMOMS, a multicenter, randomized trial, compared use of intermittent retrospective CGM (every 6 weeks) to SMBG in pregnant women with T1DM, T2DM, or insulin-treated GDM [19]. CGM use did not reduce the risk of macrosomia in studied groups, but it should be noticed that the study included a heterogeneous group and it was underpowered to detect whether women with GDM might benefit. Another smaller randomized trial compared intermittent retrospective CGM (at 28, 32, and 36 weeks' gestation) with SMBG in 50 women with insulin-treated GDM. Using CGM was associated with improved HbA1c at 37 weeks' gestation, with a reduced time spent in hyperglycemia without increasing time in hypoglycemia [20].

Some studies have assessed CGM-glycemic profiles in pregnant women with GDM in correlation with pregnancy outcomes. As CGM provides frequent glucose measurements it is obvious that it produces far more information on glucose trends than either SMBG or HbA1c. CGM provides also information about glycemic excursions related to meal and during nighttime. Law et al. detected significantly higher glucose levels for 6 h overnight (0030–0630 h) in mothers of LGA infants [21]. When analyzing different patterns of hyperglycemia and the development of maternal-fetal complications, time above range after lunch was find to increase the probability of macrosomia and large for gestational age [21]. CGM facilitate better recognition of onset of hyperglycemia and better therapeutic intervention, with more appropriate adjustments in diet and/or medication, thereby improving prognosis in women with GDM.

CONCLUSION

In last decades, GDM appears to be the most common condition in pregnancy with health consequences for mothers and offspring during ante-, intra- and post-partum periods. Identifying GDM is extremely important because with appropriate therapy fetal and maternal morbidity can be decreased. Established risk factors for GDM include ethnicity, obesity, and family history of diabetes. Knowing these factors and applying universal screening at 24-28 weeks of gestation with either one-step approach or two-step approach enable the clinician to control early the blood glucose levels and to reduce the occurrence of adverse outcomes.

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