

Screening For Gestational Diabetes Mellitus

Abstract

Gestational diabetes is a carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy. It is the most common metabolic disorder affecting pregnancy. Recognizing and treating diabetes or any degree of glucose intolerance in pregnancy results in lowering maternal and fetal complications. These patients present higher risk for excessive weight gain, preeclampsia, cesarean sections, a high risk of developing type 2 diabetes and cardiovascular disease in the future. Complications of infants are; higher risk for macrosomia, birth trauma, hypoglycemia, hypocalcemia, hyperbilirubinemia, respiratory distress syndrome, polycythemia, obesity and type 2 diabetes.

Gestational diabetes mellitus (GDM) screening should be performed at 24-28 gestational weeks and followed by definitive testing in women who are labeled as high-risk population. Two strategies are used to screen for gestational diabetes. In the two-step approach, the 50-g oral glucose challenge test (OGCT) is performed between 24 and 28 weeks of gestation in a nonfasting state. Alternatively, in the one-step approach, a 75-g glucose load is administered after measuring a fasting glucose level, and the plasma glucose levels are evaluated after 1 and 2 hours of the administration. There are the other methods for screening, including HbA1C and fasting blood glucose, but an exact approach for gestational diabetes screening has not yet been established.

Keywords: Gestational diabetes mellitus; Screening; One-step approach; Two-step approach

Review Article

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Muge Eylem Sengul¹, Elif Gozdemir^{2*} and Serap Simavli³

¹Osmaniye Merkez Number 04 Family Health Center, Turkey

²Department of Obstetrics and Gynecology, Gaziosmanpasa University School of Medicine, Turkey

³Department of Obstetrics and Gynecology, Pamukkale University School of Medicine, Turkey

***Corresponding author:** Elif Gozdemir, Gaziosmanpasa University School of Medicine, Tokat, Turkey, Tel: +905337404155; Email: dreلاكilic@gmail.com

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Abbreviations: GDM: Gestational Diabetes Mellitus; OGCT: Oral Glucose Challenge Test; IADPSG: International Association of the Diabetes and Pregnancy Study Groups; BMI: Body Mass Index; NDDG: National Diabetes Data Group; CC: Carpenter and Coustan criteria; WHO: World Health Organization; HAPO: Hyperglycemia and Adverse Pregnancy Outcomes; CDA: Canadian Diabetes Association; NICE: National Institute for Health and Clinical Excellence; NIH: National Institutes of Health; AACE: American Association of Clinical Endocrinologists; ACOG: American College of Obstetricians and Gynecologists; OGTT: Oral Glucose Tolerance Test

Introduction

GDM is a carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy [1]. GDM is an important public health problem. As older age at pregnancy become more common, GDM's prevalence is increasing as obesity and sedentary lifestyle [2-5]. If GDM is unrecognized or left unregulated, there is an important risk of maternal, fetal and neonatal implications, including increased maternal weight gain, a higher rate of caesarean section, preeclampsia, shoulder dystocia and other birth traumas, macrosomia of newborn, and neonatal hypoglycemia, among others [6]. All these perinatal complications can be prevented or reduced, if the hyperglycaemia is diagnosed early enough [7,8]. During pregnancy, hyperplasia of the pancreatic β -cells occurs, leading to increased insulin secretion, and an early increase in insulin sensitivity is followed by progressive insulin resistance due to the placental secretion of diabetogenic hormones, including growth

hormone, corticotropin-releasing hormone, placental lactogen, and progesterone. GDM screening is universal and testing for GDM is usually done between 24 and 28 weeks of gestation [9,10]. The approach to screening gestational diabetes in pregnant women will be reviewed here.

Prevalence

GDM is a common disease affecting approximately 6-7% of pregnancies, with variations in prevalence noted among different races, ethnicities, screening practises, testing methods, and diagnostic criteria [11]. The prevalence has been increasing overtime, possibly due to increases in mean maternal age and weight. The prevalence of GDM is even higher among obese patients, ranging from 7-14% [12,13]. In 2010, International Association of the Diabetes and Pregnancy Study Groups (IADPSG) criteria proposed new screening and diagnostic criteria for gestational diabetes. The use of these criteria is predicted to increase the prevalence of gestational diabetes to 18% [14].

Risk Factors

The risk factors for GDM include having a family history of diabetes mellitus type 2 (DM2), being a member of an ethnic group that is at increased risk for the development of DM2 (i.e. Hispanic, African, Native American, South Asian, East Asian, or Pacific Islands ancestry), previous GDM, a macrosomic infant (defined as 4 kgs or more), a Body Mass Index (BMI) of ≥ 30 kg/m², unexplained intrauterine foetal death, unexplained birth of a malformed infant, a maternal age of ≥ 35 years, glycosuria at

the first prenatal visit, and a medical condition associated with the development diabetes, such as polycystic ovary syndrome, metabolic syndrome, or hypertension [15]. Gestational diabetes is less likely to develop among women who are younger (<25 years of age), have a normal BMI (<25 kg/m²), are white and non-Hispanic, have no first-degree relatives with diabetes, and have no history of previous glucose intolerance [16].

Approaches to Risk Reduction

Physical activity

Nonpregnant women who engage in regular exercise have a lower risk of developing DM2 compared to nonpregnant women who are sedentary. The effects of exercise on gestational diabetes have been explored with two types of studies: observational studies and randomised trials. The value of exercise was illustrated in 2011 with a meta-analysis that included seven pre-pregnancy studies and five early pregnancy studies. These studies have reported an association between increased physical activity and reduced risk of GDM [17]. As for during gestation, a 2014 meta-analysis of six randomised trials revealed that initiating an exercise program during pregnancy did not significantly reduce the risk of developing GDM compared with routine care [18].

Weight loss

In a cohort study, obese women who lost at least 4.5 kgs between pregnancies decreased their risk of gestational diabetes relative to obese women whose weight reduced by less than 4.5 kgs between pregnancies [19].

Adverse Outcomes during Pregnancy

The risks of adverse outcomes increase as maternal fasting plasma glucose levels increase above 75 mg/dl and as the one-hour and two-hour oral glucose tolerance test (OGTT) values increase. Associated foetal risks of GDM include macrosomia, shoulder dystocia, hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, and childhood obesity. Maternal risks include preeclampsia, caesarean delivery, and increased risk of developing

DM2 and cardiovascular disease later in life. Moreover, if maternal hyperglycaemia is present during the first trimester, it causes increasing the risk of miscarriage and congenital anomalies [20-28].

History

In 1960s, O'Sullivan et al. [29] proposed diabetes improve outcomes, the first evidence that screening, diagnosis and treatment of hyperglycaemia in women not previously known to have [29]. These criteria were later modified by the National Diabetes Data Group (NDDG) in 1979 as well as by Carpenter and Coustan. The Carpenter and Coustan criteria (CC) were lower than the NDDG criteria and therefore resulted in a higher prevalence of GDM [29-31]. In 1979-1980 international panels established the 2-h 75g OGTT as the diagnostic test for diabetes and glucose intolerance [30], this recommendation was extended by the World Health Organization (WHO) to pregnant women [32]. The 2-h 75g OGTT had been little examined during pregnancy, so the US(United States) National Diabetes Data Group (NDDG) continued to use the 3-h 100g OGTT [30].

In 2000, The NDDG recommendation had been followed by The American Diabetes Association (ADA). ADA recommended the use of the Carpenter and Coustan criteria for diagnosis of GDM. Over the last 3 decades these procedures and criteria were frequently adopted as a two-step procedure: a 50g 1-h challenge test and then a 100g 3-h OGTT for those positive at screening. In 2008, the results of the "Hyperglycemia and Adverse Pregnancy Outcomes (HAPO)" study were published. 25,505 pregnant women tested with a 2-h 75g OGTT for the classification of diagnostic criteria for GDM [22]. This major observational study provided valuable information regarding the risks of adverse outcomes associated with various degrees of maternal glucose intolerance. Based on the results of this study, the International Association of Diabetes and Pregnancy Study Groups (IADPSG) proposed a new diagnostic criterion in 2010 [14,22]. The IADPSG Consensus Panel recommended the diagnostic criteria for GDM presented in Table 1 [14]. These cut points were also recommended by the ADA for a 2-h 75g OGTT in its 2011 position statement [33].

Table 1: Diagnostic Thresholds for Gestational Diabetes Mellitus.

Dignostic criteria	Step	Glucose load, g	Fasting glucose load mg/dl	1h	2h	3h	Abnormal values, n
NDDG	2-step	100	105	190	165	145	2
CC	2-step	100	95	180	155	140	2
ADA(2000-2010)	2-step	75	95	180	155	-	2
CDA(2008)	2-step	75	95	191	160	-	2
IADPSG	1-step	75	92	180	153	-	1
WHO	1-step	75	110	-	140	-	1

ADA: American Diabetes Association; CC: Carpenter–Coustan; CDA: Canadian Diabetes Association; IADPSG: International Association of the Diabetes and Pregnancy Study Groups; NDDG: National Diabetes Data Group; WHO: World Health Organization

Most commonly used diagnostic criteria for GDM

The most commonly used guidelines for the diagnosis of GDM

recommend the following diagnostic criteria [1,14,34,35] (Table 2).

Table 2: Most commonly used guidelines for the diagnosis of GDM.

Organisation	Fasting Plasma glucose, mmol/L	Glucose Challenge	1-h plasma glucose	2-h plasma glucose	3-h plasma glucose
WHO 1999*	≥7.0	75g OGTT	Not required	≥ 7.8	Not required
American Congress of Obstetricians and Gynecologists**	≥ 5.3	100g OGTT	≥ 10.0	≥ 8.6	≥ 7.8
Canadian Diabetes Association***	≥ 5.3	75g OGTT	≥ 10.6	≥ 8.9	Not required
IADPSG****	≥ 5.1	75g OGTT	≥ 10.0	≥ 8.5	Not required

*one value is sufficient for diagnosis

** two or more values are required for diagnosis

***two or more values required for diagnosis

****one value is sufficient for diagnosis

Benefits of Screening

Treating screen-detected GDM with dietary modifications, glucose monitoring, and insulin can significantly reduce the risk for preeclampsia, foetal macrosomia, and shoulder dystocia [36].

Screening for Gestational Diabetes Mellitus

A screening test has to be sensitive, simple, cheap, defined with clear criteria, noninvasive, reproducible and available. Some authors are doubtful about any health advantages in screening for GDM [37]. The Preventive Services Task Force (USPSTF), the United Kingdom National Health Service and the Canadian Task Force didn't report any sufficient high-level evidence about cost-effectiveness of routine GDM screening [38]. In the United States of America (USA), most obstetricians prefer universal screening with an initial 50-g glucose challenge test (GCT) [39-41]. Very recently, the Canadian Diabetes Association (CDA) not only recommends the same sequential universal screening approach, but also offers an alternative with one-step 75-g oral glucose tolerance test (OGTT) [42].

The National Institute for Health and Clinical Excellence (NICE) recommends selective screening in asymptomatic patients based on the risk factor assessment and does not advocate the use of the GCT, fasting glycemia, random blood glucose, or glucosuria [39]. The NICE is currently in the process of reviewing their guidelines. The Society of Obstetricians and Gynaecologists of Canada (SOGC) still recommends routine screening at 24-28 weeks' gestation with the 50-g GCT but is against screening for low-risk women with glucose testing [43].

In 2013, the National Institutes of Health (NIH) published online the draft statement that the NIH panel did not find clear evidence to support adopting the one-step model, such as that proposed by IADPSG [44]. The American Association of Clinical Endocrinologists (AACE) and the ADA in 2011 recommend

screening of all women without a pregestational diabetes at 24-28 weeks' gestation with a 75-g 2-h oGTT [40].

Screening time

Screening is recommended after 24 weeks of gestation. Screening for GDM may occur earlier than 24 weeks of gestation in high-risk women (e.g. body mass index >30 kg/m², prior history of gestational diabetes, or known impaired glucose metabolism), but there is little evidence of the benefits or harms of screening before 24 weeks of gestation. Performing oGTT before 24 weeks' gestation didn't recommended by the IADPSG Consensus Panel [45].

In the absence of early screening or if early screening is negative, universal screening is performed at 24 to 28 weeks of gestation. A recent, randomised trial had shown the benefits of treating GDM and the possible reduction in healthcare costs that could be achieved with universal screening. Therefore, in 2011, the American College of Obstetricians and Gynecologists (ACOG) and ADA recommended universal screening because of the beneficial effects of screening, diagnosis and subsequent treatment [34,36]. Before 28 weeks fetal growth acceleration has already began, so screening after 28 weeks isn't logical. For healthy women without anamnestic risk factors GDM screening and diagnosis is performed between 24 and 28 weeks [7,38-40].

United States Preventive Services Task Force (USPTF) assessment for screening time

The USPSTF concludes with moderate certainty that screening for gestational diabetes after 24 weeks of gestation causes moderate reductions in maternal and foetal complications (specifically, the collective outcomes of preeclampsia, macrosomia, and shoulder dystocia). The USPSTF concludes that the evidence to support screening for gestational diabetes before 24 weeks of gestation is insufficient, and the balance of benefits and harms of

screening cannot be determined [36].

One-step and two-step approaches

Two strategies are used to screen for gestational diabetes. In the two-step approach, a 50-g oral glucose challenge test (OGCT) is performed between 24 and 28 weeks of gestation in a nonfasting state. If the screening threshold is met or exceeded (130 mg/dL, 135 mg/dl, or 140 mg/dL), patients receive the oral glucose tolerance test (OGTT). During the OGTT, a fasting glucose level is obtained, followed by the administration of a 100-g glucose load, and glucose levels are evaluated after 1, 2 and 3 hours of the administration. A diagnosis of GDM is made when two or more glucose values fall at or above the specified glucose thresholds [36].

These screening tests exhibited various sensitivities. For example, using a threshold of 140 mg/dl in the 50-g GCT pooled an estimate of sensitivity ranging between 0.74 (95% CI 0.62-0.87) and 0.83 (95% CI 0.75-0.91). Lowering the threshold to 130 mg/dL could increase the sensitivity of the test to 0.9 [46]. This false negative result might lead to false reassurance among the patients and the physicians. In contrast, the "one-step" approach could eliminate the problem of a false negative test and the potential drop-off after a positive screening test [47]. Alternatively, in the one-step approach, a 75-g glucose load is administered after the patient reaches a fasting glucose, and the plasma glucose levels are evaluated after 1 and 2 hours of the administration. Gestational diabetes mellitus is diagnosed if one glucose value falls at or above the specified glucose thresholds.

The one-step approach (75-g oral GTT) after release of the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study findings of 2008, followed the 2010 recommendations of the IADPSG, which were endorsed by the ADA in 2011 are recommended. The most important reasoning for the shift from the 2-step to the 1-step method is the latter's ability to show GDM earlier, and thus doctors can treat the disease earlier, thereby decreasing the risks associated with the disease. In addition, proponents of the 1-step method affirm its ease of administration, its convenience for the patients, and its diagnostic accuracy.

The IADPSG recommended that a one-step 75-g OGTT be given to all pregnant women who do not have a diagnosis of overt diabetes. They also recommended that a single glucose value, rather than at least two abnormal values at or above diagnostic glucose thresholds on the OGTT, be accepted as sufficient evidence for a diagnosis of GDM. The diagnostic glucose thresholds recommended by the IADPSG were the maternal glucose values from the HAPO study that identified a 1.75-fold increase overall (adjusted odds ratio relative to the mean cohort glucose values) for gestational age, elevated C-peptides, high neonatal body fat, or a combination of these factors. In contrast, the 2-step approach to GDM screening has been shown to be more cost-effective than the 1-step approach [48].

Other screening tests for gestational diabetes mellitus

HgbA1c has limited efficacy in the diagnosis of GDM during the third trimester, demonstrating moderate sensitivity (85.7%)

and poor specificity (61.1%) [40,49]. The American Diabetes Association (ADA) and the International Association of Diabetes in Pregnancy Study Group (IADPSG) support its use during pregnancy. Four research articles evaluated the HbA1C thresholds of 5.0, 5.3, 5.5, 7.5 using different diagnostic criteria for gestational diabetes [49-52].

A threshold was lacking between the HgbA1C level and the probability of gestational diabetes across the four studies. However, O'Connor et al. [53] investigated the normal values for HgbA1c in pregnancy in non-diabetic women and identified a normal reference interval of 4.3-5.4% in the first trimester [53]. Because of the high rates of false-positive and false-negative findings, serum HbA1c values cannot be recommended for screening GDM [40] USPSTF also supports this conclusion [38].

Measuring fasting plasma glucose level has been suggested as an alternative to the OGCT. USPTF results show that a fasting plasma glucose test with a threshold of 85 mg/dL is similar to an OGCT in terms of sensitivity [40]. Herrera et al. [54] investigated the Importance of Fasting Blood Glucose (FBG) in Screening for Gestational Diabetes, and their data support the importance of incorporating a fasting blood glucose value into the initial screening or diagnostic testing for GDM [54]. The sensitivity of glucosuria for GDM screening is worse [55].

Various Studies about Screening Methods

Nine studies provided data to estimate the sensitivity and specificity of OGCT using a cut-off point of 140 mg/dL or greater. The joint estimates of sensitivity and specificity were 85% and 86%, respectively. Six studies reported results for a 50-g OGCT using a cut-off point of 130 mg/dL or greater. Their joint estimates of sensitivity and specificity were 99% and 77%, respectively. A 50-g OGCT with a cut-off point of 130 mg/dL had a higher sensitivity compared to a cut-off point of 140 mg/dL; however, the specificity of the 130 mg/dL cut-off point was lower [36,40]. A study conducted in the United Arab Emirates using an HbA1C value of 5.5% or greater had a specificity of 21% and a sensitivity of 82%. Seven studies assessed the fasting plasma glucose test by using the Carpenter and Coustan's criteria, and confirmed the efficacy of GDM. Each study compared four fasting plasma glucose thresholds, and found that the sensitivity and specificity were 87% and 52% for 85 mg/dL or greater, 77% and 76% for 90 mg/dL or greater, 76% and 92% for 92 mg/dL or greater, and 54% and 93% for 95 mg/dL or greater, respectively [36].

Recommendations from National Organisations

There is an agreement that universal GDM screening is cost-effective. In 2013, the American Congress of Obstetricians and Gynecologists recommended the 2-step approach for screening GDM in all pregnant women. ACOG, SOGC and NICE recommend routine risk-factor-based screening. ADA recommended both the 1 and 2-step approaches with thresholds proposed by the IADPGS. ADA recommends screening all women with a 75-g 2-h oral glucose tolerance test (OGTT). In 2013, an independent panel supported by the NIH Consensus Development Program considered whether using the 75-g OGTT (1-step approach), as proposed by the International Association of Diabetes and

Pregnancy Study Groups and supported by the American Diabetes Association, should be adopted instead of the 2-step approach. The panel released a statement that there is not enough evidence to support the 1-step approach over the 2-step. The American Academy of Family Physicians recommends screening for GDM in asymptomatic pregnant women after 24 weeks of gestation. It also concludes that the evidence is insufficient to assess the balance between benefits and harms that arise from screening for GDM in asymptomatic pregnant women before 24 weeks of gestation. The CAD, USPSTF, ADIPS, and DIP recommend that all asymptomatic women should be screened at 24-28 weeks' gestation. The Endocrine Society recommends universal screening for GDM using the 1-step approach. Australasian Diabetes in Pregnancy Society recommended the 1-step approach for screening GDM [36,55].

Conclusion

In all pregnant populations, screening for GDM, universal strategies are beneficial and better than the selective ones. Currently, the ACOG, the SOGC, and the NICE recommend routine risk-factor-based screening, and the CDA, the USPSTF, the ADA, the IADPSG, the ADIPS, and the ATLANTIC DIP recommend universal screening in asymptomatic pregnant women at 24-28 weeks' gestation. We have to concentrate on hyperglycemia because it is more important than trying to diagnose GDM itself. If it is possible, screening for hyperglycemia should be universally performed in every pregnant woman. The universal two-step screening is cost-effective. The best strategy would be connecting the screening with diagnosing GDM in the same procedure with 75 g of glucose at 24-28 weeks' gestation. Despite the clear doubts the 50-g 1-h GCT has been still used as the most popular screening method by a number of countries, including the USA.

In summary, there is still no exact approach to gestational diabetes screening. What is apparent is that screening and subsequent treatment are beneficial to short-term outcomes and possibly long-term outcomes. The most commonly evaluated screening test in the literature is the 2-step approach, and the most commonly used cut-off point is 140mg/dL. Furthermore, the 2-step approach is more cost effective than the 1-step approach.

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