

Screening and Diagnosis of Gestational Diabetes Mellitus



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Introduction

Pregnancy is a diabetogenic state manifested by insulin resistance and hyperinsulinemia. The resistance stems from the placental secretion of diabetogenic hormones, including growth hormone, corticotropin-releasing hormone, placental lactogen, and progesterone. Appropriate metabolic adaptations occur in normal pregnant women to ensure that the fetus has an ample supply of fuel and nutrients at all times. These adaptations are associated with large fluctuations in serum glucose and insulin concentrations depending upon whether the pregnant woman is fasting or has recently eaten. Fasting is a form of accelerated starvation, in which alternative fuels are made available to the mother while glucose is reserved for the fetus [1]. After an overnight fast, for example, maternal fasting capillary blood glucose concentrations fall to between 55 and 65mg/dL and venous plasma equivalent to 63 to 75mg/dL [2], while serum ketone and free fatty acid concentrations rise [3,4].

Gestational diabetes refers to carbohydrate intolerance that begins or is first detected during pregnancy. It occurs when a woman's pancreatic function is not sufficient to overcome the insulin resistance created by the anti-insulin hormones and the increased fuel consumption necessary to provide for the growing fetus. Diagnosis and treatment of gestational diabetes is important because hyperglycemia, especially when severe, increases the incidence of several complications, including preeclampsia, polyhydramnios, fetal macrosomia, birth trauma, operative delivery, neonatal metabolic complications (hypoglycemia, hyperbilirubinemia, hypocalcemia, erythremia, and respiratory distress), perinatal mortality, development of obesity and diabetes in offspring during childhood, and later development of diabetes mellitus in the mother.

Diabetes appearing after age 25 is typically type 2 diabetes. However, about 10% of women with gestational diabetes have circulating islet-cell antibodies; they may have a latent form of type 1 diabetes, although their risk of developing the disease is not known [5]. The human leukocyte antigen (HLA) alleles DR3 and DR4 appear to predispose women to the development of

type 1 diabetes after delivery, as does the presence of islet-cell antibodies [6]. This article is intended to convince the reader that screening and diagnosing gestational diabetes is a cost effective means to identify the pregnant woman at risk for an adverse outcome of her pregnancy. Despite the recent statement of the American Diabetes Association that recommends a two-step protocol, the evidence clearly shows that the two step delays the diagnosis and increases the risk of complications. This article also offers justification for a one step test rather than a two-step test for making the diagnosis of gestational diabetes.

Prevalence

The prevalence of gestational diabetes varies worldwide and among racial and ethnic groups. Prevalence rates are higher in black, Hispanic, Native American, and Asian women than in white women [7]. Prevalence also varies with testing methods and diagnostic criteria. Thus, the prevalence rate in the United States has varied from 1.4% to 14% in different studies [8-12].

Risk factors and selection of women for screening

Table 1: Risk factors for gestational diabetes.

S. No	Risk Factors for Gestational Diabetes
1	A family history of diabetes, especially in first-degree relatives
2	Prepregnancy weight of 110% of ideal body weight or more or weight gain in early adulthood (see "Health hazards associated with obesity")
3	Age greater than 25 years
4	A previous baby larger than 9 pounds (4.1kg)
5	History of abnormal glucose tolerance
6	Member of an ethnic group with a higher-than-normal rate of type 2 diabetes
7	A previous unexplained perinatal loss or birth of a malformed child
8	A birth weight greater than 9 pounds (4.1kg)
9	Polycystic ovary syndrome [14,15]
10	Maternal low birth weight [16]

Clues that a pregnant woman may be at high risk for gestational diabetes are listed in Table 1 [13]. But using historical risk factors alone to gauge risk will miss approximately one-half of women with gestational diabetes mellitus. There is little consensus regarding whom to test or how to test for gestational diabetes. The original threshold for an abnormal test was arbitrary and validated by the ability to predict subsequent diabetes in the mother [14-16]. Large studies to determine the best laboratory criteria for predicting maternal and neonatal morbidity have not been performed.

Selective screening

The American Diabetes Association (ADA) recommends that screening be limited to women with risk factors for gestational diabetes [17]. Specifically, the ADA suggests that it is not cost-effective to screen women who are younger than 25, have a normal body weight, no family history of diabetes, and are not at risk based on their race or ethnicity. The American College of Obstetricians (ACOG) uses similar criteria to define low-risk women [18].

A study of over 3,000 pregnant women supported a selective screening approach, and it resulted in the development of a scoring system to identify women at high risk for developing gestational diabetes [19]. Increasing age, body mass index, and race other than white or black were independent predictors of an increased risk, and points were awarded based upon these factors, up to a maximum of 10. Women who scored 0 or 1 point were not screened, allowing 35% of women to avoid screening altogether. All other women were screened with a 50-g oral glucose challenge; the threshold for a positive test and subsequent need for a glucose tolerance test (GTT) was based upon the number of points accumulated on the risk factor score. This approach resulted in a detection rate of gestational diabetes similar to that of universal screening, while decreasing the false-positive rate from 17.9% with usual care to 15.4% to 16%.

This scoring system has some inherent difficulties. First, it is difficult to define clear risk groups on the basis of race. Second, different thresholds for a positive oral glucose challenge and the need to consider whether the glucose was given while the woman was fasting or after a meal complicated the system. Finally, few women meet the criteria for exemption from screening. For example, the ADA system was studied retrospectively in approximately 18,000 predominantly white women [20]. Ninety-seven percent of women with gestational diabetes would have been diagnosed, but only 10% of the women would have avoided screening.

Universal screening

A study from Australia challenged the selective screening approach [21]. Among 2907 women who underwent a 75-g oral GTT at the beginning of their third trimester, 573 (19.7%) were considered low risk (as defined by white ethnic origin, age <25 years, and body mass index <25 kg/m²). The prevalence of gestational diabetes in the low-risk group (defined as a 2-hour

blood glucose concentration >144mg/dL) was 2.8%; these women had pregnancy outcomes similar to other women with gestational diabetes. If screening had been selective, 80% of women would still have been screened and 10% of women with gestational diabetes would have been missed.

In a comparison study, all women were screened with a 75g dose of glucose and a 1-hour blood glucose cut-off value of <140mg/Dl [22]. The test not only was an excellent screening method but also a cost-effective diagnostic test to identify high-risk pregnancies.

Recommendation

My recommendation is to perform universal screening because it is my belief that identification and treatment of gestational hyperglycemia can improve pregnancy outcome and that selective screening approaches are cumbersome and not sufficiently sensitive. This view is in contrast to that of the ADA and ACOG, who recommend that screening be limited to women with risk factors for gestational diabetes, although ACOG acknowledges that universal screening is a more practical approach. The United States Preventive Services Task Force (USPSTF) and the Canadian Task Force on Preventive Health Care both concluded that there is insufficient evidence to recommend for or against universal screening for gestational diabetes [23,24]. The USPSTF did find fair to good evidence that screening for gestational diabetes and treatment of hyperglycemia could reduce fetal macrosomia.

Screening Technique and Diagnostic Criteria

Screening is ideally performed at 24 to 28 weeks of gestation [25]. However, it can be done as early as the first prenatal visit if there is a high degree of suspicion that the pregnant woman has undiagnosed type 2 diabetes [26].

Initially a 50-g oral glucose challenge is given and venous serum or plasma glucose is measured 1 hour later; a value >140mg/dL is considered abnormal. Women with an abnormal value are then given a 100-g, 3-hour oral GTT [8]. The sensitivity of the 50-g glucose test is improved if it is performed in the fasting state or a lower serum glucose threshold (130mg/dL) is used [11,27]. At the 130mg/dL threshold, the test is positive in 20% to 25% of pregnant women and detects 90% of women with gestational diabetes; at the 140mg/dL threshold, 14% to 18% of tests will be positive and 80% of gestational diabetics will be detected [28]. Either threshold may be used [18]. Other types of screening tests have been proposed and may be better tolerated, but are less sensitive [29]. Capillary blood should not be used for screening tests unless the precision of the meter is known; it has been correlated with simultaneously drawn venous samples, and has met federal standards for laboratory testing.

Oral glucose tolerance test

Two different classification schemes for gestational diabetes based upon results of the 3-hour GTT results have been proposed. According to the Fourth International Workshop-Conference

on Gestational Diabetes, gestational diabetes is present if 2 or more of the following serum glucose values are exceeded: (1) fasting serum glucose concentration >95mg/dL, (2) 1-hour serum glucose concentration >180mg/dL, 2-hour serum glucose concentration >155mg/dL, 3-hour serum glucose concentration >140mg/dL.

These values are based upon the Carpenter & Coustan [11] modification and are lower than those proposed by the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus and the National Diabetes Data Group (NDDG), which used cutoff values of 105, 190, 165, and 145mg/dL, respectively [17]. Participants in the Fourth International Workshop on gestational diabetes also recommend further evaluation of any woman who has a random serum glucose value >200mg/dL or a fasting serum glucose value >126mg/dL, because these findings alone are strongly suggestive of diabetes.

The algorithm for screening recommended by the ADA uses the criteria from the Fourth International Workshop. However, one review suggests that this classification scheme diagnoses more women with gestational diabetes at very little benefit and potentially high cost [30]. In this retrospective review of 8857 pregnant women screened for gestational diabetes, 284 (3%) met the NDDG criteria while 438 (5%) met the Fourth International Workshop criteria. Thus, application of the more stringent Fourth International Workshop criteria to all women with positive screening test results would at best have reduced the prevalence of infants weighing over 4000 grams from 17.1% to 16.9% and the prevalence of infants weighing over 4500 grams from 3% to 2.9%.

Carbohydrate loading for 3 days has been recommended before the GTT [31], but it is probably not necessary [32-34]. An additional concern is that the oral GTT is an imprecise test with poor reproducibility [35]. A study that performed 2 oral GTTs 1 to 2 weeks apart in 64 pregnant women whose 50-g glucose challenge was >135mg/dL found 48 had normal/normal, 11 had normal/abnormal, 3 had abnormal/normal, and 2 had abnormal/abnormal results [36]. Thus, only 50 (78%) had reproducible test results.

Two-hour 75-g glucose tolerance test

A simplified 75-g GTT may be more cost-effective than the 3-hour test [22]. The ADA and the World Health Organization (WHO) have endorsed a 2-hour 75-g oral GTT for diagnosis of gestational diabetes, although they have different criteria for a positive test [37,38]. Some clinicians use this test as a 1-step approach for both screening and diagnosis [28]. The ability of this test to predict adverse pregnancy outcome was assessed in the Brazilian Gestational Diabetes Study of 5000 women who had the test at 24 to 28 weeks gestation [39]. The incidence of gestational diabetes by ADA and WHO criteria was 2.4% and 7.2%, respectively. Each group's criteria predicted an increased risk for development of macrosomia, preeclampsia, or perinatal death, demonstrating the utility of this abbreviated

test. However, very few of the women received dietary or drug treatment for hyperglycemia, so no conclusions can be drawn about the potential benefits of diagnosis and intervention in these women.

Other tests

According to the ADA, the diagnosis of gestational diabetes cannot be established without a confirmatory abnormal GTT. There are, however, other findings that can identify women at risk. As an example, a serum glucose concentration that is >140mg/dL after the 50-g glucose challenge is associated with a 25% to 30% risk of a macrosomic infant if no treatment is offered [25].

A fasting serum glucose concentration >90mg/dL at 24 to 28 weeks of gestation, along with a glycosylated hemoglobin (HbA1c) value above normal, is a highly sensitive and specific predictor of subsequent infant macrosomia in the general obstetrical population [40]. Glycosylated hemoglobin values alone were not sufficiently sensitive to predict those women at risk of delivering a macrosomic infant. In one study, the sensitivity and specificity of a fasting serum glucose value of 86mg/dL or higher for detecting gestational diabetes were 81% and 76%, respectively [41].

These observations permit a simplified approach in some women. We found that the rate of macrosomia could be reduced from 18% to 7% using only a positive serum glucose screen, without performing an oral GTT, to refer women for dietary treatment, self blood glucose monitoring, and insulin therapy if blood glucose targets were not met on the prescribed diet [42].

Universal screening using a threshold serum glucose concentration of 130mg/dL had 100% sensitivity, but 25% of women screened required a GTT and the cost per case diagnosed was \$249 [18,43]. Raising the serum glucose threshold value to 140mg/dL dropped the sensitivity to 90% with 15% of women screened requiring a GTT. In this protocol, the cost per case diagnosed was \$222. Selective screening with a 140mg/dL threshold lowered the sensitivity to 85% at a cost of \$192 per case diagnosed.

Use of glycosylated hemoglobin

HbA1c should be measured every 4 to 6 weeks after the diagnosis of gestational diabetes mellitus is made and more frequently if the woman's glycemic control is poor. Both average blood glucose concentration and the HbA1c values fall by about 20% in normal pregnant women, and similar values should be aimed for in diabetic women to minimize fetal risk. Thus the normal range for pregnancy is 4.7%±0.5%. Although HbA1c can be used to monitor and confirm glucose control, there are no norms or criteria to use HbA1c testing to diagnose gestational diabetes.

Treatment

Optimal management of glycemia begins with medical nutritional therapy. Insulin is then initiated if dietary

management fails to maintain normoglycemia (fasting <90mg/dL and/or 1-hour postprandial glucose concentrations <120mg/dL). If medical nutritional therapy does not achieve normal pre- and postprandial glucose concentrations, then insulin therapy must be initiated. Note that the use of oral agents is not indicated for the optimal treatment of type 2 diabetes during pregnancy or gestational diabetes.

Summary

Universal screening for gestational diabetes should be the optimal strategy. Although there is no consensus regarding threshold values for the glucose challenge test, the fact that a screening test is performed before a diagnostic test clear creates a delay in treatment. Time is of essence to prevent macrosomia and thus even a short delay in treatment may cause a tragic outcome for the infant. Even if a one-step test doubles the prevalence of gestational diabetes, it does not extrapolate to increased cost. One analysis evaluated the cost per case of gestational diabetes diagnosed using various screening protocols [43] and the data show that teaching two women the skills for self-care management of GDM is easier than teaching one woman at a time. There also maybe benefits for the woman to realize that GDM is a common disease, she is not alone and there are others who can help her cope. There is also no consensus regarding which criteria on the 3-hour GTT should be used to define gestational diabetes [44]. We are currently using the more stringent criteria of the Fourth International Workshop. However, this may change as more data become available regarding the consequences of this strategy or as definitive recommendations are made regarding the 75-g GTT. Therefore this author hopes that this review has convinced the reader that a one-step protocol to diagnosis gestational diabetes is the optimal path to follow [45,46].

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