SCREENING AND DIAGNOSTIC CRITERIA FOR GESTATIONAL DIABETES MELLITUS – CHANGES WORLDWIDE OVER TIME

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Abstract

Gestational diabetes mellitus (GDM) is defined as a glucose intolerance with first onset or first recognition during pregnancy. GDM is associated with higher incidence of maternal and fetal complications. Screening for GDM is recommended in most pregnant women. Assessment of risk for GDM should be performed at first prenatal visit and women at very high risk should be screened immediately using a random, fasting or post-glucose load glucose level. Most women not found to have GDM should undergo further screening at 24-28 weeks of gestation. Despite four international conferences aimed at developing a consensus definition and diagnostic criteria for GDM worldwide, the definition, screening and diagnostic criteria vary over the time making difficult to compare prevalence between countries. Most centers in Europe use World Health Organisation (WHO) diagnostic criteria which are the same as in the general population and use a 75g oral glucose tolerance test (OGTT). Current criteria used in US are based on two different protocols using one or two step-approach, 75g or 100g OGTT. Results of Hyperglycemia and Adverse Pregnancy Outcome released in 2008 have indicated a strong, continuous association between blood glucose levels below those currently used for diagnostic of diabetes and undesirable perinatal outcomes. Since the HAPO study, new, lower thresholds were proposed for the diagnostic of GDM. Implementation of these thresholds will almost double the proportion of women diagnosed with GDM.

key words*: gestational diabetes mellitus, risk factors for gestational diabetes, adverse perinatal outcome, diagnostic criteria, overt diabetes*

Gestational diabetes mellius (GDM) is defined as a carbohydrate intolerance of varying degrees of severity recognized with onset of or during pregnancy [1, 2], regardless of whether insulin is used for treatment or the condition persists after the pregnancy. This diagnosis does not apply to pregnant women with previously diagnosed diabetes. GDM has been well recognised for decades but still, recommended definitions and diagnostic criteria for GDM had varied over the time and the potential significance of the condition was controversial. Also, once the diagnosis of GDM was established in the late second or early third trimester, the optimal monitoring and care of these women still remain subject of debate [3]. GDM accounts for 90% of cases of diabetes mellitus in pregnancy, type 2

diabetes mellitus accounts for 8% of cases of diabetes mellitus in pregnancy, and given its increasing incidence, preexisting diabetes mellitus now affects 1% of pregnancies [4]. It is possible that some women with GDM may have had unrecognised diabetes, either type 1 or type 2 antedating pregnancy [5]. Because GDM is typically a disorder of late gestation, this possibility is greater if hyperglycemia is noted during the first trimester.

In recent years there has been a global increase in the prevalence of both obesity and type 2 diabetes. Recent reports provide evidence that the prevalence of GDM is population specific, it is a reflection of the underlying incidence of diabetes in that population and it will likely grow in direct proportion to that of type 2 diabetes [6]. Indications are that GDM already parallels the rapid increase in type 2 diabetes. For example, some data from US medical centers where the screening method and diagnostic criteria for GDM have remained constant, suggest that the prevalence of this complication of pregnancy doubled in the last eight years, a 12% increase per year that cannot be explained by changes in age, ethnic distribution or previous history of GDM among screened pregnancies [7]. Causal factors for the apparent increase in GDM are likely to be multiple, including the prevalence of obesity, particularly in youth (due to low levels of physical activity and high levels of caloric intake), increased maternal age at delivery and improved survival of female infants whose birth weights were at extremes of the normal range. As adults, the latter individuals have altered insulin action and/or insulin secretory capacity that may predispose them to the development of GDM [8].

GDM is associated with a higher incidence of maternal and fetal complications. The maternal complications include hypertensive disorders of pregnancy, polyhydramnios, recurrent genital and urinary tract infections, traumatic labor and higher rates of preterm deliveries and cesarean sections. The risk of subsequent gestational diabetes occuring after one pregnancy complicated by gestational diabetes is reported to be 60-90%, depending on the women's first trimester weight in the subsequent pregnancies. In addition, women with GDM are at increased risk for type 2 diabetes, impaired fasting glucose, impaired glucose tolerance and lipid abnormalities later in life [9, 10].

The incidence of fetal complications in women with GDM is lower than in women with preexisting diabetes but higher than in women with normal pregnancies. Although GDM is defined as diabetes first recognized in the current pregnancy, it may be reasonable to assume that the woman diagnosed with diabetes in the first or early second trimester may have developed this condition before pregnancy. If so, the fetus is at risk for developing congenital abnormalities. Offspring of GDM mothers problems may be neonatal (intrauterine death, fetal macrosomia, birth injuries – shoulder distocia, lung immaturity, respiratory distress syndrome, hypoglycemia, hypocalcemia, hyperbilirubinemia, polycytemia) and long term (childhood and adult obesity, type 2 diabetes, cardiovascular disease or poor neurological development) [11, 12].

Since GDM may represent an early manifestation of type 2 diabetes, diagnosing these women identifies those who might

benefit from interventions to reduce the risk of future diabetes and those who might benefit from cardiovascular risk modification. Medical care for women with GDM begins with detection. The screening for GDM could be the patient's history, clinical risk factors or a laboratory test.

The position of American diabetes Association (ADA) is to assess every pregnant women for the risk of GDM at her first prenatal visit [13, 14]. This is also recommended by American College of Obstetricians and Gynecologists (ACOG) [15]. The risk of GDM is stratified into low, average and high.

Pregnant women are classified as low risk if they meet **all** of the following criteria:

- Age younger than 25 years old,
- Normal prepregnancy body mass index (BMI) <25kg/m^2,
- No family hisory of diabetes in a first degree relative,
- Caucasian or member of ethnic group with low prevalence of gestational diabetes,
- No history of poor pregnancy outcome as unexplained stillbirth or delivery of large for gestational age (LGA) fetus [1],
- No personal history of glucose intolerance or diabetes [1].

The last two criteria were added to the low risk definition at the 1997 4th International Workshop Conference on GDM.

According to American Diabetes Association criteria [14], low risk women do not require glucose testing, unless they come from a population with a high prevalence of type 2 diabetes [19].

A woman is considered at high risk if she meets **one or more** of the following criteria [1, 14, 16, 17, 19]:

- Obesity,
- Strong family history of diabetes,
- History of GDM,
- Age ≥35 years,
- Polycystic ovary syndrome and/or hirsutism,
- Glycosuria on two or more occasions during current pregnancy,
- Polyhidramnios,
- Suspected macrosomia,
- Multiple pregnancy,
- Prior poor obstetrical outcome (pre-eclampsia/eclampsia, unexplained stillbirth, birth defects, macrosomic infant, neonatal death during previous pregnancy),
- Member of a high risk ethnic group (Hispanic, African, Native American, South or East Asian or Pacific Island ancestry),
- Corticosteroid use.

Ideally, women at high risk should be screened as soons as feasible during pregnancy and imediatly after the first visit (early first trimester). If GDM is not detected at this stage, it should be reassessed in weekes 24-28 or at first suspicious signs of diabetes [14].

Women who do not fit the criteria described are considered at average risk. These women are tested at 24-28 weeks of pregnancy [14].

Three methods of biochemical screening for GDM have been described.

GCT (glucose challenge test) is a 1-hour plasma glucose (1hPG) measurement following a 50g-glucose load given at any day time. GCT is performed in week 24-28 of gestation for patients at average risk and in early pregnancy for patients at high risk,

regardless the time of the last meal. If 1hPG is ≥185mg/dl (10.3mmol/l), GDM is confirmed, according to some authors [18]. If the 1hPG is 140mg/dl to 183mg/dl (7,8 to 10.2mmo/l), a 75g or 100g oral glucose tolerance test (OGTT) should be conducted. Some medical centers use a cutoff of 130mg/dl (7.2mmol/l) which identifies over 90% of all affected patients (the cutoff value of 140mg/dl identifies only 80% of women with GDM but decrease to 14-18% the number of women who will have GCT results that necessitate further testing) [1].

A random plasma glucose measurement at first prenatal visit >200mg/dl (>11.1mmol/l) outside the context of a formal glucose challenge test or fasting plasma glucose >126mg/dl (>7mmol/l) suggests diabetic state (universal early testing in populations with a high prevalence of type 2 diabetes is recommended, others may choose to test only high risk groups) [19].

Although **75g OGTT** is usually used as a one step diagnostic test, some investigators have reported the use of the 75g test as screening test with one-hour values ≥140mg/dl (7.8mmol/l) and 144mg/dl (8mmol/l) identifying women that need to proceed to a diagnostic 100g or 75g tolerance test [20].

The diagnostic criteria for GDM have evolved over the time, therefore, definitions of GDM used in epidemiological literature vary considerably. Currently, there are three diagnostic tests for diabetes in pregnancy.

1. **Fasting or random blood sugars**. A fasting plasma blood glucose ≥126mg/dl (7.0mmol/l), a random plasma glucose ≥200mg/dl or HbA1c ≥6.5% (DCCT/UKPDS standardized) meets the threshold for the diagnosis of overt diabetes (women with likely prepregnancy diabetes) if confirmed on a subsequent day [19].

2. **The 100 g OGTT.** The 100g three hour OGTT is in general used in North America and a few centers around the world. Diagnostic criteria (table 1) used were either the Carpenter&Coustan or National Diabetes Data Group (NDDG) conversion of the original O'Sullivan values [21]. At the 4th International Workshop Conference on GDM, it was agreed that the Carpenter and Coustan (C&C) [22] criteria should replace the NDDG criteria [23], resulting in significant lowering of the thresholds and an increase in the prevalence of GDM. Schwartz et al., based on a restrospective analysis of 8557 OGTT results, estimated that replacing the NDDG criteria with C&C criteria would increase by 54% the number of pregnant women with a diagnosis of GDM and would also increase costs, while only minimally affecting the prevalence of infant macrosomia [24].

3. **The 75 g OGTT.** The 75 g two-hour OGTT is the diagnostic test recommended by the WHO and is practiced in most of the world excluding North America where the 100g three hour OGTT is the principal diagnostic test. In 1999, WHO panel [25], although in general mantaining previous diagnostic recommendations, characterizes GDM as the joint category of diabetes and impaired glucose tolerance. After the 4th International Workshop Conference [1] on GDM, ADA [26] included in its recommendations the use of a two hour 75g OGTT. The same fasting, 1 hour and 2 hour diagnostic cut points are used in both tests. However for the 2 hour test, two of three abnormal values are required for diagnosis instead of the two of four required in 3–hour test.

Table 1. 100g OGTT Diagnostic Criteria for GDM

Time of testing	Carpenter&Coustan criteria Plasma or serum glucose level	NDDG criteria Plasma level
Fasting	95mg/dl 5.3mmol/l	105mg/dl 5.9mmol/l
1 hour after loading	180mg/dl 10mmol/l	190mg/dl 10.6mmol/l
2 hours after loading	155mg/dl 8.6mmol/l	165mg/dl 9.2mmol/l
3 hours after loading	140mg/dl 7.8mmol/l	145mg/dl 8.1mmol/l
Two or more values must be met or exceeded The test should be performed after 8-14 hours fast and following 3 days of unrestricted diet (>150g carbohydrate per day)		

Until march 2010 when International Association of Diabetes and Pregnancy Study Group (IADPSG) released the new diagnostic criteria for GDM, there was no consensus regarding the criteria for the 75g OGTT in pregnancy (table 2).

Table 2. Criteria for diagnosis of GDM with the 75g OGTT

Time of testing	WHO criteria	Fourth International Workshop/ADA	ADIPS (Australasian Diabetes in Pregnancy Society) [27]
Fasting	126[x]mg/dl (7mmol/l)	95mg/dl (5.3mmol/l)	99mg/dl (5.5mmol/l)
1 hour after loading	not measured	180mg/dl (10.0mmol/l)	Not measured
2 hours after loading	140mg/dl (7.8mmol/l)	155mg/dl (8.6mmol/l)	144mg/dl (8.0mmol/l)
Diagnostic criteria for GDM	One abnormal value met or exceeded	Two or more abnormal values met or exceeded	One or more abnormal values met or exceeded
[x] a fasting value ≥ 126mg/dl (7mmol/l) implies that diabetes preceded the pregnancy			

IADPSG was initially formed through the efforts of various study groups around the world to facilitate the HAPO study (Hyperglycemia and Adverse Pregnancy Outcomes) [19]. The objective of HAPO study was to clarify the association of levels of maternal glucose lower than those used for diagnostic of diabetes, with perinatal outcome [28, 29]. The study involved 25 000 women in 9 countries who underwent a 2–hour OGTT with a 75g glucose load at 24-32 weeks of gestation. Results were blinded unless fasting plasma glucose >105mg/dl (5.8mmol/l) and/or 2-hour plasma glucose>200mg/dl (11.1mmol/l) [28]. Primary outcomes in the blinded HAPO cohort were macrosomia (birth weight >90th percentile), primary cesarean delivery, clinical neonatal hypoglycemia and hyperinsulinemia (cord C peptide >90th percentile). Secondary outcomes were preeclamsia, preterm delivery, shoulder dystocia/birth injury, hyperbilirubinemia and intensive neonatal care. It was found that all primary outcomes, as well as secondary outcomes were associated with high maternal glucose concentrations, in continuous and graded manner across the full range of observed glucose levels, which precluded easy

identification of thresholds levels where risk for adverse outcomes rose [29, 30]. HAPO data show strong linear associations of risks for macrosomia and cord C-peptide with each of three measures of maternal glucose (FPG, 1 hour and 2 hour post 75g load) [19].

IADPSG examined the linear association between risk for neonatal outcomes and the three measures of maternal blood glucose (fasting, 1 hour OGTT, 2 hour OGTT) and set the thresholds at an odd ratio of 1.75, which identified 16,1% of the pregnant population as having GDM [19] (table 3). Also, IADPSG Consensus Panel emphasized the need to identify women with likely prepregnancy diabetes (overt diabetes) (table 4) and established the laboratory measures of glucose (fasting, random plasma glucose, HbA1c) for detection of possible cases [19].

Table 3. Proposed and current thresholds for the diagnosis of GDM using 75 OGTT

Time of testing	IADPSG proposed diagnostic threshold	Current ADA threshold
Fasting	92mg/dl (5.1mmol/l)	95mg/dl (5.3mmol/l)
1 hour after loading	180mg/dl (10mmol/l)	180mg/dl (10.0mmol/l)
2 hour after loading	153mg/dl (8.5mmol/l)	155mg/dl (8.6mmol/l)
Diagnostic criteria for GDM	One or more abnormal values met or exceeded	Two or more abnormal values met or exceeded

Table 4. Diagnosis of overt diabetes in pregnancy [19]

Measures of glycemia	Consensus threshold
Fasting plasma glucose	≥126mg/dl (7mmol/l)
A1c	≥6,5% (DCCT/UKPDS standardized)
Random plasma glucose	≥200mg/dl (11,1mmol/l) (confirmation required)

Table 5. Diagnosis of GDM (current and proposed recommendations)

Diagnostic criteria	ADA current recommendations (2000) [14, 31]	IADPSG proposed recommendations (2010)
Screening 1.in women at high risk in first trimester 2.all women (except low risk) in 24-28 weeks of pregnancy	random 50 g 1 hour oral glucose testing <140mg/dl normal (retest only if risk factors increase) ≥140mg/dl perform an OGTT	Eliminated glucose challenge test
Diagnostic test	75g or 100g OGTT	75g OGTT
Thresholds Fasting 1 hour 2 hour 3 hour (for 100g OGTT)	 95mg/dl (5.3mmol/l) 180mg/dl (10.0mmol/l) 155mg/dl (8.6mmol/l) 140mg/dl (7.8mmol/l)	 92mg/dl (5.1mmol/l) 180mg/dl (10.0mmol/l) 153mg/dl (8.5mmol/l)
GDM diagnosed if	2 values≥threshold	1 value≥threshold
Mild GDM	1 value≥threshold	Eliminated diagnosis
Identification of overt diabetes	-	In all or only high risk women at first prenatal visit (see Tabel 4)

Implementation of IADPSG thresholds (table 5) would mean that a significantly greater proportion of women would be diagnosed with GDM. HAPO data suggest this could approach 17,8% of pregnant women, compared with 8% diagnosed with current recommendations [29]. Randomized control trials in GDM suggest that rates of macrosomia, maternal weight gain, shoulder dystocia and hypertension in pregnancy should be reduced by glycemic management of women diagnosed at IADPSG [32]. Also, if the hypothesis that diabetes begets diabetes by in utero exposure to maternal hyperglycemia is true, than detecting and treating women of GDM may be an effective and attractive task for type 2 diabetes prevention.

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