

Gestational Diabetes Mellitus Diagnosed With a 2-h 75-g Oral Glucose Tolerance Test and Adverse Pregnancy Outcomes

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OBJECTIVE — To evaluate American Diabetes Association (ADA) and World Health Organization (WHO) diagnostic criteria for gestational diabetes mellitus (GDM) against pregnancy outcomes.

RESEARCH DESIGN AND METHODS — This cohort study consecutively enrolled Brazilian adult women attending general prenatal clinics. All women were requested to undertake a standardized 2-h 75-g oral glucose tolerance test (OGTT) between their estimated 24th and 28th gestational weeks and were then followed to delivery. New ADA criteria for GDM require two plasma glucose values ≥ 5.3 mmol/l (fasting), ≥ 10 mmol/l (1 h), and ≥ 8.6 mmol/l (2 h). WHO criteria require a plasma glucose ≥ 7.0 mmol/l (fasting) or ≥ 7.8 mmol/l (2 h). Individuals with hyperglycemia indicative of diabetes outside of pregnancy were excluded.

RESULTS — Among the 4,977 women studied, 2.4% (95% CI 2.0–2.9) presented with GDM by ADA criteria and 7.2% (6.5–7.9) by WHO criteria. After adjustment for the effects of age, obesity, and other risk factors, GDM by ADA criteria predicted an increased risk of macrosomia (RR 1.29, 95% CI 0.73–2.18), preeclampsia (2.28, 1.22–4.16), and perinatal death (3.10, 1.42–6.47). Similarly, GDM by WHO criteria predicted increased risk for macrosomia (1.45, 1.06–1.95), preeclampsia (1.94, 1.22–3.03), and perinatal death (1.59, 0.86–2.90). Of women positive by WHO criteria, 260 (73%) were negative by ADA criteria. Conversely, 22 (18%) women positive by ADA criteria were negative by WHO criteria.

CONCLUSIONS — GDM based on a 2-h 75-g OGTT defined by either WHO or ADA criteria predicts adverse pregnancy outcomes.

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Gestational diabetes mellitus (GDM) is defined as glucose intolerance of variable severity with onset or first recognition during pregnancy (1,2). In the U.S., the definition of GDM has been largely based on pregnancy-specific criteria applied to a 3-h 100-g oral glucose tolerance test (OGTT). In contradistinction,

World Health Organization (WHO) panels have adopted in pregnancy the same diagnostic criteria applied to a 2-h 75-g OGTT in nonpregnant individuals (2–4).

Although the American Diabetes Association (ADA) still recommends a 3-h 100-g OGTT for the diagnosis of GDM, it has recently included in its recommendations the use of a 2-h 75-g OGTT. The same fasting, 1-h, and 2-h diagnostic cut points are used in both tests. However, for the 2-h test, two of three abnormal values are required for diagnosis instead of the two of four required for the 3-h test (1,5).

A recent WHO panel, although in general maintaining previous diagnostic recommendations, now characterizes GDM as the joint category of diabetes and impaired glucose tolerance (fasting glucose ≥ 7.0 mmol/l or 2-h glucose ≥ 7.8 mmol/l) (2).

The predictive ability of these new criteria for the 2-h 75-g OGTT in terms of pregnancy outcomes has been investigated little, particularly in cases not meeting the criteria for diabetes outside of pregnancy. Thus, the objective of this report is to evaluate the new WHO and ADA criteria for GDM by characterizing their ability to predict which pregnancies will suffer macrosomic birth, preeclampsia, and perinatal death.

RESEARCH DESIGN AND METHODS — The Brazilian Gestational Diabetes Study is a cohort study conducted in general prenatal care clinics of the National Health Service in six Brazilian state capitals: Porto Alegre, São Paulo, Rio de Janeiro, Salvador, Fortaleza, and Manaus. Local institutional ethic committees approved the study protocol, and patients consented to participate after being informed about the nature of the study.

We enrolled women ≥ 20 years of age between their 20th and 28th gestational week if they had a negative history of diabetes outside of pregnancy. All women responded to a structured questionnaire,

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Abbreviations: ADA, American Diabetes Association; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; RR, relative risk; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

underwent standardized anthropometric measurements, and were invited to do a 2-h 75-g OGTT between their 24th and 28th gestational week. They were then followed through delivery and during the in-hospital postpartum period via chart review using a common structured protocol.

The OGTT used standard procedures (4). Briefly, we administered a 75-g anhydrous glucose load after a 12- to 14-h fast and obtained fasting, 1-h, and 2-h samples from an antecubital vein. We collected samples in tubes containing fluoride and kept them at 4°C until centrifugation up to 2 h later. Plasma measurements were performed with glucose oxidase methods (6), the coefficient of variation being <5%.

GDM was defined according to ADA's new recommendations for the 2-h 75-g OGTT as at least two values greater than a fasting glucose of 5.3 mmol/l, a 1-h glucose of 10 mmol/l, or a 2-h glucose of 8.6 mmol/l (1). It was additionally defined by current comparatively less stringent WHO criteria (fasting ≥ 7.0 mmol/l or 2-h ≥ 7.8 mmol/l) (2).

We defined macrosomia as a birth weight at or above the gestational age-specific (by week) 90th percentile of the study sample. The 90th percentile values, derived from gestational week-specific frequency tables of birth weight, were as follows: for week 35, 3,425 g; week 36, 3,500 g; week 37, 3,590 g; week 38, 3,700 g; week 39, 3,790 g; week 40, 3,920 g; week 41, 4,040 g; week 42, 4,200 g; and week 43, 4,080 g. Perinatal death was defined by fetal loss of >1 kg or with estimated gestational age ≥ 28 weeks, or by an early neonatal death (up to 7 days). Preeclampsia (or eclampsia), ascertained through chart review, was classified according to the National High Blood Pressure Education Program Working Group (7) as hypertension after the 20th week of gestation associated with proteinuria or convulsions, regardless of whether it was of new onset or superimposed upon chronic hypertension. We calculated BMI using reported prepregnancy weight and then grouped values into nutritional categories according to the 1997 WHO recommendations (8). We defined gestational age according to hierarchical criteria based on four clinical examinations: for 52% of the sample, ultrasound before week 26; for 15%, ultrasound after week 26 consistent with

neonatal age estimation or last menstrual period; for 23%, reported last menstrual period consistent with neonatal age estimation or uterine height; and for the remaining 10%, neonatal age estimation, ultrasound after week 26, uterine height, or last menstrual period.

The study was observational in nature. Decisions concerning management of hyperglycemia were left to the clinical judgment of the patients' attending obstetricians. Information concerning insulin and diet therapy was obtained from chart review.

Of the initial 5,564 consecutive women enrolled from May 1991 through August 1995, 4,998 (90%) concluded the scheduled OGTT. To focus risk assessment on the range of hyperglycemia that outside of pregnancy is considered impaired glucose tolerance, we excluded 21 women from the analyses who met diabetes criteria (fasting glucose ≥ 7.0 mmol/l or 2-h glucose ≥ 11.1 mmol/l). The total number of women available for specific outcome analyses varied, as detailed in RESULTS.

Because macrosomia and preeclampsia were not rare events, the crude and adjusted odds ratios estimated by logistic regression were transformed to relative risks (RRs) (9) for all outcomes. We calculated the population-attributable fraction using the following (10):

$$\frac{A}{M} \times \frac{OR - 1}{OR}$$

where A equals the number of outcomes among individuals with GDM, M equals the total number of outcomes, and OR equals the adjusted odds ratio for the association between GDM and outcome.

RESULTS— Table 1 shows the characteristics of the 4,977 women who completed the 2-h 75-g OGTT.

GDM based on ADA criteria was diagnosed in 119 (2.4%; 95% CI 2.0–2.9) women. Using WHO criteria, GDM was diagnosed in 357 women (7.2%; 6.5–7.9). Figure 1 illustrates the overlap in GDM classification obtained by these two criteria; only 97 cases (81% of total ADA cases and 27% of total WHO cases) were positive by both criteria. Women classified only by WHO criteria had lower fasting (5.0 vs. 5.7 mmol/l; $P < 0.001$) but higher 2-h (8.3 vs. 6.5 mmol/l; $P < 0.001$) plasma glucose values than

Table 1—Characteristics of the 4,977 adult pregnant women completing a 2-h 75-g OGTT in the Brazilian Study of Gestational Diabetes, 1991–1995

Ethnicity	
White	2,234 (44.9)
Mixed	2,042 (41.1)
Black	679 (13.6)
Other	21 (0.4)
Prepregnancy weight status	
Underweight (BMI < 18.5 kg/m ²)	276 (5.8)
Normal (18.5 kg/m ² \leq BMI < 25.0 kg/m ²)	3,151 (66.1)
Preobese (25.0 kg/m ² \leq BMI < 30 kg/m ²)	1,024 (21.5)
Obese (BMI ≥ 30.0 kg/m ²)	314 (6.6)
Education (years)	
<8	2,181 (44.0)
8–11	2,298 (46.2)
>11	486 (9.8)
Short stature (<150 cm)	832 (16.8)
Age (years)	
20–24	1,649 (33.1)
25–29	1,580 (31.8)
≥ 30	1,748 (35.1)
Parity	
0	1,360 (30.6)
1	1,486 (33.4)
2	844 (19.0)
≥ 3	748 (15.0)

Data are n (%). The variation in category totals results from missing information relating to the characteristic in question.

women classified only by ADA criteria. They were also younger (29.5 vs. 32.3 years; $P = 0.03$), shorter (154.2 vs. 157.6 cm; $P = 0.02$), and leaner (24.2 vs. 26.3 kg/m²; $P = 0.03$). No statistically significant differences between these two groups were observed regarding frequencies of macrosomia (ADA only, 17.7% vs. WHO only, 14.6%), preeclampsia (4.8

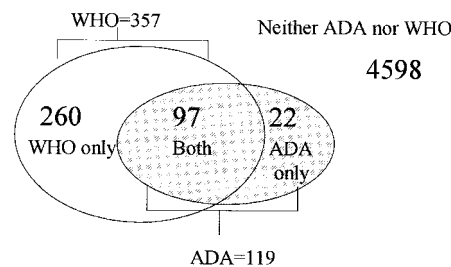


Figure 1—Overlap of cases of GDM as diagnosed by the ADA and WHO criteria for a 2-h 75-g OGTT.

Table 2—Crude and adjusted RRs of macrosomia, preeclampsia, and perinatal death associated with GDM according to ADA and WHO diagnostic criteria in the Brazilian Study of Gestational Diabetes

Outcome	Crude		Adjusted*		Population attributable fraction (%)
	RR	95% CI	RR	95% CI	
Macrosomia (n = 3,925)					
ADA	1.53	0.90–2.49	1.29	0.73–2.18	0.8
WHO	1.66	1.24–2.20	1.45	1.06–1.95	4.0
Preeclampsia (n = 4,572)					
ADA	3.62	2.05–6.19	2.28	1.22–4.16	4.8
WHO	2.43	1.57–3.70	1.94	1.22–3.03	7.9
Perinatal death (n = 4,216)					
ADA	2.97	1.40–6.07	3.10	1.42–6.47	4.8
WHO	1.66	0.91–2.96	1.59	0.86–2.90	4.5

*Adjusted through logistic regression for center, ethnicity, age, maternal height, prepregnancy BMI, weight gain to enrollment, and also, in macrosomia analyses, for neonatal sex, and in preeclampsia and perinatal death analyses, for parity and educational level. Odds ratios are corrected to estimate RRs (9).

vs. 5.0%), or perinatal death (5.9% [1/17] vs. 2.6% [6/229]).

To investigate the association of GDM with macrosomia, we analyzed data from 3,925 women (79% of those completing the OGTT). Not included were 546 women giving birth to twins or without follow-up, 214 with incomplete data on covariates, 92 with unrecorded birth weight, 198 delivering before 35 weeks' gestation, and 2 placed on insulin. Women included were similar to the 1,052 women not included with regard to age, ethnicity, educational level, nutritional status, and parity. Of the included women, 9.7% (379/3,925) gave birth to macrosomic infants.

Table 2 shows that GDM, regardless of the criteria used to classify it, predicted an ~50–70% greater risk of delivering a macrosomic infant, although when classified by ADA criteria, the increased risk was not statistically significant. For WHO criteria, a statistically increased risk persisted, although somewhat reduced (RR 1.45), after adjustment for center, ethnicity, neonatal sex, maternal height, age, prepregnancy BMI, and weight gain up to enrollment. With this adjustment, ~4% of the macrosomic infants observed could be attributed to GDM defined by WHO criteria, but <1% when defined by the less prevalent ADA GDM criteria.

To investigate the association of GDM with preeclampsia, we analyzed data from 4,572 women (92% of those completing the OGTT). Not included were the 175

women without follow-up and the 230 with incomplete data on covariates. None of the women remaining received insulin treatment. Women included were similar to the 405 women not included with regard to age, educational level, and nutritional status; women studied were more frequently white (46 vs. 35%) and nulliparous (31 vs. 24%). Among women studied, 145 (3.2%) developed preeclampsia, with 7 being cases of eclampsia and 27 cases of preeclampsia superimposed on chronic hypertension.

Table 2 shows that GDM was associated with a two to three times greater risk of preeclampsia. After adjustment for center, ethnicity, maternal height, parity, educational level, age, prepregnancy BMI, and weight gain to enrollment, statistically significant RRs of 2.28 for ADA and 1.94 for WHO criteria were present. With this adjustment, ~5% of the preeclampsia observed could be attributed to GDM as defined by ADA and ~8% to the more prevalent GDM by WHO criteria.

To investigate the association of GDM with perinatal mortality, we analyzed data from 4,216 women (85% of those completing the OGTT). Not included were 4 women with abortions (fetal loss before 28 weeks), 547 giving birth to twins or without follow-up, and 210 with incomplete data on covariates. None of the remaining women received insulin treatment. The 4,216 women included were similar to the 761 women not included with regard to age, educational

level, nutritional status, and parity; women studied were more frequently white (46 vs. 40%). A total of 102 (24/1,000) perinatal deaths occurred, with 68 (16/1,000) being fetal deaths and 34 (8/1,000) early neonatal deaths. There were 13 deaths occurring in the 331 GDM women (WHO or ADA criteria), with 7 (21/1,000) being fetal and 6 (18/1,000) early neonatal. Malformation was noted in only 1 of these 13 deaths.

Table 2 shows that women classified as having GDM based on ADA criteria presented an approximately three times greater risk of a perinatal death. Increased risk (RR 3.10, 95% CI 1.42–6.47) was maintained after adjustment for center, ethnicity, maternal height, parity, educational level, age, prepregnancy BMI, and weight gain to enrollment. With this adjustment, ~5% of the perinatal deaths observed could be attributed to ADA-defined GDM. Classification based on WHO criteria was less predictive of perinatal death (RR 1.66; 95% CI 0.91–2.96). However, because WHO-defined GDM was more prevalent, the percentage of perinatal deaths (4.5%) attributable to GDM so-defined was similar to that attributable to GDM defined by ADA criteria.

Given the less than complete overlap of GDM cases diagnosed by the two criteria, we also assessed increased risks of macrosomia, preeclampsia, and perinatal death associated with a diagnosis of GDM by only one of the two criteria against a negative diagnosis for both. Women diagnosed only by WHO criteria (n = 260) had a crude RR for macrosomia of 1.72 (95% CI 1.2–2.4), of 1.75 (1.0–3.1) for preeclampsia/eclampsia, and of 1.1 (0.5–2.6) for perinatal death. Crude RRs for diagnosis only by ADA criteria (n = 22) were 1.9 (0.7–5.4), 1.7 (0.2–11.3), and 2.6 (0.4–17.4), respectively.

Because we detected considerably more cases (357 vs. 119) of GDM using WHO criteria versus ADA criteria, we also detected 3.5 times more (45 vs. 13) subjects with GDM who later delivered macrosomic infants with WHO criteria. Similarly, we detected two times more (23 vs. 12) cases of GDM complicated by preeclampsia and 71% more (12 vs. 7) cases with eventual perinatal death.

Although none of the GDM women included in the above analyses received insulin treatment, 12 women received instructions for a hypocaloric or a normo-

caloric diet for diabetes. The frequency of such diet prescription increased with the degree of hyperglycemia: of these 12 women, 2 had a 2-h glucose level between 7.8 and 8.8 mmol/l (1% of women with glucose in this range); 4 between 8.9 and 10.0 mmol/l (6% of such women); and 6 between 10.1 and 11.0 mmol/l (26% of such women). When these diet-treated women were removed from the analyses, associations of GDM with the three outcomes changed very little, with statistical significance being unaltered.

CONCLUSIONS— We have shown that women diagnosed with GDM based on a 2-h 75-g OGTT, independently of various risk factors such as maternal age and obesity, have an increased risk of delivering a macrosomic infant, developing preeclampsia, and suffering a perinatal death. Based on ADA criteria, GDM predicted a 30% increased risk (NS) of macrosomia, a 128% increased risk of preeclampsia, and a 210% increased risk of a perinatal death. Defined by WHO criteria, GDM predicted similar increased risks of macrosomia and preeclampsia (45 and 94%, respectively) but a notably lower increased risk of a perinatal death (59%; NS).

Our results confirm that GDM is independently associated with macrosomia and preeclampsia, as previously demonstrated by two other large cohorts of American and Canadian women (11,12). More importantly, they show, to our knowledge for the first time, that GDM, independent of age, obesity, and other risk factors, predicts perinatal mortality. Although the background perinatal mortality rate in our study (24/1,000) is high compared with the current U.S. rate, probably reflecting different socioeconomic settings, the even higher rate among GDM women (39/1,000) is noteworthy.

The heterogeneity of diagnostic procedures and criteria, the large variation in research protocols adopted across studies, and the differences in obstetric care over time limit comparability of studies of GDM–pregnancy outcome associations. Yet, a few comparisons regarding the less studied GDM outcome, perinatal death, deserve attention. Our results based on ADA criteria were similar to those of O’Sullivan et al. (13). We calculated from their publication a crude RR of perinatal mortality for GDM of 4.2 ($P < 0.05$) and

an adjusted RR (for age and obesity) of 3.1, the latter not statistically significant (95% CI 0.73–12.9). Our results based on WHO criteria show a lower crude RR (1.66) than that of 2.84 ($P = 0.18$, based on a 2-h cut point of 6.7 mmol/l), calculated from reported data in Pima Indians (14).

A few interpretations from our population attributable fraction data are worth considering. The proportion of the adverse pregnancy outcomes that could be attributed or associated to GDM in our study was small (1–8%), consistent with estimates of attributable risk of macrosomia reported by Casey et al. (15) in a large U.S. cohort. Thus, assuming that GDM could have been prevented or fully controlled, only a small proportion of the adverse outcomes would have been prevented. Nonetheless, a perinatal death is a grave outcome. The fact that as many as 5% could be attributed to GDM, and thus perhaps prevented by clinical protocols for its detection and treatment, highlights the potential clinical importance of GDM, especially in settings in which perinatal mortality remains a major health problem. This interpretation, however, assumes that successful management of GDM will reduce perinatal mortality. Although macrosomia has been shown in randomized trials to be reduced through detection and metabolic control of GDM, benefit in terms of perinatal mortality is far less conclusive (16,17).

Because the risks of adverse outcomes probably increase monotonically along the continuum of the hyperglycemic range, identification of the best cut points for diagnosing GDM has been problematic. In fact, a large international cohort study designed to have the power to define risks associated with various ranges of hyperglycemia was recommended (18) and is currently in the field. The study will hopefully provide precise estimations of risks associated with different ranges of plasma glucose values obtained during a 2-h 75-g OGTT. In the meantime, it is reassuring to know that the two recent official GDM diagnostic recommendations based on a 2-h 75-g OGTT are able to identify women with increased adverse pregnancy outcomes independently of other risk factors.

The ADA and WHO criteria each present advantages and disadvantages. ADA criteria define a more stringent (2–3 vs. 7–8%) and thus logically more severe

condition. These criteria require three blood samples, as opposed to only two with the WHO criteria. The WHO criteria have the simplicity of applying the same criteria for diabetes used outside of pregnancy. Additionally, by identifying a larger number of GDM women, these criteria have a greater potential for prevention, especially of macrosomia. However, the potential benefits to be obtained through treatment of this greater number of cases need to be weighed against the increased use of resources required for their management.

Potential limitations to this study should be considered. Although incomplete follow-up could produce bias, data comparing those pregnant women analyzed with those initially enrolled indicated only small differences, suggesting that if bias were present, it would be minor. Additionally, treatment of hyperglycemia probably exerted little effect on GDM associations with outcomes. In part, as a result of agreement among investigators on the relative lack of empirical evidence to support any diagnostic criteria for GDM falling below the range of hyperglycemia defining diabetes outside of pregnancy, only two cases of GDM were treated with insulin, and both were excluded from these analyses. Hypocaloric diets or diets for diabetes were used infrequently. Reanalysis excluding these diet-treated women produced little change in the magnitude of the associations. Finally, our study, being observational in nature, cannot estimate gains to be made through diagnosis and treatment of this condition. Rather, it can only highlight the potential for such gains.

The strengths of this study merit mention. This is one of the few large studies of unselected pregnant women universally evaluated with the 75-g OGTT. Because these analyses excluded women meeting current diagnostic criteria for diabetes outside of pregnancy, the magnitude of associations here reported reflect the risk specifically for individuals with hyperglycemia in a range where the benefits of diagnosis and treatment are currently being debated. Of note, however, this exclusion resulted in a reduction of ~0.5% in the prevalence of GDM defined by each set of criteria. An additional strength of this study is that treatment of hyperglycemia was minimal, and no additional exclusions were made based on gestational criteria for hyperglycemia.

The characteristics of our study population need to be considered while generalizing these findings to other populations. Composed of urban women who sought care in public services, the study population did not include the more affluent segment of Brazilian society. The high perinatal mortality (24/1,000) among those studied, suggesting causal pathways uncommon in settings of low perinatal mortality, may limit extrapolations to low mortality settings. On the other hand, our sample amply reflected different categories of ethnicity, age, parity, and nutritional status.

In conclusion, GDM detected by a 2-h 75-g OGTT, as defined by ADA or WHO criteria, was associated with the development of adverse pregnancy outcomes. Until consensual criteria are reached, these two criteria are valid options for the detection of a glucose tolerance state predictive of adverse pregnancy outcomes. Assuming that effective treatment is available, the WHO criteria, by identifying a larger number of cases, may have greater potential for prevention.

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APPENDIX

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