Oral glucose tolerance test and pregnancy outcomes

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CONTEXT: Women with Gestational Diabetes Mellitus (GDM) were at increased risk of developing maternal, neonatal complications and postpartum diabetes mellitus. **AIMS:** The study compares relative value of antenatal criteria used for diagnosis of GDM in predicting pregnancy outcome and insulin need. **SETTINGS AND DESIGN:** The study was a longitudinal, prospective clinical trial performed in Al Ain Hospital, UAE. **METHODOLOGY:** Eligible population was made up of patients who participated in an early screening program for GDM and had a positive oral glucose tolerance test (OGTT). A total of 165 GDM patients gave birth consecutively at Al Ain Hospital, UAE (from July, 2002 to January, 2003) and were followed-up for 6 months during postpartum period. Sources of information used were maternal, neonatal hospital records and laboratory results for patients both antenatally and postnatally. Specific patient information regarding maternal and neonatal complications was collected. **STATISTICAL ANALYSIS:** The Pearson chi-squared test and/or the Fisher's exact test were used for analysis as appropriate. **RESULTS:** The number of diagnostic antenatal OGTT values obtained during diagnosis of GDM was significantly correlated with the development of maternal and neonatal complications. The number of abnormal diagnostic antenatal OGTT values using Coustan and Carpenter Criteria (CCC) significantly influenced the development of postpartum diabetes mellitus ($P = 0.044$) within six months of delivery. Number of abnormal OGTT values significantly contributed to insulin need during index pregnancy ($P < 0.05$). **CONCLUSIONS:** Number of abnormal OGTT values obtained during early GDM diagnosis influences maternal and neonatal outcomes. Antenatal OGTT abnormal values are crucial in identifying the need for insulin in GDM patients.

KEY WORDS: Criteria, glucose, oral outcomes, pregnancy, UAE

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Introduction

The study was conducted to examine the early markers for gestational diabetes mellitus (GDM) complications. The study aims to compare the relative value of antenatal criteria used for diagnosis of GDM in predicting pregnancy outcome and insulin need, by examining blood glucose threshold cut-off values from two different standards [National Diabetes Data Group criteria (NDDG) *vs.* Coustan and Carpenter criteria (CCC)], in a population of UAE nationals.

In 1964, O'Sullivan and Mahan suggested using glucose values in pregnant females, obtained during a 100-g, 3-h oral glucose tolerance test (OGTT), to diagnose GDM.[1] In 1979, NDDG recommended adjusting diagnostic thresholds upward.[2] Resulting values were recommended by American Diabetes Association (ADA) as diagnostic cut-off points for GDM until 1999.[3] However, in 1982, Coustan and Carpenter published a different set of interpretations of O'Sullivan and Mahan criteria.[4] In 1989, Sacks and co-workers also showed that correction of O'Sullivan's cut-offs may be necessary and suggested new cut-off values.[5] In 2000, ADA revised the recommendation for GDM diagnostic criteria and proposed adoption of CCC thresholds instead of NDDG thresholds.[6]

New diagnostic criteria for diabetes mellitus outside pregnancy have been recommended by ADA[7] and World Health Organization (WHO).[8] Consensus, however, is

still lacking on GDM, i.e., these bodies have not reached agreement on the criteria for GDM diagnosis, referral criteria for confirmatory OGTT, its standardization, and diagnostic cut-off point.[9,10] The ADA recommends selective screening for GDM in pregnant women who are at high risk, while other guidelines, including those of American College of Obstetrics and Gynecologists (ACOG), support screening of all pregnant women for GDM.[11,12]

The variation in prevalence of GDM worldwide depends on screening and diagnostic methods used as well as on age and ethnicity of the pregnant population.[13-19] The OGTT is usually performed between the 24th and 28th week of gestation; however, in women at increased risk, such as previous gestational diabetes, OGTT should be performed early after diagnosis of pregnancy.[19] It has been found that early glucose tolerance screening could avoid some diabetes-related complications in women with GDM.[20]

There is controversy, for example, regarding adverse maternal and foetal outcomes when there is a single elevated 100 g OGTT value.[21] However, several studies have demonstrated that even one abnormal value is associated with unfavorable neonatal and maternal outcomes.[22-24] The ADA position statement recommends use of either the 100 g OGTT with CCC or 75 g OGTT with CCC in diagnosis of GDM.[25,26] Some studies have also suggested that replacing NDDG criteria with the CCC would increase the number of pregnant women with a diagnosis of GDM, while only minimally affecting prevalence of infant macrosomia.[27]

The first population-based study of GDM prevalence, using both NDDG and CCC thresholds among a large multi-ethnic cohort, suggested that women with GDM diagnosed by CCC, who did not meet NDDG criteria, have higher rates of perinatal complications such as macrosomia, cesarean section, neonatal hypoglycemia and hyperbilirubinemia. Overall, GDM prevalence among screened women was 3.2% (95% CI 3.0-3.4) by NDDG criteria and 4.8% (95% CI 4.5-5.1) by CCC. The prevalence of GDM increased, on an average, by 50.0% with use of the CCC thresholds.[18,28] Furthermore, the CCC better reflect original O'Sullivan-Mahan glucose thresholds, which in turn had a (61.0%) predictive value for identifying women in whom overt diabetes would develop in the following 17-23 years and who may benefit from diabetes prevention strategies.[29,30] In summary, understanding the extent of GDM prevalence and associated complications is hindered by a lack of homogeneity in diagnostic criteria used in previous studies and by changes over time in recommended diagnostic glucose values.

It has been found that the number of abnormal values in 100 g diagnostic OGTT is an independent predictor of subsequent diabetes.[31,32] Other studies found that the strongest predictive factor for progression of GDM patients to postpartum diabetes was four abnormal glucose values on diagnostic antenatal OGTT.[33] Some studies have also demonstrated that plasma glucose concentrations at each point of an OGTT postpartum are predictive for the development of type 2 diabetes.[34] Recent studies have concluded that both maternal GDM risk factors and greater carbohydrate intolerance are associated with an increase in adverse neonatal outcomes.[35,36]

The fasting glucose levels from OGTTs administered during pregnancy was the factor most often examined in studies to date. The fasting glucose level on OGTTs was found predictive for development of diabetes in the majority of studies.[37-45] Although 1- and 2-h plasma glucose levels were studied less often than fasting plasma glucose levels, these were also associated with future type 2 diabetes.[46-48] The area under the OGTT curve was found to be associated with type 2 diabetes in two studies.[41,43] The commonly accepted treatment goal is to maintain a fasting capillary blood glucose level between 5.32 mmol/l and 5.88 mmol/l; the ambiguity (i.e., range) is due to imperfect data. The postprandial treatment goal should be a capillary blood glucose level of <7.8 mmol/l at 1 h and <6.7 mmol/l at 2 h. Patients not meeting these goals with dietary changes alone should begin insulin therapy.[49] A more aggressive goal of a fasting capillary blood glucose level below 95 mg/d (5.32 mmol/l) is supported by a prospective non-randomized observational study.[50,51] This more conservative goal is recommended in the most recent ACOG practice bulletin on gestational diabetes.[13] Another prospective non-randomized study has shown a reduction in operative deliveries and birth trauma in women with GDM, who are treated with insulin.[52] Most, but not all, prospective trials involving insulin therapy in women with GDM have shown a reduction in the incidence of neonatal macrosomia.[53-59]

Methodology

The study was a longitudinal prospective clinical trial approved by Research Ethics Committee (RECA/01/26), Faculty of Medicine, Emirates University in Al Ain, UAE.

The study site was Al Ain Hospital, UAE. Patients were recruited from the gynecology outpatient clinics, wards (D, E, and N) and some primary health care clinics. The eligible population was made up of all patients who participated in an early screening program for GDM, who had a positive OGTT (based on CCC). A total of 165 GDM patients gave birth consecutively at Al Ain Hospital, UAE (from July, 2002 to January, 2003) and were followed-up for 6 months during postpartum period. The sources of information used were maternal medical records, neonatal hospital records and laboratory results for patients both antenatally and postnatally. Diagnostic antenatal OGTTs (within the first 4 months of pregnancy) were conducted in fasting state with glucose analysis performed at fasting, 1, 2 and 3 h after a 100-g oral glucose load. Two sets of thresholds were applied to study population: the NDDG and the CCC [Table 1]. By both criteria, GDM is defined as at least two plasma glucose measurements during diagnostic test at or higher than reported cut-points. The antenatal OGTT values were recoded and computed according to Coustan and Carpenter diagnostic criteria in one case and to National Diabetes Data Group cut-off values in the second case. The sum of abnormal diagnostic OGTT values was calculated and computed for each patient, i.e., 1, 2, 3 or 4 abnormal values (for each of the above two cases). The Pearson chi-squared test and / or the Fisher's exact test were used for analysis as appropriate. The *P* value <0.05 was considered statistically significant. The odds ratios and 95% confidence intervals were obtained as appropriate.

Results

The study included 165 women aged between 21 and 39 years who delivered in Al Ain, UAE and who were known not to have diabetes before the index pregnancy. Overall, GDM among diagnosed women was 100.0% by Coustan and Carpenter criteria and 87.9% by National Diabetes Data Group based on the respective thresholds. The diagnostic antenatal OGTT values for GDM patients under CCC and NDGG cut-off values were as follows: Patients with two abnormal values (n = 44 *vs.* n = 41), with three abnormal values (n = 63 *vs.* n = 59), and with four diagnostic abnormal values (n = 58 *vs.* n = 45), respectively. However, patients (n = 20) under NDDG criteria had less than two diagnostic values of which seven patients had only one diagnostic value and 13 did not meet any cut-off value. Results indicated that patients [n = 20; (12.1%)] would not have been diagnosed as having GDM if NDDG criteria alone had been used for diagnosing GDM.

GDM women with more than two antenatal glucose tolerance values according to CCC were older >29 years [n = 70 (55.1%) *vs.* n = 57 (44.9%)] and revealed a higher parity >5 gravida [n = 85 (66.9%) *vs.* n = 42 (33.1%)] than those with two abnormal OGTT values by NDDG criteria. Furthermore, patients were diagnosed at an earlier gestational age of <16 weeks [n = 88 (69.3%) *vs.* n = 39 (30.7%)].

The number of antenatal OGTT values obtained during the diagnosis of GDM was significantly correlated with

Table 1: Diagnostic oral glucose tolerance test (OGTT) - number of abnormal values as determined by Coustan and Carpenter Criteria (CCC) and/or National Diabetes Data Group (NDDG) - influence on pregnancy outcomes

Pregnancy outcome	Number of antenatal OGTT values						
	0 value	1 value	2 values	3 values	4 values	Total	*P* value
No need for cesarean section (% of total)	12 (92.3)	7 (100.0)	38 (92.7)	52 (88.1)	37 (82.2)	146 (88.5)	0.471
Need for cesarean section (% of total)	1 (7.7)	0 (0.0)	3 (7.3)	7 (11.9)	8 (17.8)	19 (11.5)	
Totals (NDDG)	13	7	41	59	45	165	
No macrosomia (% of total)	-	-	36 (94.7)	58 (85.3)	44 (74.6)	138 (83.6)	0.029
Macrosomia (% of total)	-	-	2 (5.3)	10 (14.7)	15 (25.4)	27 (16.4)	
Totals (CCC)	-	-	38	68	59	165	
No macrosomia (% of total)	11 (84.6)	6 (85.7)	38 (92.7)	50 (84.7)	33 (73.3)	138 (83.6)	0.197
Macrosomia (% of total)	2 (15.4)	1 (14.3)	3 (7.3)	9 (15.3)	12 (26.7)	27 (16.4)	
Totals (NDDG)	13	7	41	59	45	165	
Not large for gestational age (% of total)	-	-	36 (94.7)	60 (88.2)	45 (76.3)	141 (85.5)	0.029
Large for gestational age (% of total)	-	-	2 (5.3)	8 (11.8)	14 (23.7)	24 (14.5)	
Totals (CCC)	-	-	38	68	59	165	
Not large for gestational age (% of total)	12 (92.3)	6 (85.7)	39 (95.1)	51 (86.4)	33 (73.3)	141 (85.5)	0.063
Large for gestational age (% of total)	1 (7.7)	1 (14.3)	2 (4.9)	8 (13.6)	12 (26.7)	24 (14.5)	
Totals	13	7	41	59	45	165	

the development of some complications. Maternal and neonatal outcomes that were shown to be influenced by the number of abnormal values as determined by CCC or NDDG criteria were as follows.

Hydramnios (P = 0.023 and 0.096), severe hyperglycemia (P = 0.045 and 0.263), need for cesarean section (P = 0.034 and 0.471), macrosomia (P = 0.029 and 0.197) and large for gestational age (P = 0.029 and 0.063), respectively.

The number of abnormal OGTT values classified under CCC had a statistically significant impact on maternal and neonatal outcomes detailed above. However, on replacing by NDDG criteria, the influence of number of abnormal OGTT values on maternal and neonatal complications was not found to be statistically significant in any case [Table 1].

The influence of timing of abnormal OGTT values on pregnancy outcomes included odds ratios and 95.0% confidence intervals were presented in Table 2. No significant influence was detected for the 1- and 2-h values. Significant influence was, however, detected with some parameters with fasting and three hour values, [Table 3].

The number of abnormal diagnostic antenatal OGTT values using CCC, significantly influenced the development of postpartum diabetes mellitus (P = 0.044) within 6 months of delivery as determined by the criteria established by Expert Committee on Diagnosis and Classification of Diabetes Mellitus.[58] The association with the development of postpartum diabetes mellitus was as follows: patients with two abnormal values [n = 4; (10.5%)], with three abnormal values [n = 12; (17.6%)], and with four diagnostic OGTT abnormal values [n = 18; (30.5%)].

The chi-squared analysis of diagnostic antenatal OGTT results revealed that timing of values obtained during diagnosis of GDM (based on CCC cut-off values) was not significantly related to development of postpartum diabetes mellitus. The influence of timing of diagnostic antenatal OGTT cut-off values (based on CCC) on insulin need during index pregnancy is presented in Table 4. The number of abnormal OGTT values significantly contributed to insulin need during index pregnancy (P < 0.05; Table 5).

Discussion

This study was undertaken to determine the impact on the study population of adopting CCC for GDM in place of the widely used NDDG criteria. The results demonstrated increased sensitivity of CCC when compared with NDDG criteria in diagnosis of GDM. The finding was consistent with that recently reported in some studies.[43,44] The results support the current practice

Table 2: Fasting plasma glucose oral glucose tolerance test (OGTT) value - as determined by Coustan and Carpenter Criteria (CCC) - influence on pregnancy outcomes

Variable	OR*	95% CI†	*P* value
Maternal outcomes			
Hydramnios	1.51	0.47-4.89	0.588
Severe hyperglycemia‖	3.43	0.75-15.69	0.152
Pre-eclampsia	0.72	0.25-2.10	0.575
Eclampsia	1.36	0.27-6.99	0.527
Need for cesarean section	4.29	1.93-19.34	0.047
Obstructed labor	2.29	0.26-20.15	0.667
Neonatal outcomes			
Macrosomia	6.88	1.56-30.29	0.003
Large for gestational age	3.61	1.03-12.72	0.049
Neonatal hypoglycemia¶ (<2.6 mmol/l)	3.77	0.46-30.99	0.277
Respiratory distress	1.13	0.34-3.79	0.554
Hyperbilirubinaemia	1.60	0.32-7.99	0.722
Premature neonate	4.00	0.88-18.09	0.061
Shoulder dystocia	1.36	0.27-6.99	0.527
Hypocalcemia	1.35	0.14-13.31	0.636
Small for gestational age	2.35	0.76-7.30	0.151

*OR = Odds ratios; †95% CI = Confidence intervals; ‖Severe hyperglycemia was defined as fasting plasma glucose >7.6 mmol/l and/or 1-h postprandial plasma glucose >7.8 mmol/l; ¶Neonatal hypoglycemia was defined as <2.6 mmol/l

Table 3: Fasting and 3-h plasma glucose oral glucose tolerance test (OGTT) value - as determined by Coustan and Carpenter Criteria (CCC) - influence on pregnancy outcomes

Pregnancy outcome	Fasting plasma glucose				Total	*P* value
	≤95 mg/dl (≤5.32 mmol/l)	≥95 mg/dl (≥5.32 mmol/l)	≤140 mg/dl (≤7.80 mmol/l)	≥140 mg/dl (≥7.80 mmol/l)		
No macrosomia (% of total)	49 (96.1)	89 (78.1)	-	-	138 (83.6)	0.003
Macrosomia (% of total)	2 (3.9)	25 (21.9)	-	-	27 (16.4)	
Totals	51	114	-	-	165	
No need for cesarean section (% of total)	49 (96.1)	97 (85.1)	-	-	146 (88.5)	0.047
Need for cesarean section (% of total)	2 (3.9)	17 (14.9)	-	-	19 (11.5)	
Totals	51	114	-	-	165	
Not large for gestational age (% of total)	48 (94.1)	93 (81.6)	-	-	141 (85.5)	0.049
Large for gestational age (% of total)	3 (5.9)	21 (18.4)	-	-	24 (14.5)	
Totals	51	114	-	-	165	
No hydramnios (% of total)	-	-	62 (96.9)	86 (85.1)	148 (89.7)	0.017
Hydramnios (% of total)	-	-	2 (3.1)	15 (14.9)	17 (10.3)	
Totals	-	-	64	101	165	
Not obstructed labor (% of total)	-	-	64 (100.0)	95 (94.1)	159 (96.4)	0.047
Obstructed labor (% of total)	-	-	0 (0.0)	6 (5.9)	6 (3.6)	
Totals	-	-	64	101	165	

Table 4: Influence of timing of abnormal diagnostic oral glucose tolerance test (OGTT) values on insulin need during the index pregnancy of gestational diabetes mellitus (GDM) patients

OGTT cut-off values	Number of patients using insulin (*n* = 91)	OR*	95% CI†	*P* value
≥95 mg/dl (5.32 mmol/l) fasting (% of 114)	84 (73.7%)	17.6	7.16-43.29	0.000
≥180 mg/dl (10.08 mmol/l) at 1 h (% of 143)	86 (60.1%)	5.13	1.79-14.69	0.001
≥155 mg/dl (8.68 mmol/l) at 2 h (% of 158)	88 (55.7%)	1.68	0.36-7.74	0.702
≥140 mg/dl (7.80 mmol/l) at 3 h (% of 101)	60 (59.4%)	1.56	0.83-2.93	0.200

*OR = odds ratios; †95% CI = Confidence intervals

Table 5: Influence of diagnostic oral glucose tolerance test (OGTT) values - number of abnormal values in the 100 g diagnostic OGTT - on insulin need during the index pregnancy of gestational diabetes mellitus (GDM) patients

Insulin	Number of antenatal OGTT values (*P* = 0.000)			
	2 values	3 values	4 values	Total
No insulin need (% of total)	32 (84.2)	34 (50.0)	08 (13.6)	74 (44.8)
Insulin need (% of total)	06 (15.8)	34 (50.0)	51 (86.4)	91 (55.2)
Totals	38	68	59	165

of using CCC in Al Ain Hospital. In the sample of GDM patients, NDDG criteria cut-off values would have failed to diagnose (*n* = 20) patients who were identified (and treated) using CCC values. A similar finding has been documented in a retrospective study in USA women.[26] Similar results were also demonstrated from a cross-sectional study of (*n* = 28,330) women aimed to estimate the magnitude of change in prevalence of GDM using the CCC thresholds as compared to the NDDG thresholds. This later study documented an increased prevalence of GDM, on an average, of 50.0% from 3.2% to 4.8% with use of CCC thresholds.[18]

However, prevalence of GDM diagnosis in present UAE population was found to be increased by only 12.1% using CCC as compared to NDDG criteria. This difference may be attributed in part to the small sample size used in this study as compared to two large studies mentioned above. Furthermore, study by Ferrara *et al*,[17] was conducted in a multiethnic 14-county region in Northern California, whereas our study was performed in a single sample of UAE nationals (i.e., in a single ethnic population). The latter is likely to be the main reason for the variation in findings.

The pregnant women with a diagnosis of GDM using CCC criteria, who did not meet NDDG criteria, had high rates of macosomia. This finding is in agreement with that previously reported.[18,26] However, rates of neonatal hypoglycemia and hyperbilirubinemia were not found to be increased significantly as reported.[18]

The number of abnormal OGTT values as determined using CCC was significantly associated with some

maternal and neonatal outcomes. These associations were, however, not statistically significant with the NDDG cut-off values. The association of complications with number of positive plasma glucose levels during OGTT increased, as number of abnormal OGTT values increased. The highest frequency for all significantly associated complications was exhibited with four abnormal OGTT values. This finding was in agreement with recently published research.[44]

The results indicated an association between some pregnancy complications with the timing of antenatal diagnostic threshold, particularly with fasting (≥95 mg/dl ≡ 5.32 mmol/l) and with 3-h interval (≥140 mg/dl ≡ 7.80 mmol/l) data. The finding concerning fasting glucose level has been widely reported by other researchers.[8,36-38,41,42] The finding concerning 3-h value is of clinical importance as has not been demonstrated in any of previous studies.

An increase in number of abnormal OGTT values was associated with an increase in number of patients developing postpartum diabetes mellitus. The finding was similar to findings reported by other researchers using different populations[30-32] and confirms association in UAE population. However, in this later study,[32] the GDM patients were followed-up for 11 years after first postpartum assessment, whereas the present study has succeeded in providing this evidence during early postpartum period.

Traditionally, insulin need in pregnancy has been determined by glycemic control during pregnancy (fasting ≥105 mg/dl and 2-h postprandial ≥120 mg/dl); however, the present study highlighted a relationship between diagnostic antenatal OGTT values and the need for insulin in GDM patients. The fasting values (≥95 mg/dl) and 1-h values (≥180 mg/dl) were significantly associated with insulin need. Moreover, use of insulin during index pregnancy was significantly influenced by number of abnormal OGTT values. The percentages of patients who needed insulin increased as the number of abnormal values increased. This finding highlights the importance of proper interpretation of diagnostic OGTT values obtained for GDM patients with regard to scheduling patients for insulin in early antenatal period before pregnancy complications ensue.

Conclusions

The CCC are superior to the NDDG criteria in the diagnosis of GDM. Use of the NDDG criteria has the potential to misdiagnose (12.1%) patients in the UAE. Such missed diagnoses have the potential to allow patients with GDM to continue with their pregnancy without proper treatment and as such increase the number of maternal and pediatric complications. The number of abnormal OGTT values obtained during the early GDM diagnosis influences some maternal and neonatal outcomes.

The present study identified for the first time, in the Al Ain, UAE population, the markers of the early development of postpartum diabetes mellitus in current GDM patients, e.g., the number of abnormal values in the 100-g diagnostic OGTT. The latter finding may help in screening programs for those at greater risk of developing diabetes, for whom it is imperative to set up a prevention program.

This research highlights the importance of antenatal OGTT abnormal values in identifying the need for insulin in GDM patients. The present work suggested that if abnormal values (fasting and 1-h values) are seen in the diagnostic OGTT, then insulin should be started immediately to try to prevent incidents of severe hyperglycemia at an early stage before GDM complications ensue.

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