

## Original Article

## Abnormal glucose tolerance is associated with preterm labor and increased neonatal complications in Taiwanese women

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## Abstract

**Objective:** To investigate the relationship between abnormal degrees of oral glucose tolerance test (OGTT) results and pregnancy outcomes. **Materials and methods:** A total of 7513 singleton pregnancies screened for gestational diabetes mellitus were enrolled in this retrospective observational study. The pregnancy outcomes of six different groups with different degrees of glucose intolerance using the OGTT were compared [both the National Diabetes Data Group (NDDG) and Carpenter and Coustan (C&C) criteria were used]. The pregnancies were classified into the following groups: the normal group, consisting of pregnancies with a negative 50-g glucose challenge test (GCT), and Grade 0, 1, 2, 3 and 4 groups, consisting of pregnancies with positive 50-g GCT, and abnormal values of 0, 1, 2, 3 and 4 from the 100-g OGTT, respectively.

**Results:** The adjusted odds ratios (95% confidence interval) for preterm labor and admission to the neonatal intensive care unit (NICU) were shown to be increased in the Grade 4 groups [3.31 (1.47–7.43) and 6.31 (3.14–12.70) by the NDDG criteria; 4.13 (2.30–7.43) and 5.25 (3.00–9.19) by the C&C criteria] compared with the normal group.

**Conclusion:** The results indicated an increased risk for preterm labor and admission to the NICU as the abnormal value of the OGTT increased. Copyright © 2013, Taiwan Association of Obstetrics & Gynecology. Published by Elsevier Taiwan LLC. All rights reserved.

**Keywords:** gestational diabetes mellitus; neonatal complications; oral glucose tolerance test; prenatal care; preterm labor

## Introduction

The prevalence of gestational diabetes mellitus (GDM) has been shown to be between 0.7% and 7.4% [1–7]. The early diagnosis of GDM is important to reduce adverse pregnancy outcomes. The current consensus on glucose tolerance testing during pregnancy involves the use of a 75-g oral glucose tolerance test (OGTT). The Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study, a large multicenter trial (15 centers with approximately 25,000 women) using the 75-g OGTT, was recently published [8], and the results of this study were supported by the International Association of Diabetes

and Pregnancy Study Groups (IADPSG) in 2010 [9] and the American Diabetes Association in 2011 [10]. However, with the OGTT one needs to fast at least 8 hours, which is difficult to administer in Taiwan because many pregnant women are only able or willing to visit the outpatient department in the afternoon or evening (unique worldwide).

Furthermore, the committee opinion by the American College of Obstetricians and Gynecologists showed that there is no evidence that the identification and treatment of women based on the new IADPSG recommendations will lead to clinically significant improvements in maternal and neonatal outcomes and also lead to a significant increase in healthcare costs. The diagnosis of GDM should be based on a two-step approach [50-g glucose challenge test (GCT) and a 100-g OGTT] [11].

Thus, the diagnostic criteria for GDM are still a matter of discussion owing to the lack of consensus and racial and social specifics in various states and the requirement for fasting [12].

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A two-step approach was used to screen for GDM and predict the risk of glucose intolerance postpartum [13,14]. There were two criteria of 100-g OGTT: the National Diabetes Data Group (NDDG) criteria [14] and the Carpenter and Coustan (C&C) criteria [15]. Previous studies showed inconsistent results regarding differences between NDDG and C&C criteria, including advantages and disadvantages [4,16,17]. Hence, both of these diagnostic systems were used in this study.

Recent studies have demonstrated a monotonic relationship between increasing maternal glycemic values and adverse pregnancy outcomes [8,18,19]. However, there were no apparent thresholds at which the risks were found to increase [8,18,19]. Some studies have classified maternal glycemia according to a normal 50-g GCT result and an abnormal 100-g OGTT result and have demonstrated a monotonic relationship using the NDDG or C&C thresholds [20–22]. For the two-step approach, two or more abnormal 100-g OGTT results served as the threshold for the diagnosis of GDM. However, it remains controversial how to most effectively care for pregnant women with only one abnormal 100-g glucose value [20–27].

The objective of this study was to investigate the relationship between abnormal degrees of OGTT results and pregnancy outcomes.

## Materials and methods

### Materials

This retrospective observational study involved the collection of all medical records from the 8014 pregnancies that were administered a 50-g GCT at 24–28 weeks of gestation and were delivered at Chia-Yi Christian Hospital (CYCH) between March 2006 and June 2011. Cases of multifetal pregnancies, prepregnancy diabetes and incomplete 100-g OGTT results were excluded ( $n = 136$ ) from this study. This study was approved by the institutional human studies committee at CYCH (institutional review board number: 100006). Owing to the study design of the retrospective medical chart review, the committee was in agreement that informed consent from each participant was not necessary.

### Glucose tolerance testing

The diagnosis of GDM was based on a 1-hour plasma glucose level  $\geq 140$  mg/dL (7.8 mmol/L) from the 50-g GCT followed by at least two abnormal values from a 100-g OGTT according to the NDDG criteria at CYCH (glucose levels were considered abnormal at or greater than 105, 190, 165, and 145 mg/dL (5.8, 10.6, 9.2, 8.1 mmol/L) for the fasting, 1-, 2- and 3-hour plasma glucose tests, respectively). Women who had 1-hour plasma glucose levels that were less than their fasting plasma glucose levels ( $n = 5$ ) and those with a positive 50-g GCT who had not received a 100-g OGTT ( $n = 360$ ) were excluded from this study. A total of 7513 women were included in this study.

The pregnancies were classified into six groups; individuals with negative 50-g GCT results were assumed to be normal in

this study, although the GCT with a cut-off value set at 140 mg/dL (7.8 mmol/L) was generally considered to have a sensitivity of 80% for GDM. Subsequently, based on a 100-g OGTT, individuals were assigned to Grade 0 to 4 groups according to the number of higher than normal values obtained using this test. For the NDDG groups, the grade was classified as Grade 0 to Grade 4 by the NDDG criteria, and the C&C criteria were used for the C&C groups. Abnormal results referred to glucose levels according to C&C criteria that were equal to or greater than 95, 180, 155, and 140 mg/dL (5.3, 10.0, 8.6, and 7.8 mmol/L) for the fasting, 1-, 2- and 3-hour plasma glucose tests, respectively.

### Maternal and neonatal complications

The outcomes of the study were related to maternal complications, such as preterm labor (delivery before 37 weeks), pregnancy-induced hypertension (PIH) or pre-eclampsia, cesarean section, vacuum extraction, prolonged labor, shoulder dystocia and third- or fourth-degree perineal laceration, and to neonatal complications, such as macrosomia (birth weights  $>4000$  g) and admission to the neonatal intensive care unit (NICU). Chronic hypertension was defined as hypertension that is present and observable before pregnancy or that was diagnosed before the 20th week of gestation. Hypertension was defined as blood pressure (BP)  $\geq 140$  mmHg systolic or  $\geq 90$  mmHg diastolic. PIH was transient hypertension of pregnancy or chronic hypertension identified in the latter half of pregnancy. Pre-eclampsia was characterized by BP of  $\geq 140/90$  mmHg after the 20th week of gestation in a women with previously normal BP and who have proteinuria ( $\geq 0.3$  g/day or  $\geq 1+$  on a urine dipstick), with or without pathological edema.

### Statistical analysis

For the statistical analysis, the baseline categorical variables (nulliparous status and chronic hypertension) were analyzed using the Chi-square test or Fisher's exact test as appropriate. The continuous variables were analyzed using the analysis of variance (ANOVA) test. The Cochran–Armitage test was used to examine the trends between the six groups and their respective outcomes. A multiple logistic regression was used to determine the relationship between the OGTT from Grades 0 to 4 and the GCT of the normal group after adjusting for maternal age, body mass index (BMI) at entry, gestational week receiving 50-g GCT, nulliparous status and chronic hypertension. Associations were described in terms of an adjusted odds ratio (aOR) with a 95% confidence interval (CI).

A two-sided  $p$ -value  $< 0.05$  was considered statistically significant. Each of the statistical analyses was performed using the SAS statistical package (Version 9.2; SAS Institute Inc., Cary, NC, USA).

## Results

Of the 7513 singleton pregnancies, 20.5% ( $n = 1542$ ) were associated with complete 100-g OGTT results. The incidence of

GDM was 3.9% ( $n = 296$ ) as diagnosed using the NDDG criteria and was 6.0% ( $n = 454$ ) as diagnosed using the C&C criteria.

The maternal characteristics and the 50-g GCT results of the NDDG groups are shown in Table 1. There were statistically significant differences for each of the maternal characteristics studied except for nulliparous status. For the groups with higher grades, maternal age, BMI at entry, chronic hypertension and birth weight were found to increase, whereas weeks of gestation was found to decrease.

The frequency of the outcomes for the NDDG and C&C groups is illustrated in Fig. 1. The frequencies of preterm labor, PIH or pre-eclampsia, cesarean section, macrosomia, and admission to the NICU showed significant trends among the six groups, especially preterm labor and admission to the NICU which increased as the grade of both NDDG and C&C groups increased (all  $p < 0.001$ ). The frequencies of vacuum extraction, prolonged labor, shoulder dystocia and third- or fourth-degree perineal laceration demonstrated no significant difference between the groups (not shown in Fig. 1). The aORs for outcomes with a significant association between the NDDG groups and C&C groups are shown in Tables 2 and 3. Each of the outcomes of interest had greater aORs among the NDDG or C&C groups compared with the normal group, except for the frequencies of cesarean section, prolonged labor, shoulder dystocia and third- or fourth-degree perineal laceration. In the NDDG groups, the women diagnosed with GDM (Grade 2–4) had increased risks for preterm labor (Grades 2, 3 and 4 with aORs of 2.40, 2.59 and 3.31, respectively) and admission to the NICU (Grades 2, 3 and 4 with aORs of 1.95, 2.97 and 6.31, respectively). The Grade 4 group was associated with a higher risk for macrosomia (aOR = 5.20, 95% CI = 1.67–16.23) compared with the normal group. The Grade 1 group was associated with a higher risk for PIH or pre-eclampsia and vacuum extraction (aOR = 2.09, 95% CI = 1.21–3.61; aOR = 1.78, 95% CI = 1.13–2.81) compared with the normal group. Similar trends were observed for the C&C groups (shown in Table 3).

## Discussion

The major focus of this study was the classification of OGTT into six different degrees as an attempt to understand the influence of abnormal OGTT values on pregnancy

outcome. A multiple regression analysis was performed after adjusting for confounding factors; in particular, GDM was classified using three levels (Grades 2–4) according to both NDDG and C&C criteria.

We found a significant association between increasingly abnormal OGTT values and pregnancy outcomes of preterm labor and admission to the NICU. The aORs for preterm labor and admission to the NICU were shown to be significantly increased in the Grade 2, 3 and 4 groups compared with the normal group by both NDDG and C&C criteria. These heightened risks indicate that it is important to receive an OGTT during the early part of pregnancy to reduce adverse pregnancy outcomes and especially preterm labor and admission to the NICU.

Most studies have only compared GDM and non-GDM groups in terms of pregnancy outcome [4,5,7]. In Sweden (1991–2003) [7], a population-based cohort study reported the aOR (95% CI) for preterm labor to be 1.71 (1.58–1.86) using the 75-g OGTT approach, and in Taiwan (2001–2008) [4], a medical center reported that the incidence of preterm labor was no different using both NDDG and C&C criteria. Furthermore, some studies had classified study participants using the two-step approach into normal (GCT negative), Grade 0, Grade 1 and GDM groups. A Turkish study found that the incidence of preterm labor was not altered by GDM status [22]; however, a Chinese study found a significant increase in this incidence as a result of this condition [21]. The aOR (95% CI) of Grades 0 and 1, GDM as determined by the C&C but not NDDG criteria, and GDM by the NDDG groups from a northern California population-based study was 1.23 (1.18–1.41), 1.53 (1.6–2.03), and 1.42 (1.15–1.77), respectively, compared with the 50-g GCT normal group [20]. Their results were found to differ for preterm labor based on the various classification systems used and the country in which the study was conducted. However, no study divided individuals with GDM into additional groups to examine the influence of abnormal 100-g OGTT values. The present study demonstrated that a greater range of abnormal OGTT values resulted in a more defined risk for preterm labor, regardless of whether the NDDG or C&C criteria were used.

In this study, there were also increased risks for admission to the NICU according to the abnormal extent of the OGTT grades. In 2008, the HAPO [8] study demonstrated a similar increasing

Table 1  
Maternal characteristics of the six NDDG groups.

	Normal	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	<i>p</i>
<i>n</i>	5971	1021	225	180	75	41	
Maternal age (y)	28.2 ± 4.5	30.0 ± 4.5	31.0 ± 4.5	31.7 ± 4.3	31.8 ± 3.7	31.5 ± 5.4	<0.001
BMI at entry (kg/m <sup>2</sup> )	26.7 ± 3.5	27.1 ± 3.7	28.2 ± 4.0	27.4 ± 3.6	27.3 ± 3.6	32.1 ± 4.5	<0.001
Nulliparous status	3093 (51.8)	530 (51.9)	102 (45.3)	88 (48.9)	33 (44.0)	22 (53.7)	0.31
Chronic hypertension	23 (0.4)	5 (0.5)	3 (1.3)	2 (1.1)	1 (1.3)	1 (2.4)	0.02
Gestational wk receiving 50-g GCT	26.8 ± 1.2	27.0 ± 1.2	26.8 ± 1.2	26.8 ± 1.2	26.9 ± 1.1	26.6 ± 1.3	<0.001
Gestational wks	38.3 ± 1.4	38.3 ± 1.4	38.0 ± 1.4	37.7 ± 1.6	37.6 ± 1.4	37.1 ± 1.7	<0.001
Birth weight (g)	3084.5 ± 396.5	3136.5 ± 392.0	3175.7 ± 410.7	3092.9 ± 471.3	3048.0 ± 471.6	3160.3 ± 632.7	<0.001

Data are presented as mean ± standard deviation or *n* (%).

BMI = body mass index; GCT = glucose challenge test; NDDG = National Diabetes Data Group.

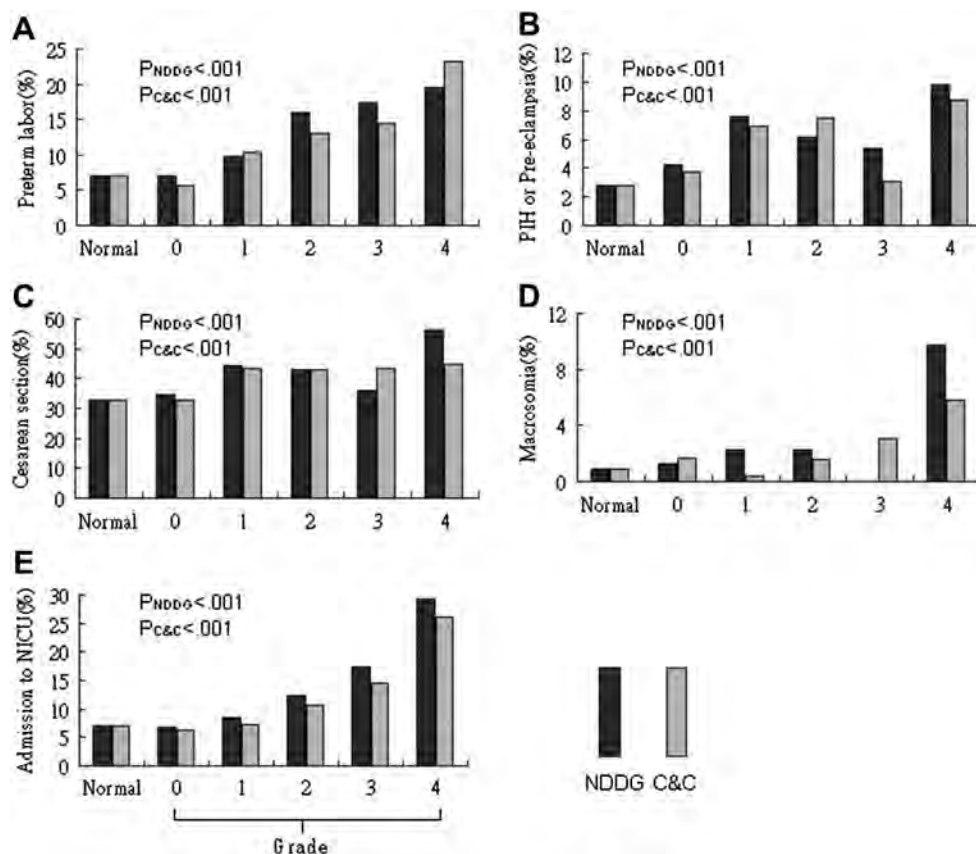


Fig. 1. The frequencies of the various outcomes compared between the NDDG and C&C groups: (A) comparison of preterm labor; (B) comparison of PIH or pre-eclampsia; (C) comparison of cesarean section; (D) comparison of macrosomia; (E) comparison of admission to the NICU. The Grade 0, 1, 2, 3 and 4 groups, consisting of pregnancies with a positive 50-g GCT, and abnormal values of 0, 1, 2, 3 and 4 from the 100-g OGTT, respectively. [ $P_{C\&C}$ ,  $p$ -value for the trend between the C&C groups;  $P_{NDDG}$ ,  $p$ -value for the trend between the NDDG groups]. C&C = Carpenter and Coustan; GCT = glucose challenge test; NDDG = National Diabetes Data Group; NICU = neonatal intensive care unit; OGTT = oral glucose tolerance test; PIH = pregnancy-induced hypertension.

relationship between the need for intensive neonatal care at the 1- and 2-hour categories and the increased plasma glucose level at 1 standard deviation, for which the aORs (95% CI) were 1.07 (1.02–1.13) and 1.09 (1.03–1.14), respectively. In 2010, Anderberg et al [18] reported a similar result using the 75-g

OGTT and categorizing the 2-hour plasma glucose concentrations into three degrees using a population-based database in southern Sweden. The aORs (95% CI) for the 2-hour plasma glucose concentrations of 155–180 mg/dL (8.6–10.0 mmol/L) and >180 mg/dL (10.0 mmol/L) were 2.1 (1.1–3.8) and 5.2

Table 2  
Adjusted odds ratios for outcomes between 50-g GCT normal and 100-g OGTT grading groups by NDDG criteria.

Outcome	Normal	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
<i>n</i>	5971	1021	225	180	75	41
Preterm labor (<37 wk)	1	0.99 (0.76–1.29)	1.37 (0.86–2.17)	2.40 <sup>a</sup> (1.58–3.65)	2.59 <sup>a</sup> (1.40–4.79)	3.31 <sup>a</sup> (1.47–7.43)
PIH or pre-eclampsia	1	1.36 (0.95–1.95)	2.09 <sup>a</sup> (1.21–3.61)	1.85 (0.96–3.58)	1.83 (0.64–5.25)	1.03 (0.34–3.15)
Cesarean section	1	0.93 (0.81–1.08)	1.18 (0.89–1.56)	1.12 (0.82–1.52)	0.83 (0.51–1.36)	1.24 (0.65–2.39)
Vacuum extraction	1	1.21 (0.93–1.56)	1.78 <sup>a</sup> (1.13–2.81)	0.93 (0.50–1.75)	1.05 (0.41–2.64)	0.42 (0.06–3.11)
Prolonged labor	1	1.09 (0.90–1.31)	0.68 (0.44–1.05)	0.76 (0.48–1.21)	1.00 (0.52–1.91)	0.28 (0.07–1.16)
Shoulder dystocia	1	0.47 (0.11–1.97)	2.21 (0.51–9.56)	3.16 (0.73–13.75)	3.97 (0.52–30.48)	— <sup>b</sup>
Third- or fourth-degree perineal laceration	1	0.80 (0.52–1.24)	1.61 (0.80–3.24)	1.05 (0.42–2.61)	0.51 (0.07–3.75)	1.07 (0.14–8.00)
Macrosomia (birth weight >4000 g) <sup>c</sup>	1	1.35 (0.72–2.52)	2.06 (0.80–5.31)	2.38 (0.84–6.79)	— <sup>b</sup>	5.20 <sup>a</sup> (1.67–16.23)
Admission to the NICU <sup>c</sup>	1	1.03 (0.79–1.34)	1.33 (0.82–2.16)	1.95 <sup>a</sup> (1.23–3.10)	2.97 <sup>a</sup> (1.61–5.48)	6.31 <sup>a</sup> (3.14–12.70)

Data are presented as adjusted OR (95% CI). Adjusted OR is the OR adjusted for group differences in maternal age, BMI at entry, gestational week receiving a 50-g GCT, nulliparous status and chronic hypertension.

CI = confidence interval; GCT = glucose challenge test; NDDG = National Diabetes Data Group; NICU = neonatal intensive care unit; OGTT = oral glucose tolerance test; OR = odds ratio; PIH = pregnancy-induced hypertension.

<sup>a</sup> 95% CI does not include 1; <sup>b</sup> There were no cases in the group; <sup>c</sup> Excluded neonatal death.



Table 3

Adjusted odds ratios for outcomes between 50-g GCT normal and 100-g OGTT grading groups by Carpenter and Coustan criteria.

Outcome	Normal	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
<i>n</i>	5971	799	289	254	131	69
Preterm labor (<37 wk)	1	0.80 (0.58–1.10)	1.53 <sup>a</sup> (1.03–2.27)	1.89 <sup>a</sup> (1.28–2.79)	2.08 <sup>a</sup> (1.25–3.46)	4.13 <sup>a</sup> (2.30–7.43)
PIH or pre-eclampsia	1	1.22 (0.81–1.85)	2.04 <sup>a</sup> (1.23–3.38)	2.57 <sup>a</sup> (1.53–4.32)	0.79 (0.28–2.20)	1.23 (0.49–3.09)
Cesarean section	1	0.87 (0.74–1.02)	1.20 (0.94–1.54)	1.15 (0.88–1.49)	1.06 (0.74–1.52)	0.91 (0.55–1.51)
Vacuum extraction	1	1.07 (0.80–1.44)	1.88 <sup>a</sup> (1.28–2.77)	1.35 (0.85–2.16)	0.98 (0.47–2.05)	0.45 (0.11–1.88)
Prolonged labor	1	1.10 (0.90–1.35)	0.97 (0.69–1.36)	0.66 (0.44–1.00)	0.91 (0.55–1.51)	0.53 (0.23–1.24)
Shoulder dystocia	1	0.58 (0.14–2.46)	0.88 (0.12–6.56)	1.06 (0.14–7.98)	4.42 (1.00–19.53)	3.47 (0.44–27.29)
Third- or fourth-degree perineal laceration	1	0.84 (0.52–1.34)	1.01 (0.49–2.09)	1.38 (0.69–2.76)	0.30 (0.04–2.20)	1.16 (0.28–4.88)
Macrosomia (birth weight >4000 g) <sup>b</sup>	1	1.75 (0.94–3.26)	0.33 (0.05–2.39)	1.72 (0.61–4.88)	3.02 <sup>a</sup> (1.05–8.67)	3.61 <sup>a</sup> (1.20–10.90)
Admission to the NICU <sup>b</sup>	1	0.95 (0.70–1.28)	1.11 (0.70–1.76)	1.70 <sup>a</sup> (1.12–2.58)	2.42 <sup>a</sup> (1.46–4.01)	5.25 <sup>a</sup> (3.00–9.19)

Data are presented as adjusted OR (95% CI). Adjusted OR is the OR adjusted for group differences in maternal age, BMI at entry, gestational week receiving a 50-g GCT, nulliparous status and chronic hypertension.

CI = confidence interval; GCT = glucose challenge test; NICU = neonatal intensive care unit; OGTT = oral glucose tolerance test; OR = odds ratio; PIH = pregnancy-induced hypertension.

<sup>a</sup> 95% CI does not include 1; <sup>b</sup> Excluded neonatal death.

(2.8–9.6), respectively, compared with the plasma glucose concentrations <155 mg/dL (8.6 mmol/L). These studies examined large populations and used potential confounding factors to adjust the risk of need for intensive neonatal care. However, these studies each used the 75-g OGTT approach to categorize maternal glycemia.

When the two-step approach was used, the incidence of hospitalization was found to be significantly different among the 50-g GCT normal group (5.9%), the Grade 0 group (9.7%), the Grade 1 group (14.8%) and the GDM group (12.3%) using the NDDG criteria in Turkey [22]. The aOR (95% CI) for neonatal admission to the intensive care nursery for individuals of Grade 1 according to the C&C criteria was 1.52 (1.04–2.22) compared with the 50-g normal group consisting of white women in the USA [28]. In our study, there was no significantly greater risk for individuals of Grade 1, but there was a minor trend (aOR = 1.11, 95% CI = 0.70–1.76). Also, there was a significant trend towards a greater risk for individuals in the Grade 2–4 groups, as determined using a multiple logistic regression after adjusting for confounding factors.

The proportion of women who were given cesarean sections has been reported to be greater for those with GDM than without [4,7], and this proportion was most significantly increased for Grade 1 [22,28] compared with the 50-g GCT normal group. Our results were also in accordance with these studies. However, after adjusting for confounding factors in a multiple regression analysis, this significance was diminished. The proportion of women with PIH or pre-eclampsia was reported to be greater for those with GDM than without [4,7], and the risk for pre-eclampsia was reported to be greater for individuals of Grade 1 than for those in the 50-g GCT normal group according to a multiple logistic regression analysis that was adjusted for potential confounding factors among white women [28]. In our study, there was a significant increasing trend for PIH or pre-eclampsia for each of the six grade groups except for Grades 2 and 3 (Fig. 1). After adjusting for confounding factors, the ORs were significantly greater for individuals in the Grade 1 group compared with those in the 50-g GCT normal group. According to multiple logistic models,

BMI at the time of entry had a more significant influence on the risk of cesarean section, PIH or pre-eclampsia than did the degree of abnormal OGTT results.

The limitations of this study were that the recorded data were not extensive enough to be properly adjusted and that BMI was recorded at delivery and not pre-pregnancy. Another possible limitation might be that negative 50-g GCT individuals might also be glucose intolerant on the 100-g test. An additional limitation was that only a few individuals were classified as Grades 3 and 4. In addition, other potential factors led to adverse outcomes irrespective of diabetes. However, we were able to demonstrate that there was an increased risk for preterm labor and admission to the NICU as the abnormal degree of OGTT results increased.

In conclusion, our results indicated an increased risk for preterm labor and admission to the NICU as the abnormal value of the OGTT increased according to the two-step approach. These findings could provide evidence for the development of an optimal approach to screening and diagnosis of GDM [11]. Further research regarding the advantages and disadvantages of screening and diagnosis of GDM are needed.

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