CEOG Clinical and Experimental Obstetrics & Gynecology

The association of impaired gestational glucose tolerance with maternal and fetal outcomes

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Summary

The aim of the present study was to examine the associations of gestational diabetes mellitus (GDM) and impaired glucose tolerance (IGT) with maternal and fetal outcomes.A total of 200 pregnant women were included in this cross-sectional study. A 50-gram oral glucose challenge test (GCT) was performed between 24 and 28 weeks of gestation, followed by glucose tolerance test (OGTT) with 100 grams of oral glucose in those with an abnormal one-hour test result. The following were not significantly different between groups. Preterm labour (PL), pregnancy induced hypertension(PIH), pre-eclampsia, polyhydramnios, and macrosomia. However, a significant increase was noted in the fetal birth weight as well as in number of cesarean deliveries among GDM subjects. Neonatal outcomes were also similar between the two groups. In conclusion, the present results suggest that single high glucose readings in OGTT may be as important as a diagnosis of GDM in terms of fetomaternal complication risk.

Key words: Gestational diabetes; Impaired glucose tolerance; Pregnancy.

Introduction

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance of variable severity, occurring or being detected for the first time during pregnancy [1]. Nearly 1% to 14% of all pregnancies (average 7%) are complicated by gestational diabetes mellitus (GDM) [2], with a strong correlation between metabolic control and feto-maternal outcomes [3, 4]. Maternal hyperglycemia has been shown to be a significant risk factor for the mother and fetus [5]. Failure to inadequately diagnose and treat this condition may lead to significant perinatal mortality and morbidity, including stillbirths, fetal macrosomia, shoulder dystocia, birth trauma, respiratory distress syndrome, neonatal jaundice, neonatal electrolyte imbalance, and polycythemia [6]. In addition, babies born to mothers with GDM are more likely to experience health problems such as hypoglycemia, hypocalcemia, hypomagnesemia, hyperbilirubinemia, and respiratory distress syndrome (RDS) during the newborn period [7]. After confirmation of the positive effects of optimally controlled GDM on perinatal outcomes in recent studies, the discussions concerning the importance of screening and treatment in this condition have subsided [8]. Current strategy for the prevention of fetal and maternal complications involves the assessment of all pregnant women between 24 and 28 weeks of gestation with a 50-gram glucose challenge test (GCT). Pregnant women with a test result of > 140 mg/dl are subjected to further assessment with oral glucose tolerance test (OGTT) [9], which allows the establishment of a final diagnosis [10]. A single value exceeding the normal range in OGTT is referred to as "glucose intolerance" or "borderline diabetes" [11] while two or more readings above the normal range are diagnostic for GDM. Pregnant women diagnosed with GDM are treated accordingly (diet, insulin, etc.) to prevent obstetric complications and postpartum type 2 diabetes [12].

Although appropriate medical care is generally provided for pregnant women with GDM due to its known effects on both the fetus and the mother, the clinical importance of a single high reading in a three-hour (100 grams) OGTT is unknown. Many studies have shown that single high reading in OGTT is a common occurrence with potential adverse feto-maternal effects [13].

In the present study, the authors' objective was to examine perinatal outcomes in that specific subset of pregnant women in whom a diagnosis of GDM could not be established, but in whom OGTT was abnormal.

Materials and Methods

This study was approved by the local ethics committee at Sifa University and written consent of the participating patients were obtained. The study design was a cross-sectional study was performed on 200 pregnant women who presented to the antenatal outpatient unit of the Sifa University, Department of Gynecology and Obstetrics between January 2012 to November 2014. Patients with a previous diagnosis of diabetes, metabolic disease, or multiple-pregnancy were excluded. A standard screening test with 50 grams of glucose was administered to all study subjects Plasma glucose

Revised manuscript accepted for publication June 22, 2015

levels were measured spectrophotometrically with a device using the hexokinase method. Patients with a blood glucose level <140 mg/dl were classified as"normal", while those with > 200 mg/dl were considered to have"GDM" and those with a glucose >140 mg were considered to have "impaired glucose tolerance (IGT)". The latter group subsequently underwent a 100-gram OGTT after eight to 14 hours of fasting. Prior to OGTT, pregnant women were instructed to consume a diet that included a minimum of 150 grams of carbohydrates for three days and the test was performed in the morning following eight to 12 hours of overnight fasting. After blood sampling for fasting blood glucose determination, a solution containing 100 grams of glucose was given to the study subjects and one-, two-, and three-hour venous glucose levels were assessed according to Carpenter and Coustan's threshold criteria, where two or more readings above the normal range were considered GDM, and one reading was considered IGT. Patients with normal glucose readings at all time-points were accepted to have "normoglycemia".

Study subjects were divided into two groups based on the result of OGGT. Group A (n=21) included patients with a single abnormal reading at OGTT (i.e. IGT group), and Group B (n=28) included women with gestational diabetes (i.e. GDM group). Gestational weeks, glucose concentrations measured during a three-hour OGTT, BMI, age, parity, birth weight, the birth method, and maternal and perinatal morbidities were assessed and recorded. All births took place in the hospital setting at the Private Sifa Hospital.

In patients diagnosed with GDM, insulin therapy was initiated when dietary treatment did not consistently maintain fasting and preprandial capillary glucose ≤ 100 mg/dl and two-hour postprandial capillary glucose ≤ 120 mg/dl. Patients were closely monitored for pregnancy related complications.

Pre-eclampsia was defined as persistently high blood pressure (systolic BP > 140 mmHg and/or diastolic BP > 90 mmHg in > two measurements) and presence of proteinuria (urinary protein > +2), and pregnancy-induced hypertension was defined according to above-stated blood pressure criteria without proteinuria.

Birth before 37 weeks of gestation, term-induced births, fetal membrane rupture with amniotomy, or administration of intravenous oxytocin infusion was considered "pre-term".

Macrosomia was defined as a birth weight exceeding 4,000 g and neonatal hypoglycemia was defined as the occurrence of a plasma glucose level of < 40 mg/dl in the first 48 hours of life [14].

Presence of a respiratory rate above 60/minute in addition to clinical findings such as subcostal retractions, grunting, and nasal flaring were considered to indicate respiratory distress. In addition, patients with lung x-ray findings suggestive of respiratory distress syndrome (RDS), pneumonic infiltration or pneumothorax were recorded.

Direct and indirect hyperbilirubinemia were measured with an auto-analyzer in venous blood samples and phototherapy was administered according to the protocol for admitted newborns with a gestational age of ≥ 35 weeks proposed by the Hyperbilirubinemia Subcommittee of the American Academy of Pediatrics [15].

Statistics

Statistical analyses were performed using Rstudio 0.98.501 software. The normality of distribution of the variables was tested using analytic methods (Kolmogorov-Smirnov/Shapiro-Wilk tests). Descriptive statistics such as mean ± standard deviation were presented for the variables. Inter-group comparisons of continuous variables without normal distribution were done using Mann-Whitney U test. For the inter-group comparisons of categorical variables, Pearson chi-Square and Fisher exact chi-square test were used. A *p*-value of less than 0.05 was considered statistically significant.

Table 1. — *Comparative descriptive statistics in IGT and GDM groups.*

Variables	IGT (n=21)	GDM (n=28)	*p*-value
BMI	26.43 ± 2.25	26.00 ± 2.25	0.521
Fasting blood glucose (mg/dl)	96.43 ± 4.24	98.43 ± 5.60	0.083
Age (years)	29.05 ± 4.02	30.32 ± 3.74	0.239
50-gram glucose challenge test	157.57 ± 12.82	168.07 ± 12.99	*0.007**
1-hour OGTT	202.10 ± 11.55	220.43 ± 20.04	*0.001**
2-hour OGTT	158.95 ± 8.63	174.46 ± 10.45	*0.0001**
3-hour OGTT	135.14 ± 4.07	143.89 ± 8.57	*0.0001**
Neonatal birth weight (kg)	3433.33 ± 379.91	3748.21 ± 381.39	*0.006* *
Parity	IGT (%)	GDM (%)	*p*-value
1	8 (38.1)	5 (17.9)	0.379
2	9 (42.9)	13 (46.4)	
3	3 (14.3)	7 (25.0)	
4	1 (4.8)	3 (10.7)	

* $p < 0.05$ was accepted as statistical significance.
OGTT: oral glucose tolerance test; GDM: gestational diabetes mellitus; IGT: impaired fasting glucose tolerance.

Results

The demographic characteristics of the groups are shown in Table 1. No significant differences were observed in BMI, parity, and age between the groups. There were no significant differences between IGT and GDM groups in terms of FBG, while significantly higher blood glucose was found at GCT and at all OGTT time-points (one, two, and three hours) in GDM group (Table 1).

The groups were also compared in terms of obstetric outcomes (Table 2), with no significant differences ($p > 0.05$) in the frequency of preterm labour (PL), pregnancy induced hypertension (PIH), pre-eclampsia, polyhydramnios, or macrosomia. However, significantly higher fetal birth weight as well as a higher occurrence of cesarean deliveries were found in GDM group (Tables 1 and 2) ($p < 0.05$).

Neonatal outcomes were compared between the two groups (Table 2), with no significant differences in the frequency of hyperbilurubinemia, hypoglycemia or RDS ($p > 0.05$) (Table 2).

Discussion

Although numerous studies on GDM have been published since its first description, the clinical significance of the milder form of the condition remains disputed, with no agreement on screening tests, diagnostic criteria, and use of oral anti-diabetics [16].

A 50-gram oral glucose challenge test may be used irrespective of the fasting state between 24 and 28 weeks of gestation in all pregnant women, although tests performed during fasting state are diagnostically more sensitive [17]. American Diabetes Association (ADA) accepts a threshold

Table 2. — *Comparative categorical data in IGT and GDM groups.*

	IGT		GDM		*p*-values
Variables	Yes (%)	No (%)	Yes (%)	No (%)	
Polyhydramnios	3 (14.3)	18 (85.7)	9 (32.1)	19 (67.9)	0.192
Delivery before 37 weeks	0 (0)	21 (100)	3 (10.7)	25 (89.3)	0.250
Vaginal birth	12 (57.1)	9 (42.9)	6 (21.4)	22 (78.6)	0.010 *
Cesarean delivery	9 (42.9)	12 (57.1)	22 (78.6)	6 (21.4)	0.010 *
Macrosomia	3 (14.3)	18 (85.7)	9 (32.1)	19 (67.9)	0.192
Pre-eclampsia	3 (14.3)	18 (85.7)	4 (14.3)	24 (85.7)	1.000
PIH	0 (0)	21 (100)	3 (10.7)	25 (89.3)	0.250
Neonatal hyperbilirubinemia	4 (19.0)	17 (81.0)	7 (25.0)	21 (75.0)	0.737
Neonatal hypoglycemia	0 (0)	21 (100)	4 (14.3)	24 (85.7)	0.125
RDS	3 (14.3)	18 (85.7)	6 (21.4)	22 (78.6)	0.714

* $p < 0.05$ was accepted as statistical significance.; RDS: respiratory distress syndrome; PIH: pregnancy-induced hypertension; GDM: gestational diabetes mellitus; IGT: impaired fasting glucose tolerance.

level of 130 mg/dl or 140 mg/l, which allows identification of the 80% or 90% of the cases, respectively [18].

From a viewpoint of patient characteristics, advanced age, increased BMI, parity, and fetal macrosomia are more prevalent in GDM patients [19, 20]. However, in the present study no significant differences in terms of age, parity, or BMI was found between the groups. On the other hand, consistent with previous studies, a parallel increase in plasma glucose and birth weight was observed [21].

Similar to a previous study [22], the risk of cesarean delivery was also high in the present patients with GDM, which could be associated with an increased likelihood of birth trauma, fetal distress, or postpartum bleeding in women with GDM. In contrast, IGT could be associated with a lower potential for planned cesarean delivery. In patients with borderline GDM, a higher frequency of amniotic fluid index exceeding 95-97.5 percentile was found [23]. However, the present study groups did not differ in this respect. Insulin resistance has been shown to be associated with the development of pre-eclampsia [24]. In this study, despite the absence of a significant threshold level, an increased risk of PIH and pre-eclampsia was found in the study group. This may be due to the small sample size. In contrast to other reports [25], no significant increase in preterm labor was found in association with GDM.

In a study by Sermer *et al.* where OGTT results of 3,637 pregnant women was examined, a linear correlation between increasing glucose levels and hyperbilirubinemia was observed [26]. In the present study, 25% and 19% of the newborns in GDM and IGT groups had hyperbilirubinemia, respectively, which was treated with phototherapy.

The leading cause of mortality in newborns of diabetic mothers is RDS, which results from fetal hyperinsulinism inhibiting the synthesis of surfactant in the fetal lung. In the study by Casey *et al.*, 3% of the 874 pregnant women with GDM had RDS [27]. In the present study, RDS occurred in 21% and 14% of the newborns of mothers in GDM and IGT groups, respectively. A major limitation of this study is the small sample size. Thus, further studies with larger sample sizes are warranted.

In conclusion, the present results suggest that single high glucose readings in OGTT may be as important as a diagnosis of GDM in terms of fetomaternal complication risk. Well-designed, larger prospective studies involving borderline GDM patients are warranted to further clarify this association.

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