

Relationship between Maternal Glucose Intolerance and Fasting Plasma Glucose with Macrosomia during Pregnancy

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Abstract

Background: In this study, the effects of various degrees of maternal glucose intolerance and Fasting Plasma Glucose (FPG) during pregnancy on the prevalence of macrosomia were addressed.

Methods: In this cohort study, we recruited 1801 pregnant women who referred to perinatal clinic between July 2004 and September 2005. Gestational Diabetes Mellitus (GDM) was diagnosed by oral glucose tolerance test (OGTT) and glucose challenge test (GCT). According to the results of GCT and OGTT, patients were assigned in four groups: 1-normal GCT (<130 mg/dl), 2-GCT \geq 130 mg/dl but normal OGTT, 3-impaired glucose test (IGT), and 4-GDM. Also, the mean values of infant birth weight (IBW) in each group were recorded. Moreover, by using FPG in the third trimester, patients were classified into four groups: FPGs \leq 85, 86-90, 91-95, and \geq 96 mg/dl; and the relationship between the mean FPGs of each group and mean IBW was determined.

Results: The prevalence of macrosomia in patients with GDM, IGT, only abnormal GCT and normal GCT was 15.8% , 6%, 3.6% and 1.1%, respectively; and the differences between the groups were significant (RR: 2.5; CI95%:1.99-3.12); also, macrosomia positively correlated with obesity before pregnancy (RR: 1.92; CI95%:1.36-2.73). Mean FPG in the third trimester in each group had statistically significant difference regarding to increase prevalence of macrosomia with increase in FPG values.

Conclusion: The lower degrees of glucose intolerance (IGT and Only abnormal GCT) rather than the Carpenter-Coustan criteria could be related with increase in the prevalence of macrosomia, and FPG itself has independent relationship with macrosomia.

Keywords: Gestational Diabetes Mellitus, Glucose intolerance, Macrosomia

Introduction

Gestational Diabetes Mellitus (GDM) is defined as any degree of glucose intolerance with onset or first recognition during pregnancy (1). GDM is screened by glucose challenge test (GCT) and then an oral glucose tolerance test (OGTT) is performed for definite diagnosis (2). Heretofore

Carpenter-Coustan's and NDDG's criteria have been utilized for diagnosis; however, these criteria are arbitrary and there is no sufficient evidence to confirm these criteria (3). Since the present criteria for diagnosis of GDM are not based on fetal outcome, here diagnostic criteria (Carpenter-Coustan and NDDG criteria) are based on O'sullivan and Mahan's criteria (4), and these criteria, were attached to the subsequent emergence of overt diabetes mellitus in mother after pregnancy rather than the outcome of the present pregnancy; so, we don't precisely know whether Plasma Glucose level could be used for diagnosing poor fetal outcome. Could adverse fetal outcomes be shown by the present GTT criteria exactly? On the other hand, does degree of maternal plasma glucose lead to fetal hyperinsulinemia?

According to review on gestational diabetes mellitus in different regions of Iran from 1992 to 2007, the prevalence of GDM ranged from 1.3% to 10% (5,6), and in Tehran, capital city of Iran, was 6.9% (3). One of the most important and prevalent complications of GDM is macrosomia in the newborn (7). During pregnancy, maternal hyperglycemia results in excessive transfer of glucose across the placenta which may lead to fetal hyperinsulinemia and subsequent increase in growth and adiposity who identify as macrosomia (8,9). Factors associated with the fetal macrosomia include: level of hyperglycemia, genetics, duration of gestation, racial and ethnicity factors, maternal obesity and maternal weight gain (10). Early diagnosis of GDM and intensive blood glucose control may prevent macrosomia (11). Fasting plasma glucose levels even in degrees lower than endorsed threshold for diagnosis of GDM have effects on macrosomia (12, 13, 14). Moreover, Impaired Glucose Tolerance (IGT) is also associated with increasing the prevalence of macrosomia (13). However, it still remains questionable what exact levels of maternal

hyperglycemia leads to fetal hyperinsulinemia and macrosomia (15, 16).

In this study, the effects of various degrees of glucose intolerance and FPG during pregnancy on the prevalence of macrosomia in four groups including: normal GCT, positive GCT and negative OGTT, IGT and GDM addressed.

Methods

In this cohort study, we recruited 1801 pregnant women aged 16-43 years old who referred to perinatal clinics of teaching hospitals affiliated to Tehran University of Medical Sciences between July 2004 and September 2005. Inclusion criteria were absence of laboratory and clinical evidences of diabetes in prepregnancy and exclusion criteria were history of diabetes mellitus before pregnancy and multiple pregnancies. In our study, 1-hour 50-gr glucose challenge test (GCT) was used for screening and GDM diagnosed by 3-hour 100 gr oral glucose tolerance test (OGTT) (2-3,5-13,15-18). According to Carpenter- Coustan's criteria, fasting plasma glucose ≥ 95 mg/dl, 1h ≥ 180 mg/dl, 2 hrs ≥ 155 mg/dl and 3 hrs ≥ 140 mg/dl after glucose loading (OGTT), considered as GDM if at least two values reach above-mentioned criteria. On the other hand, one increased value is defined as IGT (18). Of participants, 196 who were high risk as identified having each of the following criteria: glucoseuria, BMI ≥ 27 Kg/m², history of diabetes in the first-degree relatives, abortion, stillbirth, macrosomia or GDM (19) underwent screening test by a 50-g GCT in the first prenatal visit (before 20th week). If the test results were in normal range then the same was done between 24 and 28 gestational weeks. With applying ADA criteria (20), all other women should be underwent test in 24-28 gestational weeks with a 50-g GCT followed by a formal 100-g OGTT for women who identified positive (defined as a plasma glucose level ≥ 130 mg/dl). Four weeks later (32th gestational week), 100-g OGTT was done in patients with IGT (21, 22). According to the results of GCT and OGTT, patients were classified in four groups: 1- normal GCT (<130 mg/dl), 2- GCT ≥ 130 mg/dl but normal OGTT, 3- IGT and 4- GDM.

Also the mean values of birth weight in each group were recorded. Moreover, with applying

FPG in the third trimester (FPG in 50-g GCT), patients were classified into four groups as $\text{FPG} \leq 85$, 86–90, 91–95 and $\text{FPG} \geq 96$ mg/dL and the relationship between the mean FPG values of each group and median of birth weight was examined. In this study, the prevalence of macrosomia in various degrees of glucose intolerance was assessed. If patients with GDM had normal FPG, they were recommended diet therapy for 2 weeks except patients who were in the first trimester or 2 last months of pregnancy which insulin therapy were immediately considered; nonetheless in the former group if plasma glucose could not be kept in the normal range (fasting < 95 mg/dl and 2h after meals < 120 mg/dl), insulin therapy was considered (23, 24). Twenty percent of patients needed insulin therapy with multiple daily injections method (Regular before each meal and NPH at bedtime).

The patients were asked to sign an informed written consent. The data were analyzed by SPSS, Fisher's exact test and Chi-Square test for relationship between different groups; also, ANOVA for comparing different degrees of glucose intolerance with mean values of birth weight and FPG. In addition, the other causes of macrosomia expect maternal glucose intolerance were not enrolled in analysis. P-values < 0.05 were considered as statistically significant.

Results

The mean values of maternal age, weight and BMI before pregnancy were 26 ± 5 years, 64.3 ± 11.3 Kg and 25.3 ± 4.4 Kg/m², respectively. Results of glucose challenge test in 66% of pregnant women were less than 130 mg/dL. In 22.9% of all pregnant women, though GCT results were equal or higher than 130 mg/dL, OGTT results were in normal range. Also, 3.7% of women were IGT and 7.4% were identified to have GDM.

There were significant differences on mean values of maternal age, weight and BMI before pregnancy within 4 groups, and the mean values of maternal age, weight and BMI before pregnancy positively correlated with rise in glucose intolerance values (Table 1).

The mean values of gestational age (weeks) and weight gain during pregnancy were 38.9 ± 1.2 weeks and 12.3 ± 3.8 kg and the mean

of gestational age and weight gain negatively correlated with rise in glucose intolerance values (Table 1).

The mean values of neonatal birth weight in each group were recorded (Table 2). There were significant differences between the mean values of neonatal birth weight and various degrees of glucose intolerance values, and these differences with post-hoc test (Bonferroni) were between normal GCT group and the other 3 groups and between GCT abnormal-OGTT normal group and GDM group. Fifty three newborns had birth weight equal or greater than 4000 g. The prevalence of macrosomia was 2.9% and only 4 newborns had birth weight more than 4500g (0.3%). The prevalence of macrosomia in patients with GDM, IGT, abnormal GCT, and normal GCT were 15.8%, 6%, 3.6% and 1.1%, respectively and the differences between the groups were significant. The relative risk for macrosomia in normal GCT and abnormal GCT, IGT, and GDM groups were 3.5(CI 95%:1.62-7.25), 2.4(CI 95%:1.35-4.26) and 2.6(CI 95%:2-3.27), respectively; in other words, each degree rise in glucose intolerance value resulted in 2.5 times greater risk for macrosomia (CI 95%:1.99-3.12) (Table 2).

There was significant negative correlation between gestational age and neonatal birth weight (partial correlation efficient: 0.3).

In terms of BMI before pregnancy, the prevalence of normal weight ($\text{BMI} < 24.9$), overweight ($25 < \text{BMI} < 29.9$) and obese ($\text{BMI} > 30$) conditions in patients were 51.7%, 33.5% and 14.7% Kg/m², respectively and these values were positively correlated with rise in values of glucose intolerance. There were significant differences between macrosomia and various BMI values before pregnancy as 1.92 times greater relative risk observed with each degree rise in BMI values (RR:1.92; CI95%:1.36-2.73); however no significant differences were seen between macrosomia and weight-gain during pregnancy.

The mean value of Fasting Plasma Glucose in the third trimester was 82 mg/dl and with considering rise in degree of glucose intolerance values, differences between aforementioned groups were statistically significant (Table 2). Moreover, the relationship between third trimester FPG values in 4 groups and macrosomia was evaluated. The prevalence

of macrosomia in 4 classified FPG groups (FPGs ≤ 85 , 86- 90, 91-95 and ≥ 96 mg/dL) was 2.1%, 1.9%, 6.8% and 7%, respectively; so,

increase in FPG values were associated with increase in the prevalence of macrosomia.

Table 1- Comparison between the mean of age, weight, BMI before pregnancy and GA, weight gain and various degrees of glucose intolerance in pregnant women with normal GCT, abnormal GCT/ normal OGTT, IGT and GDM

Groups [§]	Normal GCT n=1189	abnormal GCT/normal OGTT n=412	IGT n=67	GDM n=133
Age [*] (years)	26 \pm 4	27 \pm 5	29 \pm 4	30 \pm 5
Weight (kg) [*]	63.5 \pm 11.1	64.7 \pm 11.6	67.6 \pm 11	68.3 \pm 11.5
BMI (kg/m ²) [*]	25 \pm 4.3	25.4 \pm 4.3	26.5 \pm 4.4	27.2 \pm 4.7
GA ^{**} (weeks)	38 \pm 1	38 \pm 1	38 \pm 1	38 \pm 1
Weight gain(kg) ^{**}	12.4 \pm 3.9	12.5 \pm 3.6	12.3 \pm 3.6	11.1 \pm 4.1

*the mean of maternal age, weight and BMI increased with rising degrees of glucose intolerance values.

**the mean of GA (gestational age) and weight gain decreased with rising degrees of glucose intolerance values.

§ All differences were statistically significant (P<0.05)

£ Participants were 1801 pregnant women.

Table 2- Comparison between the mean of birth weight, prevalence of macrosomia, mean of FPG in the third trimester and various degrees of glucose intolerance in pregnant women with normal GCT, abnormal GCT/normal OGTT, IGT and GDM

Groups [§]	Normal GCT n=1189	abnormal GCT/normal OGTT n=412	IGT n=67	GDM n=133
Mean birth weight (g)	3.2 \pm 0.3	3.2 \pm 0.3	3.3 \pm 0.4	3.4 \pm 0.5
Macrosomia [*] (%)	1.1	3.6	6	15.8
Mean FPG in the third trimester ^{**} (mg/dL)	80.3 \pm 8.7	82.7 \pm 9.6	88.2 \pm 10.6	91.3 \pm 10.9

*Increasing glucose intolerance values were associated with increasing prevalence of macrosomia

**Mean FPG increased considerably with increasing glucose intolerance values.

§ All differences were statistically significant (P<0.05)

£ Participants were 1801 pregnant women.

Discussion

In the present study, the prevalence of macrosomia in patients with GDM, IGT, only abnormal GCT and normal GCT was 15.8%, 6%, 3.6% and 1.1%, respectively; and the differences between various groups were significant. Moreover, there were statistical significant differences between the mean values of infant birth weight of normal GCT group and other groups also abnormal GCT group and GDM group. Although there was only 160 g difference between median birth weight of GDM group and normal GCT group newborns which may be attributed to drug therapy in GDM patients.

In our study, there were significant differences in the mean values of FPG among 4 groups. Furthermore, there was correlation between prevalence of macrosomia and increasing FPGs in third trimester.

Ample evidences have demonstrated relationship between various degrees of

glucose intolerance during pregnancy and macrosomia, even in lesser degrees of glucose intolerance than necessary threshold for diagnosis of GDM (14,25-30). In a retrospective cohort study of 1825 eligible pregnant women, patients were screened for GDM with the 1-hour 50-g GCT at 24-28 gestational weeks. A false-positive GCT was defined as a result greater than or equal to 135 mg/dL which followed by a normal 3-hours GTT. The false-positive GCT cohort more frequently had adverse perinatal outcomes, including macrosomia greater than 4500 g (OR: 3.66; 95% CI: 1.30- 10.32) (31). Also, Cheng *et al.* have shown that women with a GCT of ≥ 140 mg/dL had higher odds of macrosomia (OR: 1.32; 95% CI: 1.13-1.54) and shoulder dystocia (OR: 1.68; 95% CI: 1.11-2.55) (32). Ergin *et al.* showed a single abnormal test value on an oral glucose tolerance test could be regarded as a pathologic finding and that the patient with a

single abnormal test value may be treated similarly to the patient with gestational diabetes mellitus (33). Langer *et al.* showed that, if IGT left untreated, it would strongly be associated with adverse perinatal outcomes and macrosomia (34% vs. 9%) (34).

Some studies have revealed that one random maternal FPG during pregnancy is important for anticipating macrosomia; In addition, some other studies have considered that there is a significant relationship between FPG and macrosomia (8, 35-38).

In the study by Schrader *et al.* 160 pregnant women were screened for GDM at 24th to 28th gestational weeks using 50 g GCT. If the patients' challenge test were positive (140 mg/dL or higher), then a 100 g OGTT was performed. None of the GCT-negative or the GCT-positive/OGTT-negative patients received treatment. The FPG on the OGTT significantly correlated with infant birth weight ($P < 0.001$; $r = 0.94$). A value greater than 90 mg/dL has been proved to be 100% sensitive and 64% specific for infant birth weight more than 4000 g (38). Schaffer-Graf *et al.* have studied the relationship between FPG within 32th to 35th gestational weeks and macrosomia. The results of their investigation showed that each 5 mg/dl increase in FBS during week 35 led to 1.6 times increase in the probability of macrosomia in newborns (36).

Recently, the HAPO study has shown that there is a linear association between maternal fasting glucose levels below threshold for diagnosing GDM and increase in birth weight (14).

Different studies have proved that yet further studies are warranted to determine the effects of various degrees of glucose intolerance on macrosomia and to identify mothers who are at

higher risk for having macrosomic babies (35-39); so we suggest more further studies on various degrees of hyperinsulinemia in GDM, IGT and only positive GCT patients.

There are evidences which support harmfully rising glucose levels within pregnancy could affects postnatal outcomes. Nevertheless, there are also many women with lower levels of glucose intolerance whose babies are not at risk, but may become concerned and anxious as a result of classified as abnormal.

In summary, we demonstrated relationship between various degrees of glucose intolerance and FPG and macrosomia (which according to the Pederson hypothesis results from fetal hyperinsulinemia). Our results demonstrate that the lesser degrees of glucose intolerance rather than the Carpenter-Coustan criteria could be related to increasing the prevalence of macrosomia, and FPG, itself, has independent relationship to macrosomia. So, if pregnant women have only positive GCT or IGT, more carefully fetal surveillance is warranted, even if we could not diagnose GDM by current recommended criteria. This emphasizes on two points: current treatment goals in GDM are not yet suitable and lower levels of blood glucose should be considered as diagnostic threshold for diagnosis of GDM, and other causes may play role in resulting macrosomia among GDM patients.

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