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Maternal and neonatal outcomes of borderline hyperglycemia during pregnancy diagnosed with abnormal screening test

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Summary

Aim: The authors aimed to determine whether mild maternal glucose intolerance detected by abnormal screening by one-hour 50-gram glucose challenge test (GCT) and normal 100-gram oral glucose tolerance test (OGTT), which can be called as borderline hyperglycemia, is associated with increased risk of maternal and fetal adverse outcomes or not compared to normal and gestational diabetes mellitus (GDM) patients. *Materials and Materials:* Pregnant women with normal 50-gram GCT (198 cases), abnormal 50-gram GCT and normal 100-gram OGTT (160 cases), and impaired glucose tolerance (IGT) or GDM diagnosed with 100-gram OGTT (212 cases) were included. Data was collected from hospital automation system and clinical records. The authors compared demographic, obstetric, and neonatal outcomes among these three groups. *Results:* Mean maternal age (31.5 ± 5.2 years), history of GDM (4.2%), and the rate of cesarean section delivery in previous pregnancy (41,5%) were statistically higher in group 3 (IGT+GDM group) compared to both group 1 (normal 50-gram GCT) and group 2 (borderline hyperglycemia), respectively ($p < 0.01$, $p < 0.01$, and $p < 0.01$). The duration of maternal hospitalization was longer (2.40 ± 1.28 and 2.39 ± 1.25 *vs.* 1.79 ± 1.15 day, $p = 0.001$, $p = 0.001$, respectively) and postoperative hemoglobin values were lower (10.71 ± 1.44 and 10.69 ± 10.90 *vs.* 11.22 ± 1.43, $p = 0.015$, $p = 0.006$, respectively) both in groups 2 and 3 when compared with group 1. However preeclampsia was statistically more commonly developed in group 3 than in groups 1 and 2 (16% *vs.* 6.1% and 11.3%; $p < 0.05$). Neonatal hypoglycemia was more common both in groups 2 and 3 compared to group 1 (11.8%, 4.6% *vs.* 0%; $p < 0.001$, $p = 0.045$, respectively) and first minute apgar scores were higher in group 1 than in groups 2 and 3 (7.97 ± 0.55 *vs.* 7.65 ± 1.19 and 7.60 ± 1.17; $p = 0.003$, $p = 0.001$, respectively). Duration of hospitalization period for neonates was longer in groups 2 and 3 than in group 1 (2.22 ± 1.28 and 2.42 ± 1.48 *vs.* 1.82 ± 1.17 day; $p = 0.006$, $p = 0.001$). *Conclusion:* Borderline hyperglycemia can cause maternal, perinatal, and neonatal adverse outcomes. Both obstetricians and neonatologists must keep in mind the unfavorable pregnancy outcomes of borderline hyperglycemia cases and careful follow up is needed even if it is not accepted as GDM and IGT.

Key words: Borderline hyperglycemia; 50-gram GCT; Perinatal outcomes.

Introduction

The prevalence of diabetes mellitus (DM) among reproductive aged women is increasing gradually all over the world with the increase in obesity and sedentary lifestyle. Gestational diabetes mellitus (GDM) is defined as glucose intolerance with onset or first recognition during pregnancy and the prevalence of GDM ranges from 1% to 14% depending on the population screened [1, 2]. Women with GDM have increased risk of both maternal and neonatal complications. The aim of the screening and diagnosing GDM during pregnancy is to reduce the perinatal complications. For this purpose different screening approaches have recommended. Even if International Association of Diabetes and Study Group (IADPSG) recommends one step approach with 75-gram two-hour oral glucose tolerance test (OGTT), two-step approach is the most widely used approach and recommended by ACOG [3, 4]. Two step approach consist of the first step 50 gram one-hour glucose challenge test (GCT) and if the patients is screened positive, the second step three-hour 100-gram OGTT.

The maternal and neonatal risks of GDM are well documented in the literature; the risks of borderline hyperglycemia (which has not got the criteria of GDM or impaired glucose tolerance but positive 50-gram GCT results) are less clear. There are several studies showing that the risk of adverse maternal and infant pregnancy outcomes increases with increasing levels of glucose impairment [5, 6]. In this study the authors aimed to determine whether mild maternal glucose intolerance detected by abnormal screening by one-hour 50-gram GCT and normal 100-gram OGTT, which can be called as borderline hyperglycemia is associated with increased risk of maternal and fetal adverse outcomes or not, compared to normal and GDM patients.

Materials and Methods

Pregnancies screened for GDM who admitted to Zeynep Kamil Maternity and Children's Training and Research Hospital in Istanbul for routine pregnancy follow up from January 2010 to De-

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cember 2012 were included in the study. GDM screening was done by two step approach. The first step 50-gram one-hour GCT had administered at 24-28 weeks gestation as recommended by ACOG [7]. The threshold value as ≥ 140 mg/dl of serum glucose level after one hour was accepted as positive test result and patients underwent second step,100-gram three-hour OGTT. Patients with a value of 200 mg/dl or higher after 50-gram GLT were considered to have GDM and did not undergo 100-gram GTT [8]. The threshold values of serum glucose levels are determined as ≥ 95 mg/dl, ≥ 180 mg/dl, ≥ 155 mg/dl, ≥ 140 mg/dl, or higher for fasting, one, two, three hours, respectively, according to Carpenter Coustan criteria [9]. Two abnormal values meeting or exceeding the threshold values were required for the diagnosis of GDM. One positive value indicated impaired glucose intolerance and all values under the threshold level was accepted negative OGTT [10]. Data was collected from hospital automation system and clinical records. Pregnancies with fetal anomalies, previously diagnosed type I or type II diabetics, multiple gestations, autoimmune diseases, congenital uterine anomalies, history of preterm birth, and hypertension were all excluded from the study. Among total of 3,054 cases screened with 50-gram GCT, 678 had positive screening. Of them, 212 cases were diagnosed with impaired glucose tolerance or GDM with 100-gram OGTT or as 200 mg/dl or higher after 50-gram GLT. With randomized sampling, 198 cases out of 2,376 (first case in every 12 cases), 50-gram GCT negative pregnant women were included in group 1, 160 cases out of 480 (first case in every three cases) pregnant women 50-gram GCT positive but 100-gram OGTT negative were considered as group 2 (borderline hyperglycemia group) and 212 whose 100-gram OGTT abnormal were considered as group 3 (impaired glucose tolerance or GDM group). Gestational age was determined by last menstrual period which was confirmed with crown rump length (CRL) measurement at first trimester obstetric ultrasound. All cases had their periodic hospital visits and gave birth in the present hospital.

The authors compared demographic, obstetric, and neonatal outcomes among these three groups. Demographic variables and past obstetric history such as maternal age, gravidity, parity, previous mode of delivery, history of GDM, macrosomic fetus, premature delivery, and history of GDM in first degree relatives were recorded.

Maternal outcomes were duration of hospitalization period, obstetric haemorrhage (defined as difference in prepartum and postpartum hemoglobin levels higher than one gr/dl), ablatio placenta, polyhydramnios (defined as amniotic fluid index above 90 percentile at that gestational age), preeclampsia (defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg with proteinuria ≥ 300 mg in 24 hours), and the mode of delivery.

Neonatal outcomes were birth weight of newborn, macrosomia (defined as birthweight over 4,000 grams), gestational age at birth, prematurity (defined as giving birth under 37 weeks gestation), hypoglycemia (serum glucose level below 40 gr/dl within two hours from birth), polycythemia (venous hematocrit level above 65%), neonatal hyperbilirubinemia (diagnosed when total bilirubin was higher according to weight and age of newborn according to American Academy of Pediatrics clinical guideline, birth injury, shoulder dystocia, neonatal intensive care unit (NICU) admission, 1st and 5th minute apgar scores, and duration of hospitalization period of newborn were all recorded.

Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 statistical software programs were used for statistical analysis. Categorical variables are presented as percentages, and continuous variables are presented as mean followed by standard deviation and median. The normality of the variables was tested with Kolmogorov–Smirnov test. One-way ANOVA variance analysis with Tukey HDS as a post hoc test was used for comparison of continuous variables between groups. Kruskal Wallis and Mann–Whitney U test were used to compare the median of different groups. Nominal variables were compared by chi-square test, Yates Continuity Correction, and Fisher's Exact test. A p-value <0.05 was considered as statistically significant.

Results

Mean maternal age was 31.5 ± 5.2 years in group 3 which was statistically higher than groups 1 and 2 (28.2 ± 5.0 and 29.2 ± 6.1 years) ($p < 0.01$). However mean maternal ages between groups 1 and 2 were not statistically different ($p = 0.352$). History of GDM in group 3 was statistically higher than groups 1 and 2 (4.2% *vs.* 1.0% and 0.6%, $p < 0.01$) and also history of DM in the first degree relatives were statistically higher in group 3 than both groups 1 and 2, respectively (12.3% *vs.* 1.0% and 4.4%, $p < 0.01$). The rate of cesarean section delivery in previous pregnancy was statistically higher in group 3 compared to both groups 1 and 2, respectively (41.5% *vs.* 27% and 28.9 % $p < 0.01$). There were no statistically significant difference between the groups for parity, history of macrosomia, and history of premature labor. These baseline characteristics are shown in Table 1.

Comparison of both maternal and obstetrical outcomes are shown in Table 2. The duration of maternal hospitalization were longer both in groups 2 and 3 when compared with group 1 (2.40 ± 1.28 and 2.39 ± 1.25 *vs.* 1.79 ± 1.15 day, $p = 0.001$, $p = 0.001$, respectively), but no difference was seen between groups 2 and 3. Postoperative hemoglobin values were lower both in groups 2 and 3 than in group 1 (10.71 ± 1.44 and 10.69 ± 10.90 *vs.* 11.22 ± 1.43, $p = 0.015$, $p = 0.006$, respectively), whereas there were no statistically difference between the groups for preoperative hemoglobin values. Preeclampsia was statistically more commonly developed in group 3 than in group 1 and 2 (16% *vs.* 6.1% and 11.3%; $p < 0.05$). Although pre-eclampsia was commonly seen in group 2 than in group 1, the difference was not statistically significant. Cesarean section rate was statistically higher in group 3 than in groups 2 and 1 (91.3% *vs.* 66.2% and 37.8%; $p = 0.014$, $p = 0.001$) and also cesarean section rate was more common in group 2 than in group 1, which was not statistically significant ($p = 0.095$). There was no significant difference in the rate of polyhydramnios, placental ablation, preterm labor, and average gestational week at birth between the groups.

Neonatal hypoglycemia was more common in group 3 than in group 2 (11.8% *vs.* 4.6%; $p = 0.027$). There was statistically significant neonatal hypoglycemia in group 2 compare to group 1, in that there was no neonatal hypoglycemia ($p = 0.045$). First minute Apgar scores were higher in group 1 than in groups 2 and 3 (7.97 ± 0.55 *vs.* 7.65 ± 1.19 and 7.60 ± 1.17; $p = 0.003$, $p = 0.001$). Duration of hospitalization period for neonates was longer in

Table 1. — *Maternal characteristic of study groups.*

	Group 1 (n=198) Normal 50-gram GCT Mean ± SD (median)	Group 2 (n=160) Borderline GDM (screen positive, 100-gram OGTT negative) Mean ± SD (median)	Group 3 (n=212) IGT + GDM Mean ±S D (median)	*p*
Maternal age (years)	28.24 ± 5.04 (28.00)	29.22 ± 6.16 (29.00)	31.52 ± 5.24 (31.50)	< 0.001 0.001[a] 0.001[b]
Parity n (%)	1.62 ± 0.79 (1.00)	1.88 ± 1.02 (2.00)	1.77 ± 0.99 (1.50)	0.240
Previous C/S delivery, n (%)	41 (27%)	38 (28.9%)	59 (41.5%)	0.001 0.001[a] 0.001[b]
History of GDM, n (%)	2 (1.0%)	1 (0.6%)	9 (4.2%)	0.046 0.048[b]
History of macrosomia, n (%)	12 (6.1%)	8 (5%)	17 (8 %)	0.090
History of prematurity, n (%)	10 (5.1%)	5 (3.1%)	14 (6.61%)	0.320
History of DM in 1st degree relatives n (%)	12 (1.%)	7 (4.4%)	26 (12.3%)	0.001 0.002[a] 0.014[b]

[a]: Comparison of normal pregnancy and IGT+GDM (group 1-3).
[b]: Comparison of borderline GDM and IGT+GDM (group 2-3).

Table 2. — *Pregnancy complications, maternal and fetal outcomes.*

	Group 1 (n=198) Normal 50-gram GCT Mean ± SD (median)	Group 2 (n=160) Borderline GDM (screen positive, 100-gram OGTT negative) Mean ± SD (median)	Group 3 (n=212) IGT + GDM Mean ± SD (median)	*p*
Maternal Hospitalization (days)	1,79±1.15 (2)	2.40±1.28 (2)	2.39±1.25 (2)	< 0.001 0.001* 0.001[a]
Birth weight (grams)	3202.02±443.82 (3200)	3230.21±500.46 (3210)	3311.20±630.33 (3375)	0.188
Macrosomia n (%)	18 (9.1%)	16 (10%)	24 (11.3%)	0.735
Gestational age (weeks)	39.02±1.89 (39.29)	38.81±2.01 (39.00)	38.69±2.13 (39.00)	0.423
Preop Hb g/dl	12.06±1.31 (12.10)	11.81±1.27 (11.85)	11.98±1.26 (12.00)	0.261
Postop Hb g/dl	11.22±1.43 (11.30)	10.71±1.44 (11.00)	10.69±1.39 (10.90)	0.005 0.015* 0.006[a]
C/S delivery, n (%)	75 (37.8%)	106 (66.2%)	193 (91.2%)	0.001 0.095* 0.001[a] 0.014[b]
Preeclampsia, n (%)	12 (6.1%)	18 (11.3%)	34 (16.0%)	0.040 0.023[a]
Polyhydramnios, n (%)	2 (1.0%)	5 (3.1%)	8 (3.8%)	0.405
Placenta ablation, n (%)	0 (0.0%)	3 (1.9%)	3 (1.4%)	0.410
Labor injury, n (%)	2 (1.0%)	1 (0.6%)	6 (2.8%)	0.233
Shoulder distocia, n (%)	0 (0.0%)	1 (0.6%)	0 (0.0%)	0.368
Prematurity, n (%)	20 (11.2%)	15 (9.5%)	24 (11.4%)	0.383
1st min. Apgar Score	7.97±0.55 (8)	7.65±1.19 (8)	7.60±1.17 (8)	0.002 0.003* 0.001[a]
5th min. Apgar Score	9.02±0.28 (9)	8.86±1.02 (9)	8.84±0.98 (9)	0.178
Neonatal hospitalization (days)	1.82±1.17 (2)	2.22±1.28 (2)	2.42±1.48 (2)	0.001 0.006* 0.001[a]
Hyperbilirubinemia, n (%)	10 (5.2%)	14 (9.2%)	15 (7.1%)	0.480
Hypoglycemia, n (%)	0 (0.0%)	7 (4.6%)	25 (11.8%)	0.001 0.045* 0.001 [a] 0.027[b]
Polycythemia, n (%)	4(2.1%)	3 (2.0%)	13 (6.2%)	0.073
Neonatal intensive care unit admission (days)	6 (6.2%)	9 (5.7%)	13 (6.2%)	0.980

* Comparison of normal pregnancy and borderline GDM (group 1-2). [a]: Comparison of normal pregnancy and IGT+GDM (group 1-3).
[b]: Comparison of borderline GDM and IGT+GDM (group 2-3).

groups 2 and 3 than in group 1 (2.22 ± 1.28 and 2.42 ± 1.48 *vs.* 1.82 ± 1.17 day; $p = 0.006$, $p = 0.001$). The difference between groups 2 and 3 was not significant. There was no statistically difference in the rate of shoulder distocia and other birth injuries, neonatal hyperbilirubinemia, neonatal polycythemia, NICU admission, birth weight, 5th minute Apgar scores, and in the rate of macrosomia between the groups.

Discussion

This study was designed to emphasize the impact of having high glucose levels of 50-gram GCT for pregnant women who had the 100-gram OGTT results of normal in range. Although there was no criteria of GDM, mild hyperglycemia appearing as elevated 50-gram GCT may be considered to cause adverse maternal and neonatal outcomes.

In the present study, the patients who had abnormal 100-

gram OGTT results group were older, had more cesarean section in their previous pregnancies, had more GDM history in their previous pregnancies, and more DM history in their first degree relatives compared to patients who have normal and abnormal 50-gram GCT results. The GDM prevalence increases as the maternal age increases [2, 11-14]. This was similar with the present results. Previous cesarean section rate was statistically higher in abnormal 100-gram OGTT group than normal and abnormal 50-gram GCT groups. Even if Gorgal *et al.* reported similar cesarean section rates in GDM and glucose tolerant cases, the present results were consistent with the literature which had higher previous cesarean rates in diabetic groups [13, 15]. In the present study the authors found that history of GDM in previous pregnancies and DM in first degree relatives were more common in GDM cases, but there was no difference between normal 50-gram GCT and borderline hyperglycemic group. This finding was consistent with the report of Keshavarz *et al.* Family history of diabetes was more common in GDM patients in their study [13]. Cheng *et al.* also reported that prior history of GDM was less common in 50-gram GCT below 200 mg/dl than above 200 mg/dl group [14]. The present authors found that obstetric history about GDM in previous pregnancies may be helpful in the prediction of GDM in the current pregnancy but not for borderline hyperglycemia.

For obstetric outcomes, maternal hospitalization period was shorter in normal 50-gram GCT group than borderline hyperglycemia or abnormal 100-gram OGTT groups and the present authors can conclude that there was no difference between borderline hyperglycemic group and abnormal 100-gram OGTT group; both have higher risk for a longer hospitalization period. Postpartum hemorrhage was higher in borderline hyperglycemic and abnormal 100-gram OGTT group than normal 50-gram GCT group. There was no significant difference between borderline hyperglycemia and abnormal OGTT groups. Cesarean section rates were highest in abnormal 100-gram OGTT group and were higher in borderline hyperglycemic group than normal 50-gram GCT group. Preeclampsia was more common in abnormal 100-gram OGTT group than normal 50-gram GCT group (16% *vs.* 6%), whereas no difference was found between borderline hyperglycemia and abnormal 100-gram OGTT group. Postpartum haemorrhage and duration of hospitalization period were similar in abnormal 100-gram OGTT group and borderline hyperglycemia group but both were statistically higher in these groups than normal 50-gram GCT group. Although preeclampsia and cesarean section rates were higher in borderline hyperglycemia group than normal 50-gram GCT group, the differences were not statistically significant.

These adverse outcomes were reported by many reports in the literature. In an extensive and multicenter study, HAPO study, affirmed increased cesarean rates. One of the primary outcome of HAPO was that increasing maternal hyperglycemia causes increased cesarean section rates [5]. Ju *et al.* support maternal adverse outcomes of borderline hyperglycemia such as increased cesarean section rates, maternal hospitalization, pregnancy-induced hypertension, but contrary to the present study that no difference was seen in the postpartum haemorrhages rates [16]. Zhang *et al.* highlighted that there was a tendency of increasing cesarean delivery rates, macrosomia, preterm delivery, pregnancy induced hypertension from normal glucose tolerant to impaired glucose tolerant or GDM patients, even if they were not statistically significant [17]. Cheng *et al.* compared the outcomes of women with GCT < 120 mgr/dl, 130-140 mgr/dl, and ≥ 140 mgr/dl and found that compared to women with a GCT of < 120 mg/dl, women with a GCT of 130-139 mg/dl, and ≥ 140 mg/dl were more likely to have preeclampsia and operative vaginal or cesarean deliveries [18]. They concluded that even if 50-gram GCT was not abnormal, the higher levels were associated with increased perinatal morbidity. Biri *et al.* reported that there was no difference between normal 50-gram GCT and abnormal 50-gram GCT groups in the rate of preeclampsia and cesarean section, prematurity, and polyhydramnios [19]. In the present study, the authors demonstrated increased rate of postpartum hemorrhage and longer duration of maternal hospitalization in borderline hyperglycemia group compared to normal 50-gram GCT group. Even if cesarean section and preeclampsia rates were higher in borderline hyperglycemia group, they were not statistically significant.

The present authors also evaluated the neonatal outcomes in this study. Neonatal hypoglycemia was higher in abnormal 100-gram OGTT group than borderline hyperglycemic group and also higher in borderline hyperglycemic group than normal 50-gram GCT group. First minute Apgar score was higher and duration of neonatal hospitalization was shorter in normal 50-gram GCT group than borderline hyperglycemic group and abnormal 100-gram OGTT group. First minute Apgar score and duration of neonatal hospitalization were similar between borderline hyperglycemic and abnormal 100-gram OGTT groups. Although the rate of birth injury was higher in abnormal 100-gram OGTT group, this was not statistically significant. There were no statistically significant difference between groups for birth injuries, 5th minute Apgar scores, rate of hyperbilirubinemia, and NICU admission. Corrado *et al.* did not find statistically significant difference between normal 50-gram GCT group and impaired glucose tolerance group diagnosed with 100-gram OGTT for neonatal hypoglycemia, and 1st and 5th minute Apgar scores of neonates [20]. Akpak *et al.* reported that abnormal 50-gram GCT groups had increased risk of neonatal hyperbilirubinemia, polycytemia, and NICU admission rates than normal 50-gram GCT group which was contrary to the present results, but increased hospitalization rates and neonatal hypoglycemia rates correlated with the present results [21]. Ju *et al.* reported that preterm birth was

higher and neonatal duration of hospitalization, neonatal intensive care unit admission, and admission to nursery were longer in borderline hyperglycemia cases than in normal GCT cases. These were explained with increased rate of preeclampsia, cesarean section for fetal distress, and preterm birth in borderline hyperglycemia cases [16]. Korucuoglu *et al.* reported that neonatal adverse outcomes occurred more as the 50-gram GCT results increased, for neonatal hospitalization, hypoglycemia, hyperbilirubinemia, and 1st minute Apgar scores [22]. Biri *et al.* concluded that neonatal hospitalization period was shorter in normal 50-gram GCT group than in abnormal 50-gram and abnormal 100-gram OGTT groups, similar to the present study [19]. Hypoglycemia was higher in abnormal 100-gram OGTT group than in normal 50-gram GCT group, but did not especially mention the difference between abnormal 50-gram GCT group and the others. Hyperbilirubinemia was higher in abnormal 100-gram OGTT group than normal 50-gram GCT group. First minute Apgar scores was higher in normal 50-gram GCT group than others, but no difference was found in 5th minute Apgar scores as in the present study [19].

It was reported that variations in the maternal glucose metabolism, even within the normal range can effect growth and development of the fetus [23]. Frequent antenatal visits with close monitoring of fetal growth and lowering of blood glucose levels with diet therapy was advised in patients with higher levels of mid-pregnancy HbA1c and pre-pregnancy BMI in patients with borderline hyperglycemia who had abnormal 50-gram GCT and normal 100-gram OGTT results. Although the present authors had similar neonatal birth weight and rate of macrosomia between groups, they had increasing rate of neonatal hypoglycemia from groups 1 to 3 which may be related to level of glucose intolerance in borderline hyperglycemia to IGT+GDM cases. Increased duration of neonatal hospital stay and lower 1st minute Apgar scores in borderline hyperglycemia group may also be related to mild glucose intolerance.

Conclusion

Pregnant women who have abnormal 50-gram GCT results which can be defined as borderline hyperglycemia, can be candidates for maternal, perinatal, and neonatal adverse outcomes. Even if they are not diagnosed as GDM and IGT, both obstetricians and neonatologists must keep in mind the unfavorable pregnancy outcomes and careful follow up is needed.

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