Influence of Hypoglycemia During The 100-G Oral Glucose Tolerance Test on Obstetrics Outcomes

İlknur İNEGÖL GÜMÜŞ[1], Feridun KARAKURT[2], Ayşe KARGILI[2], Neslihan CARDA SEÇKİN[1], Hasan KAFALI[1] Nilgün ÖZTÜRK TURHAN[1]

Ankara, Turkey

OBJECTIVES: We aimed to investigate the impact of hypoglycemia during 100-g oral glucose tolerance test on perinatal outcomes.
STUDY DESIGN: Obstetrics records of 411 pregnants who delivered singletons at our institution were reviewed. 31/411 (7,5 %) of patients who were diagnosed as Gestational Diabetes Mellitus were excluded from the study. The study group was consisted of pregnant women who experienced hypoglycemia defined as a plasma glucose level of 60 mg/dL or less during the 100-g oral glucose tolerance test. This group were compared with women who had normal glucose levels during 50-g oral glucose loading test (glucose challenge test) and who had normal values and had no hypoglycemia during 100-g OGTT.
RESULTS: We identified 62 hypoglycemic patients (15 %) on 100-g oral glucose tolerance test and 318 non-hypoglycemic patients (77,3 %) as control group. Gestational weight gain was statistically higher in hypoglycemic group. The mean birth weight was 3419±421,9 g in the study group and 3275±491,7 g in the control group (p=0.042). Rates of babies admitted to NICU were similar in both groups.
CONCLUSIONS: Women who experience hypoglycemia during the OGTT have a significantly higher incidence of gestational weight gain and higher neonatal birth weights as well. As a result if a pregnant has hypoglycemia during OGTT we should monitorize her and the fetus as well carefully.

Key Words: 100-g oral glucose tolerance, Hypoglycemia, Obstetrics outcomes

Gynecol Obstet Reprod Med;14:2 (84 - 88)

Introduction

Clinical hypoglycemia rarely occurs in healthy human beings, but it is a fact of life for people with diabetes mellitus. It is feared by many patients not only because of the associated physical discomfort, but mainly because of the risk of cognitive function deterioration that may lead to loss of personal control and adequate conscious behavior, and eventually to coma. Despite recent advances in treatment of Diabetes mellitus, hypoglycemia remains the principal barrier to obtaining true glycemic control, and microvascular and macrovascular complications of diabetes associated with chronic hyperglycemia are to a certain extent the consequence of hypoglycemia.[1]

It is a wellknown phenomenon that a significant number of women experience hypoglycemia or occasional hypoglycemic reaction including tachycardia, faintness, nausea, and perspiration during the 3-hour oral GTT which is the accepted method for diagnosing GDM during pregnancy.[2] Increased materno-fetal morbidity associated with GDM has been demonstrated, but we did not have enough knowledge about the impact of low blood glucose levels or hypoglycemia during the OGTT on obstetrics outcomes. To our knowledge it has been established only in one literature.[2] In our clinical observation we noticed that hypoglycemic patients during 100-g OGTT on 3 hours show some smilar the clinical feature with gestational diabetes mellitus, despite of fact that their OGTT values were in normal ranges according to diagnostic criteria of GDM of the fourth international workshop-conference on gestational diabetes mellitus.[3]

In the present study we aimed to investigate whether hypoglycemia during 100-g OGTT have an effect on perinatal outcomes.

Material and Method

In this retrospective study, between January 2002 and April 2006, all pregnant patients attending outpatient clinic of Department of Obstetrics and Gynecology of Fatih University Hospital were screened for gestational diabetes (GDM), with a 50 g oral glucose loading test (glucose challenge test [GCT] between 24 and 28 weeks' gestation. If the screening plasma glucose value was ≥130 mg/dL, the patient underwent a stan-

[1]*Department of Obstetrics and Gynecology and* [2]*Endocrinology Fatih University School of Medicine, Ankara*

Adress of Correspondence: *İlknur İnegöl Gümüş*
Fatih University School of Medicine
Department of Obstetrics and
Gynecology Emek, Ankara
ilknurinegol@yahoo.com

Submitted for Publication: *08. 05. 2008*
Accepted for Publication: *24. 06. 2008*

dart, 3 hour oral glucose tolerance test (OGTT). The test was performed after 3 days of unrestricted diet with at least 150 g of carbonhydrates daily and after an overnight fast of not less than 8 hours. Patients were classified as gestationally diabetic if two or more of four the plasma glucose concentrations equaled or exceeded the following values: fasting blood sugar 95 mg/dL; one-hour level 180 mg / dL; two hour level 155 mg /dL; and three hour level, 140 mg / dL [3]. 31/411 (7,5 %) of patients who were diagnosed as Gestational Diabetes Mellitus were excluded from the study.

The study group was consisted of pregnant women who experienced hypoglycemia defined as a plasma glucose level of 60 mg/dL or less during the 100-g oral glucose tolerance test on 3 hours (n=62). This group were compared with women who had normal glucose levels during 50-g oral glucose loading test (glucose challenge test) and who had normal values and had no hypoglycemia during 100-g OGTT on 3 hours (n=318).

The two groups were compared for the prevalance of family history of diabetes mellitus, pre-pregnancy body mass index (BMI), gestational weight gain, nullipara, obstetric complications such as premature delivery, macrosomia, polyhydramnios, hypertension, mode of delivery. We also compared the two groups for the infants' birth weight, proportion of babies admitted to neonatal intensive care (NICU).

Data analysis was performed by using SPSS for Windows (version 11.5). Data were presented as mean±std.deviation. Comparison of continuous variables were made by using Student's t-test or Mann-Whitney-U test, and categorical comparisons were evaluated by Chi-square or Fisher's exact probability test. A p value of <0.05 was accepted as statistically significant.

Results

The records of 411 pregnant patients who had been followed and gave birth in the Obstetrics and Gynecology Department of Fatih University Hospital were reviewed. 31 of 411 (7,5 %) patients were diagnosed as GDM and excluded from study. The data of 380 patients were suitable for evaluation. 133 patients were positive for 50-g glucose challenge test (GCT) and negative for OGTT (32,3 %) and 185 patients were negative for GCT (45 %).

We identified 62 hypoglycemic patients (15 %) on 100-g oral glucose tolerance test who had level ≤ 60 mg/dL level of blood glucose on 3 hours and 318 non-hypoglycemic patients (77,3 %) as control group who had normal glucose levels during 50-g oral glucose loading test (glucose challenge test) and who had normal values and had no hypoglycemia during 100-g OGTT. Maternal data was showed in table 1.

Table 1: Maternal Data

	Hypoglycemia group (n=62)	Non hypoglycemia group (n=318)	P
Age (years)	29,4 ± 4,6	29,1 ± 6,4	0.313
Gravidity	2,14 ± 1,18	2,16 ± 1,37	0.620
Parity	0,98 ± 0,96	0,90 ± 1,1	0.262
Pre-pregnancy BMI (kg/m^2)	25,4 ± 9,5	23,1 ± 3,4	0.586
Post-pregnancy BMI (kg/m^2)	32,9 ± 9,9	28,5 ± 3,8	0.030*
Gestational weight gain	15,8 ± 3,8	14,6 ± 4,3	0.019*
Family history of DM (%)	15 (24,2 %)	76 (23,9 %)	0,960
Nulllipara (%)	20 (%32,3)	127 (%40,1)	0,249

Data are presented as mean ± Standard deviation
** $p < 0.05$*

In hypoglycemic group the mean values of fasting, 1 hour, 2 hours and 3 hours on OGTT were 76,5 ± 6,6; 141,7 ± 34,0 ; 106,3 ± 23,4; 53,5 ± 6,7 respectively. Gestational weight gain, post-pregnancy BMI were significantly higher in hypoglycemic group. The mean birth weight was 3419±421,9 g in the study group and 3275±491,7 g in the control group (p=0.042). Rates of babies admitted to NICU were similar in both groups. Pregnancy and neonatal outcomes were showed in table 2.

Table 2: Pregnancy and Neonatal Outcomes

	Hypoglycemia group (n=62)	Non hypoglycemia group (n=318)	P
Composite adverse perinatal outcome	15 (24,2%)	84 (%26,4)	0,715
Preeclampsia	0 (0%)	7 (2,2%)	0.605
Hypertension	8 (12,9%)	24 (7,5%)	0,165
Polyhydramnios	9 (14,5%)	25 (7,9%)	0,093
Macrosomia (>4000 g)	7 (11,3 %)	28 (8,8 %)	0,287
Delivery < 37 weeks	8 (12,9%)	31 (9,7%)	0,454
Birth trauma	2 (3,2%)	8 (2,5%)	0,670
Frequency of admission to NICU	2 (3,2%)	15 (4,7%)	0,455
Induction of labor	37 (59,7%)	166 (52,2%)	0,280
Gestation at delivery (weeks)	38,4±1,24	38,3±1,83	0,689
Cesarean delivery	36 (58,1%)	162 (50,9%)	0.305
Birthweight (g)	3419 ± 421.91	3275 ± 491.77	0,042*

** $p < 0.05$*

Discussion

Hypoglycemia is a clinical and biological entity defined as an abnormal decrease in plasma glucose concentrations and the clinical consequences thereof. Hypoglycemia-related symptoms are multiple, non specific and with many guises,

and thus cannot be used to define hypoglycemia. Their only common feature is that they can be reverted by glucose administration. However, it is also difficult to set a plasma glucose level to define hypoglycemia.[4,5]

In various reports 50 mg/dL was considered to be a suitable glucose consentration for the diagnosis of hypoglycemia.[6,7] Because Clinical symptoms of hypoglycemia such as tachycardia, sweating, tremor, dizziness, headache and faintness ususally manifest at a plasma glucose level 50 mg/dL. On the other hand it is welknown that there is no clear cutoff blood glucose level for experiencing hypoglycemic symptoms; some patients may exhibit a hypoglycemic reaction at a 'normal' glucose range whereas others may be unaware of hypoglycemia even at very low blood glucose concentrations.[2,8] In the present study Cutoff level was chosed as 60 mg/dL because biochemical reactions to hypogycemia manifest at this glucose level. The first event to be elicited by a progressive decrement in plasma glucose levels is an inhibition of insulin secretion,for a mean arterialised venous glucose of 4.5 mmol/l (0.80 g/l). This inhibition has amajor role in the defence against hypoglycemia, as recovery is negatively correlated with peripheral and portal insulin levels. [9] The second event is counterregulatory hormone release, which occurs at a glucose threshold of 3.3 to 3.6mmol/l (0.60 to 0.65 g/l). Glucagon is the first line of defence, mainly for correcting brief hypoglycemia.[10]

Glucagon stimulates a cascade of phosphorylation, inducing an increase in hepatic glucoseproduction by stimulation of glycogenolysis and neoglucogenesis. Epinephrine becomes of primary importance when glucagon secretion is deficient, and is important in correctingprolonged hypoglycemia, by direct and indirect mechanisms. Epinephrine increases hepaticglucose output by stimulation of glycogenolysis and neoglucogenesis, directly and throughits action on insulin and glucagon secretion. Epinephrine increases substrates forneoglucogenesis (lactates, alanine).[11]

In the normal nonpregnant individual declining blood glucose levels trigger an organized sequence of responses first and foremost insulin secretion is suppressed when blood glucose levels fall within the physiological range. The resultant reduction in peripheral glucose uptake and increase in hepatic glucose production usually terminates the decline in blood glucose and prevents true hypoglycemia. In addition, the fall in intra-islet insulin appears to have a signaling role for the glucagon response to hypoglycemia by alleviating its suppressive effect on pancreatic a-cells, thus permitting glucagon release. It promotes hepatic glucose production by stimulation of glycogenolysis and gluconeogenesis.[1]

Hypoglycemic episodes are more common during pregnancy because of the physiological changes that take place: basal insulin levels are increased, while glucagon release is suppressed by estrogen, progesterone, human placental lactogen, and probably other mediators.[12] The result is that pregnant women may experience postprandial hypoglycemia more often. Some pregnant women may be more prone to this condition and may react with an exaggerated response.

The occurrence of hypoglycemia and occasional hypoglycemic reaction during the 3-hour oral GTT is a well-known phenomenon. However, its incidence and possible effect on perinatal outcome have not been directly addressed. Searching the literature we find only one literature about this question.[2] In that study, the incidence of hypoglycemia during the 100-g oral GTT was found 15 %. No cases of fasting hypoglycemia were observed (after fasting of at least 8 hours). All hypoglycemic events were reported to occur 3 hours after the glucose ingestion. In the present study we have found an somewhat higher incidence of 15% of hypoglycemia during the 100-g oral GTT hovewer if we look at the curves presented in the original report by O'Sullivan and Mahan[13] it can be seen that approximately 25% of the patients showed a glucose values below 50 mg/dL in the third hour during 100-g oral GTT.

What is the clinical implication of maternal reactive hypoglycemic events during OGTT for fetal well-being? There is a scarcity of data concerning this question. In some studies they had been suggested that relative maternal hypoglycemia was associated with growth restriction.[14-17] Nevertheless in these studies the definition of maternal hypoglycemia was drawn from the OGTT rather than from the glicemic profile in pregnancy. In our study there was no baby below 2500 gr in hypoglycemia group. In the control group there were 13 (4,08 %) pregnants who delivered < 2500 gr babies.

Weissman et al[2] showed the newborns' birth weights in women with hypoglycemia were significantly lower than in the control group although the gestational ages at deliveries were similar. They speculated that difference was not due to a higher rate of SGA, but to a lower rate of LGA infants. They have also reported a lower rate of cesarean delivery with indication of macrosomia in patient who showed reactive hypogycemia In the present study, contrary to former study birth weight in women with hypoglycemia were found higher than control group but rate of cesarean delivery with indication of macrosomia was found smilar. This can be explained by the fact that study was retrospective and did not consider some variables that could potentially affect fetal growth such as obesity, weight gain during pregnancy. In the present study gestational weight gain, post-pregnancy BMI were found significantly higher in hypoglycemic group so higher birthweight in women with reactive hypogylcemia can be associated with excess weight gain in pregnancy on the other hand perhaps it can be speculated that reactive hypoglycemia may be carbonhydrate intolerance of different type with onset or first recog-

nition during pregnancy.

There is limited information about the impact of low blood glucose levels or hypoglycemia during the OGTT on obstetrics outcomes. Although Weissman et al[2] claimed that hypoglycemia during OGTT is not unusual, is transitory, and carries a favorable prognosis in terms of obstetric outcome including lower incidence of GDM, lower birth weights, and a lower rate of cesarean deliveries for macrosomia ,we do not think the event so simply. If such a phenomenon may occur more frequently in women who experience during the OGTT and sometimes these hypoglycemic attack become deep and more than fetal brain sparing mechanism it is easly cause fetal mortality or morbidity.

In a conclusion, pregnants who experienced hypoglycemia during OGTT should be monitorized during and after pregnancy. The impact of maternal hypoglycemia during OGTT on perinatal outcomes requires prospective and larger further studies.

100-G Oral Glukoz Tolerans Testi Sırasında Hipogliseminin Obstetrik Sonuçlara Etkisi

İlknur İNEGÖL GÜMÜŞ, Feridun KARAKURT
Ayşe KARGILI, Neslihan CARDA SEÇKİN
Hasan KAFALI, Nilgün ÖZTÜRK TURHAN

Ankara, Türkiye

Gebelikte 100-g oral glukoz tolerance testi (OGTT) sırasında gelişebilecek hipogliseminin perinatal sonuçlara etkisini araştırmak.
Bu retrospektif çalışmada 411 gebe değerlendirildi. Gestasyonel diabetes mellitus tanısı alan 31 hasta (%7,5) ekarte edildi. Çalışma grubunu 100-g oral glukoz tolerans testi 3.saat sırasında 60 mg/dL ve altı espit edilen hastalar, kontrol grubunu ise hipoglisemi tespit edilmeyen hastalar oluşturdu.
100-g oral glukoz tolerans testi sırasında 62 hipoglisemik (%15) hasta tespit edildi. Kontrol grubu olarak 318 hasta toplandı. Gebelikte toplam alınan kilo hipoglisemik grupta daha fazla tespit edildi (p=0.019). Ortalama bebek doğum ağırlığı hipoglisemik grupta 3419±421,9 g, kontrol grubunda 3275± 491,7 g idi (p=0.042). Yenidoğan yoğun bakıma kabul oranı iki grupta da benzer idi.
OGTT sırasında hipoglisemi tespit eden gebelerde gebelikte alınan toplam kilo daha fazla bebek doğum ağırlığı daha fazla tespit edildi. OGTT sırasında hipoglisemi tespit edilen gebeler daha dikkatlice takip edilebilir.

Anahtar Kelimeler: 100-g oral glukoz tolerans testi, Hipoglisemi, Obstetrik sonuçlar

References

1. De Galan BE, Schouwenberg BJ, Tack CJ, Smits P: Pathophysiology and management of recurrent hypoglycemia and hypoglycemia unawareness in diabetes Neth J Med. 2006;64:269-79.
2. Amir Weissman, Ido Solt, Moshe Zloczower, Peter Jakobi: Hypoglicemia during the 100-g Oral glucose tolerance test: Incidence and Perinatal Significance. Obstet Gynecol 2005;105:1424-8.
3. Organizing Committee, B.E. Metzger, D.M. Coustan: Summmary of recommendations of the Fourth International Wok-shop-Conference on Gestational Diabetes Mellitus Diabetes Care 1998;21:161-7.
4. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulation systems are higher than thresholds for symptoms. J Clin Invest. 1987;79:777-81.
5. Mitrakou A, Fanelli C, Veneman T, Perriello G, Calderone S, Platanisiotis D et al. Reversibility of unawareness of hypoglycemia in patients with insulinomas. N Engl J Med 1993;329:834-9.
6. Unawareness of hypoglycemia (Editorial). N Engl J Med 1995;333:1771-2.
7. Field JB: Hypoglicemia: definition, clinical presentations, classification, and laboratory tests. Endocrinol Metab Clin North Am 1989;18:27-43.
8. Palardy J, Havrankova J, Lepage R, Matte R, Belanger R, D'Amour P, et al. Blood glucose measurements during symptomatic episodes in patients with suspected postprandial hypoglycemia. N Eng J Med 1989;321:1421-5.
9. Fanelli C, Pampenelli S, Epifano AM, et al. Relative role of insulin and hypoglycemia on induction of neuroendocrine responses to symptoms of and deterioration of cognitive function in hypoglycemia in male and female humans. Diabetologia 1994;37:797-807.
10. Heller SR, Cryer PE: Reduced neuroendocrine and symptomatic responses to subsequent hypoglycemia after one episode of hypoglycemia in nondiabetic humans. Diabetes 1991;40:223-6.
11. Cryer PE. Glucose counterregulation: the prevention and correction of hypoglycemia in humans. Am J Physiol 1993; 264:149-55.
12. Phelps RL, Metzger BE, Freinkel N: Carbohydrate metabolism in pregnancy: diurnal profiles of blood glucose, insulin, free fatty acids, triglycerides, cholesterol, and individual amino acids in late normal pregnancy. Am J Obstet Gynecol 1981;140:730-6
13. O'Sullivan JB, Mahan CM, D'Agostino RB, Charles D. Glucose disposal rates and the glucose challenge in pregnant women. J Clin Endocrinol Metab 1974;39:1067-71.
14. Owens JA, Falconer J, Robinson JS. Glucose metobolism in pregnant shep when placental growth is restricted. Am J Physiol 1989;257:350-7.
15. Langer O, Damus K, Maiman M, Divon M, Levy J,

Bauman W. A Link between relative hypoglycemia-hypoinsulinemia during oral glucose tolerance tests and intrauterine growth retardation. Am J Obstet Gynecol 1986;155:711-6.

16. Sokol RJ, Kazzi GM, Kalhan SC, Pillay SK. Identifying the pregnancy at risk for intrauterine growth retardation: possible usefulness of the intravenous glucose tolerance test. Am J Obstet Gynecol 1982;143:220-3.

17. Khouzami VA, Ginsburg DS, Daikoku NH, Johnson JW. The glucose tolerance test as a means of identifying intrauterine growth retardation. Am J Obstet Gynecol 1981;139:423-6.