

# Does Maternal Glycemic Regulation Affect Perinatal Outcome In Women with Gestational Diabetes Mellitus?

## GESTASYONEL DİABETES MELLİTUSU OLAN KADINLARDA MATERNAL GLİSEMİK REGÜLASYON PERİNATAL SONUÇLARI ETKİLER Mİ?

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### Summary

**Objective:** The aim of the study is to determine the significance of maternal glycemic regulation in the fetal outcomes in pregnancies complicated by gestational diabetes mellitus.

**Materials and Methods:** The records of 117 consecutive pregnancies complicated with gestational diabetes mellitus were evaluated retrospectively. The patients with gestational diabetes mellitus were treated either with diet or diet in combination with insulin. The mean glucose level was calculated by dividing the total sum of the glucose levels by the number of measurement during the days of hospitalization. The patients were divided in two groups: In group A the mean glucose level was lower than 100 mg/dL (n=52) and in group B higher than 100 mg/dL (n=65).

**Results:** Cesarean section was performed significantly more often in group B than the group A (53.8% versus 34.6%, p=0.03). Preterm delivery was found to be significantly higher in group B (26.2% versus 5.8%, p=0.003). A total of 18.5% of babies delivered in group B were admitted to the neonatal unit compared to 9.6% in group A (p=0.17). Low Apgar scores at 5 minutes occurred in 6 babies born in group B compared to 2 babies in group A. Only one macrosomic newborn with birthweight higher than 4500 g was found in group B.

**Conclusion:** Adverse perinatal outcomes seems to be higher in the gestational diabetics with poor glycemic control.

**Key Words:** Gestational diabetes mellitus, Perinatal outcome, Glycemic control

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### Özet

**Amaç:** Bu çalışmanın amacı gestasyonel diabetes mellitus ile komplike olmuş gebeliklerde maternal glisemik regülasyonun önemini ortaya koymaktır.

**Materyel ve Metod:** Gestasyonel diabetes mellitus ile komplike olmuş 117 ardışık gebeliğin kayıtları retrospektif olarak incelendi. Gestasyonel diabetes mellitus olan hastalara diet ya da diet ile kombine insulin tedavisi uygulandı. Ortalama glukoz düzeyi tüm glukoz ölçümlerinin hospitalizasyon süresince yapılan ölçüm sayısına bölünmesi ile hesaplandı. Hastalar iki gruba ayrıldı: Grup A'ya ortalama glukoz düzeyi 100 mg/dL (n=52) altında olan hastalar, grup B'ye 100 mg/dL (n=65) üzerinde olan hastalar alındı.

**Bulgular:** Sezaryen ile doğum grup B'de grup A'ya göre anlamlı olarak daha yüksek saptandı (%11.5'a karşılık %7.7, p=0.34). Preterm doğum grup B'de grup A'ya göre anlamlı olarak daha yüksek bulundu (%26.2'ye karşılık %5.8, p=0.003). Grup B'de bebeklerin %18.5'i yenidoğan ünitesine yatırılırken, grup A'da bebeklerin %9.6'sı yenidoğan ünitesine yatırıldı (p=0.17). Beşinci dakika düşük Apgar skoru grup B'de 6 bebekte ve grup A'da 2 bebekte saptandı. Grup B'de 4500 kg üzerinde doğum ağırlığı olan tek bir bebek bulundu.

**Sonuç:** Kötü glisemik kontrolü olan gestasyonel diabetes mellituslu hastalarda kötü perinatal sonuçlar daha yüksek izlenmektedir.

**Anahtar Kelimeler:** Gestasyonel diabetes mellitus, Perinatal sonuç, Glisemik kontrol

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Gestational diabetes mellitus (GDM) is a disorder with elevated circulating glucose. The approach to GDM has altered markedly in the last decade; it is guided by universal screening and an impetus to establish 24-hour euglycemia in these women, through serial measurements of blood glucose by home monitoring and glycosylated hemoglobin (1). Moreover, it has been clearly established that tight glycemic control can serve as the primary prevention for these women in terms of fetal disease (2-5). Additionally, in the presence of hyperglycemia, the offspring of GDM mothers are at increased risk for perinatal mortality (6).

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The aim of the present study is to assess fetal outcome in gestational diabetic mothers with regard to glycemic control.

### Material and Methods

In Ege University Hospital screening with 50 g oral glucose challenge was administered routinely to consecutive pregnant women at the time of their first antenatal visit. Patients with abnormal screening results, defined as a serum glucose level  $\geq 140$  mg/dL, were later administered standard 100 g oral glucose load, and plasma glucose level was measured in the baseline fasting state

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and at 1-, 2- and 3-hours intervals after glucose ingestion. GDM was considered if  $\geq 2$  values met or exceeded the following cutoff points: fasting, 105 mg/dL, 1-hour 190 mg/dL, 2-hours 165 mg/dL, and 3-hours 145 mg/dL. In those cases with a normal result of the 50 g oral glucose challenge or an abnormal screening result but normal result of the 100 g glucose load, women underwent repeated testing at 24 to 28 weeks' gestation with the same criteria to define an abnormal screening test result and GDM. Plasma glucose was obtained by venipuncture and analyzed by the glucose oxidase method.

Between January 1998 and December 2000, 117 patients with gestational diabetes mellitus diagnosed by the criteria outlined above were reviewed from medical records and birth records retrospectively. The following data were registered: Gestational week at diagnosis and birth, glucose concentrations at 3 hours oral glucose tolerance test, age parity, birthweight, mode of delivery, maternal and neonatal morbidity. All the women in the study delivered at Ege University Hospital. Women who delivered elsewhere, multiple pregnancies and cases of pre-gestational diabetes were excluded from the study.

After diagnosis of GDM was made, patients were hospitalized and glycemic profile measuring venous glucose level was performed before and 2 hours after each main meal. The mean glucose level was calculated by dividing the total sum of the glucose levels by the number of measurement during the days of hospitalization. For all the patients the range of hospitalization was 4-7 days. The patients were divided in two groups: In group A the mean glucose level was lower than 100 mg/dL (n=52) and in group B higher than 100 mg/dL (n=65). If the preprandial glucose concentration was  $<105$  mg/dL and the postprandial glucose concentration was  $<120$  mg/dL, women were given only dietary recommendations. If these values were exceeded, insulin treatment was initiated. Nineteen patients received insulin therapy. In only one patient insulin therapy was required despite prior control of hyperglycemia by diet. Insulin therapy was initiated in 10 patients at the 24-28 weeks of gestation and 9 patients in 28-32 weeks of gestation. Blood was obtained in the fasting state, and glycosylated hemoglobin concentration was determined by standard automated methods.

Ninety-eight gestational diabetes patients were treated with diet alone, 19 were treated with diet plus insulin. The women were offered clinic visits with intervals of 2 weeks and ultrasound examinations were performed at intervals of 4 weeks from diagnosis. Labor was induced at 40 weeks of gestation if spontaneous labor had not occurred.

Blood glucose was measured in the newborns of diabetic mothers 1/2 hour after delivery. In case of hypoglycemia, measurements were repeated every second hour until stable values above 2.5 mmol/L were obtained.

The hypoglycemic infants were treated with early feeding (breast or formula) and if necessary intravenous infusion of glucose was given.

Pre-eclampsia was defined as persistently elevated blood pressure (systolic pressure  $>140$  mm Hg and/or diastolic pressure  $> 90$  mm Hg on more than two measurements) and proteinuria ( $>2+$  in a urine protein test, equal to 1.0 g/L). Pregnancy-induced hypertension was diagnosed if the blood pressure met the above mentioned criteria without the presence of proteinuria. Chronic hypertension was defined by antihypertensive medication before the time of conception and fundal findings of the eye. The present study determined the overall frequency of hypertensive disorders (pre-eclampsia, pregnancy induced hypertension and chronic hypertension).

Preterm delivery was defined as delivery before the 37th week of gestation and term-induced labor included artificial rupture of membranes and intravenous infusion of oxytocin. Macrosomia was defined as birth weight  $>4500$  g, neonatal hypoglycemia was defined as a minimum blood glucose value  $< 2.0$  mmol/L during the first 48 h of life. Apgar scores  $< 7$  after 5 minutes were considered low.

Statistical analysis was performed by a commercial statistical package program (SPSS, Chicago, IL) using unpaired student t test, chi-square and Fisher's exact test accepting  $p<0.05$  as significant. The results are given as mean  $\pm$  standard deviations for normally distributed data and as frequencies (n) and percentages (%) for nominal data.

## Results

Maternal age, parity and initial 50 g glucose tolerance test results of both groups are summarized in Table 1. The two groups were similar with respect to maternal age ( $p > 0.05$ ); but primigravidas were found to be significantly higher in group A ( $p=0.0002$ ). Gestational age at the time of oral glucose tolerance test was similar in both groups ( $p > 0.05$ ). The percent of gestational diabetes in previous pregnancy was 13.5% and 36.9% in group A and B, respectively. The mean hemoglobin A<sub>1c</sub> level in group B was insignificantly higher than group A ( $4.9\pm 1.1$  versus  $4.6\pm 0.6$ ,  $p=0.1$ ). Maternal outcomes of both groups are summarized in Table 2. Hypertensive disorders were tended to be more frequent in group A but the difference was insignificant (11.5% versus 7.7%,  $p=0.34$ ). Cesarean section was performed significantly more often in group B than the group A (53.8% versus 34.6%,  $p=0.03$ ). Preterm delivery was found to be significantly higher in group B (26.2% versus 5.8%,  $p=0.003$ ). Also the frequency of the polyhydramnios and oligohydramnios were higher in group B.

Perinatal outcomes in both groups are shown in Table 3. Gestational age at birth was significantly higher in group

**Table 1.** Maternal age, parity and 50 g oral glucose tolerance test of the gestational diabetic women

	Group A (n=52)	Group B (n=65)	P value
Maternal age (years)	30.6±5.4	31.1±4.9	0.59
Parity = 0	28 (53.8%)	14 (21.5%)	0.0002
Parity = 1	16 (30.8%)	39 (60.0%)	0.001
Parity ≥2	8 (15.4%)	12 (18.5%)	0.66
50 g GTT	164.3±26.1	169.0±32.0	0.38
Gestational age at OGTT	28.1±5.5	26.9±5.4	0.26

GTT: Glucose tolerance test, GDM: Gestational diabetes mellitus

**Table 2.** Maternal outcomes in gestational diabetic women

	Group A (n=52)	Group B (n=65)	P value
Hypertensive disorders	6 (11.5%)	5 (7.7%)	0.34
Cesarean delivery	18 (34.6%)	35 (53.8%)	0.03
Preterm delivery	3 (5.8%)	17 (26.2%)	0.003
IUGR	1 (1.9%)	1 (1.5%)	0.69
Polyhydramnios	1 (1.9%)	2 (3.1%)	0.58
Oligohydramnios	1 (1.9%)	3 (4.6%)	0.39

IUGR: Intrauterine growth restriction, GDM: Gestational diabetes mellitus

**Table 3.** Perinatal outcomes in gestational diabetic women

	Group A (n=52)	Group B (n=65)	P value
Gestational age at birth (weeks)	38.2±2.1	37.1±3.3	0.003
Birthweight (g)	3285±543	3216±915	0.6
Macrosomia (BW ≥4500 g)	0	1 (1.5%)	0.55
Apgar < 7 at 5 minute	2 (3.8%)	6 (9.2%)	0.22
Admission to a neonatal unit	5 (9.6%)	12 (18.5%)	0.17
Congenital malformation	2 (3.8%)	2 (3.1%)	0.6

BW: Birthweight, GDM: Gestational diabetes mellitus

A. A total of 18.5% of babies delivered in group B were admitted to the neonatal unit compared to 9.6% in group A ( $p=0.17$ ). Low Apgar scores at 5 minutes occurred in 6 babies born in group B compared to 2 babies in group A. Congenital malformations was not different between the two groups. Only one macrosomic newborn with birthweight higher than 4500 g was found in group B.

### Discussion

In pregnancies complicated by GDM optimum maternal glucose levels should be maintained to prevent perinatal morbidity and mortality. When the mean blood glucose level is  $>105$  mg/dL, there is greater risk for the development of large for gestational age infants when compared with a control population (4-6). Also, there is an increased incidence of macrosomia and respiratory distress syndrome in untreated GDM patients (7). In the series of Langer et al (5), in which women having GDM were kept under strict metabolic control, morbidity followed either an L-shaped pattern for hyperbilirubinemia (higher incidence among small for

gestational age than among appropriate for gestational age and large for gestational age infants) and a U-shaped pattern for neonatal intensive care unit stay (higher incidence among small for gestational age and large for gestational age infants than among appropriate for gestational age infants). It should be noted that apart from the level of glycemic control, prematurity had an independent and significant association with the occurrence of neonatal morbidity (8).

Hyperglycemia (fasting plasma glucose level  $>105$  mg/dL) at diagnosis or presentation for care was associated with an increased risk of anomalies in general and with anomalies involving multiple organ systems without a preferential increase in involvement of specific organ system in GDM patients (9).

Hyperinsulinism has a major role for the development of fetal macrosomia (10,11). Fetal size may be excessive in pregnancies complicated by GDM, despite only modest elevation of maternal blood glucose. Macrosomic infants of nondiabetic mothers also have hyperinsulinemia at birth (12,13).

In the 1996 Clinical Practice Recommendations of the American Diabetes Association (6) it was emphasized that fasting plasma glucose  $>105$  mg/dL and 2-h postprandial values  $>120$  mg/dL are associated with fetal morbidity such as macrosomia. The American Diabetes Association further states that the offspring of mothers who experience both fasting ( $>105$  mg/dL) and postprandial ( $>120$  mg/dL) hyperglycemia are at greatest risk for intrauterine death or neonatal mortality (6). If diet therapy does not consistently maintain near-normoglycemic levels, the American Diabetes Association recommends that insulin therapy be considered. As a requirement for effective insulin therapy, American Diabetes Association recommends that self-monitoring of blood glucose be performed frequently each day to achieve near-normoglycemia (14). Self monitoring of blood glucose may identify a subset of women with GDM whose fetal outcome may benefit by earlier initiation of insulin therapy (14).

In the study of Rudge et al (15) despite treatment, the diabetic pregnant women and those with daily hyperglycemia presented higher mean blood glucose levels compared to controls ( $76.6 \pm 10.2$  mg/dl). The pregnancies complicated by diabetes and by daily hyperglycemia were characterized by a high incidence of prematurity, macrosomia, large for gestational age newborn infants, malformation and fetal and neonatal death, with consequent perinatal mortality. Likewise, in the present study despite diet plus insulin therapy premature delivery was found in 26.2% of patients in group B.

In the present study gestational age at the time of oral glucose tolerance test was similar in both groups ( $p > 0.05$ ). The percent of gestational diabetes in previous pregnancy was 13.5% and 36.9% in group A and B, respectively. The mean hemoglobin  $A_{1c}$  level in group B was insignificantly higher than group A ( $4.9 \pm 1.1$  versus  $4.6 \pm 0.6$ ,  $p=0.1$ ). Cesarean section was performed significantly more often in group B than the group A (53.8% versus 34.6%,  $p=0.03$ ). Preterm delivery was found to be significantly higher in group B (26.2% versus 5.8%,  $p=0.003$ ). Also the frequency of the polyhydramnios and oligohydramnios were higher in group B.

In conclusion, adverse perinatal outcomes seems to be higher in the gestational diabetics with poor glycemic control. The pregnancies complicated by GDM and the mean glucose level higher than 100 mg/dL were characterized by a high incidence of prematurity and cesarean delivery.

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