

## Gestational diabetes mellitus is as innocent as you think?

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### ABSTRACT

**Background:** We aimed to compare fetal outcomes, fetal hypoxia, acidemia and maternal characteristics including hemoglobin A1c, doppler indices between gestational diabetes mellitus (GDM) and pregestational diabetes mellitus (DM) among pregnant women treated with insulin.

**Methods:** Data of pregnant patients with diagnosis of pregestational diabetes (type 1 and 2) and GDM who were treated with insulin (GDM A2 in White classification) was retrospectively collected and compared. Patients with active chronic systemic disease, multiple pregnancies, lost to follow up and detected fetal malformations were excluded. Maternal characteristics, umbilical doppler indices and amnion fluid index, gestational age at delivery, delivery characteristics (including vaginal delivery, or cesarean section) and newborn characteristics such as birth weight, Apgar score and umbilical cord pH were all recorded.

**Results:** A total of 130 patients (67 patients with GDM and 63 pregestational DM) were recruited to the study. There were no significant difference regarding type of delivery, fetal birth weight, umbilical cord Hb and gestational birth age. No other significant difference in frequency of low Apgar scores and fetal acidosis or metabolic acidosis were reported. HbA1c and blood glucose levels and insulin dosage were significantly statistically higher in pregestational group.

**Conclusions:** The frequency of fetal distress parameters and poor fetal outcome were similar between groups although pregestational diabetic patients had higher HbA1c rates. Therefore, patients with GDM (A2) should be followed up as closely as pregestational (overt) diabetic patients.

**Keywords:** Fetal hypoxia, Gestational diabetes mellitus, Hemoglobin A1c, Pregestational diabetes

### INTRODUCTION

Gestational diabetes mellitus (GDM) is a common multisystemic disease affecting 6-7% pregnancies in western countries.<sup>1,2</sup> GDM is a type of carbohydrate intolerance with onset or first diagnosed during pregnancy depending on the diagnostic criteria used.<sup>3</sup> Pregestational diabetes (diabetes mellitus type 1 and 2) is also one of the common chronic metabolic disorders resulting with four times relative risk for fetal death and higher risks of complications such as hypertension, preeclampsia, genital trauma and cesarean delivery.<sup>1,4-6</sup>

Type 1 diabetes mellitus (DM) is a kind of pancreas  $\beta$  cell destruction while type 2 DM is characterized as insufficient insulin release leading insulin resistance.<sup>7</sup> The antenatal follow-up in diabetic pregnant women is important to control blood glucose levels, treat chronic complications and to monitor the fetus. In addition to routine pregnancy antenatal follow up, glucose impairment is the most focused issue to manage and identify the complications of pregnancy in GDM patients.

It is well known that pregestational DM has higher congenital fetal malformations including caudal

regression or cardiac diseases compared to GDM (typically have rare diabetes-related vasculopathy due to short exposure time of the disorder and late pregnancy onset).<sup>8</sup> Moreover, pregestational diabetes would have a more severe glycemic disturbance and increased risk of both maternal and neonatal complications; however, little has been reported regarding differences in pregnancy outcomes between these groups. In this study, we aimed to compare fetal outcomes, fetal hypoxia, acidemia and maternal characteristics including hemoglobin A1c, doppler indices between GDM and pregestational DM among pregnant women treated with insulin.

## METHODS

This retrospective cohort study was conducted between January 2014 and June 2015 at a tertiary referral Center in Kayseri, Turkey. Informed written consent was obtained from all participants. The study was approved by ethics committee of Erciyes School of Medicine. All the procedures followed were in accord with the ethical standards of the committee on human experimentation stated at the Declaration of Helsinki.

### *Patients selection and study design*

Data of pregnant patients followed in our department with diagnosis of pregestational diabetes (type 1 and 2) and GDM who were treated with insulin (GDM A2 in White classification) was retrospectively collected and compared. Singleton pregnancies aged between 18-45 were included. Patients with active chronic systemic disease, lost to follow up and detected fetal malformations were excluded. Collected data included maternal characteristics (age, parity, pre-pregnancy body mass index (BMI)), gestational age at delivery, delivery characteristics (including vaginal delivery, or cesarean section) and newborn characteristics such as birth weight, Apgar score and umbilical cord pH. Gestational age was defined by the number of weeks since the last menstrual period or the ultrasound assessment of crown-rump length if discordance was recognized. Maternal laboratory values including blood glucose, Hemoglobin A1c, thyroid stimulating hormone (TSH) and insulin doses were also recorded.

Due to our clinic protocol, blood glucose screening test was performed at 24–28 weeks with 50 g glucose loading test with a 135- mg/dL cutoff point. If the 50 g screening was positive, then a diagnostic 100 g oral glucose tolerance test (OGTT) was performed according to Carpenter and Coustan (CC) criteria.<sup>9</sup> If blood glucose level was above 190 mg/dL at 50 gr glucose test or two or more values were above the cutoff levels in the OGTT, these women were considered to have pregestational DM. 2-hours postprandial blood glucose profile was assessed accompanying diet treatment (30kcal/kg) every 2 weeks. All diabetic pregnant women in this study were hospitalized at 37 weeks and monitored by nonstress test. Estimated fetal weight, amniotic fluid volume and fetal

umbilical Doppler examination of all patients were evaluated.

In uncomplicated cases, either elective induction of labor or cesarean section was scheduled between 38 weeks 3 days and 39 weeks. After the delivery, an umbilical cord segment was double-clamped, and a venous blood gas sample was obtained using 1 mL heparinized syringe by an assistant and sent immediately for analysis in our intensive care laboratory. Patients with acute fetal distress, umbilical cord prolapsus, and ablatio placentae were not included in the study. Umbilical venous pH and base deficit cutoff levels of 7.23 and 6.3mmol/L, were used respectively, which corresponds to more than 1% probability of fetal acidemia and metabolic acidosis.<sup>10,11</sup>

All patients with newly diagnosed GDM during pregnancy were checked with 75-gr OGTT six weeks after delivery to confirm the diagnosis.

### *Statistical analysis*

The clinical features of both groups were compared with the Statistical Package for Social Sciences (SPSS) for Windows, version 18.0 (SPSS Inc. IL, USA). The Shapiro-Wilk and Kolmogorov Smirnov tests were used to test for the distribution of data. Normally distributed baseline characteristics were presented as mean±standard deviation, and abnormally distributed data were presented as median (min-max). To assess the differences in variables between groups, the independent t test was used. Results with non-normal distribution, Kruskal-Wallis, Mann-Whitney U-test and Bonferroni correction were used. Values of  $p < 0.05$  was accepted as statistically significant.

## RESULTS

A total of 130 patients (67 patients with GDM and 63 pregestational DM) were recruited to the study. There was no significant difference regarding age, gravida, parity and BMI between groups. Ultrasound indices (Umb Pi, Umb s/d and amnion fluid index) of groups were also similar. HbA1c and blood glucose levels were significantly statistically higher in pregestational group while TSH values were similar. Insulin dosage needed for treatment was also higher in pregestational group as expected. There was no significant difference regarding type of delivery, fetal birth weight, umbilical cord Hb and gestational birth age. No other significant difference in frequency of low Apgar scores and fetal acidosis or metabolic acidosis were reported. Comparison of maternal and fetal characteristics between groups were summarized in Table 1. Cesarean delivery rates were high in both groups. There was neither fetal or maternal mortality nor severe ketoacidosis episodes.

There were 18 patients with type 1 and 45 patients with type 2 in pregestational DM group. The mean time (year)

of diabetic history was 8.8 and 4.6 in type 1 and 2, respectively.

**Table 1: Comparison of maternal and fetal characteristics between groups.**

	GDM (n=67)	Pregestational DM (type 1 and 2 diabetes) (n=63)	P value
Age (y)	33.8 (±5.9)	32.9 (±7.1)	0.4
Gravida	3.5 (±1.7)	3.6 (±2.0)	0.8
Parity	2.1 (±1.4)	2.3 (±1.7)	0.4
BMI (kg/m <sup>2</sup> )	33.7 (±7.2)	33.8 (±5.0)	0.8
Insulin dosage*	16 (4-130)	40 (4-160)	0.002
HbA1c	5.4 (±0.9)	5.9 (±1.0)	0.005
TSH	1.7 (±1.0)	1.9 (±1.3)	0.2
Blood glucose (mg/dL)	105.2 (±14.5)	110.7 (±15.5)	0.05
Umb Pi	0.9 (±0.2)	0.96 (±0.2)	0.1
Umb s/d*	2.2 (1.4-5.3)	2.5 (1.6-7.6)	0.9
Amnion fluid index (AFI) (ml)	185 (±7.1)	233 (±21.8)	0.09
polyhydramnios (AFI>240 mm)	17	19	0.5
Type of delivery			
Vaginal delivery	12	10	0.7
Cesarean	55	53	
Fetal birth weight (gr)	3509 (±527)	3633 (±556)	0.2
Umb cord Hb (g/dL)	15.6 (±1.6)	15.8 (±1.6)	0.5
Gestational birth age (w)	38.5 (±0.4)	38.4 (±0.3)	0.2
1min Apgar score ≤7	7	7	0.9
5 min Apgar score ≤7	1	0	0.3
fetal acidosis venous pH<7.23	9	7	0.6
metabolic acidosis (base deficit >6.3 mmol/L)	18	11	0.1

\*Median (min-max), BMI: Body mass index, TSH: Thyroid stimulating hormone Pi: pulsatility index, Hb: hemoglobin

## DISCUSSION

This study implies that patients diagnosed with GDM and needed insulin therapy should be followed up as pregestational DM during antenatal period. Although blood glucose and HbA1C values were significantly different between pregnancies with GDM(A2) and pregestational DM, similar results were obtained in terms of fetal distress parameters.

In a recent study, they analyzed and compared the course and outcome of pregnancy in the patients with diabetes in relation to the group of healthy women regarding preterm delivery, perinatal morbidity and mortality.<sup>12</sup> They also

evaluated pregnancy outcomes in the patients with pre-existing diabetes type 1 and the patients with gestational and diabetes type 2. Their study resulted that a higher incidence of perinatal fetal morbidity (hypoglycemia, jaundice, respiratory distress syndrome) in the patients with type 1, type 2 and GDM than in the healthy controls. Moreover, there was a higher incidence of cesarean section in the patients with type 1 diabetes than in those with type 2, gestation diabetes and healthy controls. Although there was no significant difference in the frequency of preterm delivery, they mentioned that poorer glycaemic control resulting higher values of HbA1c in third trimester was related to preterm delivery.<sup>12</sup> In present study all patients were treated with insulin and we compared antenatal ultrasound (amnion fluid index (AFI), umbilical doppler etc.) and peri and postnatal maternal and fetal outcomes in patients with GDM and pregestational DM including type 1 and 2. We did not have control groups since we wanted to compare GDM A2 and pregestational diabetic results. It is well known that diabetes affects pregnancy in one way or another.

In another study, consequences of gestational and pregestational diabetes on placental function and birth weight were evaluated.<sup>13</sup> It was said that the placental structure was altered in pregestational and GDM. In addition, it was shown that oxygen supply was reduced in the maternal-placental in diabetic patients.<sup>14</sup> Due to impaired oxygen supply, more fetal oxygen was required. Low fetal oxygen levels affect and accelerate the transcription synthesis of proangiogenic factors such as leptin, vascular endothelial growth factor (VEGF) or fibroblast growth factor 2 (FGF2).<sup>15,16</sup> Therefore, both types of diabetes (GDM and in type 1 DM) were characterized by increased vascularisation.<sup>14</sup> In present results, HbA1c and blood glucose levels were significantly statistically higher in pregestational group while fetal outcomes were similar regarding fetal distress. This may be explained by other preangiogenic factors mentioned above. In fact, we could not trust HbA1c levels only due to this metabolism.

Tan et al. evaluated abnormal umbilical artery resistance index (UARI) in 50 randomly selected diabetic patients and a matched control group of 50 non-diabetic pregnancies.<sup>17</sup> They showed that abnormal UARI on Doppler study in diabetic pregnancy was not associated with a significantly higher incidence of than non-diabetic pregnancy. Authors have also performed umbilical doppler in all patients at least once per week, beginning from 36 weeks' gestation and could not find any difference between groups. Umbilical doppler parameters including Umb Pi and Umb s/d were not a useful tool to predict subsequent fetal outcome in diabetic pregnancies.

In our study, there was no significant difference among AFI between groups. In fact, there was no other significant differences in frequency of polyhydramnios (AFI>240 ml). Idris et al. revealed that pregestational

diabetic pregnancy with polyhydramnios was associated with poor diabetic control and resulting with significant increase in adverse perinatal outcome in these pregnancies, apart from a higher iatrogenic preterm birth rate.<sup>18</sup> In present study, there was no significant difference regarding fetal distress parameters and poor fetal outcome between groups even though higher HbA1c rates in pregestational diabetic patients. We think that in studies with larger numbers, polyhydramnios scores may be different.

Importantly, a limitation of current study is that it included only diabetic women treated with insulin. The second, the small sample size of cases with low apgar scores presented a limitation to the analyses of the data collected. However, a particular strength of the present study was that this was the first study investigating and comparing maternal characteristics including doppler and laboratory parameters and fetal outcome between GDM (A2) and pregestational diabetes.

In conclusion, the frequency of fetal distress parameters and poor fetal outcome were similar between groups although pregestational diabetic patients had higher HbA1c rates. Therefore, patients with GDM (A2) should be followed up as closely as pregestational (overt) diabetic patients and careful attention should be paid to end organ damage.

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