

# Predictive Risk Factors in the Treatment of Gestational Diabetes Mellitus

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## ABSTRACT

**OBJECTIVE:** This study aims to investigate predictive risk factors in the treatment of gestational diabetes mellitus (GDM).

**PATIENTS AND METHODS:** A total of 256 pregnant women who underwent 75 g oral glucose tolerance test (OGTT) during 24–28 weeks of pregnancy were included according to the World Health Organization criteria. Demographic characteristics of the patients, including age, parity, family history of diabetes, body weight before pregnancy, and body weight at the diagnosis of GDM, were recorded. Fasting insulin and hemoglobin A1c (HbA1c) values at the time of diagnosis were evaluated. The patients were divided into two groups: those requiring insulin treatment (insulin group,  $n = 89$ ) and those receiving diet therapy (diet group,  $n = 167$ ) during pregnancy according to the American Diabetes Association recommendations.

**RESULTS:** A total of 34.76% of the pregnant women with GDM required insulin treatment. The mean age of these patients was significantly higher compared to the diet group ( $34.9 \pm 0.6$  years vs.  $31.9 \pm 0.6$  years;  $P = 0.004$ ). Body mass index before pregnancy was also significantly higher in the insulin group than that in the diet group ( $32 \pm 0.9$  kg/m<sup>2</sup> vs.  $29 \pm 0.7$  kg/m<sup>2</sup>;  $P = 0.004$ ). Fasting blood glucose (FBG) during OGTT was  $105.6 \pm 2.1$  mg/dL and  $96.7 \pm 1.1$  mg/dL in the insulin group and diet group, respectively ( $P < 0.001$ ). There was no significant difference in fasting plasma glucose during OGTT between the groups ( $P = 0.069$ ), while plasma glucose at two hours was  $161.1 \pm 6.8$  mg/dL in the insulin group and  $145.1 \pm 3.7$  mg/dL in the diet group ( $P = 0.027$ ). At the time of diagnosis, HbA1c values were significantly higher in the insulin group compared to the diet group ( $5.3 \pm 0.1$  vs.  $4.9 \pm 0.1$ ;  $P = 0.001$ ). There was no significant difference in FBG and homeostasis model assessment-insulin resistance values between the groups ( $P = 0.908$ ,  $P = 0.073$ ).

**CONCLUSION:** Our study results suggest that age, family history of diabetes, body weight before pregnancy, FBG, and HbA1c values are predictors for the necessity of insulin treatment.

**KEYWORDS:** fasting blood glucose, pregnancy, obstetric outcome, oral glucose tolerance test, hemoglobin A1c

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## Introduction

Gestational diabetes mellitus (GDM) is one of the most common metabolic disorder diagnosed during pregnancy, and it refers to carbohydrate intolerance in various levels.<sup>1</sup> The rate of pregnant women with GDM is rising.<sup>2</sup> It is possible to protect the fetus from macrosomia, a possible long-term obesity, and to prevent the fetus from birth injury by diagnosing and treating pregnant women with GDM.

It is hard to make a comparison of GDM prevalence among various populations because there is no common agreement on universal screening and diagnosing. According to the American Diabetes Association (ADA), GDM accounts for 4% of pregnant women. However, it may vary between 1% and 14% in different populations.<sup>2,3</sup> Screening of GDM is often performed at 24–28 weeks during pregnancy, whereas high-risk patients are recommended to be screened at the onset of pregnancy.<sup>4</sup> Similar to the rest of the world, a two-stage

screening test with 50 g oral glucose tolerance test (OGTT) and 100 g OGTT has been performed for many years in Turkey. However, in recent years, a single-stage screening with 75 g OGTT has been adopted.<sup>5,6</sup>

Fetal and maternal complication risks should be minimized by following treatment and monitoring protocols in patients with GDM.<sup>3</sup> The first-line treatment of GDM is medical diet therapy and exercise. However, insulin therapy can be initiated if diet and exercise alone are inadequate, based on individual fasting blood glucose (FBG) and postprandial blood glucose (PPBG) levels. Basal-bolus insulin regimen (0.8–1 kg/day) is administered to patients with an FBG level of  $>95$  mg/dL, a one-hour PPBG level of  $>140$  mg/dL, and a two-hour PPBG level of  $>120$  mg/dL besides diet and exercise.<sup>7</sup>

The aim of this study is to investigate predictive risk factors in the treatment of GDM.



## Materials and Methods

**Patients.** Between December 2013 and December 2014, a total of 970 pregnant women were screened for GDM with 75 g OGTT at 24–28 weeks of pregnancy at Istanbul Medipol University Hospital, gynecology and obstetrics outpatient clinic. Of these women, 256 women who were diagnosed with GDM according to the World Health Organization (WHO) criteria (defined as FBG >126 mg/dL; two-hour PPGT >140 mg/dL) were included.<sup>8,9</sup> Women with multiple pregnancies, type 1 and type 2 diabetes, grand multipara (greater than four births), and systemic diseases were excluded. After 8–12-hour fasting, venous blood samples were collected at 08.00 a.m. from all patients. Hemoglobin A1c (HbA1c), glucose, and insulin levels were measured according to anamnesis and FBG measures in the first trimester of pregnant women. Based on homeostasis model assessment-insulin resistance (HOMA-IR), an insulin resistance score was calculated using the following formula: fasting plasma glucose (mmol/L) times fasting serum insulin (mU/L) divided by 22.5.<sup>10</sup> A threshold of 2.7 was considered for HOMA-IR.<sup>11</sup> Insulin level was measured using chemiluminescent microparticle immunoassay (Architect System; Abbott), while glucose level was measured using hexokinase method and HbA1c values were measured using immunoturbidimetry. Demographic characteristics of the patients, including age, parity, family history of diabetes, body weight before pregnancy, and body weight at the diagnosis of GDM, were recorded. The patients were divided into two groups: those requiring insulin treatment (insulin group;  $n = 89$ ) and those receiving diet therapy (diet group;  $n = 167$ ) during pregnancy.

The first-line treatment was medical diet for patients with GDM. Daily calorie intake was calculated based on body mass index (BMI) values. A diet program consisting of three main meals and four snacks was scheduled for obese patients (24 kcal/kg) and nonobese patients (35 kcal/kg) as of the second trimester of pregnancy. All the patients were followed with FBG tests and PPBG at one and two hours. The mean duration of blood glucose monitoring in patients on diet was 15 days. Insulin treatment was initiated in patients

with an FBG level of 95 mg/dL and a one-hour PPBG level of  $\geq 140$  mg/dL despite diet and exercise. Treatment goals were based on the ADA recommendations.<sup>6</sup>

Insulin treatment was initiated with basal-bolus or bolus alone, based on the individual FBG levels. Neutral protamine hagedorn (NPH) insulin was administered to patients with high levels of FBG, whereas NPH with crystallized insulin was administered to those with high levels of FBG and PPTT. Target value for blood glucose with insulin treatment was <95 mg/dL, one-hour PPTT <140 mg/dL, and two-hour PPTT <120 mg/dL.<sup>6</sup>

**Statistical analysis.** Statistical analysis was performed using the SPSS v18.0 software (SPSS Inc.). Categorical data were expressed in number and percentage, while numerical data were expressed in mean and standard deviation (minimum and maximum, where applicable). Chi-square test was used to compare categorical data, whereas independent  $t$ -test was performed to compare numerical data. The Mann-Whitney  $U$  test was used if the assumptions were not met. Logistic regression analysis was performed to identify the insulin group. A  $P$ -value of <0.05 was considered statistically significant. The risk factors of logistic regression analysis were FBG and HbA1c, which required insulin treatment.

## Results

The mean age of the 256 pregnant women was  $34.9 \pm 0.6$  years (range, 25–45 years). Of these women, 32% were above 35 years of age. The mean BMI value before pregnancy was  $30 \pm 5.6$  kg/m<sup>2</sup>, and 45.3% of the patients were deemed as obese.

A total of 34.76% pregnant women with GDM required insulin treatment. The mean age of these patients was significantly higher compared to the diet group (Table 1). Insulin treatment was required for 49% of patients above 35 years of age and 26% of patients below 35 years of age. BMI before pregnancy was also significantly higher in the insulin group compared to the diet group ( $32 \pm 0.9$  kg/m<sup>2</sup> vs.  $29 \pm 0.7$  kg/m<sup>2</sup>;  $P = 0.004$ ). Insulin treatment was required for 43.1% of patients having a BMI >30 kg/m<sup>2</sup> and 20.4% of patients having a BMI <30 kg/m<sup>2</sup>. However, weight gain was higher in the diet group compared to the insulin group until the time

**Table 1.** Demographic, anthropometric, and clinical characteristics of the patients.

	INSULIN GROUP ( $n = 89$ )	DIET GROUP ( $n = 167$ )	P-VALUE
Age (year)	$34.9 \pm 0.6$	$31.9 \pm 0.6$	0.004
Parity	$2.9 \pm 0.2$	$2.2 \pm 0.1$	0.003
GDM history	4 (8.8%)	10 (12%)	0.58
Family history of type 2 diabetes	35 (77.7%)	41 (49.4%)	0.001
Baseline BMI (kg/m <sup>2</sup> )	$32 \pm 0.9$	$29 \pm 0.7$	0.004
Baseline BMI >35	17 (37.8%)	13 (15.7%)	0.006
Weight gain (kg)	$6.3 \pm 0.8$	$8.4 \pm 0.6$	0.039

**Abbreviations:** BMI, body mass index; GDM, gestational diabetes mellitus.

**Table 2.** Biochemistry results of the patients.

	INSULIN GROUP (n = 89)	DIET GROUP (n = 167)	P-VALUE
FBG (mg/dL)	105.6 ± 2.1	96.7 ± 1.1	<0.001
OGTT at 2 h mg/dL	161.1 ± 6.8	145.1 ± 3.7	0.027
Fasting insulin (IU/mL)	9.7 ± 0.8	9.5 ± 1.1	0.908
HOMA-IR (unit)	2.4 ± 1.2	1.9 ± 1	0.073
HbA1c (%)	5.3 ± 0.1	4.9 ± 0.1	0.001

**Abbreviations:** FBG, fasting blood glucose; OGTT, oral glucose tolerance test; HOMA-IR, homeostasis model assessment-insulin resistance; HbA1c, hemoglobin A1c.

of the diagnosis of GDM ( $P = 0.039$ ) (Table 1). In the insulin group, parity was  $2.9 \pm 0.2$ , while it was  $2.2 \pm 0.1$  in the diet group. The difference between the parities was significant ( $P = 0.003$ ). Considering the family history of type 2 diabetes, there was a significant difference between the two groups ( $P = 0.001$ ) (Table 1).

FBG during OGTT was  $105.6 \pm 2.1$  mg/dL and  $96.7 \pm 1.1$  mg/dL in the insulin group and diet group, respectively ( $P < 0.001$ ). There was no significant difference in the fasting plasma glucose during OGTT between the groups ( $P = 0.069$ ), while plasma glucose during OGTT at two hours was  $161.1 \pm 6.8$  mg/dL in the insulin group and  $145.1 \pm 3.7$  mg/dL in the diet group ( $P = 0.027$ ). At the time of GDM diagnosis, HbA1c values were significantly higher in the insulin group compared to the diet group ( $5.3 \pm 0.1$  vs.  $4.9 \pm 0.1$ ;  $P = 0.001$ ). There was no significant difference in FBG and HOMA-IR values between the groups (Table 2).

Logistic regression analysis revealed that a higher number of patients with increased FBG and HbA1c required insulin treatment. Each one-unit increase in FBG increased the probability of insulin use by 1.062-fold (95% confidence interval (CI): 1.021–1.104), whereas each one-unit increase in HbA1c increased the probability by 3.1-fold (95% CI: 1.185–8.164). Age-adjusted regression analysis also showed that each one-year increase in age increased the probability of insulin use by 1.109-fold (95% CI: 1.018–1.209) (Table 3).

## Discussion

GDM risk factors may be maternal or pregnancy related. Some of these factors are history of diabetes mellitus in family, elderly pregnancy, obesity, macrosomic infant in previous delivery, and multiparity.<sup>12</sup> Diagnosing GDM is paramount

to prevent prenatal and maternal complications.<sup>9,13</sup> WHO adopted the two-hour 75-g OGTT during pregnancy and recommended the same diagnostic cutoff points established for the diagnosis of impaired glucose tolerance in nonpregnant women.<sup>14</sup> Untreated GDM was associated with significantly higher perinatal mortality rate compared to those with normal glucose tolerance.<sup>15</sup> Also, with the modern management of GDM, lower morbidity rate can be expected in the infants of diabetic mothers.<sup>16</sup> Changing lifestyle, diet, and additional insulin treatment have shown better perinatal outcomes.<sup>17,18</sup>

In the present study, we identified risk factors based on the WHO diagnostic criteria among patients requiring insulin for the treatment of GDM. In the insulin group, the number of parity was higher with an increased number of family history of type 2 diabetes, increased BMI, and age indicating a significant difference. We also found that each one-unit (1 mg/dL) increase in the FBG at the time of diagnosis increased the probability of insulin use by 1.062-fold and each one-unit increase in HbA1c increased it by 3.1-fold.

Similarly, Pertot et al<sup>19</sup> demonstrated that family history of diabetes, body weight before pregnancy, and BMI were determinant factors for insulin treatment. In another study, Ouzounian et al<sup>20</sup> reported that overweight and obese women with GDM had an increased need for medical nutrition therapy for glycemic regulation and insulin treatment.

In our study, FBG, two-hour OGTT, and HbA1c values were higher in the insulin group compared to the diet group, which are consistent with other reports in the literature. In a study including 300 women with GDM, Bakiner et al<sup>21</sup> showed that 36.7% required insulin treatment with a higher incidence among patients with elevated FBG and HbA1c values. The authors reported that an FBG level of  $\geq 89.5$  mg/dL and an HbA1c value of  $\geq 5.4$  were positive predictors for GDM. In another study, the authors found that an FBG level of  $>105$  mg/dL might be used to identify high-risk pregnant women requiring insulin treatment.<sup>22</sup> In addition, Clayton et al<sup>23</sup> demonstrated that increased HbA1c, FBG, and BMI values were positively associated with insulin treatment among patients with GDM. Another study showed that the majority of pregnant women with a one-hour OGTT of  $\geq 190$  mg/dL needed insulin treatment.<sup>20</sup>

**Table 3.** Factors affecting insulin need in patients with GDM.

VARIABLE	P-VALUE	OR	95% CONFIDENCE INTERVAL
FBG (mg/dL)	0.003	1.062	1.021–1.104
HbA1c	0.021	3.110	1.185–8.164
Age	0.017	1.109	1.018–1.209

**Note:** Only significant values via regression analysis are presented.  
**Abbreviations:** FBG, fasting blood glucose; HbA1c, hemoglobin A1c.



In this study, a significantly higher number of patients with increased two-hour OGTT, FBG, and HbA1c values required insulin treatment than those in the diet group. However, logistic regression analysis revealed that two-hour OGTT was not a predictor for the insulin need. The analysis also showed that each one-unit increase in FBG at the time of diagnosis increased the probability of using insulin by 1.062-fold and each one-unit increase in the HbA1c increased it by 3.1-fold.

In conclusion, we found that advanced age and increased BMI values before pregnancy were more frequent among patients receiving insulin treatment for GDM. Based on logistic regression analysis, FBG (odds ratio (OR), 1.062), HbA1c (OR, 3.110), and age (OR, 1.109) were found to be predictors for insulin treatment. The close monitoring of patients with GDM during pregnancy is essential for the early prediction of fetal and maternal complications.

### Consent

Written informed consent was obtained from all the participants. Local ethics committee approval was not needed because of noninvasive retrospective clinical study.

### Author Contributions

Conceived and designed the experiments: LHA, BY. Analyzed the data: LHA, BY. Wrote the first draft of the manuscript: LHA, BY, NK, YKA. Contributed to the writing of the manuscript: LHA, BY, NK, YKA. Agree with manuscript results and conclusions: LHA, BY, NK, YKA. Jointly developed the structure and arguments for the paper: LHA, BY, NK, YKA. Made critical revisions and approved final version: LHA, BY, NK, YKA. All authors reviewed and approved of the final manuscript.

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