ARE THE FACTORS AFFECTING ADVERSE PREGNANCY OUTCOMES DIFFERENT IN OBESE GESTATIONAL DIABETES PREGNANT WOMEN RECEIVING DIET OR INSULIN TREATMENT?

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Abstract

Context. We aimed to examine the factors affecting adverse gestational outcome in gestational diabetes (GDM) patients, who were grouped as obese and normal-weight, having only-diet, or insulin treatments.

Subjects and Methods. The study included 373 patients, treated with diet or insulin. These patients were sub-grouped as obese and non-obese, and examined retrospectively. The variables affecting adverse gestational outcome in obese GDM patients having dietary and/ or insulin treatments were detected with multiple regression analysis.

Results. The weight gained during pregnancy in the GDM group having insulin treatment was more than the one in only-diet treated GDM group ($p=0.004$). Pre-pregnancy body mass index, the weight gained during pregnancy, hemoglobin A1C levels in the second and third trimesters, caesarian rates were higher in the insulin-treated obese patients than in the other groups ($p<0.001$). The odds ratio for fasting blood glucose level in insulin-treated obese GDM group was 1.081 (95% CI = 1.004 - 1.163) ($p=0.039$); and it was 0.982 (95% CI = 0.924 - 1.002) ($p=0.048$) for the weight gained during pregnancy, in only-diet treated obese GDM patients.

Conclusion. The control of weight gained during pregnancy, and of fasting blood glucose levels in obese patients having GDM, is important to decrease adverse gestational outcome.

Key words: obese gestational diabetes, adverse pregnancy outcomes, weight gain during pregnancy, diet therapy, insulin therapy.

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common medical complications of pregnancy (1). The insulin resistance, which reaches a peak during the 24-28th gestational weeks, increases during gestation (2). GDM has the same risk factors observed for type 2 diabetes, such as obesity and increased

age (3). The prevalence of GDM may range between 1- 14 % (4). It is very well known that women who are overweight or obese in the pre-pregnancy period have an increased risk of GDM. Recently, obesity has become a global health problem due to a sedentary lifestyle and changes in dietary habits. Torloni *et al.* observed a two-fold increase in GDM in over-weight women and a four-fold in obese ones (5). There are many studies which observed the increased GDM risk in obese women as compared to women of normal weight (6, 7).

GDM increases maternal complications like preeclampsia, cesarean rate, cardiovascular disease, obesity, and diabetes after pregnancy and neonatal complications like macrosomia, hypoglycemia, hyperbilirubinemia, delivery trauma, shoulder dystocia, and adult-onset obesity, and diabetes (1). The maternal and fetal complications are notably increased in obese GDM patients (7). Dietary regimens and exercise are applied in GDM patients to reach target blood glucose levels, and insulin treatment is used in patients who are not successful with the mentioned methods.

In this study, we aimed to observe the factors affecting adverse pregnancy outcomes in the obese and non-obese GDM patients who were treated only with diet or with insulin; and benefit via strict control of these factors during antenatal follow-up.

MATERIALS AND METHODS

Pregnant patients diagnosed with GDM in our clinic between 2013 and 2016 were included in the study. The screening test used was an O'Sullivan 50-g glucose load, given orally at any time of the day with plasma glucose measured one hour later between the 24-28th week. If the 1-hour value was over 140 mg/dL (7.8 mmol/L), 100g oral glucose tolerance test (OGTT) was done in the morning following overnight fasting between 8 and 14 hours. OGTT (100g) has at least two different

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glucose algorithms that are used for diagnosis of GDM (8). Cut off levels of Carpenter Coustan criteria for glucose for fasting, 1st, 2nd, and 3rd hours were 95 mg/dL, 180 mg/dL, 155 mg/dL, and 140, respectively. In the beginning, 535 patients had positive glucose tolerance test results and therefore diagnosed as GDM. They initially received a general healthy dietary recommendation, as the caloric intake of 2000–2500 calories per day with a breakdown of 45% carbohydrates, 20 % protein, and 35 % fat (9). The patients were treated with diet and exercise for up to 2 weeks depending upon the fasting and the postprandial blood glucose levels to achieve excellent glycemic control before the insulin therapy. When diet and exercise therapy failed in achieving satisfying glycemic control, insulin therapy was started. Insulin treatment was started in pregnant women with postprandial satiety sugar $\geq$ 140 mg/dL. Blood glucose levels of patients were followed according to the recommendations of The Endocrine Society (10). Pre-pregnancy BMI was obtained by dividing pre-pregnancy body weight in kilograms by the square of height in meters. BMI <30 kg/m² non-obese and BMI ≥ 30 kg/m² as obese were evaluated according to their pre-pregnancy weight. The GDM groups having only-diet, and insulin regimens were sub-grouped into obese and non-obese groups.

Exclusion criteria included infectious diseases, use of medications known to alter insulin secretion or action, and lipoprotein metabolism, hypertension, family history of cardiovascular disease, and endocrinopathies including diabetes, Cushing syndrome, androgen-secreting tumors, late-onset 21-hydroxylase deficiency, thyroid dysfunction, autoimmune diseases, multiple fetuses, and epilepsy. All patients included in the study were matched for age, gestational age, smoking, and pre-pregnancy body mass index (BMI). The Institutional Review Board approved this study (approval number: 07.11.2017/22), and the universal principles of the Helsinki Declaration (as revised in 2000) were applied.

Gestational age was confirmed in all participants by a routine ultrasonographic examination performed during the first-trimester gestation. All analysis was conducted in the hematology and biochemistry laboratory of our hospital with the use of a Beckman Coulter (High Wycombe, UK) Gen-S automated analyzer. Plasma glucose levels were determined with the glucose hexokinase method. Hemoglobin-A1c (HbA1c) levels were determined by Glucose GOD-PAP, Roche Diagnostics GmbH, Germany analyzer.

The adverse pregnancy outcomes criteria were APGAR score <7 , fetal weight <2500 g, or > 4500 g,

polyhydramnios (amniotic fluid index > 25 cm).

We planned delivery with normal blood glucose regulation, biophysical profile, and non-stress test between 40-406/7 in GDM pregnant women with only-diet. Also, we proposed delivery of normal blood glucose regulation, biophysical profile, and non-stress test between 38-396/7 in GDM pregnant women with insulin therapy.

Statistical analysis

Data analysis was performed by using SPSS for Windows, version 17 (SPSS Inc., Chicago, IL, United States). Continuous variables were shown as the mean $\pm$ standard deviation (SD) or mean $\pm$ Confidence Interval, and a number of cases and (percentage), where applicable. Student's t-test compared the mean differences between groups. Pearson's Chi-Square test analyzed nominal data. The variables of sub-groups were evaluated with one-way ANOVA test. Multiple logistic regression analyses were applied for calculating odds ratios and 95% confidence intervals for prediction of adverse pregnancy outcomes in subgroups of obese GDM patients, like the ones having only-diet treatment, and the ones using insulin. Correlation analysis was applied for adverse pregnancy outcomes and variables of these groups. A $p < 0.05$ was considered statistically significant.

RESULTS

The study included 535 patients, who had been diagnosed with GDM at their 24th -28th weeks, and was followed up till delivery. Three hundred and seventy-three of these patients were treated only with diet, and 162 of them had to use insulin. Table 1 presents the anthropometric, biochemical, and ultrasonographic parameters of the groups. Groups were homogenized for age, BMI, gravity, and delivery weeks. The weight gained during pregnancy in the insulin group was significantly higher than the other one ($p = 0.004$). The HbA1c level in the second and third trimesters was significantly higher in the patients using insulin ($p < 0.001$, and $p < 0.001$, respectively). Ultrasonographic parameters were evaluated; the insulin group had a significantly higher abdominal circumference (AC)/biparietal diameter (BPD) ratio than the only-diet group ($p < 0.001$). There was no difference between the groups when the amniotic fluid index and Doppler measurements were compared (Table 1).

There was no difference in fetal gender and birth weights, and APGAR scores of 1st and 5th minutes

Table 1. The anthropometric, biochemical and ultrasonographic parameters of the groups

	Only-Diet (n=373)	Insulin (n=162)	p-value
Age (year)*	31.5±6.0	30.6±5.9	0.647
Pre-pregnancy body mass index*	27.74±3.9	28.17±4.1	0.269
Gravity**	3 [1 – 10]	3 [1 – 12]	0.352
Birth week*	38.2±2.0	37.9±1.7	0.052
Weight gain *	14.5±7.1	16.6±8.0	0.004
Smoking***	24 (6.5%)	12 (7.5%)	0.826
Postprandial blood glucose level**	89 [57 – 211]	91.3 [59 – 206]	0.290
HbA1c of 2 nd trimester **	5.3 [4.0 – 8.4]	5.8 [5.0 – 9.1]	<0.001
HbA1c of 3 rd trimester**	5.3 [3.5 – 9.8]	5.8 [4.1 – 8.1]	<0.001
Amniotic fluid index***	Normohydramnios Oligohydramnios Polyhydramnios	104 (69.8%) 11 (7.4%) 34 (22.8%)	0.149
Umbilical Artery Doppler*	2.15±0.62	2.26±0.65	0.080
Abdominal circumference/biparietal diameter**	1.009[0.89-1.14]	1.021[0.92-1.17]	0.001
Apgar 1/5***	< 7 ≥ 7	18 (4.82%) 7 (4.32%)	0.339
Birth weight*	3353.6±617.8	3437.6±564.0	0.140
Fetal gender***	Female Male	163 (45.5%) 77 (48.7%)	0.501
50g OGTT*	150.2± 30.8	174.4± 26.3	<0.001
	Fasting blood glucose	83.6±12.7	<0.001
100g OGTT*	OGTT 1. hour	175.7±38.7	<0.001
	OGTT 2. hour	134.3±31.3	<0.001
	OGTT 3. hour	88.0±28.5	0.013

*Results were analyzed by independent Sample t-test (Mean ± SD), **Kruskal Wallis Test (Median [min-max]), ***Pearson chi-square test (%). p< 0.05 statistically significant. Statistically significant p values are marked as bold text. OGTT; oral glucose tolerance test, HbA1c; Hemoglobin A1c.

between the groups. The results of 50g and 100g OGTT results were significantly higher in the group using insulin (Table 1).

GDM patients were divided into subgroups according to their pre-pregnancy weight. When these groups were sub-grouped as BMI <30 kg/m², and BMI >30 kg/m², 60 patients (16.08%) of the group treated only with diet was obese, and 313 (83.91%) of the patients were non-obese. On the other hand, 48 patients (29.6%) of the insulin-treated group were obese, whereas 114 (70.4%) of them were not (Table 2). Weight gained during pregnancy, 2nd and 3rd-trimester HbA1c levels, AC/BPD ratio were significantly higher in the obese insulin-using patients when compared to only- diet using group (p<0.001) (Table 2).

The cesarean ratio was significantly higher in obese patients using insulin than in the non-obese group using insulin, and in the group treated only with diet (p=0.010). The result of 50g OGTT was significantly higher in the obese insulin-treated sub-group when it was compared to the group treated only with diet. Besides, in the group treated only with diet, it was higher in the obese sub-group than in the non-obese participants (p<0.001). The fasting blood glucose level was significantly higher in the obese patients of the

insulin-treated group when compared to the other ones (p<0.001). The results of 100g OGTT test in the 1st, 2nd, and 3rd hours were significantly higher in obese sub-groups when compared to their non-obese counterparts, and significantly higher in the obese patients of the insulin-treated group than in the other groups (Table 2).

Multivariate logistic regression analysis was used to evaluate the relation of anthropometric and laboratory parameters on adverse pregnancy outcomes in obese sub-groups. OR for fasting, blood glucose was 1.081 (95% CI =1.004-1.163) in obese insulin-using patients. Only the fasting blood glucose level had high predictivity for the adverse pregnancy outcomes in the insulin group (p=0.039). The OR for weight gained during pregnancy in the obese sub-group of the group treated with diet was 0.982 (95% CI =0.924-1.002) which had high predictivity for the adverse pregnancy outcomes (p=0.048) (Table 3).

Pre-pregnancy BMI and weight gain during pregnancy were correlated to an adverse outcome, in obese GDM sub-group treated only with diet (r=0.309, p=0.003; r=-0.195, p=0.012, respectively). Only the fasting blood glucose level was positively related to adverse pregnancy outcomes, in obese insulin-treated sub-group (r=0.328, p=0.030) (Table 4).

Table 2. The comparison of obese and non-obese subgroups of study groups

Obese (1) N=60 (16.08%)	Diet		Insulin		p-value*	p-value**
	Non-obese (2) n=313 (83.91%)	Obese (3) n=48 (29.6%)	Non-obese (4) n=114 (70.4%)			
Age (year)	32.27 ±5.166	31.13 ± 6.10	32.56 ±5.45	32.28 ±5.99	p(12)=ns p(13)=ns p(14)=ns p(23)=ns p(24)=ns p(34)=ns	0.342
Gravity	3.00[1-10]	2.81 [1-10]	3.44 [1-8]	3.03 [1-12]	p(12)=ns p(13)=ns p(14)=ns p(23)=0.019 p(24)=ns p(34)=ns	0.107
Birth Week	38.02 ± 2.008	38.27 ± 1.94	37.68 ±1.76	38.10 ± 1.64	p(12)=ns p(13)=ns p(14)=ns p(23)=ns p(24)=ns p(34)=ns	0.311
Weight gain	14.68 ± 7.67	14.68 ±6.96	20.65 ±8.99	14.85 ± 6.81	p(12)=ns p(13)<0.001 p(14)=ns p(23)<0.001 p(24)=ns p(34)<0.001	<0.001
Smoking	0.26 [0-10]	0.36 [0-20]	0.94[0-20]	0.35[0-10]	p(12)=ns p(13)=ns p(14)=ns p(23)=ns p(24)=ns p(34)=ns	0.237
Postprandial blood glucose	94.16 ±24.59	96.84 ±25.01	19.49 ±29.05	98.03 ±29.83	p(12)=ns p(13)=ns p(14)=ns p(23)=ns p(24)=ns p(34)=ns	0.088
HbA1c of 2 nd trimester	5.36 ±0.66	5.36 ±0.57	6.24 ±0.62	5.73 ±0.88	p(12)=ns p(13)=0.002 p(14)=ns p(23)<0.001 p(24)=0.028 p(34)=0.039	<0.001
HbA1c of 3 rd trimester	5.27 ±0.64	5.26 ± 0.63	6.01 ±0.84	5.77 ±0.655	p(12)=ns p(13)<0.001 p(14)<0.001 p(23)=ns p(24)<0.001 p(34)=ns	<0.001
Umbilical artery doppler	2.14[1.2-3.60]	2.14[1.0-3.41]	2.34[1.16-3.96]	2.21[1.0-3.70]	p(12)=ns p(13)=ns p(14)=ns p(23)=0.048 p(24)=ns p(34)=ns	0.215
Abdominal circumference / biparietal diameter	1.01 ± 0.036	1.00 ±0.035	1.03 ±0.053	1.01 ±0.04	p(12)=ns p(13)=0.023 p(14)=ns p(23)<0.001 p(24)=0.022 p(34)=0.030	<0.001

Obese (1) N=60 (16.08%)		Diet		Insulin		p-value*	p-value**
		Non-obese (2) n=313 (83.91%)	Obese (3) n=48 (29.6%)	Non-obese (4) n=114 (70.4%)			
Apgar 1/5	< 7	4 (6.77%)	12 (3.83%)	3(6.25%)	2 (1.75%)	p(12)=0.024 p(13)=ns p(14)=0.017 p(23)=ns p(24)=ns p(34)=ns	0.058
	≥ 7	55 (93.22%)	301 (96.16%)	45(93.75%)	112(98.27%)		
Birth weight		3319.54±678.10	3369.00±594.33	3500.43 ±570.31	3411.75 ±561.88	p(12)=ns p(13)=ns p(14)=ns p(23)=ns p(24)=ns p(34)=ns	0.353
Birth type	Vaginal birth	21(35.59%)	112 (35.78%)	7 (14.58%)	36 (31.57%)	p(12)=ns p(13)=0.004 p(14)=ns p(23)=0.001 p(24)=ns p(34)=0.020	0.010
	Cesarean	38 (64.40%)	201 (64.21%)	41 (85.41%)	78 (68.42%)		
Fetal gender	Female	26 (44.06%)	165 (52.71%)	26 (54.16%)	55 (48.24%)	p(12)=ns p(13)=ns p(14)=ns p(23)=ns p(24)=ns p(34)=ns	0.790
	Male	33 (55.93%)	148 (42.28%)	22 (45.83)	59 (51.75%)		
50g OGTT		156.03 ± 27.50	148.01 ±31.81	178.19 ±29.70	172.98 ± 25.02	p(12)=0.034 p(13)<0.001 p(14)<0.001 p(23)<0.001 p(24)<0.001 p(34)=ns	<0.001
100g OGTT	Fasting blood sugar	87.06 ±14.13	84.58 ±17.89	117.71 ±30.40	100.67 ±29.61	p(12)=ns p(13)<0.001 p(14)<0.001 p(23)<0.001 p(24)<0.001 p(34)<0.001	<0.001
	OGTT 1 st hour	180.55 ± 36.37	178.50 ±65.96	188.95 ±44.33	202.16 ± 29.97	p(12)=ns p(13)=ns p(14)=0.016 p(23)=ns p(24)=0.002 p(34)=ns	0.015
	OGTT 2 nd hour	138.54 ±29.70	133.93 ±34.00	166.17 ±41.75	157.63 ±33.99	p(12)=ns p(13)=0.002 p(14)=0.001 p(23)<0.001 p(24)<0.001 p(34)=ns	<0.001
	OGTT 3 rd hour	92.32 ±27.35	86.36 ±28.86	109.00 ±37.46	95.09 ±36.08	p(12)=ns p(13)=0.044 p(14)=ns p(23)=0.004 p(24)=ns p(34)=ns	0.014

**p-value; between groups, *p-value; within groups. p < 0.05, statistically significant. Results were analyzed by One Way ANOVA (Brown-Forsythe), Post-hoc Test (LSD-Games Howell). Statistically significant p-values are marked as bold text. OGTT; oral glucose tolerance test, HbA1c; Hemoglobin A1c.

Table 3. Multiple regression analysis for adverse pregnancy outcomes in obese sub-groups

	Adverse pregnancy outcomes		Insulin Group OR (95% CI)	p value*
	Only-Diet Group OR (95% CI)	p value*		
Age	1.020 (0.973-1.070)	0.405	1.007 (0.793-1.278)	0.954
Pre-pregnancy body mass index	1.053 (0.980-1.131)	0.159	1.024 (0.788-1.329)	0.861
Weight gain	0.983 (0.924-1.002)	0.048	1.036 (0.930-1.154)	0.523
Postprandial blood glucose	1.002 (0.091-1.013)	0.750	1.008 (0.972-1.045)	0.658
Fasting blood glucose	1.002 (0.98-1.021)	0.874	1.081 (1.004-1.163)	0.039
50g OGTT	0.998 (0.983-1.012)	0.757	0.978 (0.926-1.033)	0.422
100g OGTT 1 st Hour	1.003 (0.998-1.009)	.259	0.996 (0.972-1.020)	0.738
100g OGTT 2 nd Hour	0.998 (0.989-1.006)	0.598	1.006 (0.981-1.033)	0.629
100g OGTT 3 rd hour	0.999 (0.989-1.009)	0.890	1.014 (0.986-1.043)	0.339
HbA1c of 2 nd trimester	0.810 (0.03-3.232)	0.765	1.515 (1.030-1.826)	0.894
HbA1c of 3 rd trimester	0.956 (0.517-1.767)	0.885	2.177 (1.252-2.799)	0.479

*p < 0.05 statistically significant. OGTT; oral glucose tolerance test, HbA1c; Hemoglobin A1c.

Table 4. Correlation analysis for variables on adverse pregnancy outcomes in obese patients using only- diet and treated with insulin

	Adverse Pregnancy Outcome Obese GDM Using Only Diet	Obese GDM Using Insulin
Age	r=0.170 p=ns	r=-0.112 p= ns
Pre-pregnancy body mass index	r=0.309 p=0.003	r=0.227 p=ns
Weight gain	r=0.195 p=0.012	r=-0.088 p=ns
Postprandial blood glucose	r=-0.161 p=ns	r=0.121 p=ns
50g OGTT	r=-0.074 p=ns	r=-0.110 p=ns
Fasting blood glucose	r=0.055 p=ns	r=0.328 p=0.030
100g OGTT1. Hour	r=-0.026 p=ns	r=-0.142 p=ns
100g OGTT 2. Hour	r=-0.054 p=ns	r=0.119 p=ns
100g OGTT 3. Hour	r=-0.046 p=ns	r=0.237 p=ns
HbA1c	r=0.214 p=ns	r=0.112 p=ns

HbA1c; Hemoglobin A1c.

The results of each adverse pregnancy outcome were evaluated by multiple regression analysis in obese pregnant women who received only diet therapy. 50g OGTT was independently associated with fetal weight < 2500 g in obese only-diet group (OR: 0.970, 95% CI: 0.942-0.999, p=0.040). Increased fasting blood glucose was independently associated with fetal weight >4500 g in the obese only-diet group (OR: 1.068, 95% CI: 1.014-1.124, p=.013). None of the laboratory or clinical variables were associated with polyhydramnios and APGAR score < 7 in the obese only-diet group (Table 5).

The results of each adverse pregnancy outcomes were evaluated by multiple regression analysis in obese

pregnant women who received insulin treatment only. Pre-pregnancy BMI was independently associated with polyhydramnios in obese insulin treatment group (OR: 1.205, 95% CI: 1.011-1.436, p=.037). None of the laboratory or clinical variables were associated with APGAR score < 7, fetal weight <2500g and fetal weight > 4500g in obese insulin treatment group (Table 6).

Additionally, a total of 27 (45%) pregnant women had adverse pregnancy outcomes in the GDM group receiving obese diet therapy (5 (18.51%) APGAR <7, 1 (3.70%) fetal weight <2500g, 7 (25.92%) fetal weight > 4500g and 14 (51.85) polyhydramnios). A total of 29 (60.1%) pregnant women had negative results in the GDM group receiving obese insulin

Table 5. Multiple regression analysis for each adverse pregnancy outcome in obese only-diet group

	Adverse pregnancy outcomes							
	APGAR score <7		Fetal weight <2500g		Fetal weight > 4500g		Polyhydramnios	
	OR (95% CI)	p value*	OR (95% CI)	p value*	OR (95% CI)	p value*	OR (95% CI)	p value*
Age	0.949 (0.834-1.080)	0.431	0.981 (0.857-1.124)	0.785	1.114 (0.938-1.324)	0.220	1.065 (0.977-1.160)	0.152
Pre-pregnancy body mass index	1.044 (0.898-1.213)	0.577	0.968 (0.814-1.152)	0.718	1.160 (0.980-1.373)	0.085	1.021 (0.924-1.128)	0.686
Weight gain	0.968 (0.880-1.065)	0.504	1.024 (0.925-1.133)	0.649	1.103 (0.974-1.249)	0.121	0.987 (0.929-1.049)	0.682
Postprandial blood glucose	0.978 (0.935-1.024)	0.344	0.982 (0.939-1.028)	0.439	1.004 (0.971-1.038)	0.835	0.974 (0.945-1.004)	0.085
Fasting blood glucose	1.033 (0.988-1.079)	0.153	0.941 (0.869-1.018)	0.130	1.068 (1.014-1.124)	0.013	1.005 (0.974-1.038)	0.749
50g OGTT	0.986 (0.957-1.015)	0.335	0.970 (0.942-0.999)	0.040	1.008 (0.971-1.047)	0.665	1.006 (0.988-1.024)	0.518
100g OGTT 1st Hour	1.016 (0.975-1.059)	0.453	1.007 (0.974-1.041)	0.683	1.017 (0.960-1.077)	0.577	0.995 (0.979-1.011)	0.536
100g OGTT 2nd Hour	1.013 (0.966-1.061)	0.606	0.995 (0.957-1.035)	0.815	1.013 (0.948-1.082)	0.704	0.993 (0.973-1.013)	0.473
100g OGTT 3rd hour	1.000 (0.949-1.053)	0.989	0.983 (0.933-1.036)	0.527	1.007 (0.941-1.077)	0.846	0.988 (0.965-1.011)	0.295
HbA1c of 2nd trimester	1.097 (0.101-11.903)	0.903	1.052 (0.689-1.658)	0.453	1.808 (0.999-3.287)	0.276	1.203 (0.094-1.398)	0.992
HbA1c of 3rd trimester	5.664 (0.970-7.846)	0.111	0.355 (0.064-1.982)	0.238	3.680 (0.499-7.148)	0.201	0.627 (0.213-1.848)	0.397

*p < 0.05 statistically significant. OGTT; oral glucose tolerance test, HbA1c; Hemoglobin A1c.

Table 6. Multiple regression analysis for each adverse pregnancy outcome in obese insulin group

	Adverse pregnancy outcomes							
	APGAR score <7		Fetal weight <2500g		Fetal weight > 4500g		Polyhydramnios	
	OR (95% CI)	p value*	OR (95% CI)	p value*	OR (95% CI)	p value*	OR (95% CI)	p value*
Age	0.890 (0.716-1.105)	0.290	1.295 (0.760-2.204)	.641	1.049 (0.711-1.548)	0.808	0.960 (0.856-1.073)	0.470
Pre-pregnancy body mass index	1.048 (0.802-1.371)	0.730	0.942 (0.520-1.705)	.843	1.348 (0.013-1.405)	0.991	1.205 (1.011-1.436)	0.037
Weight gain	1.010 (0.892-1.143)	0.875	1.061 (0.902-1.249)	.474	0.597 (0.225-1.583)	0.300	0.981 (0.916-1.051)	0.584
Postprandial blood glucose	1.040 (1.000-1.082)	0.052	0.877 (0.701-1.098)	.252	1.012 (0.955-1.072)	0.682	1.031 (0.991-1.036)	0.242
Fasting blood glucose	1.013 (0.977-1.051)	0.475	0.928 (0.808-1.065)	.288	1.121 (0.947-1.328)	0.185	1.018 (0.997-1.040)	0.089
50g OGTT	1.014 (0.973-1.057)	0.501	0.881 (0.687-1.132)	.322	0.736 (0.120-0.751)	0.853	1.005 (0.981-1.030)	0.678
100g OGTT 1st Hour	1.038 (0.991-1.087)	0.117	0.991 (0.947-1.038)	.706			0.977 (0.947-1.008)	0.139
100g OGTT 2nd Hour	1.024 (0.992-1.058)	0.148	0.981 (0.903-1.065)	0.647			0.999 (0.975-1.024)	0.966
100g OGTT 3rd hour	1.109 (0.942-1.305)	0.214	0.943 (0.837-1.061)	0.328			1.004 (0.978-1.031)	0.753
HbA1c of 2nd trimester	1.938 (0.69-5.471)	0.698					2.318 (0.277-9.410)	0.438
HbA1c of 3rd trimester	1.732 (0.173-7.319)	0.640	0.213 (0.010-4.735)	0.328	1.147 (0.406-3.239)	0.152	2.389 (0.796-7.166)	0.120

*p < 0.05 statistically significant. OGTT; oral glucose tolerance test, HbA1c; Hemoglobin A1c.

therapy (3 (10.34%) APGAR <7, 1 (3.44%) fetal weight <2500g, 11 (37.93%) fetal weight > 4500g and 14 (48.27%) polyhydramnios).

The mean maternal age and pre-pregnancy BMI of pregnant women with adverse gestational outcomes were significantly higher than those without adverse pregnancy outcomes in the only-diet GDM group (32.08 ± 6.06 vs. 30.69 ± 5.99 , $p=.041$ and 27.43 ± 4.19 vs. 26.13 ± 3.79 , $p=.004$, respectively). Also, the gestational week was significantly earlier in the only-diet GDM group with adverse pregnancy outcomes compared to the only-diet GDM group without adverse pregnancy outcome (37.27 ± 2.12 vs. 39.04 ± 1.17 , $p<.001$) (Table 7).

The only gestational week was earlier in the GDM group receiving insulin treatment with adverse

pregnancy outcomes than in the GDM group receiving insulin treatment without adverse pregnancy outcomes (37.04 ± 1.76 vs. 38.76 ± 1.01 , $p<.001$) (Table 8).

DISCUSSION

GDM is related to serious maternal and fetal complications in both antenatal and postnatal periods. In obese patients, the risk of GDM with related complications has increased. The risk of GDM has been seen more recently, as a result of the increasing incidence of obesity. In this study, we aimed to determine the risk factors affecting adverse maternal and fetal outcomes in pregnant women with obese gestational diabetes. We observed increased pre-pregnancy BMI in both obese using only diet and obese insulin-treated sub-groups.

Table 7. Comparison of only-diet GDM groups with and without adverse pregnancy outcomes

	Only-Diet Adverse pregnancy outcome	Non-adverse pregnancy outcome	p-value
Age (year)*	32.08 ± 6.06	30.69 ± 5.99	0.041
Pre-pregnancy body mass index*	27.43 ± 4.19	26.13 ± 3.79	0.004
Gravity**	2.85 ± 1.69	2.89 ± 1.75	0.847
Birth week*	37.27 ± 2.12	39.04 ± 1.17	<0.001
Weight gain *	13.98 ± 7.47	14.57 ± 6.83	0.461
Smoking***	10 (7.5%)	10 (5.1%)	0.255
Postprandial blood glucose level**	96.96 ± 26.92	95.05 ± 23.23	0.513
HbA1c of 2 nd trimester **	5.41 ± 0.64	5.32 ± 0.59	0.616
HbA1c of 3 rd trimester**	5.20 ± 0.52	5.33 ± 0.77	0.134
Fasting blood glucose	84.30 ± 14.84	87.60 ± 20.73	0.094
50g OGTT*	149.71 ± 29.87	151.91 ± 32.35	0.571
OGTT 1. hour	174.03 ± 42.64	185.93 ± 81.99	0.190
OGTT 2. hour	136.69 ± 35.34	133.07 ± 28.23	0.457
OGTT 3. hour	89.25 ± 28.47	87.88 ± 28.56	0.747

*Results were analyzed by independent Sample t-test (Mean $\pm$ SD), **Kruskal Wallis Test (Median [min-max]),***Pearson chi-square test (%). $p<0.05$ statistically significant. Statistically significant p values are marked as bold text. OGTT; oral glucose tolerance test, HbA1c; Hemoglobin A1c.

Table 8. Comparison of treated with insulin GDM groups with and without adverse pregnancy outcomes

	Insuline treatment Adverse pregnancy outcome	Non-adverse pregnancy outcome	p-value
Age (year)*	33.32 ± 5.74	33.12 ± 5.94	0.837
Pre-pregnancy body mass index*	29.00 ± 5.58	27.48 ± 4.02	0.063
Gravity**	3.03 ± 1.80	3.22 ± 1.52	0.493
Birth week*	37.04 ± 1.76	38.76 ± 1.01	<0.001
Weight gain *	16.59 ± 7.32	15.60 ± 8.40	0.453
Smoking***	6	5	
Postprandial blood glucose level**	98.86 ± 31.37	99.14 ± 26.31	0.955
HbA1c of 2 nd trimester **	5.54 ± 0.43	6.20 ± 0.99	0.060
HbA1c of 3 rd trimester**	5.96 ± 0.78	5.71 ± 0.65	0.088
Fasting blood glucose	100.16 ± 25.05	114.97 ± 36.23	0.005
50g OGTT*	176.85 ± 25.57	174.78 ± 25.09	0.682
OGTT 1. hour	200.58 ± 28.92	201.94 ± 36.67	0.852
OGTT 2. hour	154.68 ± 27.72	168.88 ± 38.71	0.059
OGTT 3. hour	109.21 ± 40.88	87.24 ± 30.46	0.008

*Results were analyzed by independent Sample t-test (Mean $\pm$ SD), **Kruskal Wallis Test (Median [min-max]),***Pearson chi-square test (%). $p<0.05$ statistically significant. Statistically significant p values are marked as bold text. OGTT; oral glucose tolerance test, HbA1c; Hemoglobin A1c.

Obese GDM patients using insulin were found to have increased weight gain during pregnancy and higher levels of HbA1c in the 2nd and 3rd trimesters, in our study. Also, weight gain during pregnancy was associated with adverse pregnancy outcomes in the GDM group receiving dietary therapy, and elevated fasting blood glucose levels were associated with adverse pregnancy outcomes in the GDM group receiving insulin therapy. High levels of 50 g OGTT were the most important risk factors affecting infants with fetal weight <2500g in the GDM group receiving obese diet therapy, whereas the increase in fasting blood glucose level was the most important risk factor in infants with fetal weight > 4500g. Pre-pregnancy BMI was a risk factor associated with polyhydramnios in obese GDM pregnant women receiving insulin therapy.

In a study performed in Sweden on 151,025 women between 1992 and 2001, and increased risk of adverse pregnancy outcomes was observed in patients having 3 or more units of increase in BMI, than in patients having 1 unit of increase (11). Gao *et al.* showed an increased risk of adverse pregnancy outcomes with increased pre-pregnancy BMI, and weight gained during pregnancy (12). They also observed a positive relationship between fetal birth weight and weight gained during pregnancy.

We observed a significantly increased cesarean rate and 50g OGTT results in the obese GDM subgroup using insulin than in the other sub-groups. Miao *et al.* supported this result with their researches in which 832 nulliparous GDM patients were examined retrospectively (13). Cesarean delivery rate was significantly higher in the obese and overweight GDM group than the non-obese group. Similarly, Cossonet *et al.* in their study of 15,551 singleton pregnant women stated that the rate of the cesarean section did not change in obese and overweight pregnant women with GDM compared to control group (14).

We observed the predictive value of weight gained during pregnancy on adverse pregnancy outcomes in the obese sub-group using the only diet. Pre-pregnancy BMI was also positively correlated to adverse outcome in this sub-group. The same was observed for fasting blood glucose level in obese insulin-treated sub-group. Boney *et al.* showed the increased risk of metabolic syndrome in the children of obese or overweight mothers had GDM (15). Cypryk *et al.* examined the increased risk of macrosomia, and risk of developing diabetes in the future lives of the children of mothers, who are obese or overweight and having GDM (16). The weight control of obese pregnant

patients with diet and lifestyle modification improves the adverse pregnancy outcomes risk (17, 18). Zilberlicht *et al.* observed the high risk of adverse pregnancy outcomes in patients having high pre-pregnancy BMI and increased weight gain during pregnancy (19). Meiramova *et al.* stated that pre-pregnancy BMI was higher, and gestational hypertension rate was higher in the GDM group compared to the control group. They also reported that the rate of cesarean section, birth induction, birth trauma, diabetic fetopathy were significantly higher in the GDM group compared to the control group, and the 5th minute APGAR score of the newborn was substantially lower (20).

In conclusion, both GDM and obesity are important risk factors for adverse pregnancy outcomes. Control of fasting blood glucose level in obese GDM patients using insulin and regulation of weight gain in GDM patients using only the diet may improve adverse pregnancy outcomes. These factors should be emphasized in the follow-up of GDM patients.

Conflict of interest

None of the authors received any financial support that could be considered a potential conflict of interest regarding the manuscript or its submission

Statement of Informed Consent.

Informed consent was obtained from all patients for being included in the study.

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