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ORIGINAL ARTICLE

The effect of maternal metabolic factors and lipid profile on birth weight in pregnant women with gestational diabetes and normal glucose tolerance

[1]Lütfiye UYGUR
[2]Gizem BOZ İZCEYHAN
[3]Ceren ÜNAL
[1]Işıl AYHAN
[4]Murat MUHÇU

[1]Division of Perinatology, Department of Obstetrics and Gynecology, University of Health Sciences, Türkiye. Zeynep Kamil Maternity and Children's Training and Research Hospital, İstanbul, Türkiye

[2]Department of Obstetrics and Gynecology, University of Health Sciences, Türkiye. Zeynep Kamil Maternity and Children's Training and Research Hospital, İstanbul, Türkiye

[3]Department of Obstetrics and Gynecology, Koç Univesity Faculty of Medicine, İstanbul, Türkiye

[4]Division of Perinatology, Department of Obstetrics and Gynecology, Ümraniye Research Hospital, İstanbul, Türkiye

ORCID ID
LU : 0000-0002-6325-1910
GBİ : 0000-0002-3358-6250
CÜ : 0000-0003-3485-5843
IA : 0000-0002-8160-7853
MM : 0000-0001-7039-375X

ABSTRACT

Objective: The objective of the study is to investigate the impact of maternal metabolic syndrome parameters and lipid profiles on fetal growth in pregnancies with gestational diabetes and with normal glucose tolerance. The second aim was to compare the metabolic profiles of pregnant women with gestational diabetes mellitus and with normal glucose tolerance.

Material and Methods: Pregnant women who applied for an oral glucose tolerance test were recruited and followed up prospectively. They were also examined for metabolic syndrome, including serum lipid profile between 24th and 28th weeks. The group diagnosed with gestational diabetes and those with normal glucose tolerance were compared in terms of obesity, hypertension, serum lipid profile, and neonatal birth weight. Hypertriglyceridemic and normotriglyceridemic patients were compared regarding maternal metabolic syndrome criteria and neonatal birthweight.

Results: Diabetic pregnant women had significantly higher body mass index (BMI) and triglyceride levels and lower high-density lipoprotein (LP) levels than non-diabetics. The hypertension rate was also higher; however, it was not statistically significant. Those with hypertriglyceridemia had higher BMI, hemoglobin (HbA1c) level, and neonatal birth weight in the diabetic group, whereas triglyceride level did not impact neonatal birthweight in non-diabetic patients. Obesity, high HbA1c, and triglyceride levels, and low high-density LP levels were the parameters leading to fetal macrosomia in gestational diabetes.

Conclusion: Increased accumulation of glucose toward the fetus is not the only mechanism of macrosomia. Parameters of metabolic syndrome affect fetal growth concomitantly. Diabetic women should be evaluated in the context of metabolic syndrome.

Keywords: Birth weight, fetal growth, gestational diabetes, hypertriglyceridemia, metabolic syndrome, obesity.

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Correspondence: Lütfiye UYGUR, MD. Türkiye Sağlık Bilimleri Üniversitesi, Zeynep Kamil Kadın ve Çocuk Hastalıkları Eğitim ve Araştırma Hastanesi, Kadın Hastalıkları ve Doğum Kliniği, Perinatoloji Bölümü, İstanbul, Türkiye.
Tel: +90 555 705 44 24 **e-mail:** lutfiyeuygur@gmail.com
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INTRODUCTION

Gestational diabetes mellitus (GDM) is acquired glucose intolerance during pregnancy. It is known to be one of the most prevalent pregnancy complications. Due to the increased obesity prevalence and sedentary lifestyles, the prevalence of pregestational diabetes mellitus (PDM) and GDM has become evident in all age groups. The overall prevalence of PDM and GDM is 1%, and 1.7–15.7% of all pregnancies, respectively.[1]

GDM is correlated with metabolic disorders like, obesity, insulin resistance, hyperlipidemia, and hypertension. Pre-pregnancy body mass index (BMI) and severity of GDM are independently and significantly associated with an increased risk of hypertensive diseases during pregnancy (HDP).[2] Pregnancy leads to physiological changes to ensure the accumulation of maternal serum contents toward the fetus to support its growth. Maternal blood levels of triacylglycerol (TG), free fatty acids (FFA), cholesterol, lipoprotein (LP), and phospholipids rise consistently after a dip during the first 8 weeks of pregnancy. Pregnancy-related physiological hypertriglyceridemia is thought to be caused by increased estrogen levels and insulin resistance.[3,4] This physiological change mimicking metabolic syndrome is exaggerated in women with GDM. Women with GDM have higher TG levels but lower low-density LP (LDL) levels. Concentrations of total cholesterol, high-density LP (HDL), and apolipoprotein do not alter significantly.[5,6] The diminished oxidation of dietary TG in GDM may result in an increase in TG and free fatty acid buildup in the fetoplacental unit, which may lead to macrosomia. Maternal and fetal adverse outcomes such as cesarean delivery, neonatal hypoglycemia, premature delivery, shoulder dystocia, birth injuries, intensive neonatal care admission, and hyperbilirubinemia show continuous linear associations with maternal fasting and postprandial glucose levels. They are direct results of fetal macrosomia and hyperinsulinemia.[7]

This study aimed to investigate the impact of maternal metabolic syndrome parameters and lipid profiles on intrauterine fetal development in pregnancies with gestational diabetes and with normal glucose tolerance. The second aim was to compare the metabolic profiles of pregnant women with GDM and those with normal glucose tolerance.

MATERIAL AND METHODS

This prospective observational cohort study was approved by the local ethics committee of a tertiary maternity hospital (decision date: January 04, 2013, No: 005). Patients who participated in the research provided informed consent. Pregnant women who presented in outpatient clinics for routine follow-up and screened for GDM at Zeynep Kamil Training and Research Hospital between 2012 and 2013 were recruited for the study. Exclusion criteria were chronic hypertension, thyroid dysfunction, PDM, multiple pregnancies, fetal anomalies, or regular drug use.

Demographic data were recorded, including height and weight, medical and surgical history, prior macrosomic delivery, history of GDM, drug use, and smoking. Between the 24 and 28 weeks of gestation, two-stage universal GDM screening was carried out, as recommended in the ACOG 2013 bulletin.[8] An extra blood sample was taken to assess serum lipid concentrations while assessing fasting blood glucose before loading 50 g of glucose as routine protocol.

The non-diabetic group (NGT) included those whose serum glucose levels were <140 mg/dL in the blood sample taken on the 1st h of the 50-g oral glucose tolerance test (OGTT). Those whose serum glucose levels were higher than 140 mg/dL were undergone to 100-g OGTT. GDM was diagnosed in 100 g OGTT according to the Carpenter-Coustan criteria.[8] Glycosylated hemoglobin (HbA1c) was evaluated after the 35th week in the group with GDM to assess glycemic control. Glycooxidase has been used to evaluate the plasma glucose concentration, and the Cobas Integra® equipment was used to perform a colorimetric enzyme test to measure the serum triglyceride, cholesterol, and HDL levels. The Friedewald formula was used to calculate LDL levels. Using a turbidimetric inhibition immunoassay, the HbA1c values were calculated.

The weight of patients at the time of delivery was recorded, and the data on the newborn and pregnancy outcomes were obtained from the hospital records. The patients who delivered before 37 weeks of gestation were excluded. The last menstrual period and the first-trimester ultrasound measures were used to confirm the gestational age (GA).

GDM and NGT groups were compared in terms of demographic characteristics, some metabolic syndrome parameters, namely TG level, HDL level, blood pressure, and BMI, and maternal-neonatal pregnancy outcomes. The patients were examined for the metabolic syndrome criteria excluding the "waist circumference" as the pregnancy affects that criteria irrespective of metabolic syndrome. To assess the impact of dyslipidemia on neonatal birth weight and maternal outcomes, hypertriglyceridemic and normotriglyceridemic patients were compared in both GDM and NGT groups. We used the reference values of our laboratory, which were developed in a non-pregnant population, as the upper limit for TG results because there are no normal lipid level threshold values generated by taking into account the metabolic responses in the lipid profile during pregnancy.

The Statistical Package for Social Sciences 21.0 program was used for statistical analysis. Mean, standard deviation, minimum-maximum, median, ratio, and frequency values were calculated in the descriptive statistics of the data. The distribution of the variables was determined by the Kolmogorov–Smirnov test. To analyze the quantitative data, an independent sample t-test, and Mann–Whitney U test were used. The Chi-square test was used to evaluate the qualitative data. At the effect level, regression analysis was performed. The 95% confidence level and $p<0.05$ significance level were used to assess the findings.

RESULTS

A total of 212 patients were recruited for the study. Thirteen patients were lost to follow-up and were excluded. Sixteen patients from the GDM group and seven from the NGT group delivered preterm secondary to preeclampsia, abruption of the placenta, preterm premature rupture of membranes, and spontaneous preterm delivery. Therefore, they were also excluded, and 93 cases of NGT and 83 cases of GDM were evaluated.

When the groups were compared in terms of demographic features, it was detected that the mean maternal age, parity, history of a previous macrosomic baby, and pre-pregnancy BMI were signifi-

Table 1: Demographic data of the study population

	NGT (n=93)	GDM (n=83)	p
Age (Mean±SD)	28.3±5.7	33.0±5	<0.001
Median (min–max)	28 (19–39)	33 (19–42)	
Parity	1 (0–2)	1 (0–5)	<0.001
History of macrosomic baby	1 (1.1%)	19 (22.9%)	<0.001
Smoking	2 (2.2%)	5 (6%)	0.189
BMI	23.8±4.3	27.3±4.6	<0.001
Final maternal weight	79.1±10.9	83.9±13.2	0.013
Total weight gain	15.9±5.8	13.6±4.8	0.005

Independent sample test/Mann–Whitney U test/Chi-square test; NGT: Normal glucose tolerance; GDM: Gestational diabetes mellitus; n: Sample number; SD: Standard deviation; p: Significance value; BMI: Body mass index.

Table 2: Lipid profile, HbA1c, and rate of hypertensive diseases in the NGT and GDM groups

	NGT (n=93)	GDM (n=83)	p
TG (mg/dL)	181.1±62.8	245.1±90.1	<0.001
	176 (80–375)	226 (115–522)	
LDL (mg/dL)	135.5±41.8	124.3±52.0	0.121
	130 (60–305)	116 (33–420)	
Total cholesterol (mg/dL)	250.4±45.6	226.0±47.8	0.001
	245 (155–392)	226 (66–342)	
HDL (mg/dL)	81.4±21.2	59.6±16.0	<0.001
	78 (47–187)	59 (33–107)	
HbA1c (%)		5.7±0.8	
		6 (5–10)	
HDP	7 (7.5%)	13 (15.7%)	0.090

NGT: Normal glucose tolerance; GDM: Gestational diabetes mellitus; n: Sample number; p: Significance value; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; HbA1c: Hemoglobin A1 c; HDP: Hypertensive disease of pregnancy.

cantly greater in the GDM group (p<0.05). Although the NGT group significantly gained more weight than the GDM group, the final maternal weight was significantly higher in the GDM group (Table 1).

Serum lipid profile and rate of HDP were compared between the groups (Table 2). TG level was significantly higher (p<0.05), and total cholesterol and HDL levels were significantly lower in the GDM group (p<0.05). LDL levels did not differ between the groups (p>0.05). Since our laboratory calculates LDL using the Friedewald algorithm,

Table 3: Comparison of the pregnancy outcomes between GDM and NGT groups

	NGT (n=93)	GDM (n=83)	p
GA at birth	38.6±1.1	38.8±1.2	0.190
Birth weight	3424±356	3652±556	0.002
	3500 (2580–4330)	3690 (2340–5390)	
LGA newborn	13 (14%)	36 (43.4%)	<0.001
Cesarean section	32 (34.4%)	45 (54.2%)	0.008

Independent sample test/Mann–Whitney U test/Chi-square test; NGT: Normal glucose tolerance; GDM: Gestational diabetes mellitus; n: Sample number; p: Significance value; LGA: Large for gestational age.

Table 4: Comparison of the hypertriglyceridemic and normotriglyceridemic groups among the NGT patients

	TG <200 (n=67)	TG ≥200 (n=26)	p
Age	27.3±5.6	30.7±5.5	0.009
	27 (19–39)	32 (21–39)	
BMI	23.1±4.3	25.5±4.1	0.012
	23 (17–37)	25 (19–37)	
Total weight gain	16.7±5.4	14.0±6.3	0.037
	18 (4–30)	14 (0–28)	
Birth weight	3417±370	3441±330	0.761
	3450 (2650–4330)	3500 (2580–4100)	
LGA newborn	8 (12.3%)	5 (17.9%)	0.479
HDP	3 (4.6%)	4 (14.3%)	0.105

Independent sample test/Chi-square test; NGT: Normal glucose tolerance; GDM: Gestational diabetes mellitus; n: Sample number; p: Significance value; TG: Triglyceride; BMI: Body mass index; LGA: Large for gestational age; HDP: Hypertensive disease of pregnancy.

patients with TG levels exceeding 400 mg/dL could not have their LDL levels calculated. Therefore, LDL results could not be obtained in four patients, all in the GDM group. Although HDP complicated the GDM patients more frequently, the difference between the groups was insignificant.

The mean birth weight in the GDM and NGT groups were 3652±556 g and 3424±356 g, respectively, and the difference was statistically significant (p=0.002). The GDM group had a significantly higher large for GA (LGA) newborn rate compared to the NGT (43.4% vs. 14%, respectively, p=0.000). GDM group had a significantly higher rate of cesarean section compared to the NGT group (54.2% vs. 34.4%, respectively, p=0.008) (Table 3).

Table 5: Comparison of the hypertriglyceridemic and normotriglyceridemic groups among the GDM patients

	TG <200 (n=26)	TG ≥200 (n=57)	p
Age	31.9±5.6	33.4±4.6	0.200
	32 (19–42)	33 (23–42)	
BMI	25.1±3.2	28.4±4.8	0.001
	25 (20–32)	27 (20–41)	
Total weight gain	12.6±4	14.1±5	0.194
	14 (6–22)	14 (6–30)	
HbA1c (%)	5.4±0.5	5.8±0.9	0.013
	5 (5–6)	6 (5–10)	
Birth weight	3492±368	3725±612	0.077
	3510 (2890–4020)	3700 (2340–5390)	
LGA newborn	10 (38.5%)	26 (45.6%)	0.779
HDP	2 (7.7%)	11 (19.3%)	0.177

Independent sample test/Chi-square test; NGT: Normal glucose tolerance; GDM: Gestational diabetes mellitus; n: Sample number; p: Significance value; TG: Triglyceride; BMI: Body mass index; LGA: Large for gestational age; HDP: Hypertensive disease of pregnancy.

Table 6: Factors impact on the neonatal birth weight in the patients with normal glucose tolerance

	Univariate analysis		
	β	SE	p
Age	-9.0	6.6	0.174
BMI	-19.7	8.4	0.020
Prepregnancy weight	-4.9	3.2	0.126
Final maternal weight	1.2	3.4	0.719
Total maternal weight gain	24.1	5.9	0.000
TG	0.7	0.6	0.209
LDL	0.6	0.9	0.484
HDL	4.7	1.7	0.006
Total cholesterol	1.2	0.8	0.129
History of macrosomia	379.9	358.1	0.292
Hypertension	-505.1	130.5	0.000
Smoking	51.9	256.1	0.840
GA at birth	190.8	28.0	0.000

SE: Standard error; BMI: Body mass index; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; GA: Gestational age; β: Standard error; p: Significance value.

Neither in GDM nor in NGT patients, no statistically significant difference was detected in macrosomia and HDP between the hypertriglyceridemic group and the normotriglyceridemic group (Table 4, 5). In NGT patients, the hypertriglyceridemic group had more advanced maternal age; however, maternal age did not differ between the TG groups in GDM pregnant women (p=0.200). BMI was higher in the hypertriglyceridemic group in both GDM and NGT patients (p=0.001 and p=0.012, respectively). Maternal weight gain was lower in the hypertriglyceridemic group in NGT patients; however, it did not differ between TG groups in GDM patients. In GDM patients, the hypertriglyceridemic group had higher HbA1c levels than the normotriglyceridemic group. Neonatal birth weight did not differ between TG groups in NGT pregnancies. In GDM patients, hypertriglyceridemia was related to higher neonatal birthweight, although it did not reach statistical significance (Table 5).

Univariate regression analysis was performed in GDM and NGT groups to find out the maternal factors that impact neonatal birthweight. In the NGT group, GA at birth, maternal BMI, total weight gain in pregnancy, and HDL level were the variables positively affecting birth weight, while HDP had a negative effect (Table 6). In the GDM group, maternal age, GA at birth, total maternal weight gain, and HDP were not found to have an effect on birth weight, whereas BMI, pre-pregnancy weight, final maternal weight, history of a macrosomic newborn, levels of TG, LDL, total cholesterol, HDL and HbA1c had a significant effect on birth weight in univariate analysis (Table 7).

Table 7: Factors affecting the neonatal birth weight in the patients with GDM

	Univariate analysis		
	β	SE	p
Age	13.6	12.3	0.272
BMI	45.4	12.4	0.000
Prepregnancy weight	19.1	4.5	0.000
Final maternal weight	19.6	4.2	0.000
Total maternal weight gain	17.5	12.8	0.176
TG	1.8	0.7	0.008
LDL	-2.4	1.2	0.044
HDL	-8.8	3.7	0.020
Total cholesterol	-3.6	1.2	0.005
HbA1c	365.6	66.2	0.000
History of macrosomia	687.9	124.6	0.000
Hypertansion	115.1	168.5	0.496
Smoking	108.4	257.8	0.675
GA at birth	-25.9	50.9	0.612

SE: Standard error; BMI: Body mass index; TG: Triglyceride; LDL: Low-density lipoprotein; HDL: High density lipoprotein; GA: Gestational age; β: Standard error; p: Significance value.

DISCUSSION

Several maternal lipid and carbohydrate metabolism changes occur during the pregnancy to support intrauterine fetal growth. Numerous physiological and biochemical changes take place throughout pregnancy, which is a period of adaptation. This study aimed to examine the interaction of these maternal metabolic changes with each other and the impact of some of these changes, which are considered physiologic to some extent, on fetal growth. These metabolic changes were evaluated within the context of parameters included in the diagnosis of metabolic syndrome and studied in patients with and without GDM. It was detected that the extension of these changes differs depending on the GDM status.

We found that maternal age, parity, BMI, and final maternal weight of pregnant women with GDM were substantially higher than those with NGT. These findings were in accordance with the existing literature and support the suggestion that advanced maternal age and obesity are among the leading risk factors for GDM.[9–11] NGT patients gained more weight than GDM patients, consistent with the other studies in the literature.[10,12–15] This can be related to lifestyle changes after the diagnosis of GDM. Another reason can be the insulin resistance in diabetic and obese pregnant which prevents insulin's lipogenic impact and results in decreased maternal weight gain and increased glucose flow to the fetoplacental unit.

When the perinatal outcomes of the two groups were examined, the GDM group had significantly higher birth weight and LGA infant ratio than the NGT group. This also resulted in a significantly higher cesarean rate in the GDM group. Maternal hyperglycemia accumulates an abnormally high glucose level toward the fetus, resulting in macrosomia through fetal hyperinsulinemia in diabetic mothers, as well described in the literature.[7,16,17] Pregnancy-related hypertension was more common in the GDM group (15.7%) than in the NGT group (7.5%), although the difference was not statistically significant (p=0.09) (Table 3). One of the most important factors contributing to premature birth in diabetic pregnant women is hypertensive diseases, and several studies in the literature have shown that diabetic pregnant are more likely to develop gestational hypertension.[18–20] As we excluded preterm deliveries due to preeclampsia, the difference in hypertension rates between GDM and NGT groups could not reach statistical significance.

We found that GDM patients have higher serum TG levels than their non-diabetic counterparts. This was consistent with the literature.[21,22] The other studies in the literature did not report any difference in total cholesterol and HDL levels. In contrast, we detected significantly lower total cholesterol and HDL levels in GDM pregnant compared with the NGT pregnant. The lower total serum cholesterol of the GDM group seems to be related to considerably lower HDL levels. This result supports the speculation that GDM can be accepted as a temporary status of metabolic syndrome, which also withholds the patients from benefiting from the antiatherogenic effects of HDL, preventing endothelial damage.

To understand the impact of hypertriglyceridemia on newborn weight and pregnancy outcomes, we compared the maternal features and neonatal outcomes of the patients with TG level>200 mg/dL and with TG level <200 mg/dL. The patients with hypertriglyceridemia had considerably higher maternal age and BMI but lesser weight gain in the NGT group (Table 4). This result can be secondary to dietary control in obese patients who were also hypertriglyceridemic. In GDM patients, BMI, HbA1c level at term, and the percentage of patients with hypertension were all higher in patients with hypertriglyceridemia than the ones with normal TG levels, although only BMI and HbA1c at term attained statistical significance (Table 6). Hypertriglyceridemia was related to obesity in both patient groups. This relationship was exaggerated and correlated with higher HbA1c and birth weight in GDM patients. Although birth weight did not differ significantly between the hypertriglyceridemic and normotriglyceridemic group (Table 5), elevated TG level was among the significant factors affecting birth weight along with obesity, history of macrosomia, higher HbA1c and lower HDL level in univariate analysis (Table 7). On the other hand, no impact of high triglyceride levels was detected on neonatal birth weight in non-diabetic pregnancies. None of the serum lipid levels were related to birth weight in the NGT patients. This result was in accordance with the other studies in the literature and supported the synergistic impact of the components of metabolic syndrome on higher neonatal birthweight in insulin-resistant pregnant.[12,23–25] The previous studies could not reveal the impact of HDL on birth weight; however, we found a negative correlation between HDL level and neonatal birth weight.[16]

Maternal insulin resistance leads to increased mobilization from fat reserves and increased free fatty acid and TG levels in the blood. This is a physiologic change for the mother to utilize fat as a source of energy and to accumulate glucose and amino acids towards the fetoplacental unit. However, in obese and diabetic pregnant, this change becomes excessive, leading to hypertriglyceridemia, which results in indirect atherogenic consequences for the mother and macrosomia for the fetus.[26] Changes in lipid metabolism in GDM patients are proportionate to insulin resistance, which may explain the association between hypertriglyceridemia and elevated birth weight in GDM patients, despite the fact that maternal triglycerides cannot pass the placenta. The connection between hypertriglyceridemia and obesity seems to be a result of their shared association with insulin resistance.[23] Furthermore, fetal overgrowth is caused by the transport of maternal fatty acids through the placenta by LP receptors, fatty acid binding proteins, and different lipase activities that match triglycerides.[27–29]

The studies in the literature report that despite adequate glycemic control proved by standardized measures like fasting, 1st-h, and 2nd-h blood glucose levels or HbA1c level, macrosomia rates is higher in GDM pregnant women than in NGT pregnant women. This raises the question of whether there are other factors leading to macrosomia in insulin-resistant patients. In the research by Langer et al.,[30] additional insulin therapy that was given to obese GDM pregnant women who were actually able to maintain normal glucose levels with diet or oral anti-diabetic medications decreased the risk of macrosomia in the insulin-therapy group. This may be owing to insulin's antilipolytic impact.[30–32] Insulin treatment might have lowered maternal levels of FFA and triglycerides and potentially prevented overgrowth.

CONCLUSION

When the pregnancy is considered as a "testing period," certain pathologies that were present before the pregnancy but were not diagnosed or covered up may become obvious due to these physiological changes after conception. Moreover, these alterations can be permanent after the pregnancy. Patients with GDM experience more dramatic and progressive alterations.

GDM is a pathology related to several metabolic disorders, such as obesity, insulin resistance, hyperlipidemia, and high blood pressure. All of these disorders are components of metabolic syndrome interacting with each other, changing the intrauterine environment and leading to fetal macrosomia. The prevention of obesity in reproductive age, the prevention of excessive weight gain throughout pregnancy, and more liberal use of anti-diabetic agents to avoid the lipolytic effects of insulin resistance in GDM treatment, instead of insisting on long-term dietary restrictions, may decrease the macrosomia risk.

GDM is also a significant risk factor for major morbidity and mortality in women, including type 2 diabetes, metabolic syndrome, and cardiovascular disease in later life. In this study, BMI and TG levels were significantly higher, and HDL was significantly lower in the group with GDM. The hypertension rate was not significantly higher due to the design of the study. As these patients are more likely to have metabolic syndrome after giving birth, they should be closely followed up for not only type 2 diabetes but also hypertension, obesity, hyperlipidemia, and heart disease, and they should be strongly encouraged to lifestyle changes.

Statement

Ethics Committee Approval: The Zeynep Kamil Maternity and Children's Training and Research Hospital Clinical Research Ethics Committee granted approval for this study (date: 04.01.2013, number: 005).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – LU; Design – LU; Supervision – MM; Resource – LU; Materials – GBİ; Data Collection and/or Processing – LU; Analysis and/or Interpretation – IA; Literature Search – CÜ; Writing – LU, GBİ, CÜ; Critical Reviews – LU.

Conflict of Interest: The authors have no conflict of interest to declare.

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