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Vascular effects of gestational diabetes can be recognized by carotid intima-media thickness: a prospective case-control study

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Abstract

Gestational diabetes mellitus (GDM) is a systemic disease that has poor maternal and fetal health outcomes. Patients who aree diagnosed with GDM are more likely to encounter cardiovascular system diseases during pregnancy and after birth. Carotid intima-media thickness (CIMT) is used as an early indicator of diseases such as coronary artery disease. This study aims to define the effects of hyperglycemia at an early term using CIMT, maternal and fetal doppler flows in patients diagnosed with GDM. The study included 132 pregnant women who had reached the 24th gestational week. (GDM group n=65, Control group n=67) Comparisons were performed between women with similar demographic characteristics who received a 100-gr oral glucose test (OGT) and GDM diagnosis and who did not. The participants' routine hemograms and biochemical tests were done during OGT. Fetal biometrics, amniotic fluid index, uterine artery doppler flow, and bilateral CIMT measurements were performed during the obstetric examinations. Gravida, para, and live birth rates of the GDM group participants were higher than those of the control group (p=0.003, 0.002, 0.002 respectively). The amniotic fluid index was found to be higher in the GDM group (p<0.001). Fasting glucose values and platelet counts were higher in the GDM group (p=0.031 and p<0.001). Other laboratory data demonstrated no statistically meaningful differences between the groups (p>0.05). When the doppler measurements were compared, umbilical artery pulsatility index values were discovered to be similar between the groups (p=0.509). While the right uterine artery (UtA) pulsatility index was higher in the GDM group (p<0.001), no statistically significant differences were found between the groups in terms of the left UtA pulsatility index (p=0.485). Right and left CIMTs were higher in the GDM group (p=0.001, p<0.001, p<0.001 respectively). While in the GDM group there was a positive correlation between the thrombocyte level and uterine artery resistance (r=0.336, p=0.006; r=0.397, p=0.044 respectively), no similar correlations were found in the control group. This study found that GDM patients had inflammation, increased resistance in uterine artery flow, and increased CIMT. It has been shown, there is a correlation between CIMT and glucose levels and between thrombocytosis and UtA resistance in GDM patients. Uterine artery doppler data and CIMT measurements could be used as an indicator of systemic inflammation and cardiovascular disease in patients with GDM.

Keywords: Cardiovascular disease, carotid intima-media, gestational diabetes

Introduction

The definition of gestational diabetes mellitus (GDM) is any degree of glucose intolerance with onset or first recognition during pregnancy [1]. Since diabetes screening is rarely done in women at reproductive age, it is sometimes difficult to diagnose hyperglycemia emerging in pregnancy as gestational diabetes mellitus. The ratio of complicated pregnancies with any kind of diabetes was reported at 7%, and approximately 87% of these pregnancies were proven to be GDM [2]. The

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prevalence of gestational diabetes in society varies depending on the characteristic of the population and the criteria used for diagnosis. The prevalence of GDM ranges between 9% and 26% [3]. After giving birth, females diagnosed with GDM were found to experience a decrease in insulin sensitivity, atherogenic lipid profile and increased Carotid intima-media thickness (CIMT) and cardiovascular risks [4-6].

Coronary artery disease (CAD) is a crucial reason for death worldwide, and hypertension, diabetes, smoking, and lipid profile disorders are listed as important risk factors. Coronary angiography is the golden classic diagnosis method of CAD [7]. This invasive method brings along some risks. CAD happens as a result of the atherosclerotic process, and CIMT, a non-invasive and easily applicable marker, is used for the diagnosis of atherosclerosis [8]. A study that investigated CIMT and inter-adventitial thickness (IAT) of healthy pregnant women found that CIMT and IAT increased with the progression of the gestational week, and even if IAT returned to its previous condition after birth, CIMT could return to its previous thickness after 2.7 years [9]. Although CIMT was reported to increase in patients with GDM history, it cannot return to normal in postpartum 2.7 years like CIMT physiologically increasing in pregnancy [10]. This condition could decrease the reliability of CIMT as a reliable marker in pregnancy for CAD. Evaluation of uterine artery (UtA) blood flow of healthy pregnant and pregnant women diagnosed with GDM together with CIMT may increase the reliability of CIMT. Thus, individuals at risk for atherosclerotic diseases can be detected by CIMT measured during pregnancy.

Materials and Method

The study was conducted with pregnant women who were followed up in the Cardiovascular Surgery and Obstetric Clinic at the Medical Faculty Hospital of Amasya University between 2020 and 2021. Before starting the study, ethics committee approval was obtained from the non-interventional ethics committee of Amasya University, dated 05.12.2019 and numbered 51. The investigation, which was created as a case-control study, contained healthy pregnant females in the third trimester who had a body mass index of below 25 and who accepted GDM screening. Of all the women who were followed up in the clinic, those aged 40 and over; had diabetes, previous gestational diabetes, or preeclamptic findings; were hypertensive or diagnosed with any kind of cardiovascular diseases; used oral anticoagulant or heparin-derivatives; diagnosed with autoimmune diseases and had lipid profile disorder were excluded.

The week of pregnancy of the patients was decided by examining similar studies that had been done before. And pregnant women who completed their 24th gestational week were included in the study. Pregnant women with a gestational week between 24 and 28 who wanted to have the screening test initially received a 50gr oral glucose challenge test (OGCT). Those who had high OGCT were administered a 100gr oral glucose test following the appropriate fasting duration and diet. While fasting blood of patients was analyzed during both tests, routine hemogram (Sysmex XN 1000) and biochemical tests were also analyzed (Beckman Coulter AU 5800). Measurements included obstetric fetal biometrics, fetal-uterine doppler flows (fetal uterine doppler Mindray DC-7), and in the same session CIMT (Philips innosight diagnostic ultrasound system) of pregnant women in the 25th to 28th gestational weeks. The clinician who performed ultrasound measurements was blind to GDM status of patients and experienced in obstetric sonography and vascular sonogram methods. All sonographic measurements were performed by the same clinician. Fetal biometric measurements included biparietal diameter, femur length, and abdominal circumference [11]. The gestational weeks of the participants were determined according to crown-rump length (CRL) and gestational age was not defined by the last menstrual period. Four quadrants of amniotic pocket measurement were utilized during the analysis of amniotic fluid volume [12]. During the obstetric sonography, umbilical artery flow was analyzed distant from the placenta and umbilicus, and umbilical artery pulsatility index values were recorded [13]. Pregnant women's bilateral UtA doppler measurements were performed abdominally from the iliac artery division, and the pulsatility indices were recorded [14]. Maternal bilateral CIMT was measured and recorded when all the obstetric and maternal doppler measurements were performed. CIMT was measured from the common carotid artery, 5 mm proximal to the carotid bifurcation.

All statistical analyses were conducted with SPSS 15.0 for Windows (SPSS, IBM Inc., Chicago, IL, USA). As the sample size analysis, the Cohen effect size was decided using prior studies in the existing literature [15]. For the two-side minimum 90% power hypothesis, 0.05 margin of error, and 0.7 effect size, a minimum of 36 participants were needed for the control and study groups respectively. The conformity of the variables to the normal distribution examined using visual (histogram and probability graphs) and analytical methods (Kolmogorov Smirnov/Shapiro Wilk tests). Descriptive analyzes performed using the mean and standard deviations for normally distributed variables, and median minimum and maximum values for non-normally distributed variables. Since Neutrophil Count, Lymphocyte, neutrophil-lymphocyte ratio (NLR), Blood Urine Nitrogen, Aspartate Aminotransferase and Alanine Aminotransferase variables showed normal distribution, these parameters analyzed using the student t-test. Statistical analyzes of other variables performed using the man Whitney u test, as they did not show normal distribution.

The correlation analysis between the doppler values and other analysis parameters was conducted by the Spearman correlation test. A P-value of 0.05 was thought statistically significant.

Results

The study included 132 pregnant women, 67 in the control group

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and 65 in the GDM group. The demographic characteristics of the groups are presented in Table 1. The participants' age and body mass index were similar to each other (p>0.05). Obstetric history demonstrated statistically significant differences. The participants in the GDM group had higher gravida, parita, and live birth rates in comparison to the control group (p=0.003, 0.002, 0.002 respectively). The amniotic fluid index was found to be higher in the GDM group (p<0.001). The baseline hemogram and biochemical parameters of the groups were compared (Table 2). Among these parameters, fasting glucose values and platelet counts were found to be higher in the GDM group (p=0.031 and p<0.001). The groups indicated no statistically important differences in terms of other laboratory data (p>0.05). Pulsatility indices of the umbilical artery and UtA doppler measurements were compared between the groups (Table 3). There were no significant differences between umbilical artery pulsatility index values (p=0.509). While the right UtA pulsatility index was higher in the GDM group (p<0.001), there was no statistically significant difference between the left UtA pulsatility indices (p=0.485). Maternal CIMT were compared between the groups. Maximum (max), minimum (min), and average (aav) values of the right and left CIMT were higher in the GDM group in comparison to the control group (p=0.001, p<0.001, p<0.001 respectively). Correlation analysis of the Carotid artery measurements with other parameters was performed separately in the control and GDM groups (Table 4 and Table 5). The control group demonstrated no significant correlational relationships between the gestational week and Carotid artery measurements (p>0.05), In the control group, except for left CIMT measurement (p<0.05), all the other glucose levels and right and left CIMT indicated a statistically significant, positive correlation (p>0.05) (Table 4). As for the GDM group, glucose levels indicated a statistically significant, positive correlation only between the right CIMT max and left CIMT min measurements (r=0.269, p=0.030; r= 0.332, p= 0.007 respectively) (Table 5). In the control group, there was no statistically significant correlation between umbilical artery pulsatility index values and CIMT measurements (p>0.05). In the GDM group, there was a statistically significant, positive correlation between the umbilical artery pulsatility index values and left CIMT min and aav measurements (r=0.274, p=0.027; r=0.258, p=0.038 respectively). In the control group, a significant, positive correlation was found between the right UtA pulsatility index and right CIMT max ve aav values (r=0.379, p=0.002; r=0.296, p=0.015 respectively). None of the CIMT measurements of the left UtA pulsatility index indicated a significant correlation relationship in the control group (p>0.05). In the GDM group, significant correlation values were found with both right and left UtA pulsatility values of right CIMT max measurement (r=0.298, p=0.016; r=0.381, p=0.002 respectively). The GDM group demonstrated no significant correlation relationship between other CIMT measurement values and UtA pulsatility indices (p>0.05). Since there was a difference in platelet counts between the groups; Correlation analysis was performed between Doppler findings, CIMT measurements and platelet counts. There was a statistically meaningful, positive correlation between both right UtA and left UtA pulsatility index and platelet count in the GDM group (r=0.336, p=0.006; r=0.397, p=0.044 respectively). Bilateral CIMT measurements and umbilical artery pulsatility index were not significantly correlated with platelet counts in the GDM group (p>0.05). In the control group, none of the doppler measurements and CIMT measurements indicated a significant correlation relationship with the platelet count values (p>0.05).

Table 1. Demographic Characteristics and Fetal Biometrics of the Groups

	Control Group (n=67) (Median. min-max)	Gestational Diabetes Group (n=65) (Median. min-max)	P value
Age (Year)	28.0 (18.0-38.0)	27.0 (22.0-39.00)	0.223
Body Mass Index (kg/m2)	22.5 (20.2-24.00)	21.9 (19.5-24.4)	0.103
Gravida	1.0 (1-3.0)	1.0 (1-4.0)	0.003
Para	0 (0-1.0)	0 (0-2..0)	0.002
Live Pregnancy Count	0 (0-1.0)	0 (0-2.00)	0.002
Abortus	0 (0-1.0)	0.00 (0-1.0)	0.105
Gestational Week (Femur Length)	26.0 (24.0-37.0)	28.0 (24.0-32.0)	0.006
Amniotic Fluid Index	91.0 (55.0-170.0)	125.0 (69.0-202.0)	<0.001
Fetal Heart Rate	89.0 (65.0-108.0)	90.0 (73.0-105.0)	0.398
Maternal Heart Rate	140.0 (120.0-154.0)	135.0 (128.0-151.0)	0.014

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Table 2. Laboratory Results of Groups

	Control Group (n=67) (Mean±Std) (Median. min-max)	Gestational Diabetes Group (n=65)(Mean±Std) (Median. min-max)	P-value
Hemoglobin (g/dl)	11.6 (8.9-14.2)	11.7 (9.1-13.3)	0.412
Platelet Count(109/L)	203.0 (149.0-288.0)	223.0 (155.0-297.00)	0.031
Neutrophil Count (109/L)	4.2±1.1	4.4±1.2	0.410
Lymphocyte (109/L)	1.8±0.2	1.9±0.1	0.114
NLR	2.4±0.8	2.4±0.6	0.774
PLR	115.2 (90-196.3)	110.7 (81.5-174.5)	0.533
Glucose (mg/dl)	78 (65.0-99.0)	89.0 (70.0-117.0)	<0.001
Blood Urine Nitrogen (mg/dl)	15.4±3.4	16.1±2.9	0.858
Creatinine (mg/dl)	0.6 (0.4-0.9)	0.8 (0.4-1.0)	0.101
Aspartate Aminotransferase (U/L)	21.7±6.2	23.3±7.2	0.343
Alanine Aminotransferase (U/L)	25.2±7.8	24.6±6.9	0.758

NLR- Neutrophil-to-lymphocyte ratio; PLR- Platelet-to-lymphocyte ratio

Table 3. Doppler and Carotid Artery Parameters of Groups

	Control Group (n=67) (Median. min-max)	Gestational Diabetes Group (n=65) (Median. min-max)	P value
Umbilical Artery PI	0.81 (0.51-1.49)	0.90 (0.55-1.33)	0.509
Right Uterine Artery PI	0.83 (0.55-1.06)	0.94 (0.61-1.02)	<0.001
Left Uterine Artery PI	0.77 (0.47-1.15)	0.61 (0.51-1.15)	0.485
Right Carotid Artery Max	0.06 (0.03-.0.09)	0.07 (0.02-.0.11)	0.001
Right Carotid Artery Min	0.03 (0.03-.0.30)	0.05 (0.01-.0.62)	<0.001
Right Carotid Artery Aav	0.04 (0.02-.0.06)	0.05 (0.02-.0.58)	<0.001
Left Carotid Artery Max	0.04 (0.01-.0.11)	0.07 (0.03-.0.87)	<0.001
Left Carotid Artery Min	0.02 (0.01-.0.04)	0.03 (0.01-.0.05)	<0.001
Left Carotid Artery Aav	0.02 (0.01-.0.10)	0.05 (0.01-.0.7)	<0.001

PI: Pulsatility index, Min: Minimum, Max: Maximum, Aav: Average Value

Table 4. Correlation analysis of Carotid Artery Diameters with other parameters in Control Group

		RCA max	RCA min	RCA Aav.	LCA max	LCA min	LCA Aav
Gestational Week	p	0.085	0.553	0.369	0.247	0.080	0.304
	r	0.212	0.074	0.111	-0.143	0.215	-0.127
Glucose	p	<0.001	0.021	0.005	0.013	0.025	0.071
	r	0.623**	0.281*	0.338**	0.302*	0.274*	0.222
Umbilical Artery PI	p	0.855	0.736	0.822	0.092	0.208	0.303
	r	-0.023	0.042	-0.028	-0.208	0.156	-0.128
Right Ut.A. PI	p	0.002	0.212	0.015	0.785	0.249	0.644
	r	0.379**	0.154	0.296*	0.034	0.143	0.058
Left Ut.A. PI	p	0.705	0.788	0.319	0.920	0.658	0.207
	r	0.047	-0.033	0.124	0.013	0.055	0.156

Ut. A. PI: Uterine Artery Pulsatility Index, RCA: Right Carotid Artery, LCA: Left Carotid Artery Min: Minimum, Max: Maximum, Aav: Average Value *. Correlation is significant at the 0.05 level **. Correlation is significant at the 0.01 level

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Table 5. Correlation analysis of Carotid Artery Diameters with other parameters in Gestational Diabetes Group

		RCA max	RCA min	RCA Aav.	LCA max	LCA min	LCA Aav
Gestational Week	p	0.978	0.341	0.737	0.041	0.379	0.994
	r	-0.003	0.120	0.043	-0.255*	0.111	-0.001
Glucose	p	0.030	0.379	0.232	0.683	0.007	0.808
	r	0.269*	0.111	0.150	0.052	0.332**	-0.031
Umbilical Artery PI	p	0.489	0.559	0.899	0.066	0.027	0.038
	r	0.087	-0.074	0.016	-0.229	0.274*	0.258*
Right Ut.A. PI	p	0.016	0.663	0.082	0.293	<0.001	0.004
	r	0.298*	0.055	0.217	-0.132	0.444**	0.355**
Left Ut.A. PI	p	0.002	0.299	0.081	0.244	0.242	0.459
	r	0.381**	0.131	0.218	-0.147	0.147	0.093

Ut. A. PI: Uterine Artery Pulsatility Index, RCA: Right Carotid Artery, LCA: Left Carotid Artery Min: Minimum, Max: Maximum, Aav: Average Value*. Correlation is significant at the 0.05 level **. Correlation is significant at the 0.01 level

Discussion

This investigation aims to determine the effects of hyperglycemia at CIMT and doppler flow in patients with GDM. And to evaluate whether there is a difference in CIMT between patients with GDM and other pregnant women. This study compared GDM patients with healthy pregnant women. In the GDM group, the number of pregnancies and amniotic fluid index were higher. In the GDM group, thrombocytosis was significant; there was resistance in unilateral UtA blood flow; and again bilateral CIMT were high. A relationship was found between the resistance increase in UtAs and maternal CIMT, and this positive correlation was more significant in the GDM group.

Hyperglycemia, increased femur length measurement and polyhydramnios determined in the GDM group in this study could be an indicator of poor glycemic control, which is in line with the current literature. There is a vigorous association between GDM and macrosomia; it is observed more significantly in late-diagnosed mothers and pregnant women with poor glycemic control; and the probability of clavicle fractures, femur head fractures, and brachial plexus damage is higher during birth [16]. The relationship between GDM and polyhydramnios was determined, and sonographic assessments showed that fetal biometrics, as well as amniotic fluid measurements, could be used in GDM screening [17,18].

The literature includes doppler studies with GDM, indicating complicated results. This study compared pulsatility indices showing umbilical artery resistance, and no meaningful differences were discovered between the groups (Table 3). A prospective doppler study that was performed to predict GDM patients' perinatal outcomes showed that Middle Cerebral Artery Pulsatility Index could be an indicator; parallel to the current investigation, it found no important differences in umbilical artery values and reported that they cannot be used as an indicator [19]. A case-control study that evaluated early hemodynamic changes in the fetus aged 18-22 weeks old reported a decrease in the Middle Cerebral Artery peak systolic velocity values of the GDM group, and similar to our study, umbilical artery doppler parameters indicated no differences between the groups [20]. In addition to doppler measurements, maternal UtA doppler measurements are used to predict perinatal and maternal outcomes. Our study compared both right and left UtA doppler pulsatility indices between the groups, and a resistance increase was detected in the GDM group. A prospective study that evaluated UtA pulsatility indices values in patients with GDM in the first trimester detected an increase in pulsatility indices values in the group that developed preeclampsia, and no increase was detected in the group that did not develop preeclampsia [21]. None of the patients included in this study had hypertensive or preeclamptic findings, but there was a resistance increase in the UtA doppler of the GDM group. This condition could be an early indicator of trophoblastic invasion disorders of spiral arterioles, inflammatory disorders, and placentation disorders.

While the GDM group in this study had thrombocytosis, no increase was detected in other inflammation markers such as NLR and the platelet-lymphocyte ratio (PLR). Thrombocytosis that developed in GDM patients was reported in another retrospective case-control study, and it was reported that chronic inflammation could play a role in the pathogenesis in this group [22]. This condition could be an early indicator of trophoblastic invasion disorders of spiral arterioles, inflammatory disorders, and placentation disorders.

Previous research showed that GDM patients in the postpartum period encountered type 2 diabetes, metabolic syndrome, hypertension, and cardiovascular diseases [23,24]. This study demonstrated that CIMT, a marker of atherosclerotic and vascular diseases, was increased in the GDM group. Possible inflammation-induced thrombocytosis and increased UtA

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resistance may be associated with cardiovascular risks. A case-control study conducted between the 24th and 28th gestational weeks reported higher CIMT thickness and homocysteine levels in the GDM group in comparison to healthful pregnant women [15]. This finding overlaps with the outcomes of our analysis. The literature reports raised atherosclerosis and cardiovascular diseases in patients with proven systemic inflammation [25,26]. The effects of GDM continue after pregnancy as well.

Women who gave birth after GDM diagnosis had increased pulse wave velocity value in Carotid arteries, namely matrix metalloproteinase 1 levels, markers of resistance, and inflammation [27].

There are some limitations of this study. The first limitation is the limited number of patients included in the study, which is one of the obstacles to the generalization of the results to the population. Another limitation is that the CIMTs of the patients were not measured after delivery. Therefore, it cannot be commented on whether there is a change in the CIMT values of the patients after delivery.

Examining CIMT in pregnant women with GDM may be beneficial in terms of determining atherosclerotic risks. It may contribute to the prevention of future atherosclerotic diseases. In future studies, long-term follow-up of pregnant women with GDM will provide a more clear indication of the increased CIMT and the risk of atherosclerotic disease in these individuals.

Conclusion

This study showed inflammation, resistance in uterine artery flows, and CIMT increase in both groups. We found that CIMT was correlated with glucose levels free of patient diagnosis. We also found a correlation between thrombocytosis, namely inflammation, and UtA resistance in GDM patients. Uterine artery doppler data and CIMT measurements could be used as an indicator of systemic inflammation and cardiovascular disease. Thus, early detection of risk patients can be achieved. Although the evaluation of maternal vascular status seems possible with CIMT and UtA doppler flows, prospective studies with larger participation are needed to evaluate perinatal outcomes.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Amasya University Medical Faculty Ethics Committee (dated 05.12.2019 and decision number: 51).

Patient informed consent :
Consent forms were obtained from all patients included in the study.

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