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Second-trimester Uterine Artery Doppler Parameters but not Triple Test Analytes, May Predict Gestational Diabetes Mellitus

Filiz Yarşılıkal Güleroğlu[1], Murat Ekmez[2], Fırat Ekmez[3], Senem Karacabey[2], Ali Çetin[1]

[1]University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Obstetrics and Gynecology, Division of Perinatology, İstanbul, Turkey
[2]University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Obstetrics and Gynecology, İstanbul, Turkey
[3]Private Clinic, Şırnak, Turkey

ABSTRACT

Introduction: Gestational diabetes mellitus (GDM) presents major health concerns due to its unfavorable impact on pregnancy outcomes and it has no established predictive test. The objective of this research is to determine out the value of triple test analytes and second-trimester uterine artery (UtA) Doppler analysis together in the estimation of GDM.

Methods: In this retrospective study, the clinical data of 87 women with GDM and 723 women with normal glucose tolerance (NGT) were compared. Maternal triple test analytes [human chorionic gonadotropin (hCG), estriol, and alpha-fetoprotein (AFP)] as multiples of the median values and second-trimester UtA Doppler examination for the presence or absence of notching, the left and right UtA pulsatility index (PI), and mean UtA PI was recorded for the NGT and GDM groups.

Results: In terms of maternal serum hCG, estriol, and AFP, the study groups were found as similar. The presence of UtA notching was considerably higher in the women who developed GDM. The mean UtA PI provided good diagnostic accuracy for predicting GDM with an optimal cut-off point of >1,195 with a sensitivity of 66.7% and a specificity of 77.3%. Multivariate logistic regression revealed that the presence of a history of GDM and bilateral UtA notching was found to be a predictor of the development of GDM.

Conclusion: Second-trimester UtA Doppler ultrasonography but not the triple test analytes has a place for predicting GDM in some pregnant populations, especially in women for whom GDM screening cannot be carried out because of the hesitancy of the oral glucose tolerance test.

Keywords: Doppler ultrasonography, gestational diabetes, predictive value of test, prenatal screening, uterine artery

Introduction

Diabetes mellitus (DM) detected after 24 weeks of pregnancy is referred to as gestational diabetes mellitus (GDM), assuming that overt diabetes was excluded before becoming pregnant or at the latter in the early stages of pregnancy (1). GDM affects around 7% of all pregnant women worldwide (2). GDM presents major health concerns due to its unfavorable short-term impact on pregnancy outcomes and its potential long-term implications for mother-baby dyads, including macrosomia, preeclampsia, and type 2 diabetes (3).

It is crucial to estimate the danger of GDM early in pregnancy to allow for initial measures to the prevent adverse outcomes of GDM. Therefore, the most effective means of GDM screening in early pregnancy is still being researched. Numerous models and algorithms have been created and evaluated to screen for disease processes that result in morbidity to develop novel modalities for prediction and screening (4-6). For this purpose, maternal clinical risk factors have historically been used. However, this method is constrained by the fact that these risk variables are often used in a binary manner that results in low sensitivity and specificity values (7). Using a representative model that combined maternal factors including ancestral background history of diabetes, history of GDM, parity, body mass index (BMI), ethnicity, mean arterial pressure, pregnancy-associated plasma protein A (PAPP-A), and uterine artery (UtA) pulsatility index (PI) in the first trimester, prediction of GDM provided a detection rate of 82.7% (8).

The analysis of the proteins human chorionic gonadotropin (hCG), alpha-fetoprotein (AFP), PAPP-A, inhibin-A, and estriol is used in the routine screening for maternal serum aneuploidy between 11 and 20 weeks of gestation (9). As placental function markers, these proteins have been linked to unfavorable pregnancy outcomes such as growth restriction, hypertension, miscarriage, premature delivery, and fetal demise (10).

There is still no consensus among the perinatal experts on the value of Doppler examination for the prediction and regulation of DM in pregnant

Address for Correspondence: Filiz Yarşılıkal Güleroğlu MD, University of Health Sciences Turkey, Haseki Training and Research Hospital, Clinic of Obstetrics and Gynecology, Division of Perinatology, İstanbul, Turkey
Phone: +90 530 968 24 76 **E-mail:** filizyarsilikal@gmail.com **ORCID ID:** orcid.org/0000-0003-4577-3368

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women. Doppler examination, including the UtA, can provide valuable information about the status of fetal development and well-being. It may also help in the selection of the high-risk group of women with DM who need close follow-up and labor (11). In the current literature, there is no reliable data for the usage of UtA Doppler indices in the second-trimester for estimating GDM.

Considering that the assessment of results of the triple test and second-trimester UtA Doppler ultrasonography may be useful in the prediction of GDM, we analyzed their clinical values as well as other obstetric variables.

Methods

Study Population

This retrospective study was conducted after the affirmation of the Ethic Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital (approval number: 116-2022, date: 08.06.2022) in accordance with the current Helsinki Declaration between June 2020 and December 2021 at the Perinatology Service of University of Health Sciences Turkey, Haseki Training and Research Hospital in İstanbul. This study was registered in the ClinicalTrials database (NCT05488197). Study participants were selected consecutively from pregnant women who had a detailed maternal-fetal ultrasound examination at 18-23 weeks of pregnancy, and all participants provided written informed consent. Inclusion criteria were having a maternal age of 18-42 years, a triple test at the 15-20 weeks of pregnancy, a Doppler ultrasound examination of uterine arteries at the 18-23 weeks of pregnancy, and a 75-g, 24-h oral glucose tolerance test (OGTT) at the 24-28 weeks of pregnancy. The exclusion criteria were hypertensive disorders of pregnancy, pregestational diabetes, placental and amniotic fluid abnormalities, family history of DM, fetal growth restriction, fetal congenital malformations, severe systemic disease, and multiple pregnancies.

GDM was identified during prenatal treatment when at least one of the three 75-g, 24-h OGTT threshold values met or exceeded in pregnant women who had performed the test: Fasting 92 mg/dL, 24-h 180 mg/dL, or 24-h 153 mg/dL at 24-28 weeks of gestation (12). Consequently, 810 pregnant women were evaluated as participants in the study and splitter with the following two groups in accordance with their diabetic statuses: pregnant women with normal glucose tolerance (NGT) as NGT group (n=723) and pregnant women with GDM as the GDM group (n=87).

Study Parameters

Maternal obstetric characteristics, ethnicity, pre-pregnancy BMI, gestational age at examination (week), the localization of the placenta on ultrasound (anterior, posterior, left side, right side), mode of delivery, gestational age at delivery (week), newborn birthweight, and fetal gender were reviewed retrospectively using electronic medical records.

Maternal serum glycated hemoglobin A1c (HbA1c) value and second-trimester triple test analytes (hCG, estriol, and AFP) as multiples of the median (MoM) values were also recorded. Additionally, from the records of detailed maternal-fetal ultrasound examination at the 18-23 weeks of pregnancy, Doppler ultrasound parameters of the uterine arteries were collected. All the ultrasound examinations had were performed using a high-definition ultrasonography machine with a 2.0-7.0 MHz convex probe by a professional perinatologist (FYG). Color Doppler was used to illustrate where the UtA crossed both external iliac arteries in the parauterine region of the lower uterine segment. Pulsed-wave Doppler was employed to obtain UtA waveforms at 30° insonation and 60 cm/s peak systolic velocity. Each side captured three identical waveforms consecutively. In addition to recording the presence or absence of notching, the left and right UtA PI values were obtained, and the mean UtA PI was calculated (13).

Statistical Analysis

The IBM SPSS v25 for Windows (IBM SPSS, Armonk, NY, USA) was used to conduct the descriptive and analytic evaluation of research parameters. The numerical variables as median with minimum and maximum, mean with standard deviation, or number with percentage were listed as accommodately. By analyzing the mundaneness of numerical variables using the Kolmogorov-Smirnov test, t and Mann-Whitney tests were used for their comparisons as appropriate. The chi-square test was performed to determine whether categorical data were significant. Initially, univariate logistic regression models were employed to determine the affiliation between the presence of GDM and each potential variable, including maternal age, gravidity, history of GDM, pre-pregnancy BMI, presence of male gender, birth weight, HBA1c, triple test analytes including hCG, estriol, and AFP, UtA notching (unilateral and bilateral), and UtA mean PI individually. A receiver-operating characteristic (ROC) curve was plotted with MedCalc version 15.0 for Windows (MedCalc Software, Ostend, Belgium) to evaluate the diagnostic performance of the mean UtA PI in GDM prediction. The determinants that were remarkable at the $p<0.10$ level in the univariate model were involved in the multivariate logistic regression model to identify factors independently associated with the existence of GDM. The regression coefficients and confidence intervals at 95% for the identified parameters substantially linked with GDM were calculated. If the p-value was lower than 0.05, the statistical results were significant.

Results

Table 1 presents the outline and clinical parameters for the NGT and GDM groups. In comparison to the NGT group, the GDM group's ratio of obstetric history was considerably higher ($p<0.05$). The median values of gestational age at delivery and neonatal birthweight were considerably higher in the NGT group compared with the GDM group [39 (28-41) vs 38 (31-41), respectively; $p<0.05$ and 3,230 (1,578-4,300) vs 2,980 (1,230-4,460), respectively; $p<0.05$]. Regarding the median values of gravidity, parity, maternal age, gestational age at examination, and pre-pregnancy BMI, no important distinction was found among the study groups. The rates of smoking status, ethnicity, types of conception and delivery, localization of the placenta on ultrasound, and male newborns were found to be similar among the study groups ($p>0.05$).

The maternal laboratory and ultrasonographic findings for the NGT and GDM groups are displayed in Table 2. In comparison to the NGT group, the HbA1c mean value was considerably greater in the GDM group ($p<0.05$). The mean values of hCG, estriol, and AFP did not significantly

Table 1. The selected baseline and clinical parameters of the NGT and GDM groups

	NGT (n=723)	GDM (n=87)	p-value
Maternal age (years)	29 (18-42)	30 (19-42)	0.055
Gravidity	2 (1-10)	2 (1-8)	0.312
Parity	1 (0-9)	1 (0-5)	0.511
Ethnicity, n (%)			
Native	706 (97.6%)	86 (98.9%)	0.516
Emigrant	17 (2.4%)	1 (1.1%)	
History of GDM, n (%)			
Yes	7 (1%)	8 (9.2%)	0.001
No	716 (99%)	79 (90.8%)	
Smoking, n (%)			
Yes	7 (1%)	2 (2.3%)	0.263
No	716 (99%)	85 (97.7%)	
Natural pregnancy, n (%)			
No	19 (2.6%)	0 (0%)	-
Yes	704 (97.4%)	87 (100%)	
Pre-pregnancy BMI (kg/m^2)	26.5 (17.6-41.4)	26.4 (20-35.8)	0.821
Gestational age at examination (weeks)	21 (18-23)	21 (18-23)	0.787
Placental localization			
Anterior	372 (51.5%)	48 (55.2%)	0.098
Posterior	334 (46.2%)	35 (40.2%)	
Left side	7 (1%)	0	
Right side	10 (1.4%)	4 (4.6%)	
Mode of delivery, n (%)			
No delivery	258 (35.6%)	32 (36.7%)	0.652
Vaginal	216 (29.9%)	22 (25.3%)	
Cesarean	249 (34.4%)	33 (37.9%)	
Gestational age at delivery (weeks)	39 (28-41)	38 (31-41)	0.002
Birthweight (g)	3,230 (1,578-4,300)	2,980 (1,230-4,460)	0.043
Fetal gender, n (%)			
Female	353 (48.8%)	43(49.4%)	0.706
Male	370 (51.2%)	44 (51.2%)	

NGT: Normal glucose tolerance, GDM: Gestational diabetes, BMI: Body mass index. A median with minimum and maximum values or counts with percentages were used to present the data

differ among the NGT and GDM groups ($p>0.05$). The ratios of the presence of unilateral and bilateral UtA notching were dramatically higher in the GDM group compared with the NGT group (35.6% vs 13.6%, respectively; $p<0.05$ and 27.6% vs 2.9%, respectively; $p<0.05$). The median value of mean UtA PI was significantly higher in the GDM group compared with the NGT group [1.3 (0.7-2.3) vs 1.0 (0.6-2.3), respectively; $p<0.05$]. The ROC curve analysis indicated that the mean UtA PI had good diagnostic accuracy for GDM (area under the curve=0.75, 95% confidence interval=0.721-0.782, $p<0.05$), with an optimal cut-off point of >1.195, resulting in a sensitivity of 66.7% and a specificity of 77.3% (Figure 1).

To further investigate potential GDM risk variables, univariate and multivariate logistic regression analyses were performed (Table 3). Univariate logistic regression analysis demonstrated that the selected parameters were related to GDM, including maternal age, history of GDM, HbA1c, UtA notching (unilateral and bilateral), and mean UtA PI ($p<0.05$). Furthermore, after regulating for all variables, multiple regression analyses of the examined parameters revealed a meaningful correlation, and among them, only a history of GDM and bilateral UtA notching provided meaningful associations with GDM. Consequently, the main study parameters, including mean UtA PI and triple test analytes, were not found among the independent predictors of GDM.

Discussion

In this study, the values of triple test analytes including hCG, estriol, and AFP, and second-trimester UtA Doppler ultrasonographic parameters including mean UtA PI and notching, were assessed to determine whether they could be used to predict the development of GDM. The baseline clinical determinants of the NGT and GDM groups were considerably similar, but the delivery of gestational age and neonatal

Table 2. Laboratory and ultrasonographic findings of the NGT and GDM groups

	NGT (n=723)	GDM (n=87)	p-value
HbA1c (%)	5.1±0.38	5.3±0.45	0.016
hCG (MoM)	1±0.5	0.9±0.5	0.482
Estriol (MoM)	0.9±0.4	0.9±0.4	0.889
AFP (MoM)	1.1±0.4	1.2±0.6	0.615
UtA notching			
No	604 (83.5%)	32 (36.8%)	0.001
Unilateral	98 (13.6%)	31 (35.6%)	
Bilateral	21 (2.9%)	24 (27.6%)	
Mean UtA PI	1.0 (0.6-2.3)	1.3 (0.7-2.3)	0.001

NGT: Normal glucose tolerance, GDM: Gestational diabetes mellitus, AFP: Alpha-fetoprotein, MoM: Multiples of the median, UtA: Uterine artery, PI: Pulsatility index. Data are shown as counts with percentages, median with minimum and maximum values, and mean with standard deviation

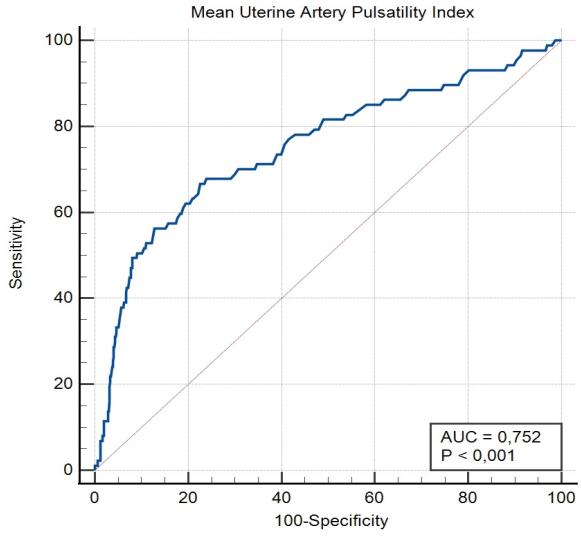

Figure 1. The ROC curve for the accuracy of the gestational diabetes mellitus (GDM) in participants. The overall predictive accuracy of the mean uterine artery pulsatility index for GDM was 0.75 (95% CI: 0.721-0.782, p<0.05), and the sensitivity and specificity were 66.7% and 77.3%, respectively

ROC: Receiver-operating characteristic, CI: Confidence interval

birthweight were higher in the NGT group. We thought that this might be regarding the close follow-up of pregnant women with GDM and their delivery before completing 39 weeks of gestation. The presence of UtA notching and serum HbA1c was considerably higher in the women who got GDM. In terms of maternal serum hCG, estriol, and AFP, the women who developed GDM have similarities with women who did not develop GDM. The mean UtA PI was higher in the women who developed GDM. Additionally, ROC curve analysis revealed that the mean UtA PI provided meaningful diagnostic accuracy for predicting GDM with an optimal cut-off point of >1,195 with a sensibility of 66.7% and a specificity of 77.3%. Univariate and multivariate logistic regression analyses showed that only clinical parameters including, the presence of a history of GDM and bilateral UtA notching, were found as a predictors of development of GDM but not our study parameters as a whole.

There have been concerns raised about screening for GDM after the 24th gestational week and diagnosing GDM in the last weeks of the second trimester due to the potential delay in achieving the favorable impact of pharmacological therapy, diet, and exercise on fetal development and maternal complications (14). Predicting gestational diabetes early allows for possible action to lower the risk of negative effects for the mother and fetus, since it may provide more time for measures that can reduce both GDM and its associated morbidities if patients at risk for GDM are identified early in the gestation among low-risk pregnancies. The diagnosis of GDM is frequently performed using OGTT techniques. However, these procedures may be more time-consuming, uncomfortable, and expensive in some populations. As a result, current investigations have focused on alternative predictive procedures.

In a recent study, Zhang et al. (15) performed a study on the estimation of GDM in the first-trimester. Maternal age, parity, BMI, serum lipid profile, blood pressure, and inflammatory parameters were evaluated as predictive factors. They found that women older than 35 and those with abnormal triglyceride values had 5.5% and 2.1 times, respectively, higher risk for GDM development. Zheng et al. (16) developed a model unifying maternal age, BMI, fasting blood glucose, and triglyceride levels between 8 and 20 weeks of pregnancy to foresee the risk of GDM. They concluded that their prediction model had a considerably good predictive value.

Several studies were performed in the first and early second trimesters to predict GDM by biomarkers such as fetuin-A, high-sensitivity C-reactive protein (17), adiponectin (18), sex hormone -binding globulin (19), placental protein 13, pentraxin 3, soluble fms-like tyrosine kinase-1, myostatin, and follistatin (20). All these studies concluded that developing prediction models to aid in the development of highly sensitive and specific testing should be the focus of future research in the first and early second trimesters.

To predict the likelihood of GDM in nulliparous women early in pregnancy, Snyder et al. (21) assessed the clinical efficacy of first and second-trimester prenatal screening biomarkers. GDM was related to lower first-trimester PAPP-A levels and higher second-trimester estriol and inhibin-A levels. The researchers concluded that PAPP-A, estriol, and inhibin-A had limited clinical usefulness for predicting the risk of GDM in nulliparous women. Sperling et al. (9) similarly used second-trimester maternal serum analytes to predict GDM. They found that rising levels of maternal AFP, hCG, and estriol in the second trimester were linked

Table 3. Logistic regression analysis of selected factors associated with the presence of GDM

	Univariate				Multivariate			
	p-value	OR	95% CI		p-value	OR	95% CI	
Maternal age (years)	0.048	1.04	1.00	1.09	0.885	1.01	0.94	1.08
Gravidity	0.244	1.09	0.94	1.26	-	-	-	-
History of GDM	<0.001	11.80	4.28	32.57	0.004	12.00	2.26	63.58
Pre-pregnancy BMI (kg/m^2)	0.742	0.98	0.87	1.11	-	-	-	-
Fetal gender, male	0.916	0.98	0.63	1.52	-	-	-	-
Birthweight (g)	0.129	1.00	1.00	1.00	-	-	-	-
HbA1c (%)	0.019	2.92	1.20	7.14	0.076	2.54	0.91	7.10
hCG (MoM)	0.474	0.56	0.12	2.71	-	-	-	-
Estriol (MoM)	0.886	0.87	0.14	5.50	-	-	-	-
AFP (MoM)	0.607	1.52	0.31	7.50	-	-	-	-
UtA notching	<0.001	-	-	-	0.004	-	-	-
Unilateral	<0.001	5.97	3.49	10.23	0.473	1.54	0.48	4.94
Bilateral	<0.001	21.57	10.87	42.80	0.011	5.70	1.48	21.98
Mean UtA PI	<0.001	20.29	9.70	42.48	0.077	4.67	0.84	25.86

GDM: Gestational diabetes mellitus, BMI: Body mass index, HbA1c: Glycated hemoglobin A1c, AFP: Alpha-fetoprotein, MoM: Multiples of the median, UtA: Uterine artery, PI: Pulsatility index, CI: Confidence interval, OR: Odds ratio

with a lower risk of GDM. However, they did not significantly improve the predictive model when combined with the clinical risk factors of age, BMI, and race. In contrast to these investigations, we were unable to detect a significant difference in the second-trimester serum analytes of women who would later develop GDM or not.

Overall, the results of the aforementioned studies focused on the clinical and laboratory parameters that were obtained during routine clinical care but that were not directly related to the development of GDM. Their predictive performance was found to be moderately adequate for routine clinical care. This subject seems to require studies examining the clinical parameters providing higher success rates for GDM prediction. Within this perspective, the current study examined for the first time the combination of parameters of second-trimester triple test analytes and second-trimester UtA PI.

Doppler ultrasonography, including UtA in the first (22) and second trimesters (23), is commonly used to predict unfavorable pregnancy outcomes such as premature birth, preeclampsia, and intrauterine growth restriction. Previously, researchers noted that in pregnant women with current or previous GDM, the findings of arterial stiffness and endothelial dysfunction were found to have increased (24,25). We thought that this condition may contribute to the clinical presentation of GDM earlier than its overt appearance in pregnant women who are candidates for developing GDM. In a study that involved the first trimester of pregnancy, Savvidou et al. (25) found that while there was no statistically significant difference in UtA PI MoM among women with and without GDM, there was an increased UtA PI in women with GDM who developed pre-eclampsia. Kim et al. (26) performed research to determine the relationship between maternal obesity and the UtA PI in the third trimester, as well as to predict the value of the UtA PI for the occurrence of adverse outcomes. They showed that obese women with increased UtA PI had an increased risk of GDM occurrence. The current study, however, was distinctive in that it examined the impact of mean UtA PI on the estimation of GDM in the second trimester. Our findings revealed that higher mean UtA PI values were linked to a higher risk of GDM.

Study Limitations

As a limitation of this study, no inclusion of placental laterality in the grouping of women with NGT and GDM can be considered a confounding factor that can reduce the value of the results of UtA PI measurements. Nevertheless, the fact that the comparison of the rate of placental localization type provided no difference between the women with or without GDM supports no meaningful influence of placental localization on the UtA PI values. UtA notching has a relationship with the development of pre-eclampsia, and this study had an exclusion criterium of hypertensive diseases of pregnancy. In further studies, with the inclusion of pregnant women with hypertensive diseases of pregnancy, the value of early second-trimester Doppler analysis for predicting development of GDM can be clarified.

Conclusion

In conclusion, our findings support the importance of second-trimester UtA Doppler ultrasonography but not the triple test analytes for predicting GDM. The UtA Doppler analysis may be an important contributor to the protocol of perinatal follow-up in women in whom GDM screening cannot be carried out because of the hesitancy of mothers about OGTT. addition, although there are first-trimester candidate parameters for predicting GDM, in some antenatal care settings, clinicians cannot have predictors obtained by early tests.

Ethics Committee Approval: This retrospective study was conducted after the affirmation of the Ethic Committee of University of Health Sciences Turkey, Haseki Training and Research Hospital (approval number: 116-2022, date: 08.06.2022).

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