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75-g oral glucose tolerance testing does not affect fetal cardiac doppler parameters in low-risk pregnant women

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Abstract

The study aimed to examine whether acute hyperglycemia, caused by the 75-g oral glucose tolerance test (OGTT) can produce fetal cardiac adverse effects that are detectable with fetal cardiac Doppler ultrasound in healthy low-risk pregnancies. Healthy low-risk pregnant women who underwent 75-g OGTT during the gestational period of 24 to 28 weeks were considered eligible and during the test, they were examined with fetal ultrasound at the fasting and 1- and 2-h timepoints. The study findings included the parameters of umbilical artery pulsatility index, uterine artery, fetal heart rate, middle cerebral artery (MCA) peak systolic velocity (MCA-PSV), MCA pulsatility index, and fetal cardiac Doppler parameters including myocardial performance index, left isovolumetric contraction and relaxation times, K-index, filling time, mitral E- and A-wave velocities, and E/A ratio. The data of 53 women without gestational diabetes mellitus were used for statistical analyses. There was no statistical significance among the three-time points of OGTT regarding all the Doppler parameters ($p>0.05$). The median MCA-PSV measured at the fasting of OGTT was significantly higher than the values measured at the first and second hour of OGTT [28 (22-42) vs. 26 (18-39) and 26 (18-38), respectively; $p<0.05$]. This increase provided no relationship with other study parameters ($p>0.05$). Overall, 75-g OGTT does not affect fetal cardiac Doppler parameters in healthy pregnant women except for abnormal findings of MCA-PSV. The results of the current study can provide significant support to clinicians in reducing the hesitations of women with low-risk pregnancies regarding gestational diabetes screening.

Keywords: Diabetes mellitus, fetal cardiac function, fetal doppler ultrasound, gestational diabetes mellitus, myocardial performance index, oral glucose tolerance test

Introduction

During antenatal care, gestational diabetes mellitus (GDM) as a special type of diabetes has an increasing prevalence in the world and emerges as impaired glucose intolerance only in the second half of pregnancy. Among the screening methods developed specifically for GDM, the oral glucose tolerance test (OGTT) including 75-g oral glucose load is more widely used [1].

Doppler ultrasonographic applications are non-invasive, reliable, and useful tools for assessing fetal well-being. It is a non-invasive technique for measuring blood flow that detects frequency changes in reflected sound. It has been used in obstetrics since 1977 to study fetoplacental circulation [2,3].

The waveforms of umbilical cord and fetal cerebral arteries are affected by maternal glucose challenge in an OGTT [4,5]. As a result, different fetal well-being test results affect clinical decisions in pregnancies complicated by fetal growth restriction (FGR).

High maternal glucose levels during pregnancy are linked to fetal hyperinsulinemia, which causes structural and functional changes in the cardiovascular system [6]. OGTT results in a temporary rise in maternal blood sugar levels, leading to a brief episode of hyperglycemia. This sudden increase in blood sugar triggers the expansion of blood vessels in the endothelium, boosts insulin production, and reduces the levels of epinephrine and norepinephrine in the body [7].

CITATION
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Fetal hyperinsulinemia leads to an augmentation in the synthesis of proteins, fats, and glycogen within the myocardium, which in turn induces hyperplasia and hypertrophy of myocardial cells. These processes also influence the interventricular septum [6,8]. The myocardial performance index (MPI) is a valuable measurement within the fetal cardiac Doppler context, evaluating the comprehensive functioning of the cardiac muscle during systolic and diastolic activities [9-11]. The fetal MPI offers a dependable assessment of fetal cardiac function and has the capability to anticipate unfavorable perinatal outcomes in pregnancies with heightened risk [12,13]. Elevated fetal MPI, indicating potential fetal cardiac impairment, has been recorded in certain studies involving complicated pregnancies [9,11,14-16].

Based on the observed prolongation of isovolumetric contraction time (IVCT) in women with systolic failure, as well as isovolumetric relaxation time (IVRT) in both systolic and relaxation abnormalities, Tei et al. [17] concluded that systolic failure is correlated with an increase in both IVCT and IVRT. The MPI is calculated by dividing the total of IVCT and IVRT by the ejection time (ET). This integrates both cardiac systolic and relaxation functions without relying on geometric assumptions and provides a convenient measure of overall cardiac function. In instances of abnormal cardiac function, isovolumetric time becomes prolonged and end-tidal volume decreases, leading to an elevation in MPI [17].

High blood glucose levels and inadequate glucose regulation play a substantial role in the processes that lead to fetal demise among diabetic mothers [18]. Nevertheless, it's essential to acknowledge the potential involvement of other factors in stillbirth cases, and investigations into fetal death among diabetic mothers, which comprehensively assess the reasons behind fetal demise, suggest that unmanaged hyperglycemia could be a contributing factor in roughly 50% of such occurrences [19].

Many articles have been published on the effect of OGTT on fetal Doppler findings [20-23]. None of them interpreted the effect of acute hyperglycemia on fetal cardiac parameters in low-risk settings. Although there is research data suggesting harmful effects on the fetal heart due to elevated blood glucose in diabetic pregnancies, there is no clinical information on fetal cardiac adverse effects due to OGTT. In this regard, clarifying whether there may be fetal cardiac adverse effects due to OGTT may reduce the hesitation experienced by patients in clinical practice. The objective of this research was to seek the impact of acute increase in blood glucose induced by the 75-g OGTT on functional alterations in the fetal heart among healthy low risk pregnancies.

Material and Methods

In this cross-sectional investigation, the participants were 102 pregnant women who experienced a 75-g OGTT during the gestational period of 24 to 28 weeks. This study took place at a tertiary hospital's maternal-fetal center in the year 2023. Before starting this study, the approval was obtained from the Human Research Ethics Committee of Haseki Training and Research Hospital (Dated: August 09, 2023 and Registered: 107-2023), and every participant gave their explicit written consent to take part in the study.

As stated in the ACOG practice bulletin [24] regarding gestational diabetes, the population at low risk was identified. Healthy pregnant women with normal singleton pregnancies were included. The gestational age based on the last menstrual period was used during antenatal care. Pregnant women with a history of GDM or macrosomia, systemic diseases, GDM diagnosed by OGTT during the current pregnancy, multiple pregnancies, pregnancies with a diagnosed or suspected fetal anomaly, FGR, polyhydramnios, and oligohydramnios were excluded. Selected clinical variables including maternal age, gravidity, parity, gestational age, weight, and height were recorded.

In accordance with the recent international guideline and cut-off values of blood glucose [7], every participant received a 75-gram oral glucose dose following an overnight fast, and their fasting blood glucose levels were assessed, along with measurements taken at the 1- and 2-h timepoint and they were coded as OGTT0 for blood glucose at fasting timepoint, OGTT1 for blood glucose at the 1-h timepoint, and OGTT2 for blood glucose at the 2-h timepoint during presentation of findings. The cutoff values for the 75-g OGTT at the three timepoints were as follows, in sequence: >92 mg/dL, >180 mg/dL, and 153 mg/dL.

An experienced perinatologist (A.Ö.) conducted all ultrasound scans to gather fetal size measurements and Doppler assessments. Doppler assessments were taken when fetal body or breathing motions were absent. Additionally, the angle of ultrasound beam was maintained below 20 degrees. As per the ISUOG practice guideline, measurements of standard fetal biometry including biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC), femur length (FL), and estimated fetal weight (EFW); assessment of amniotic fluid quantity; and Doppler assessments including cardiac parameters were carried out [25]. At the outset, the initial assessment took place in the morning after a fasting period of 12 hours. The participants were then given the 75 g of glucose orally, and the ultrasound examination was repeated after 1- and 2-h timepoints of OGTT. Firstly, fetal cardiac Doppler parameters were measured, then the peak systolic velocity (PSV) and pulsatility index (PI) obtained using the color Doppler view of middle cerebral artery (MCA) as well as PI of umbilical and uterine arteries were measured at each timepoint.

Regarding the left MPI, the Doppler sampling gate was positioned in the left ventricle as seen in the apical 4-chamber view, enabling the simultaneous visualization of both the aortic and mitral valves (Figure 1).

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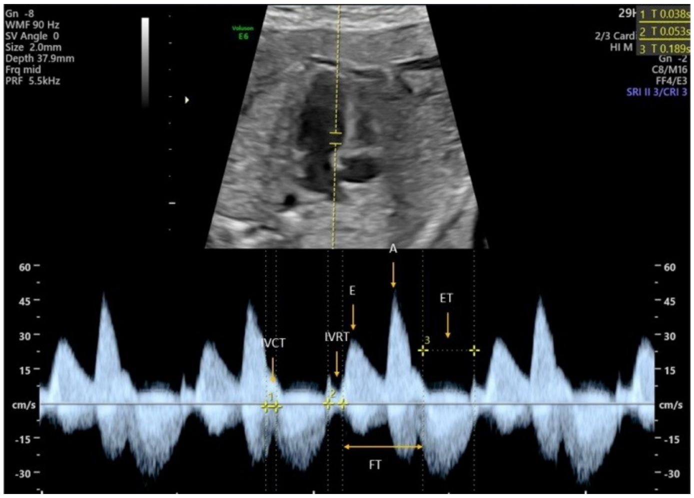

Figure 1. A representative image indicating measurements of myocardial performance index, IVCT: isovolumetric contraction time, IVRT: isovolumetric relaxation time. FT: filling time, E: mitral E wave velocity, A: mitral A wave velocity, ET: ejection time

Simultaneously, the inflow and outflow waveforms of the left ventricle were obtained. In addition, mitral E- and A-waves were identified, and their peak velocities, as well as their ratio (left E/A), were determined. For the left MPI calculation, three time intervals were measured: the left IVCT, IVRT, and ET [17]. Utilizing the left ventricular filling time for evaluating cardiac performance is of utmost importance. Drawing from this principle, Ahsan et al. [26] introduced a novel index for measuring the MPI as the K-index (KI) that is computed by dividing the combined IVRT and IVCT by the ventricular filling time (FT). The KI exhibits a strong correlation with the rise in placental blood flow, making the evaluation of MPI based on FT instead of ET more clinically meaningful. KI represents a subtype of MPI developed by Ahsan et al., with a primary focus on assessing the relaxation function of the left ventricle [26].

The following parameters were considered to calculate the sample size of study: Cohen's F effect size to be 0.20, established a type I error rate of 0.05, set a prior power level of 0.85, assumed a correlation of 0.5 among the repeated measurements, and applied a non-sphericity correction factor of 1. Based on these parameters, the minimum necessary participant count for the study design was computed as 48 individuals. Accounting for a potential dropout rate of 10%, the final accepted sample size was determined to be 53 participants.

Statistical analysis

Analyses were performed by using IBM SPSS v22.0 for Windows (USA). For descriptive statistics, the values of mean with standard deviation (SD) and median with range or 25-75% interquartile range (IQR) were used to present numeric data. After Kolmogorov-Smirnov test to examine the normality of clinical and Doppler ultrasound parameters, the comparisons of timepoints of OGTT were performed. To analyze the Doppler ultrasound variables that were measured three times in the women undergone OGTT, the repeated measures Friedman ANOVA with post hoc Mann-Whitney test was performed. To determine significances, a p value of less than 0.05 was chosen.

Results

Pregnant women who attended maternal-fetal clinic of the hospital and underwent a 75-g OGTT were enrolled. In all of the 102 eligible pregnant women, the 75-g OGTT was completed, however, data analysis was conducted on a total of 53 subjects for whom all ultrasound parameters could be measured, and who were not diagnosed with gestational diabetes mellitus (GDM). Out of the remaining 49 subjects, they were excluded either due to incomplete fetal ultrasound examination or the diagnosis of GDM.

As presented in the Table 1, the baseline clinical characteristics of the subjects were as follows. The mean (SD) values for maternal age were 29.9 (6) years, body mass index was 28.3 (4.3), OGTT0 was 80 (6.3) mg/dL, OGTT1 was 147 (20.3) mg/dL, and OGTT2 was 115 (15.5) mg/dL. The median (IQR) values for gravidity were 2 (2-3), parity was 1 (0-2), gestational age was 26 (25-27) weeks, BPD was 25 (25-26.5) weeks, HC was 25 (24-27) weeks, AC was 25 (24-27) weeks, FL was 25 (24-26) weeks, and EFW was 810 (750-965) g.

Table 1. Baseline clinical characteristic of the study population.

	Mean (SD)	Median with IQR
Maternal age (years)	29.9 (6)	
Gravidity		2 (2-3)
Parity		1 (0-2)
Gestational age (weeks)		26 (25-27)
BMI	28.3 (4.3)	
BPD		25 (25-26,5)
HC		25 (24-27)
AC		25 (24-27)
FL		25 (24-26)
EFW (g)		810 (750-965)
OGTT0 (mg/dL)	80 (6.3)	
OGTT1 (mg/dL)	147 (20.3)	
OGTT2 (mg/dL)	115 (15.5)	

BMI: body mass index, SD: standard deviation, IQR: interquartile range, BPD: biparietal diameter, HC: head circumference, AC: abdominal circumference, FL: femur length, EFW: estimated fetal weight
For 75-g oral glucose tolerance test, OGTT0, OGTT1, and OGTT2 are the fasting and first and second hours of OGTT

Figure 2 shows the violin graphs of PI of umbilical artery, mean PI of uterine arteries, and MCA PI, and MCA-PSV. There were no significant differences of umbilical artery PI, mean uterine artery PI, and MCA PI measured at the fasting and 1- and 2-h timepoints of OGTT (p>0.05). However, the MCA-PSV value measured at the fasting timepoint of OGTT was significantly higher than those measured at the 1- and 2-h timepoints of

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OGTT (p<0.05). No significant difference was detected between the MCA-PSV values measured at the 1- and 2-h timepoints of OGTT (p>0.05).

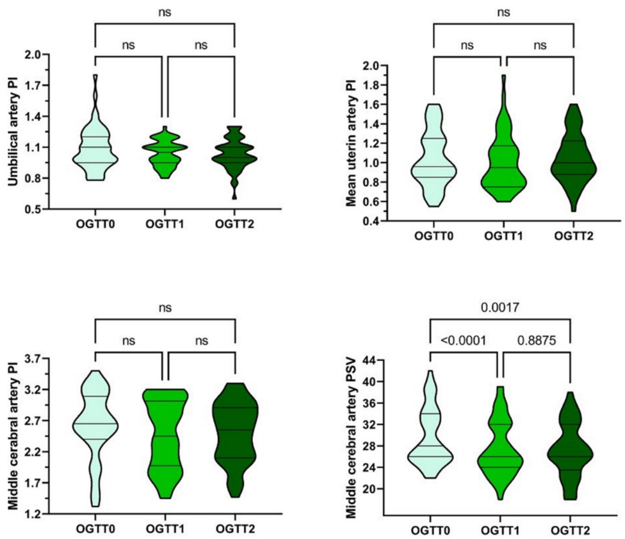

Figure 2. Violin graphs of Doppler values of umbilical artery pulsatility index (PI), mean uterine artery PI, middle cerebral artery PI, and middle cerebral artery peak systolic velocity (PSV). Data were presented as median with 25-75% interquartile range. Statistical significances were presented on the graphs. ns, no significance (p>0.05). OGTT0, OGTT1, and OGTT2 are the fasting and first and second hours of OGTT

Figure 3 presents the violin graphs of Doppler values of mitral E and A wave velocities, ratio of mitral E/A, and fetal heart rate. There were no significant differences in the Doppler values of mitral E and A wave velocities, the ratio of mitral E/A, and the fetal heart rate measured at the fasting and 1- and 2-h timepoints of OGTT (p>0.05).

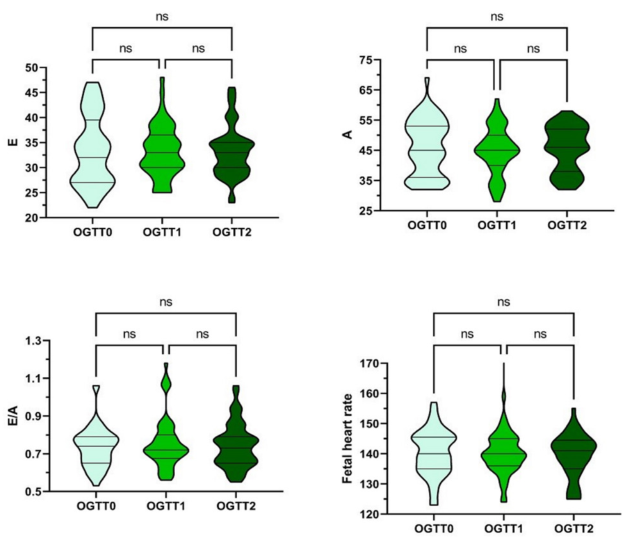

Figure 3. Violin graphs of Doppler values of mitral E and A wave velocities, ratio of mitral E/A, and fetal heart rate. Data were presented as median with 25-75% interquartile range. Statistical significances were presented on the graphs. ns, no significance (p>0.05). OGTT0, OGTT1, and OGTT2 are the fasting and first and second hours of OGTT. E: mitral E wave velocity (cm/sec), A: mitral A wave velocity (cm/sec), E/A: mitral E/A ratio

Figure 4 depicts the violin graphs of Doppler values of IVCT, IVRT, ET, and FT. There was no significantly difference in these parameters measured at the fasting, and 1-, and 2-h timepoints of OGTT (p>0.05).

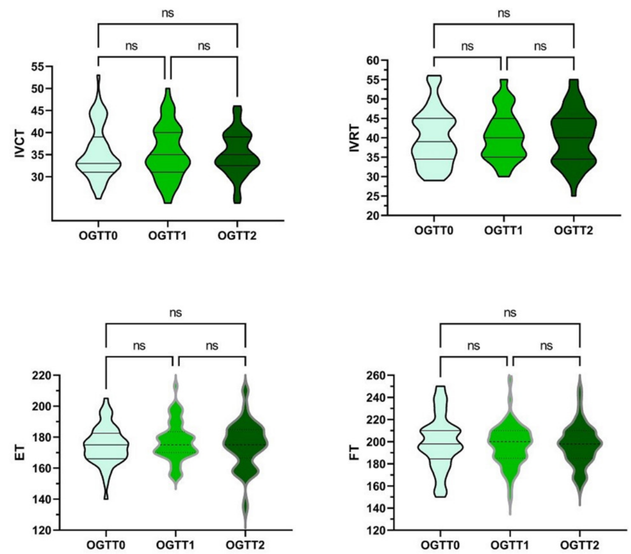

Figure 4. Violin graphs of Doppler values of IVCT, IVRT, ET and FT. Data were presented as median with 25-75% interquartile range. Statistical significances were presented on the graphs. ns, no significance (p>0.05). OGTT0, OGTT1, and OGTT2 are the fasting and first and second hours of OGTT

Figure 5 presents the violin graphs of Doppler values of MPI, and KI. The MPI and KI values measured at the fasting and 1- and 2-h timepoints of OGTT were found comparable (p>0.05).

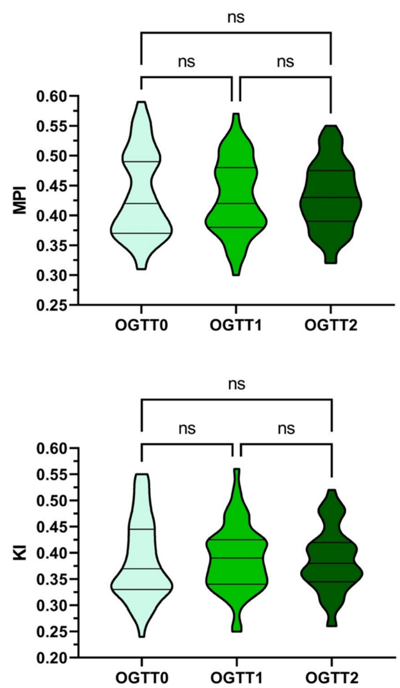

Figure 5. Violin graphs of Doppler values of MPI, and KI. Data were presented as median with 25-75% interquartile range. Statistical significances were presented on the graphs. ns, no significance (p>0.05). OGTT0, OGTT1, and OGTT2 are the fasting and first and second hours of OGTT

Discussion

This study seeking fetal cardiac functional changes in patients who underwent 75-g OGTT during the gestational period of 24 to 28 weeks and who were in low-risk population demonstrated that the test did not have a negative impact with its acute hyperglycemia effect on fetal cardiac parameters as measured by Doppler examination. Although the MCA-PSV value measured in the fasting OGTT was significantly higher than the values measured in the 1 h and 2 h OGTT, no significant difference was found between the MCA-PSV values measured in the 1st and 2nd hour of OGTT. Considering that the other parameters measured were similar, overall, these significant differences were not considered to have a clinically important meaning.

Doppler ultrasonography has been regarded as a highly valuable technique for exploring the status of fetal health abnormalities like FGR or anemia. However, its effectiveness when considering other pregnancy complications remains a topic of discussion. It is widely acknowledged that external factors can impact fetal blood circulation, potentially leading to changes in blood flow patterns. Patrick et al. provided evidence indicating that heightened fetal breathing time subsequent to maternal meals could be attributed to elevated maternal glucose levels [27].

Diabetes leads to pathophysiological alterations within the placental vascular system that are primarily functional in nature, differing from the structural changes seen in cases of FGR. Elevated blood glucose levels can lead to an imbalance between thromboxane and prostacyclin, potentially resulting in increased placental vascular resistance among individuals with GDM [28]. Consequently, the atypical Doppler waveforms observed in the umbilical artery and MCA in cases of FGR might not manifest. Additionally, hyperglycemia in pregnancies complicated by GDM can lead to sudden fetal acidosis and even fetal demise. Regrettably, routine assessments of fetal well-being, like the non-stress test or biophysical profile, may not be able to identify this abrupt outcome [1]. Considering the findings of this study, although chronic hyperglycemia may cause sudden unexplained fetal deaths, it can be said that acute hyperglycemia during OGTT does not significantly impair fetal cardiac functions in healthy pregnancies and may not cause sudden fetal deaths.

Certain researchers noted a notable reduction in MCA PI subsequent to the administration of OGTT, while contrasting findings from other studies indicated the absence of significant disparities. Furthermore, these studies revealed that UA values remained unaltered in relation to fetal weight [5,20,22,23]. This study found that only the MCA-PSV value reduced significantly among all the studied Doppler parameters.

The study's limitations include the lack of analysis of pregnancy outcomes and the relatively small number of cases. Due to the importance of fetal cardiac position in cardiac Doppler evaluation, nearly twice as many pregnancies were evaluated to reach this number of cases. In addition, cases in which the fetal cardiac position was not suitable for examination were excluded. However, the study's strengths are its prospective design and the fact that all Doppler ultrasound measurements in this study were performed by an experienced perinatologist to minimize measurement variations. Another significant advantage of this research is that it is the first to investigate cardiac Doppler parameters in low-risk populations undergoing a 75-g OGTT. The fact that the extent of fetal cardiac compromise according to the course of the OGTT was measured three times in the study may be considered important in increasing the reliability of the study results.

Conclusion

In summary, overall, the 75-g OGTT does not exhibit significant alterations in Doppler findings including fetal cardiac parameters within low-risk, healthy pregnancies. When the test results were within the normal range, the administration of the 75-g OGTT did not yield any impact on the Doppler parameters of either the mother or the fetus, including fetal cardiac performance. Considering that this study was conducted in healthy pregnancies without any risk of diabetic pregnancy, further research on the fetal cardiac adverse effects of OGTT in participants with high risk of diabetic pregnancy may provide new insights that can be transferred to clinical practice.

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
Haseki Training and Research Hospital Clinical Research Ethics Committe Decision 09.08.2023 Decree No: 107/2023.

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