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Role of ultrasonographic measurement of the fetal epicardial fat pad and cardiac interventricular septal thickness in predicting the outcome and prevent various complications of gestational diabetes mellitus

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Abstract

Background Gestational diabetes mellitus (GDM) is one of the most common medical conditions affecting pregnancy and increasing the risk for maternal and perinatal complications. The present study aimed at determining the role of ultrasonographic measurement of fetal epicardial fat pad thickness (f EFT) and fetal cardiac interventricular septal thickness (f IVST) at 24–32 weeks of gestation in the prediction of GDM.

Results A prospective observational case–control study was conducted including a total of 35 GDM patients and 35 normal pregnancies who were subjected to ultrasonographic measurement of the f EFT and f IVST at 24–32 weeks of gestation. Statistical analysis and the receiver operating characteristic curves were used to find out the cutoff value, sensitivity, specificity and diagnostic accuracy of these two parameters for the prediction of GDM. When an f EFT value of 1.3 was accepted as a cutoff value, GDM could be predicted with a sensitivity of 68.6% and specificity of 91.4%, PPV of 88.9%, NPV of 74.4% and diagnostic accuracy of 80%. When an f IVST value of 2.6 was accepted as a cutoff value, GDM could be predicted with a sensitivity of 80%, specificity of 77.14%, PPV of 77.8%, NPV of 79.4% and diagnostic accuracy of 78.5%.

Conclusion The ultrasonographic measurements of fetal epicardial fat pad thickness and fetal cardiac interventricular septal thickness were statistically significantly higher in GDM pregnancies (p value < 0.0001) as compared to the controls. Thus, these two parameters can serve as excellent ultrasonographic markers in the prediction of GDM.

Keywords Epicardial fat pad thickness, Fetal, Gestational diabetes mellitus, Interventricular septal thickness

Background

Gestational diabetes mellitus (GDM) is defined as the new onset of various degrees of glucose intolerance during pregnancy. This definition applies to whether insulin or only diet modification is used for treatment and whether the condition persists after pregnancy. It is diagnosed following a population screening for hyperglycemia in pregnant women [1, 2].

In India, the prevalence rate of GDM is 10–14.3% which is much higher than in the western population.

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The incidence of GDM follows the incidence of insulin resistance and type 2 diabetes mellitus in each country's population [3]. Hence, the incidence of GDM in India is expected to increase to 20%, i.e., one in every 5 pregnant women will have GDM. With this increase in the incidence of GDM, the various complications, i.e., maternal (postpartum hemorrhage, need for cesarean section, birth trauma, prolonged and obstructed labor, infection) as well as fetal (congenital anomalies, stillbirths, intrauterine death, birth injuries, neonatal hypoglycemia, respiratory distress), will become even more dreadful for the entire health system. Also, children of mothers with uncontrolled diabetes are four times more likely to develop diabetes in adulthood leading to worse long-term outcomes [4].

The timing and severity of maternal diabetes play a critical role in determining the effects on fetal metabolic state and fetal cardiovascular development. In pre-gestational diabetes, there is first-trimester hyperglycemia leading to adverse effects on fetal organogenesis and neural crest migration resulting in typical conotruncal cardiac defects. However, GDM in the 2nd and 3rd trimesters put the fetus at risk for myocardial hypertrophy and diastolic impairments with increased fetal cardiac interventricular septal thickness, which is the most common structural abnormality in GDM. [5] Also, 40% of the infants born to such diabetic mothers develop hypertrophic cardiomyopathy out of which 5% become symptomatic. [6] It may occur due to worsened metabolic state or due to neonatal hyperinsulinemia with increased expression and affinity of insulin receptors leading to the proliferation of cardiac myocytes.

Fetal epicardial fat is the layer of visceral fat between the myocardium and visceral pericardium, derived from the brown fat tissue. The physiological role of epicardial fat lies in acting as an immune barrier, mechanical protection of coronary arteries, local source of fatty acids to the myocardium and providing a thermogenic role [7]. Recently, it has been found that epicardial fat is metabolically very active and it could serve as a reliable marker of visceral adiposity [8]. Hence, it has been linked to the pathogenesis of many diseases including coronary artery disease, hypertension and insulin resistance resulting in metabolic syndrome. As GDM also manifests due to an altered response to increased insulin resistance in pregnancy, there should be some effect on the epicardial fat thickness in such fetuses. Therefore, measurement of fetal epicardial fat thickness may aid us in the diagnosis and monitoring of such pregnancies.

The cardiac function evaluation of the fetus provides essential information on the hemodynamic status and the cardiovascular adaptation for associated perinatal adverse effects. Fetal electrocardiography and

echocardiography are simple and noninvasive procedures that can best evaluate the fetal cardiac structures and functions [6].

The insight into the effect of GDM on fetal metabolic state and fetal heart at the time of pregnancy is still lacking. The ultrasonographic measurement of fetal epicardial fat (f EFT) and cardiac interventricular septal thickness (f IVST) may serve as novel markers for altered fetal metabolism and its consequences on the fetal heart.

The present study aimed to estimate and compare the ultrasonographic measurement of f EFT and f IVST in GDM and normal pregnancies at 24–32 weeks of gestation and evaluate the diagnostic efficacy in the prediction of GDM.

Methods

This was a prospective observational case–control study in a tertiary care center with approval from an institutional ethical committee (S No. IEC/VMMC/SJH/Thesis/October/2018-76) for a duration of 18 months from December 2018 till June 2020. All the pregnant women who were referred to our department between 24 and 32 weeks of gestation were examined to measure f EFT and f IVST, after informed written consent during the study period. The diagnostic criteria used for GDM were a one-step approach using the 75-g oral glucose tolerance test (OGTT), with glucose assayed at fasting and after 1 and 2 h, as recommended by The International Association of the Diabetes and Pregnancy Study Groups (IADPSG)[9] with threshold values of 92 mg/dl, 180 mg/dl and 153 mg/dl, respectively. GDM was defined by the presence of one or more OGTT values exceeding these thresholds. According to the OGTT results, we constituted the GDM and control groups. The control group consisted of randomly selected healthy pregnant with similar age and BMI values in the GDM group. Using the standard formula, 35 GDM patients and 35 control subjects were included in the present study.

Women with diseases known to affect fetal growth, uncertain gestational age, multiple pregnancies, pregnancies conceived by assisted reproductive technology, use of antenatal steroids before delivery, amniotic fluid index less than 10 or more than 25, fetuses with congenital anomalies and intrauterine growth restriction were excluded from the study.

Ultrasound examination

The ultrasound data in this study was collected following standardized protocols for data acquisition, using a high-resolution transabdominal ultrasound transducer (Philips IU22 3–5 MHz curvilinear probe). All ultrasounds were performed by a single radiologist. Standard fetal biometry parameters were recorded including biparietal

diameter, head circumference, abdominal circumference and femur length. Estimated fetal weight (EFW) was calculated using the Hadlock formula.

Fetal epicardial fat thickness (f EFT) was measured on a standardized four-chamber view at the end-diastole in 3 cardiac cycles through the available wall of the right ventricle in the fetus. The highest value measured from the perpendicular wall of the right ventricle across the ultrasound ray vertical to the aortic annulus was taken [5]. It was measured as a hypoechoic space just outside the myocardium anterior to the right ventricle (Fig. 1). This hypoechoic space was also evaluated on color Doppler to avoid any confusion between fetal epicardial fat and pericardial fluid. If any signal was detected, the case was excluded from the study. f IVST was measured in a transverse four-chamber view, midway between the apex and

the crux of the heart, with a cursor perpendicular to the interventricular septum (Fig. 2).

Statistical analysis

Continuous variables were presented as mean \pm SD and median. Normality of data was tested by Kolmogorov–Smirnov test. If the normality was rejected, then the non-parametric test was used. Quantitative variables were compared using the independent *t*-test/Mann–Whitney test (when the data sets were not normally distributed) between the two groups. Pearson correlation coefficient was used to assess the correlation of various parameters with gestational age. The receiver operating characteristic curve was used to find out the cutoff value of the average f EFT and f IVST (mm) for the prediction of the diagnosis of GDM.

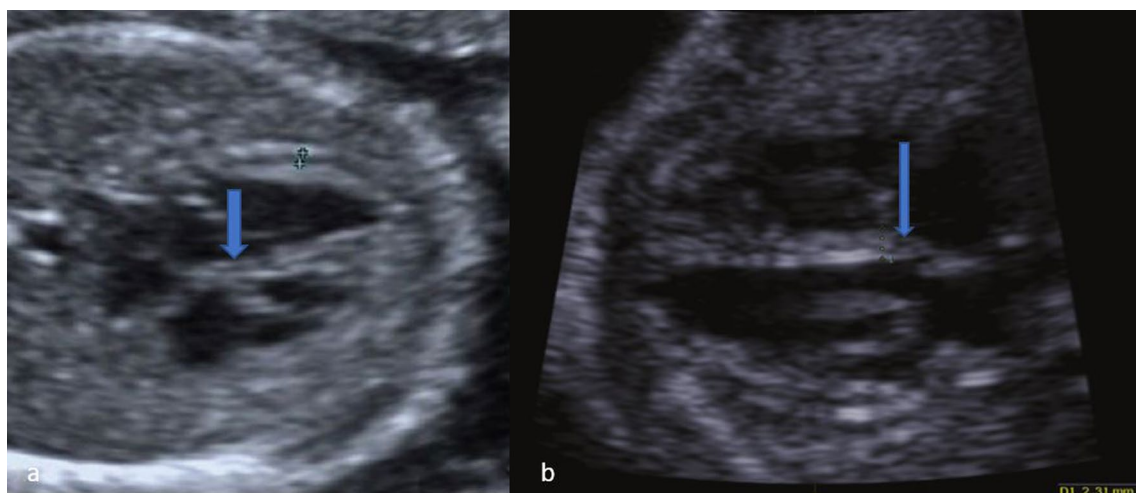


Fig. 1 Greyscale USG images of a normal pregnant female 28w2d with **a** f EFT 1.1 mm **b** f IVST systole 2.3 mm

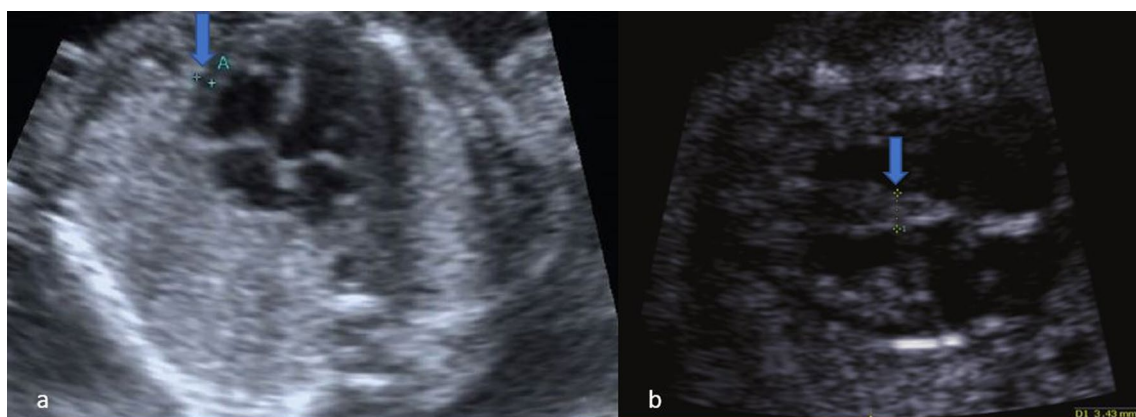


Fig. 2 Greyscale USG images of a pregnant female 28w0d with GDM **a** f EFT 2.1 mm **b** f IVST diastole 3.5 mm

Table 1 Comparison of the average fetal epicardial fat pad thickness (mm) between cases and controls

Average epicardial fat pad	Case (n = 35)	Control (n = 35)	Total	P value
Mean ± SD	1.54 ± 0.33	1.15 ± 0.2	1.35 ± 0.33	< .0001
Median (IQR)	1.53 (1.317–1.81)	1.13 (1.023–1.283)	1.3 (1.108–1.533)	
Range	0.7–2.1	0.73–1.7	0.7–2.1	

Test performed: Mann–Whitney test; 172

A *p* value of <0.05 was considered statistically significant. The data was entered in the MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

Results

The study comprised 70 pregnant women including 35 GDM patients and 35 healthy controls, between 24 and 32 weeks of gestation. The average maternal age was 26.89 ± 4.14 years in GDM and 24.43 ± 3.22 years in the control group with no significant statistical variation (*p* value 0.629). The most common fetal presentation was cephalic (80% and 77%) in GDM and controls, respectively. Most of the patients had anteriorly located placentae (58% in each group). The mean amniotic fluid index (AFI) was 15.37 ± 2.17 cm in GDM and 13.03 ± 2.05 cm in the control group and this difference was statistically significant (*p* value 0.0001). The average gestational age was 31 ± 1.5 weeks in GDM and 30.8 ± 1 weeks in the control group (no significant variation, *p* value 0.09).

The mean f EFT measurement of the whole population was 1.35 ± 0.33 mm; 1.54 ± 0.33 mm in GDM and 1.15 ± 0.2 mm in the control group. The mean f EFT values of the GDM patients were significantly higher than those of the control group (*p* value < 0.0001). The mean and median values of f EFT measurements and the changes in subgroups are tabulated in Table 1.

The mean f IVST measurement of the whole population was 2.91 ± 0.65 mm; 3.49 ± 0.91 mm in GDM and 2.45 ± 0.65 mm in the control group. The mean f IVST values of the GDM patients were significantly higher than those of the control group (*p* value < 0.0001). The mean and median values of f IVST measurements and the changes in subgroups are tabulated in Table 2.

The ROC curve analysis of average fetal epicardial fat pad thickness (mm) and average fetal cardiac interventricular septal thickness (mm) for predicting GDM are tabulated in Table 3. An f EFT value of 1.3 was accepted as a cutoff value, the presence of GDM diagnosis could be predicted with a sensitivity of 68.6%, specificity of 91.4%, PPV of 88.9%, NPV of 74.4% and diagnostic accuracy of 80% (Fig. 3). When an f IVST value of 2.6 was accepted as a cutoff value, the presence of GDM diagnosis could be predicted with a sensitivity of 80%, specificity of 77.14%,

Table 2 Comparison of the average fetal cardiac interventricular septum (mm) between cases and controls

Average interventricular septum(mm)	Case (n = 35)	Control (n = 35)	Total	P value
Mean ± SD	3.49 ± 0.91	2.45 ± 0.65	2.97 ± 0.95	< .0001
Median (IQR)	3.65 (2.85–4.005)	2.45 (1.938–2.625)	2.82 (2.225–3.682)	
Range	1.83–5.3	1.48–4.22	1.48–5.3	

Test performed: Mann–Whitney test; 229

Table 3 Receiver operating characteristic curve of the average epicardial fat pad thickness (mm) and average interventricular septum (mm) for predicting GDM

GDM	Average epicardial fat pad	Average interventricular septum (mm)
The area under the ROC curve (AUC)	0.86	0.813
Standard error	0.0451	0.0514
95% Confidence interval	0.756 to 0.931	0.702 to 0.896
P value	< 0.0001	< 0.0001
Cutoff	> 1.3667	> 2.625
Sensitivity (95% CI)	68.57%	80%
Specificity (95% CI)	91.43%	77.14%
PPV (95% CI)	88.9%	77.8%
NPV (95% CI)	74.4%	79.4%
Diagnostic accuracy	80.00%	78.57%

PPV of 77.8%, NPV of 79.4% and diagnostic accuracy of 78.5% (Fig. 4).

Discussion

The present study was carried out to evaluate the diagnostic efficacy of fetal epicardial fat pad thickness and fetal cardiac interventricular septal thickness for predicting the development of gestational diabetes mellitus. Gestational diabetes mellitus (GDM) is one of the most common complications in pregnancy leading to various metabolic abnormalities in the fetus apart from

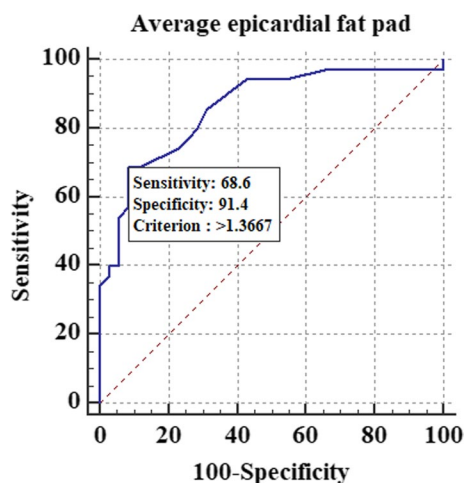


Fig. 3 ROC curve of the average fetal epicardial fat pad thickness (mm) for predicting GDM

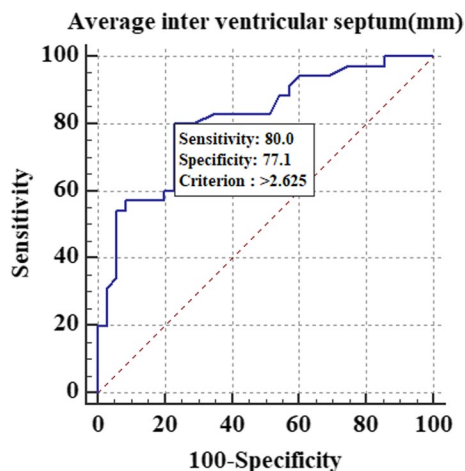


Fig. 4 ROC curve of the average fetal cardiac interventricular septal thickness (mm) for predicting GDM

structural abnormalities. Prior knowledge of fetal metabolic derangement can help the obstetrician to predict the outcome and to plan the pregnancy accordingly to prevent various complications.

The monitoring of glycemic control in GDM is usually done by serial blood glucose levels and HbA1c levels. However, in the present study, HbA1c levels were raised only in 1 pregnancy, hence it is not a reliable indicator of maternal and fetal metabolic status. On the other hand, the f EFT and f IVST were significantly higher in GDM pregnancies which occur due to the anabolic effect of hyperinsulinemia on the fetus and reliably reflect the fetal metabolic state in the early third trimester itself. Thus, these parameters can reliably predict the onset of complications in GDM pregnancies.

Most of the placentae in the present study were located anteriorly ($n=40$), followed by fundal location and the least common location was a left laterally located placenta. As per Vanuccini et al. also, anteriorly located placentae were the most common, followed by fundal location. [10]

The mean AFI was 15.37 ± 2.17 cm for cases and 13.03 ± 2.05 for controls and it was significantly higher in cases than in controls. Similar results were observed in a previous study, the maximum vertical pocket was found to be 6.1 ± 1.5 cm in the cases and 5.1 ± 0.52 cm in the controls. [11]

In the current study, the mean epicardial fat thickness was 1.54 ± 0.33 mm for cases and 1.15 ± 0.2 mm for controls which means that the mean epicardial fat thickness was significantly higher for cases than controls (p value < 0.0001). Similarly, in a previous study, the mean epicardial fat thickness was higher in cases (1.45 ± 0.19 mm) as compared to that of controls (1.30 ± 0.14 mm) (p value < 0.001). [9] In another study by Jackson et al., the epicardial fat thickness was higher in diabetic mothers (1.43 mm) as compared to controls (1.15 mm) (p value 0.02). They also found a correlation of f EFT with abdominal circumference and estimated fetal weight. Only 14 patients had availability of HbA1c levels, hence this parameter could not be studied. [12] Maternal HbA1c levels were also recorded in the current study; however, only 1 patient with GDM had raised HbA1c value, hence no relationship was found between f EFT and HbA1c. In another study by Akkurt et al., a positive correlation was found between GDM and maternal as well as fetal epicardial fat thickness (p value 0.009) between 24 and 28 weeks of gestation. They also found a positive correlation between fetal EFT and a 2-h oral glucose tolerance test. [13] A recent study by Aydin et al. established a cutoff value of f EFT as 0.95 mm to predict the presence of GDM with a sensitivity of 65% and specificity of 88% (odds ratio = 13) [14].

Thus, the results of the present study agree with the previous studies, and at a cutoff value of 1.3 mm, the fetal epicardial fat thickness can serve as a predictor of gestational diabetes mellitus with a sensitivity of 68.6%, specificity of 91.4%, PPV of 88.9%, NPV of 74.4% and diagnostic accuracy of 80%.

In the present study, the fetal interventricular septal thickness during systole was found to be significantly higher in the GDM group with a mean value of 3.9 ± 1.02 mm than in the control group with a mean value of 2.91 ± 0.82 mm (p value < 0.0001). Similarly, there were significantly higher values of fetal interventricular septal thickness during diastole with a mean value of 3.08 ± 0.86 mm in the GDM group and a mean value

of 2 ± 0.59 mm in the control group. Hence, the average interventricular septal thickness was also significantly higher in the GDM group (mean value of 3.49 ± 0.91 mm in cases versus 2.45 ± 0.65 mm in controls). Russel et al. did a study to evaluate the fetal interventricular septal thickness and ventricular wall thickness and found similar results with higher values in GDM with a mean value of 6.42 ± 1.36 mm in the systole and 5.30 ± 1.27 mm in the diastole as compared to 5.43 ± 1.01 mm in systole and 4.63 ± 0.88 mm in diastole in the controls. [15]

Ren et al. studied fetal interventricular septum thickness in controlled GDM and uncontrolled GDM and compared it with normal pregnancies. The values were 4.00 ± 1.04 mm in diastole, 5.34 ± 1.78 mm in systole in uncontrolled GDM; 3.96 ± 1.16 mm in diastole, 5.17 ± 1.22 mm in systole in controlled GDM and 2.85 ± 0.73 mm in diastole, 3.96 ± 0.83 mm in systole in normal pregnancies. Thus, higher values are seen in GDM but there was no increased thickness with poor glycemic control. [16]

The results of the present study were also concordant with another study conducted in India by Garg et al. in which the f IVST measured 3.77 ± 0.95 mm in end-diastole, 4.96 ± 1.08 mm in end-systole in uncontrolled GDM; 3.74 ± 0.98 mm in end-diastole, 4.97 ± 1.12 mm in end-systole in controlled GDM and 2.77 ± 0.86 mm in end-diastole and 3.84 ± 0.75 mm in end-systole in normal pregnancies. [17]

Miranda et al. also found that fetuses of mothers with diabetes had thicker interventricular septum compared with controls (median of 4.25 mm [interquartile range – 3.87–4.50 mm] in cases versus a median of 3.67 mm [interquartile range – 3.40–3.93 mm] in controls) [18]. The results of the current study were also in concurrence with other similar studies. [19–22]

According to the results of the present study, at a cutoff value of 2.6 mm, the average cardiac interventricular septal thickness can serve as a predictor of gestational diabetes mellitus with a sensitivity of 80%, specificity of 77.14%, PPV of 77.8%, NPV of 79.4% and diagnostic accuracy of 78.57%. This cutoff value is slightly less in comparison with a recent study, in which the f IVST cutoff value of 4.7 mm was established with a sensitivity of 78.57%, specificity of 57.20%, PPV of 15.94% and NPV of 96.27%. [23]

Thus, the present study has found fetal epicardial fat thickness and fetal interventricular septal thickness to be significant predictors of the diagnosis of GDM and their further use in detecting fetal metabolic derangement. Also, these parameters can be measured accurately early in the third trimester, thus providing greater scope for the prevention of complications. Fetal epicardial fat thickness is more accurate than other fat

reserves because it is a visceral fat deposit (hence more active metabolically active) and there are fewer chances of overestimation unlike other parameters like subcutaneous fat thickness in which skin thickness may result in faulty measurement.

The changes in f EFT and f IVST and their metabolic effects are a relatively new fact-finding research and very few studies have focused on the evaluation of these two parameters in the prediction of GDM concurrently.

The strength of this study was that it was a prospective study and a single observer was involved, thus eliminating inter-observer bias. The main limitation was that it had a small sample size and is a single-center study. Further studies with larger sample sizes and multi-institutional settings are recommended to validate the accuracy. Also, in this study, the subjects were from a homogenous population of Indian females and whether these results can be extrapolated to other ethnic groups remain to be further validated.

Conclusions

The present study was an endeavor to estimate and compare the f EFT and f IVST in GDM and normal pregnancies in early third trimester and both these parameters were found to be statistically significantly higher in GDM pregnancies. These changes occur due to anabolic effect of hyperinsulinemia on the fetus and f EFT and f IVST measurements are extremely valuable in determining the impact of changes in the intrauterine environment in GDM on fetal metabolic status. Thus, these two ultrasonographic parameters can serve as excellent markers in depicting fetal metabolic derangement in GDM pregnancies, thus preventing further complications.

Abbreviations

GDM	Gestational diabetes mellitus
f EFT	Fetal epicardial fat pad thickness
f IVST	Fetal interventricular septal thickness
PPV	Positive predictive value
NPV	Negative predictive value

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Author contributions

NB is the corresponding author, designed and revised the work, interpreted the data and submitted the case. NB has approved the submitted version for publication. GG has drafted the work and approved the submitted version for publication. RC has revised the manuscript and approved the submitted version for publication. AM and RM have revised the work. HG provided the patients for the study and helped in designing the study. No disclosure. All authors read and approved the final manuscript.

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Availability of data and materials

The cases and the images are available from the Department of Radiodiagnosis, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.

Declarations**Ethics approval and consent to participate**

A written approval was obtained from the subject.

Consent for publication

The authors consented for the submission of the manuscript and publication. The authors disclosed no competing interests and no relevant relationships. A written consent and approval was obtained from all the subjects included in this study.

Competing interests

The authors declare that they have no competing interests.

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