



Fetal Epicardial Fat Thickness: Its Role as Marker for Gestational Diabetic Mellitus

Amandeep Singh¹  Amitojveer S. Josan¹ Kamlesh Gupta¹ Sangeeta Pahwa²

¹Department of Radiodiagnosis and Imaging, Sri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Punjab, India

²Department of Obstetrics and Gynaecology, Sri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Punjab, India

Address for correspondence Amandeep Singh, MD (Radiodiagnosis), Department of Radiodiagnosis and Imaging, Sri Guru Ram Das Institute of Medical Sciences and Research, Vallah, Punjab, India (e-mail: dr.amancs@gmail.com).

Indian J Radiol Imaging 2023;33:302–308.

Abstract

Background There are very few studies on the association between fetal epicardial fat thickness (EFT) and gestational diabetes mellitus (GDM).

Aims To evaluate the role of fetal epicardial fat thickness as a marker and use it in pregnancies to screen for GDM.

Settings and Design A cross-sectional analytical study was conducted in the Department of Radiodiagnosis and Imaging at Sri Guru Ram Das Institute of Medical Sciences and Research, Amritsar, after the due clearance from the institutional research and ethics committee.

Materials and Methods The study included pregnant patients at 24 + 0/6 to 28 + 0/6 weeks of gestation scheduled for a 75 g oral glucose tolerance test from December 1, 2020 to March 30, 2022. Antenatal ultrasound was performed on Voluson E8 Expert BT12 (Wipro GE) ultrasound machine. Out of 180 patients, 60 patients were selected, that is, 30 patients with raised 75 g OGTT results (cases of GDM) and 30 patients with normal 75 g OGTT results.

Statistical Analysis The collected data were transformed into variables, coded, and entered into Microsoft Excel. Data were analyzed using the Shapiro–Wilk normality test, student's *t*-test or Mann–Whiney *U* test, chi-square test, or Fisher's exact test and statistically evaluated using the SPSS-PC-25 version.

Results Fetal EFT was found to be significantly more in the GDM group in comparison to controls without GDM, and the increased fetal EFT was positively associated with 2-hour OGTT serum glucose values.

The mean fetal epicardial fat thickness (EFT) in mothers with GDM was significantly larger, i.e., 0.17 ± 0.02 cm than in mothers without GDM, i.e., 0.12 ± 0.01 cm ($p < 0.001$). The receiver operating characteristic (ROC) curve plotted from values calculated from our results shows high sensitivity (i.e., 96.67%) and specificity (i.e., 90%) of fetal EFT as a predictor for GDM with an AUROC value of 0.96 and 95% confidence interval of 0.92 to 1.0.

Keywords

- ▶ epicardial fat thickness
- ▶ fetal
- ▶ gestational diabetes

article published online
March 4, 2023

DOI <https://doi.org/10.1055/s-0043-1762936>.
ISSN 0971-3026.

© 2023. Indian Radiological Association. All rights reserved.
This is an open access article published by Thieme under the terms of the Creative Commons Attribution-NonDerivative-NonCommercial-License, permitting copying and reproduction so long as the original work is given appropriate credit. Contents may not be used for commercial purposes, or adapted, remixed, transformed or built upon. (<https://creativecommons.org/licenses/by-nc-nd/4.0/>)
Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Conclusions EFT was significantly higher in fetuses of diabetic versus nondiabetic mothers. The mean difference in EFT of GDM cases and controls was relatively small but was statistically significant. The study concluded that measuring the epicardial fat thickness in fetuses can serve as a novel marker in GDM.

Introduction

Epicardial fat is located between the visceral pericardium and myocardium, mostly distributed adjacent to the right ventricle and adds significantly to myocardial energy production.^{1,2} It is an active and complex endocrine organ that secretes multiple anti-inflammatory and proinflammatory molecules.^{3,4} Gestational diabetes mellitus (GDM) is a disorder of metabolism that results in resistance to insulin during pregnancy.⁵ Its diagnosis is necessary, as it results in fetal, neonatal, and maternal problems.^{6–8} The resistance to insulin precedes the detection of an increase in glucose levels in the blood.^{9,10} There have been studies on the association of epicardial fat thickness (EFT) measured on ultrasonography and insulin resistance in the adult population; however, there are limited data on EFT in fetuses and GDM.

Previous studies show that EFT is increased in fetuses of mothers with GDM.^{11,12} These studies were limited by a small sample size and the lack of a standardized measurement method. Results were not controlled by gestational age. The newer ultrasound technique enables us to identify and measurement of fetal EFT accurately. Using a standardized method, we conducted a cross-sectional study of fetal EFT measurement between 24 + 0/6 and 28 + 0/6 weeks of gestation. We hypothesized that fetal EFT differs significantly between diabetic and nondiabetic pregnancies, reflecting maternal diabetic status, and correlated its values with blood glucose values obtained during a scheduled 75 g oral glucose tolerance test (OGTT) according to the American Diabetes Association criteria (fasting ≥ 92 mg/dL, 1 hour ≥ 180 mg/dL, or 2 hour ≥ 153 mg/dL).

The aim of our study was to standardize the fetal epicardial fat thickness measurement and ascertain its role in the diagnosis and effective prediction of GDM and correlate the results with OGTT results.

Methods

A cross-sectional analytical study was conducted after due approval and clearance from the ethics committee of the institute. Pregnant patients at 24 + 0/6 to 28 + 0/6 weeks of gestation who were scheduled for a 75 g oral glucose tolerance test (OGTT) according to the American Diabetes Association criteria (fasting ≥ 92 mg/dL, 1 hour ≥ 180 mg/dL, or 2 hours ≥ 153 mg/dL) from December 1, 2020 to March 30, 2022 were included in the study. As OGTT is performed as a routine test in every pregnancy between 24 weeks to 28 weeks of gestation, it did not add any extra cost to the patient. Proper prior informed consent was taken from the patient before performing the ultrasound. The ultrasound

examination of these patients was performed before the results of the OGTT to eliminate the information bias to the sonographer. Out of 180 patients in this time frame, 30 patients with raised 75 g OGTT results (cases of GDM) and 30 patients with normal 75 g OGTT results were randomly included as a convenient sample size. Patients with pre-existing type 1 or type 2 diabetes, congenital fetal anomalies, and women on medications except for oral iron supplementation or multivitamins were excluded from this study because pre-existing diabetes mellitus, and medications act as confounding factors and congenital anomalies can also alter the results as these patients will have an already raised fetal EFT due to pre-existing diabetes, and effect of medications can also alter the metabolism. Gestational age was calculated from the last menstrual period confirmed by gestational age according to ultrasound well-being scan as gestational age according to ultrasound depicts more accurate growth and development of the fetus.

Ultrasound technique used: Ultrasound was performed on Voluson E8 Expert BT12 (Wipro GE) ultrasound machine transabdominally using a linear 5 to 10 MHz probe and convex rab 6D (2–7) MHz probe. Ultrasound was done by radiologists with more than 10 years of experience in fetal imaging.

The left ventricle outflow (LVOT) view is ideal to visualize the space between the myocardium and epicardium along the right ventricle. EFT represented by the hypoechogenic area between the visceral pericardium and myocardium was identified. A reference line passing through the right ventricular wall, aortic annulus, and descending aorta was drawn. EFT was measured at the end-diastole of the cardiac cycle. Dynamic and static images were stored due to a lack of control over the cardiac cycle. The calipers measured the inner-to-inner aspect of the hypoechoic area through the available wall of the right ventricle nearest to the reference line. The maximum EFT along the reference line passing through the aortic annulus and intersecting the right ventricular wall was measured at 90 degrees to the wall (**Fig. 1**). A major prerequisite for this measurement included in this study was the anterior position of the fetal heart to minimize the limitations of reproducibility of previous studies.

The reproducibility of the technique has been investigated before the initiation of the study. A blinded investigator measured EFT in 20 randomly selected normal fetuses. The images were stored separately in the same ultrasound machine, and EFT was remeasured from the stored images after 2 weeks by the same investigator. The mean of these two measurements performed by the same investigator was

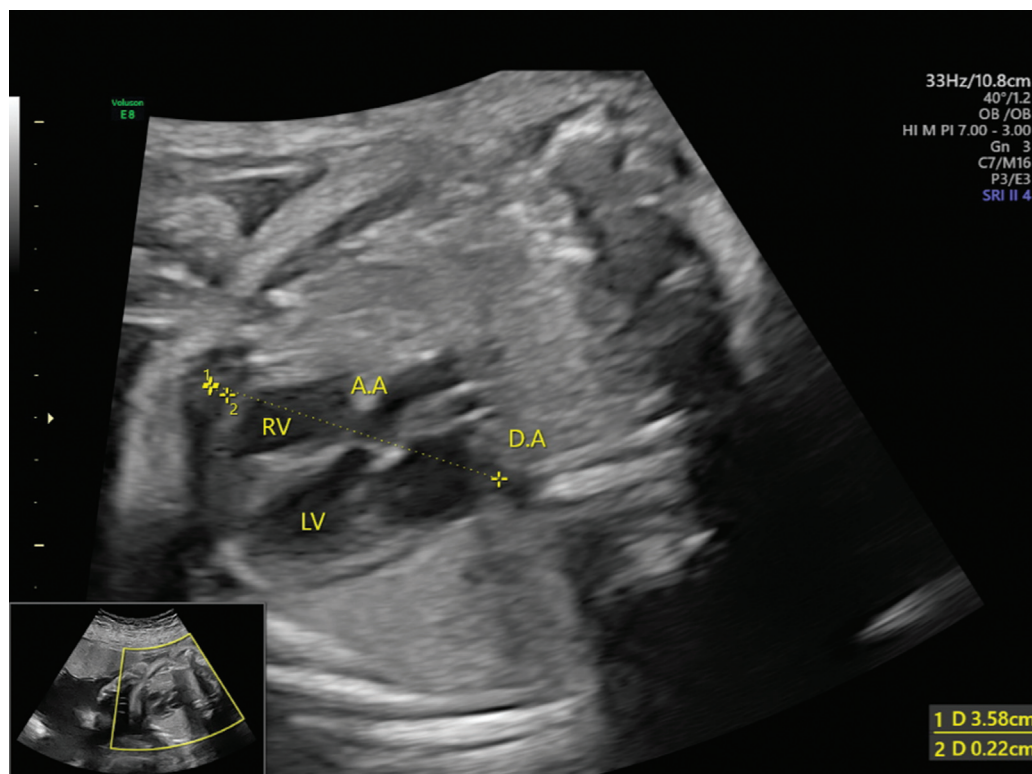


Fig. 1 Transabdominal ultrasound image representing ideal view for fetal epicardial fat thickness measurement. (D.A = descending aorta, A.A = aortic annulus, LV = left ventricle, RV = right ventricle, Calliper 1 represents the reference line to be drawn, Calliper 2 represents measurement of epicardial fat thickness from inner to inner aspect).

calculated. This mean EFT value was used for the final analysis of the results.¹³

The fetal EFT values obtained in patients with raised OGTT test results were compared with those patients having normal OGTT test results.

Data Entry and Statistical Analysis

The collected data were transformed into variables, coded, and entered in the Microsoft Excel. Data were analyzed and statistically evaluated using the SPSS-PC-25 version.

The normal distribution of different parameters was tested by the Shapiro–Wilk normality test.

Quantitative data are expressed as mean \pm standard deviation or median with interquartile range and depends on the normality difference between the mean of two groups and were compared by student's *t*-test or Mann–Whiney *U* test.

Qualitative data are expressed in frequency and percentage, and statistical differences between the proportions were tested by the chi-square test or Fisher's exact test.

ROC curve was prepared using fetal EFT to differentiate between GDM and non-GDM and based on that, the cut-off value was calculated. Sensitivity, specificity, PPV, and NPV of fetal EFT were calculated. *P*-value less than 0.05 was considered statistically significant.

Results

During the study period, 30 cases of GDM and 30 non-GDM patients were identified after the application of inclusion

and exclusion criteria. The mean gestational age of cases (26.53 ± 1.27 weeks) were matched with that of controls (26.22 ± 1.37 weeks) (**Table 1**).

The mean fetal EFT in mothers with GDM was significantly higher, i.e., 0.17 ± 0.02 cm than in mothers without GDM, i.e., 0.12 ± 0.01 cm ($p < 0.001$) (**Table 2**).

The 2 hours OGTT results of cases had an average value of 178.21 ± 9.73 mg/dL and controls had an average 2 hours OGTT value of 125.70 ± 15.31 mg/dL (**Table 3**).

In the study, among the mothers who had raised OGTT value (i.e., GDM), one of them did not have increased fetal EFT. Among controls, we had two mothers in whom the 2 hours OGTT value was normal but had relatively increased fetal EFT measurement. We also inferred from our results that fetal EFT increased as gestational age advanced in both cases and controls.

The receiver operating characteristic (ROC) curve plotted from values calculated from our results showed high

Table 1 Comparison of mean gestational age between both groups (GDM - nt = gestational diabetes mellitus not present, GDM + nt = gestational diabetes mellitus present)

	GDM-nt (n = 30)	GDM + nt (n = 30)	p-Value
Mean gestational age in weeks	26.22 ± 1.37	26.53 ± 1.27	0.37

Table 2 Comparison of mean fetal epicardial fat thickness between both groups (GDM-nt = gestational diabetes mellitus not present, GDM + nt = gestational diabetes mellitus present, cm = centimeters, IQR = interquartile range)

	GDM-nt (n = 30)	GDM + nt (n = 30)	p-Value
Mean fetal epicardial fat thickness (in cm)	0.12 ± 0.01	0.17 ± 0.02	<0.001
Median (IQR)	0.12 (0.11–0.13)	0.17 (0.16–0.19)	

Table 3 Comparison of OGTT test results between both groups (GDM-nt = gestational diabetes mellitus not present, GDM + nt = gestational diabetes mellitus present, mg/dL = milligrams per deciliter)

	GDM - nt (n = 30)	GDM + nt (n = 30)	p-Value
OGTT test result (mg/dL)	125.70 ± 15.31	178.21 ± 9.73	<0.001

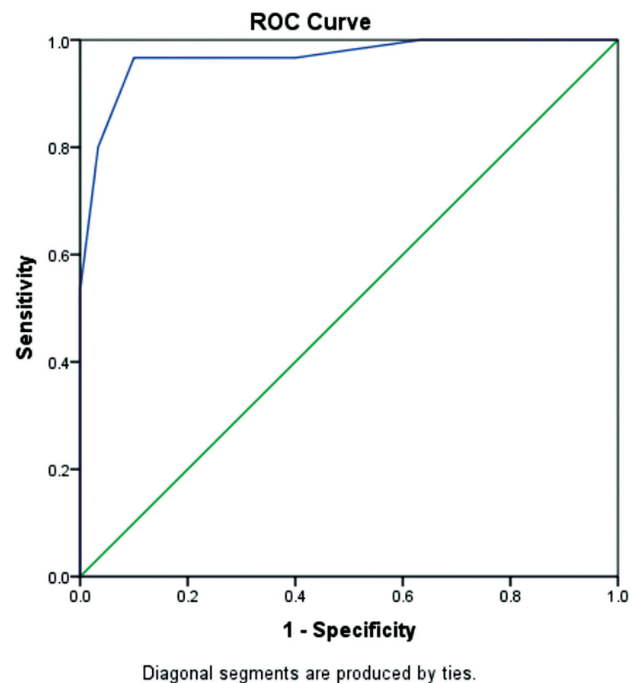


Fig. 2 ROC curve using epicardial fat thickness for the prediction of GDM.

sensitivity (i.e., 96.67%) and specificity (i.e., 90%) of fetal EFT as a predictor for GDM (→ **Fig. 2**) (→ **Table 4**).

Unadjusted linear regression analysis for factors affecting fetal EFT (→ **Table 5**), followed by the adjusted linear regression analysis (→ **Table 6**) was also done, which revealed a p-value < 0.001 of OGTT and p-value = 0.004 of BMI in unad-

Table 4 Diagnostic accuracy of fetal epicardial fat thickness for predicting GDM (CI = confidence interval)

	Fetal epicardial fat thickness
Area under curve	0.96
95% Confidence interval	0.92–1.0
Cut off value	0.145
Sensitivity (95% CI)	96.67% (82.78–99.92)
Specificity (95% CI)	90.0% (73.47–97.89)
PPV (95% CI)	90.62 (76.73–96.59)
NPV (95% CI)	96.43 (79.66–99.47)
Accuracy (95% CI)	93.33 (83.80–98.15)

Table 5 Unadjusted linear regression analysis for factors affecting fetal epicardial thickness

	Beta value	p-Value	95% CI
OGTT value	0.001	<0.001	0.001–0.001
Gestational age	0.001	0.69	–0.005 to 0.008
BMI	0.008	0.004	0.003–0.013
Maternal age	0.002	0.05	0.000–0.003

Table 6 Adjusted linear regression analysis for factors affecting fetal epicardial thickness

	Beta value	p-Value	95% CI
OGTT value	0.001	<0.001	0.001–0.001
Gestational age	–0.002	0.39	–0.006 to 0.002
BMI	0.007	<0.001	0.003 to 0.010
Maternal age	–0.001	0.31	–0.002 to 0.001

Note: Bolded values represent statistically significant data.

justed analysis. The OGTT and BMI had a p-value < 0.001 in the adjusted analysis.

Fetal EFT was found to be significantly higher in the study group with GDM, in comparison to the group without GDM (→ **Figs. 3** and **4**). Our data show that increased fetal EFT was positively associated with 2 hours of OGTT serum glucose values.

Discussion

It has been observed from the study that fetal EFT was higher in pregnant patients with GDM as compared with normal control patients. Hence, the fetal EFT can serve as a novel marker for the early detection of GDM and potentially help in the early initiation of treatment to gestational diabetic mothers to prevent complications for mother and child.

In the adult population, EFT has been calculated as a reliable marker to determine cardiovascular risk.¹⁴ Earlier

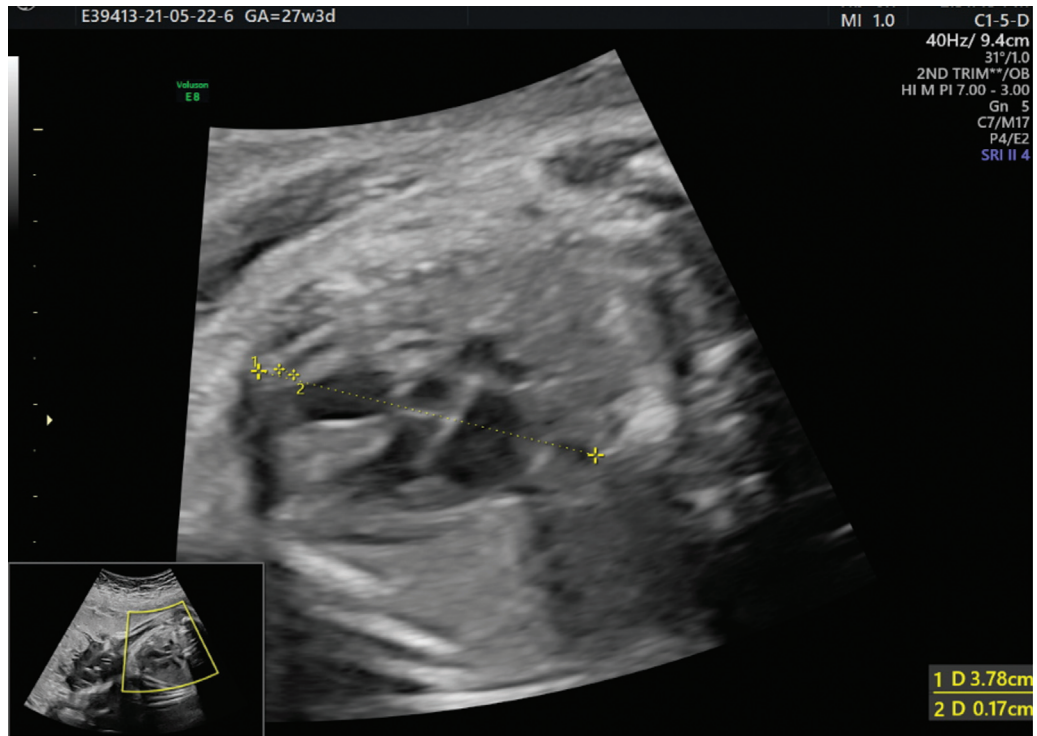


Fig. 3 Transabdominal ultrasound image at 27 weeks and 3 days of gestation. Left ventricular outflow tract view of fetal heart shows increased epicardial fat thickness. The OGTT result of this patient was found to be raises.

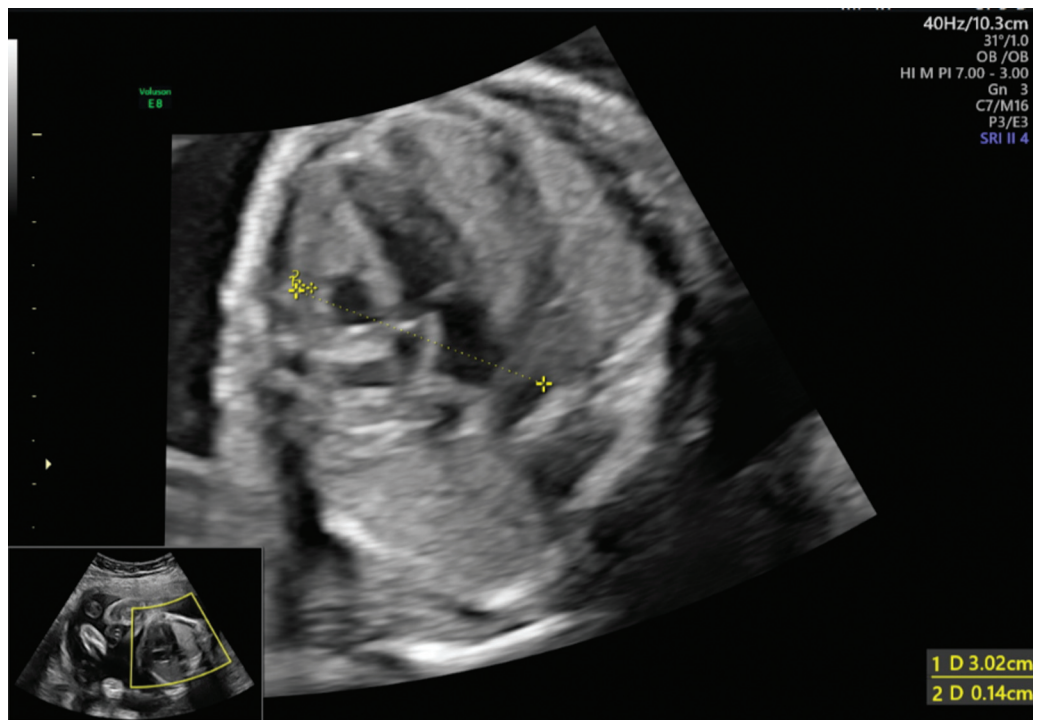


Fig. 4 Transabdominal ultrasound image at 24 weeks and 6 days of gestation. Left ventricular outflow tract view of fetal heart shows normal epicardial fat thickness. The OGTT result of this patient was found to be within normal range.

studies have shown an association between higher EFT with obesity and diabetes.^{3,15} Also, there has been an association between increased value of EFT and altered glucose in fasting state in non-diabetics.¹⁶ Such studies and their results suggest the importance of EFT measurement in fetuses.

In the present study, it was seen that fetal EFT increased with advancing gestational age. Similar findings have been documented in studies in past by Aydin et al.¹⁷

Yavuz et al, in their study, found similar findings of significantly increased epicardial fat thickness in fetuses of diabetic mothers. However, their measurement method was not standardized and they did not consider contributing factors such as the gestational age of the fetus.¹⁴

After controlling for gestational age, the present study demonstrated that EFT can be an individual marker for gestational diabetes. The pathophysiology of the regulation of insulin is same as in PDM (pre-gestational diabetes mellitus) and GDM, manifestations of insulin resistance occur in the later stages of gestation in GDM.¹⁵ This is why an increase in EFT in GDM is more evident in the third trimester.

Epicardial fat is involved in energy production for the myocardium and has increased fatty acid synthesis and lipogenesis due to insulin as compared with other types of fat. In cases with raised insulin, epicardial fat serves as a buffer to scavenge the extra toxic fatty acids. Therefore, in cases with raised fetal glucose levels, EFT will be increased long before other fat deposition occurs.^{16,17} Insulin resistance occurs before increased glucose levels induce lipogenesis.¹⁷

An increase in abdominal circumference and thickness of subcutaneous fat act as an indicator for more glycogen and fat deposition in the liver and subcutaneous tissue; however, the use of these markers in the second trimester is limited due to the incapacity of the fetus to store fat in mid-trimester. Increased fetal EFT can be a potential early marker and can be measured as early as 24 weeks of gestation to timely detect early altered fetal metabolism as a result of raised glucose before complications are apparent.

In a study by Akkurt et al, fetal EFT was measured by a standardized method by obtaining a LVOT view as described in our study.¹³ This method does not require any additional training and there is no significant increase in the scan time. This method is reliable and easily reproducible.

This technique, however, had limitations that include the posterior position of the fetal heart, which gives a non-satisfactory view and compromised poor image quality. This will further add to interobserver variability for fetal EFT measurement and compromises reproducibility of this technique. In their study, another limitation was related primarily mainly to its retrospective design. In our study, in addition to the standardization of LVOT view for fetal EFT measurement, we also standardized the anterior position of the fetal heart to overcome these limitations and produce as accurate and reliable results as possible.

Studies in the literature have demonstrated the original description of the technique of measuring the EFT in end systole to avoid possible changes due to compression of

epicardial fat in diastole.¹⁵ However, many studies have recommended measuring EFT during end-diastole as it is reproducible and have the potential for a reproducible result from other modalities, that is CT and MRI.^{1,18} Retrospective studies in the literature have not been able to control cardiac cycle because of a lack of dynamic imaging. Ours was a prospective study where we measured EFT during end-diastole. Previously, the only prospective study has been done by Yavuz et al with the same results.

Hence, the prospective design of our study and standardization of the fetal EFT measurement technique have been the major plus points of the study. One of the limitations of our study is its limited sample size. However, the standardization of the technique leaves very little scope for measurement errors and has good reproducibility.

In conclusion, EFT is a reliable marker for GDM. Measurement of EFT is reproducible, does not require any additional training, and does not adds to scan time.

Conflict of Interest

None declared.

References

- Nelson AJ, Worthley MI, Psaltis PJ, et al. Validation of cardiovascular magnetic resonance assessment of pericardial adipose tissue volume. *J Cardiovasc Magn Reson* 2009;11(01):15
- Sacks HS, Fain JN. Human epicardial adipose tissue: a review. *Am Heart J* 2007;153(06):907–917
- Bertaso AG, Bertol D, Duncan BB, Foppa M. Epicardial fat: definition, measurements and systematic review of main outcomes. *Arq Bras Cardiol* 2013;101(01):e18–e28
- Iacobellis G, Barbaro G. The double role of epicardial adipose tissue as pro- and anti-inflammatory organ. *Horm Metab Res* 2008;40(07):442–445
- Cetin M, Cakici M, Polat M, Suner A, Zencir C, Ardic I. Relation of epicardial fat thickness with carotid intima-media thickness in patients with type 2 diabetes mellitus. *Int J Endocrinol* 2013; 2013:769175
- American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2009;32(Suppl 1):S62–S67
- Noussitou P, Monbaron D, Vial Y, Gaillard RC, Ruiz J. Gestational diabetes mellitus and the risk of metabolic syndrome: a population-based study in Lausanne, Switzerland. *Diabetes Metab* 2005; 31(4 Pt 1):361–369
- König AB, Junginger S, Reusch J, Louwen F, Badenhoop K. Gestational diabetes outcome in a single center study: higher BMI in children after six months. *Horm Metab Res* 2014;46(11): 804–809
- Asemi Z, Karamali M, Esmailzadeh A. Favorable effects of vitamin D supplementation on pregnancy outcomes in gestational diabetes: a double blind randomized controlled clinical trial. *Horm Metab Res* 2015;47(08):565–570
- Drynda R, Peters CJ, Jones PM, Bowe JE. The role of non-placental signals in the adaptation of islets to pregnancy. *Horm Metab Res* 2015;47(01):64–71
- Jackson D, Deschamps D, Myers D, Fields D, Knudtson E, Gunatilake R. Fetal epicardial fat thickness in diabetic and non-diabetic pregnancies: A retrospective cross-sectional study. *Obesity (Silver Spring)* 2016;24(01):167–171
- Yavuz A, Akkurt MO, Yalcin S, Karakoc G, Varol E, Sezik M. Second trimester fetal and maternal epicardial fat thickness in gestational diabetic pregnancies. *Horm Metab Res* 2016;48(09):595–600

- 13 Akkurt MO, Turan OM, Crimmins S, Harman CR, Turan S. Increased fetal epicardial fat thickness: a novel ultrasound marker for altered fetal metabolism in diabetic pregnancies. *J Clin Ultrasound* 2018;46(06):397–402
- 14 Chun H, Suh E, Byun AR, Park HR, Shim KW. Epicardial fat thickness is associated to type 2 diabetes mellitus in Korean men: a cross-sectional study. *Cardiovasc Diabetol* 2015;14:46
- 15 Iacobellis G, Willens HJ. Echocardiographic epicardial fat: a review of research and clinical applications. *J Am Soc Echocardiogr* 2009;22(12):1311–1319, quiz 1417–1418
- 16 Iacobellis G, Barbaro G, Gerstein HC. Relationship of epicardial fat thickness and fasting glucose. *Int J Cardiol* 2008;128(03):424–426
- 17 Aydin S, Fatihoglu E. Fetal epicardial fat thickness: can it serve as a sonographic screening marker for gestational diabetes mellitus? *J Med Ultrasound* 2020;28(04):239–244
- 18 Mookadam F, Goel R, Alharthi MS, Jiamsripong P, Cha S. Epicardial fat and its association with cardiovascular risk: a cross-sectional observational study. *Heart Views* 2010;11(03):103–108