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Fetal Epicardial Fat Thickness in Intrahepatic Cholestasis of Pregnancy

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ABSTRACT

Our aim will focus on evidence suggesting a role for fetal epicardial fat thickness (fEFT) as a quantifiable independent risk factor for intrahepatic cholestasis of pregnancy (ICP).

A prospective case-control study was conducted in pregnancies complicated with ICP. During the same period, healthy pregnant women at similar gestational weeks were randomly selected as the control group.

A total of 84 pregnant women participated in this study and we recruited 42 patients with ICP as study group and 42 healthy pregnant women as control group. Pregnant women in study group had significantly higher fEFT values and higher AST, ALT, direct and indirect bilirubin concentrations than those in control group ($p<0.05$). Study population was divided into two groups based on serum fasting total bile acid (TBA) levels of ≥ 40 μmol/L and <40 μmol/L as mild (n=30) and severe (n=12). The only significant parameter was direct bilirubin as higher levels in severe ICP group ($p<0.05$). The ROC curve analysis for assessing the performance of fEFT value in predicting ICP revealed that the area under the curve was 0.793 for ICP. The optimal fEFT cut- off value for predicting ICP was found as 0.085 mm with a sensitivity of 78.6% and specifity of 71.4% .

The present study has shown that higher fEFT levels can be associated with prediction of ICP, and the study justifies the inclusion of fEFT as an aid in diagnosis alongside AST, ALT and bilirubins, as measurement of TBA levels is time consuming and expensive.

Keywords: Intrahepatic cholestasis of pregnancy, fetal epicardial fat thickness, total bile acid, bilirubin, diagnosis

Introduction

Intrahepatic cholestasis of pregnancy (ICP) is the most common liver disease specific to pregnancy a varied global incidence (from <1 to 27.6 percent worldwide), both geographically and with ethnicity (1). It is characterized by maternal pruritus, raised serum bile acids and increased rates of adverse fetal outcomes. The etiology of ICP is complex and not completely understood, but it is probably caused by elevated bile acids secondary to a combination of genetic predisposition (2), sex steroid hormones (3, 4), environmental factors (5) and underlying liver disease (6). Many studies from previous and recent years on pregnant women with cholestasis of pregnancy have shown that serum inflammatory cytokines are altered in patients with ICP (1, 7-9).

Epicardial adipose tissue (EAT) is the term used to describe the adipose tissue that is found between the outer wall of the myocardium and the visceral layer of the pericardium. EAT is identified as the anechoic space between the outer wall of the myocardium and the visceral layer of the pericardium (Figure 1). It has the same embryological origin as mesenteric and omental adipocytes. EAT is far more than a fat depot composed of adipocytes, as it also contains nerve and nodal tissue, as well as inflammatory, stromal and immune cells (10, 11). EAT is an extremely metabolically active organ secreting anti-inflammatory adipokines during healthy conditions as well as pro-inflammatory cytokines under metabolic insults, as has been demonstrated in various endocrinological diseases (12, 13).

The association between EAT and chronic inflammation in adults has been clearly established (14). In a systematic review and metanalysis, it has been shown that maternal epicardial fat thickness (EFT) is increased in patients with gestational and pregestational diabetes mellitus and pregnancy-related hypertensive disorders compared with healthy controls (15). Furthermore, emerging data have suggested that fetal EFT (fEFT) was also

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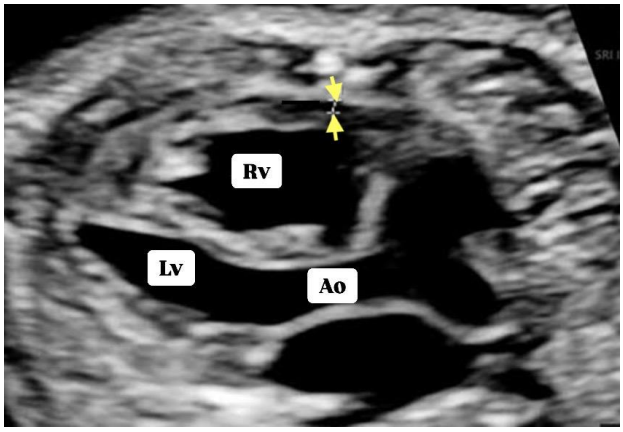

Fig. 1. Sonographic imaging and measurement of epicardial fat thickness. LV: left ventricle; RV: right ventricle; Ao: aorta

affected by perinatal abnormalities, increasing in gestational diabetes mellitus (GDM)(16, 17), preterm pre-labor rupture of membranes (PPROM)(18) and large for gestational age fetuses (19), while it decreases in fetal growth restriction (FGR) (20).

We hypothesized that EAT might play a role in ICP because serum inflammatory cytokines were impaired in it. Therefore, this prospective study will focus on evidence suggesting a role for fEFT as a quantifiable independent risk factor for ICP, as well as describing the relationship it may have as an active player in disease severity and the relationship to laboratory markers.

Material and Methods

This prospective case-control study was conducted in Ankara Bilkent City Hospital between August, 2022 and January, 2023. Ethics approval was obtained from the institutional review board (No. E2-21-465). All participants provided written informed consent and the study was conducted in accordance with the Declaration of Helsinki (21).

We performed a power analysis with G-Power® to define the minimum number of participants included in the study and 35 patients were found to be necessary with a power of 95% according to the study published by Yakut et al. (18, 20, 22). The diagnostic criteria for ICP was in accordance with: fasting total bile acids > 10 μmol/L with pruritus after exclusion of other causes of elevated bile acids (23). Gestational age was confirmed using first-trimester sonographic dating.

Participants with associated pregnancy complications (e.g. GDM and other abnormalities of glucose metabolism, gestational hypertensive disorders, FGR, PPROM, and chorioamnionitis), known hepatobiliary or coexisting chronic systemic disease, abnormal prenatal screening results, and nonsingleton pregnancies were excluded from both study and control group. The control group consisted of gestational age matched pregnant women with no defined maternal and fetal risks who had similar clinical characteristics.

The following information were recorded by the researchers: maternal age; gravidity; parity; number of living children; previous miscarriages; pre-pregnancy body mass index (BMI); gestational age at diagnosis; gestational age at delivery; mode of delivery; birth weight; APGAR scores; fetal epicardial fat thickness (EFT); laboratory findings: serum fasting total bile acid levels (TBA), aspartate aminotransferase (AST), alanine aminotransferase (10), white blood cell count (WBC), neutrophil count, eosinophil count, lymphocyte count, monocyte count, platelet count. Blood samples were drawn from participants from antecubital vein simultaneously before initiation of any treatment and medication. All recorded demographic, clinical characteristics and laboratory findings were compared between the study and the control groups. The study group was also divided into 2 subgroups according to TBA levels. TBA levels from 10 to 39 μmol/L were considered as mild ICP, while patients with TBA ≥ 40 μmol/L were considered as severe ICP, as no increase in stillbirth risk was detected in ICP patients with TBA levels < 40 micromol/L (24). All laboratory findings and EFT measurements were also compared between subgroups.

All sonographic measurements were performed by a single investigator (AA). The Voluson S10 (GE Medical Systems) ultrasonography device and a 3.5 MHz convex transducer (6C1-PVT-375BT) transabdominal probe were used for the measurements. The left ventricular outflow tract view was obtained, which is ideal for viewing the space (epicardial fat) between the myocardium and epicardium by the right ventricle. fEFT was measured outher surface of the myocardium to the inner surface of the epicardium, adjacent to the right ventricular wall (Figure 1).

Statistical analyses were performed using the SPSS (IBM SPSS Statistics 27) package program. Frequency tables and descriptive statistics were used to interpret the findings. Parametric methods were used for measurement values suitable for normal distribution. In accordance with parametric methods, "Independent Sample-t" test

Table 1: The Baseline Characteristics of The Study and Control Groups

Variable	Study (n=42)	Control (n=42)	p value
Maternal age (years) (mean ± SD)	31.07±6.35	28.83±5.29	0.087
Gestational week at examination (median) (min–max)	34.5 (22.4-37.9)	34.5 [24.1-39.6]	0.546
Gravidity (median) (min–max)	1 (0-7)	1 [0-5]	0.412
Parity (median) (min-max)	0 [0-4]	0.5 [0-3]	0.953
Living child (median) (min-max)	0 [0-4]	0 [0-3]	0.925
Previous miscarriage (median) (min-max)	0 [0-3]	0 [0-3]	0.085
Pre-pregnancy BMI (kg/m2) (mean ± SD)	26.10±5.43	22.71±3.32	0.008
Gestational week at delivery (median) (min–max)	36 [34-39]	39 [30-41]	<0.001
Route of delivery			
Normal spontaneous vaginal (n, %)	15 (35.7%)	17 (40.5%)	0,653
Cesarean section (n, %)	27 (64.3%)	25 (59.5%)	
Birth Weight (gram) (mean ± SD)	2853.94±385.61	3104.48±489.58	0.001
Apgar at 1st minute (median, min-max)	7 [6-9]	8 [6-8]	0.173
Apgar at 5th minute (median, min-max)	9[7-10]	9 [4-9]	0.284

SD: standart deviation; BMI: body mass index; Bold values are statistically significant ($p < 0.05$)

Table 2: Comparison of the fEFT and Biochemical Markers Among Study and Control Groups

Variable	Study (n=42)	Control (n=42)	p value
fEFT (mm; min-max)	1.1±0.3 (0.3-1.7)	0.7±0.3 (0.2-1.7)	<0.001
AST (U/L)	146.78±175.94	14.45±7.18	<0.001
ALT (U/L)	207.61±224.48	17.12±9.99	<0.001
Direct Bilirubine (mg/dl)	0.31±0.29	0.11±0.04	<0.001
Indirect Bilirubine (mg/dl)	0.47±0.25	0.36±0.13	0.028
WBC (x109/L)	9.42±2.60	10.20±2.66	0.163
NEU (x109/L)	7.02±2.18	7.41±1.75	0.239
LYM (x109/L)	1.66±0.59	1.85±0.69	0.284
MON (x109/L)	0.50±0.19	0.52±0.22	0.766
PLT (x109/L)	280.10±82.99	243.85±64.24	0.119

EFT: epicardial fat thickness; mm: milimeters; AST: aspartate aminotransferase; ALT: alanine aminotransferase; WBC:white blood cell; CBC: complete blood count; NEU, neutrophil; EOS, eosinophil; LYM, lymphocyte; MON: monocyte; PLT: platelet

Variables are presented as mean and standard deviation values, and bold values are statistically significant ($p<0.05$).

(t-table value) method was used to compare the measurement values of two independent groups. Nonparametric methods were used for measurement values that were not suitable for normal distribution. In compliance with nonparametric methods, "Mann-Whitney U" test (Z-table value) method was used to compare the measurement values of two independent groups. "Pearson-$\chi 2$" cross-tabulations were used to examine the relationship between two qualitative variables. "Spearman" correlation coefficient was used to examine the relationship between two quantitative variables that do not have normal distribution. In analyzing the factors affecting the disease, "Binary logistic regression: Backward LR model" was used.

Results

A total of 84 pregnant women participated in this prospective case-control study and we recruited 42

Table 3: Comparison of the fEFT and Biochemical Markers Among Subgroups

Variable	Mild (n=30)	Severe (n=12)	p value
EFT (mm; min-max)	1.1±0.3 (0.3-1.7)	1.1±0.3 (0.6-1.5)	0.571
AST (U/L)	116.66±126.78	219.58±251.95	0.912
ALT (U/L)	176.52±203.16	282.75±263.58	0.240
ALP (U/L)	164.93±54.70	213.50±84.69	0.063
Direct Bilirubine (mg/dl)	0.23±0.19	0.50±0.42	0.006
Indirect Bilirubine (mg/dl)	0.41±0.14	0.62±0.38	0.112
WBC (x109/L)	9.77±2.55	8.62±2.66	0.204
NEU (x109/L)	7.43±2.21	6.31±1.88	0.075
LYM (x109/L)	1.61±0.50	1.79±0.76	0.402
MON (x109/L)	0.52±.21	0.46±0.17	0.496
PLT (x109/L)	283.00±94.81	273.33±47.79	0.616

EFT: epicardial fat thickness; mm: milimeters; AST: aspartate aminotransferase; ALT: alanine aminotransferase; ALP: alkaline phosphatase; WBC:white blood cell; CBC: complete blood count; NEU, neutrophil; EOS, eosinophil; LYM, lymphocyte; MON: monocyte; PLT: platelet
Variables are presented as mean and standard deviation values, and bold values are statistically significant ($p<0.05$).

Table 4: ROC curve analysis to assess the performance of fetal EFT value in ICP

Variable	AUC	Sensitivity (%)	Specificity (%)	p value
EFT	0.793	78.6	71.4	<0,001

patients with ICP as study group and 42 healthy pregnant women as control group. ICP group was divided into two groups as mild (n=30) and severe (n=12) according to TBA levels.

The baseline characteristics of the study and control groups are shown in Table 1. There were no statistically significant differences in maternal age, gravidity, parity, number of living children, previous miscarriages among the groups, while pre-pregnancy body mass indexes of pregnant woman was significantly higher in study group ($p<0.05$).

Comparison of ultrasound and laboratory findings between the groups is summarized in Table 2.

Pregnant women in study group had significantly higher fEFT values and higher AST, ALT, direct bilirubine and indirect bilirubine concentrations than those in control group ($p<0.05$).

Study population was divided into two groups based on TBA levels of ≥ 40 μmol/L and <40 μmol/L as mild (n=30) and severe (n=12). The only significant parameter was direct bilirubine as higher levels in severe ICP group ($p<0.05$).

The ROC curve analysis for assessing the performance of fetal EFT value in predicting ICP is shown in Table 4 and Figure 2. The area under the curve was 0.793 ($p<0.001$, 95% CI: 0.69–0.89) for ICP. The optimal fetal EFT cut- off value for predicting ICP disease was found as 0.085 mm with a sensitivity of 78.6% and specifity of 71.4% (Figure 2).

Discussion

To the best of our knowledge, the present prospective case-control study is first to demonstrate inflammatory properties of epicardial adipose stores in fetuses with maternal ICP diagnosis independent of co-morbidities as diabetes, hypertension. The use of ultrasonography is now an integral part of daily clinical practice in pregnancy; thus we summarized the utility of fEFT measurement such as laboratory biomarkers used in diagnosis of ICP. In particular, we focused on the evaluation of fEFT that could become a diagnostic and prognostic factor able to help clinicians to identify the patients at risk or not to develop intrahepatic cholestasis of pregnancy, and to provide information on their clinical and therapeutic outcomes.

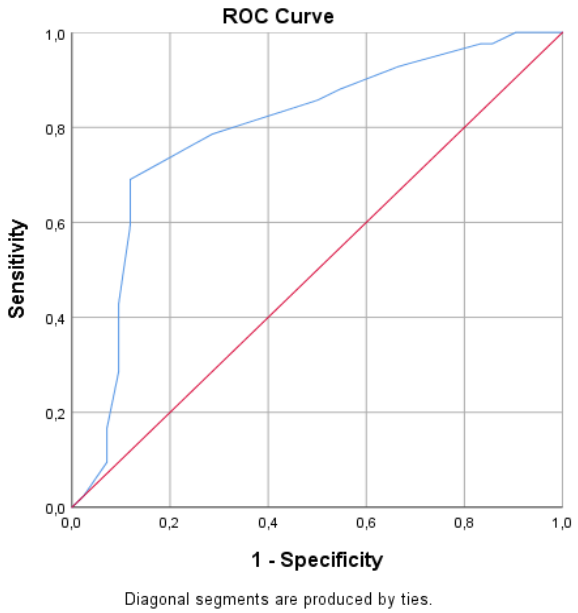

Fig. 2. ROC curve for fetal EFT value in ICP

Main purpose of this prospective study is to analyze the EFT measuements of fetuses and its pathological correlations with attention to presence and severity of disease. ICP is generally considered as "mild" when TBA levels are from 10 to 39 μmol/L and "severe" with TBA ≥ 40 μmol/L (24). Additionally we purposed the relationship of fEFT with severity of ICP and simultaneos laboratory measurements.

In this prospective case-control study, the fEFT value was found statistically higher in the maternal ICP group when compared with the control group. In addition, we investigated the predictive value of EFT in ICP patients and we determined a cut off value, sensitivity, and specificity in the ICP. We found an fEFT cut-off value of 0.085mm with a sensitivity of 78.6% and specifity of 71.4% accurately predicted ICP patients. Thus, our method can be regarded as a useful and easy method for predicting ICP patients. Further studies with larger participants may confirm this hypothesis.

As mentioned earlier, in the literature review, there are only a few studies to investigate fetal epicardial fat thickness. In the study conducted by Iskender et al., higher fEFT values were found in the fetuses diagnosed with gestational diabetes mellitus (16). Supportingly, Singh et al. found higher EFT values in fetuses diagnosed with GDM when compared to pregestational diabetes mellitus and healthy pregnant women (17). In another study Sakcak et al. found high fEFT values in the pPROM group compare to the controls (18).

ICP is associated with adverse obstetric outcomes. Most important one is the risk for fetal death, which has been reported to affect 2-4% of ICP pregnancies (25). Although the exact mechanism of fetal death that is associated with ICP is unknown, there is evidence to suggest that it may be related to a fetal cardiac event. Stacy et al. found a significant difference in the PR interval between fetuses of women with ICP and fetuses of normal control subjects (26). Also, Shih-jie et al. found that the PR interval, P wave duration and inter-atrial conduction block were associated with the amounts of epicardial fat, which might imply an effect for arrhythmogenesis (27). In the light of our study result about fEFT in ICP, further investigation is needed to determine whether fetal echocardiography can help to predict which fetuses are at risk for death that is associated with ICP.

Prospective design, the combination of laboratory measurements with fEFT are the main strengths of the current study. However, the present study has some limitations. The relatively low number of cases and the monocentric design are the main limitations. Thus, further studies focused on multicentric and larger populations might indicate more precisive results.

In conclusion, the present study has shown that higher fEFT levels can be associated with prediction of ICP, and considering the results of the present study as inferential, our study justifies the inclusion of fEFT as an aid in diagnosis alongside AST, ALT and bilirubins, as measurement of TBA levels is time consuming and expensive.

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Statements & Declarations

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All authors read and approved the final manuscript.Ethical approval: Ethics approval was obtained from the institutional review board. The study was conducted in accordance with the Declaration of Helsinki.

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