Fetal pulmonary artery Doppler parameters in pregnancies complicated with intrahepatic cholestasis of pregnancy: a prospective case-control study

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Abstract

Objective: The primary aim of this study was to determine whether pulmonary artery acceleration time (AT) to ejection time (ET) ratio (PATET) was altered in fetuses of mothers with intrahepatic cholestasis of pregnancy (IHCP). The secondary aim was to investigate the association between fetal pulmonary artery Doppler parameters with neonatal outcomes in pregnancies complicated by IHCP.

Material and Methods: This prospective case control study was conducted in a tertiary perinatal-neonatal center. A total of 18 fetuses whose mothers' pregnancies were complicated by IHCP were included as the study group and a total of 37 fetuses of mothers with healthy pregnancies were selected as controls. Fetal pulmonary artery Doppler parameters (AT; ET; AT/ET ratio) were assessed and neonatal outcomes were evaluated.

Results: Mean pulmonary artery AT, ET and PATET were significantly different between the groups ($p=0.001$, $p=0.024$ and $p=0.003$, respectively). The mean PATET value in the IHCP group was 0.217 ± 0.029 while in the control group it was 0.180 ± 0.020. While PATET values were correlated with gestational age at birth, respiratory distress and need for neonatal intensive care admission were not correlated with PATET.

Conclusion: Higher values of PATET may be a useful biomarker of fetal lung damage, secondary to IHCP. (J Turk Ger Gynecol Assoc 2022; 23: 249-54)

Keywords: Acceleration time, ejection time, intrahepatic cholestasis, pulmonary artery

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Introduction

Intrahepatic cholestasis of pregnancy (IHCP) is the most common hepatobiliary system disease of pregnancy and generally occurs in the late second and third trimesters, with a variable incidence of between 0.4% and 5% (1). IHCP is diagnosed with new-onset pruritus, particularly in the palms and soles of the feet, and elevated maternal serum bile acids and/or liver function enzymes. Furthermore, in the latest articles it has been reported that IHCP may be predicted in the first trimester by using the ratio of aspartate aminotransferase (AST) to platelet ratio index (2). Even though IHCP is generally a benign condition that resolves in two or three weeks after delivery, it is associated with adverse perinatal and neonatal outcomes (3-6). Due to the severity of the disease, a higher incidence of obstetric complications, such as preterm delivery, meconium staining of amniotic fluid, respiratory distress, fetal bradyarrhythmia and fetal demise, has been observed (1,3). It has been suggested that the underlying pathophysiological mechanism to explain these complications is raised bile acids in fetal tissues (7). As in bile acid accumulation in fetal myocardium, chronic exposure to bile acids disrupts fetal pulmonary development and function by blocking surfactant production (1,7). Moreover, in the literature, higher bile acid

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concentration has been detected in cord blood and amniotic fluid and this is associated with lower levels of pulmonary surfactant production so that respiratory distress syndrome (RDS) may be observed more often in affected newborns (8,9). RDS which may even complicate newborns after term delivery, still remains the major cause of neonatal intensive care unit (NICU) admissions, neonatal morbidity and mortality (10). Due to the importance of RDS, prediction of respiratory complications before delivery has been proposed using a range of invasive techniques, such as assessment of lecithin/sphingomyelin ratio in amniotic fluid. However, in the last decade, pulmonary artery acceleration time (AT) to ejection time (ET) ratio (PATET) has been investigated as a non-invasive method for evaluating pulmonary lung maturation (10-13). It has been reported that a low PATET ratio is a reliable ultrasonographic parameter for assessment of fetal lung immaturity, and has been particularly studied in preterm, small-for-gestational age fetuses (10,11).

Based on published evidence, we hypothesized that the effect of IHCP on fetal lung maturation might be detected by evaluating the impact of IHCP on fetal pulmonary artery Doppler parameters. The primary aim of this study was to investigate changes in PATET in the fetuses of mothers with pregnancies complicated by IHCP and to compare these with healthy pregnancies. The secondary aim was to investigate the association between fetal pulmonary artery Doppler parameters with neonatal outcomes in pregnancies complicated by IHCP.

Material and Methods

This prospective, case-control study was conducted in a tertiary perinatal-neonatal center, between June 2020 and December 2020. The study was approved by the Institutional Review Board of University of Health Sciences Turkey, Ankara City Hospital Ethics Committee (approval number: E2-20-89). The research related to humans complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Declaration of Helsinki, and has been approved by the authors' institutional review board or equivalent committee. After verbal and written information about the study, all eligible and voluntary participants gave informed consent.

Eligibility criteria of participants included singleton pregnancies, maternal age between 17 and 45 years, having no chronic systemic diseases except for IHCP. Exclusion criteria included multiple pregnancies, preexisting maternal systemic disease, such as diabetes mellitus, chronic liver disease, hepatitis, chronic renal failure, and rheumatological disease, and maternal hepatotoxic drug use. Additionally, fetal growth restriction or macrosomia, known fetal structural malformation and/or karyotype abnormality, and pregnancies complicated with preterm delivery, premature preterm rupture of membranes, preeclampsia, or pregnancy-induced hypertension were excluded.

The gestational age was determined according to crown-rump length measurement between 11th and 14th gestational weeks. The medical records of every eligible case was reviewed and the following variables were recorded to dataset: maternal demographic characteristics (age, body mass index in kg/m^2), obstetric histories (gravidity, parity, miscarriage, living children), pregnancy associated plasma protein A MoM values that were obtained in the first trimester aneuploidy screening, maternal liver function enzymes including (AST in U/L), (alanine aminotransferase in U/L) and maternal serum bile acid values that were reported at the time of diagnosis. The birth characteristics (type of delivery, gestational age at birth, birth weight, APGAR scores first and fifth minutes), NICU admission and the parameters of umbilical cord venous blood samples to determine acidbase status of the newborns were also recorded. Neonatal acidemia at birth was defined as either pH <7.2 or base deficit ≥12 mEq/L, in agreement with the neonatology clinic.

All ultrasonographic measurements were performed using a Voluson E8 Expert ultrasound (GE Healthcare, USA) with a multi-frequency convex transducer at 3-9 mHz. After admission of participants for delivery, fetal biometric measurements (biparietal diameter, head circumference, abdominal circumference, femur length, thoracic circumference), estimated fetal weight, fetal wellbeing, amniotic fluid index, Doppler flow and velocity indices of umbilical artery, middle cerebral artery, ductus venosus and fetal main pulmonary artery flow waveforms were assessed by a single observer (B.Y.).

A standardized measurement technique, previously described by Azpurua et al. (13), was used for fetal main pulmonary artery flow waveforms. After obtaining a four-chamber view of the fetal heart, a slight probe rotation was performed to maintain the short axes view that revealed the main pulmonary artery and its branches. The sample volume gate was set between two and three millimeters and was placed above the pulmonary valve. The angle of insonation was maintained under 20 degrees. The time interval between the beginning of the ventricular systole and the first peak was defined as AT. The time interval of ventricular systole was defined as ET (Figure 1). These measurements were repeated three times and mean values were recorded. The PATET ratio was obtained by dividing the AT by the ET. Using the same flow-trace, the main pulmonary artery pulsatility and resistance indices were calculated.

Immediately after delivery, the umbilical cord was clamped bilaterally and umbilical venous blood samples from the placental side were drawn into a heparinized syringe. Umbilical

venous blood pH, partial oxygen (pO_2) and carbon dioxide (pCO_2) saturation, bicarbonate, lactic acid, and base excess were recorded.

Statistical analysis

The statistical analyses were conducted using the SPSS version 22 (IBM Inc. Armonk, NY, USA). The normality of distribution was evaluated with histograms, probability plots and Kolmogorov-Smirnov test. The quantitative data were summarized as mean ± standard deviation. Parametric comparisons were made by using the Student's t-test. For all statistical analysis, a p-value <0.05 with a 95% confidence interval was considered significant. Correlation analysis was conducted using Pearson analysis.

Results

This sample consisted of 55 cases, of which 18 were IHCP and 37 were controls. Comparison of demographic features is summarized in Table 1. There was no statistically significant difference between IHCP and control groups in terms of maternal demographic characteristics and obstetric history, with the exception of parity (p=0.02).

Umbilical artery, middle cerebral artery and pulmonary artery Doppler flow indices are summarized in Table 2. Mean pulmonary artery AT, ET, PATET and peak systolic velocity values were significantly different between the groups (p=0.001, p=0.024 and p=0.003, respectively). The mean PATET value in the IHCP group was 0.217±0.029 while in the control group it was 0.180±0.020. Mean maternal serum bile acid value was 27.8±16.3 mmol/L.

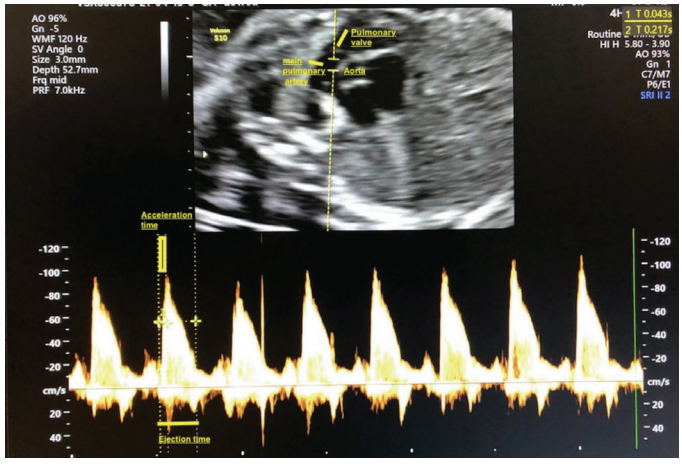

Figure 1. Fetal main pulmonary artery Doppler flow-trace

In Table 3, birth characteristics, umbilical venous blood gas analysis, NICU admission and respiratory distress values are compared. There was no difference in terms of type of delivery, administration of antenatal corticosteroid, APGAR scores at the first and fifth minutes and respiratory distress between the two groups but gestational age at birth and birthweight were significantly different (p=0.001 and p=0.034). Furthermore, significantly lower pH values and higher pCO_2 values were found in the IHC group. Acidemia was not detected in any pregnancy in either group.

In the IHCP group, 8 (44.4%) of newborns were admitted to NICU and 5 (27.7%) had respiratory distress. In comparison, 3 (8%) of newborns in the control group were admitted to NICU due to respiratory distress. When NICU admission and respiratory distress values were compared, NICU admission was significantly different (p=0.012) but respiratory distress was not (p=0.096). APGAR score at the fifth minute, gestational age at birth and respiratory distress were significantly correlated with NICU admission. Moderate negative correlations were identified for gestational age at birth (r=-0.471, p=0.001) and APGAR score at five minutes (r=-0.294, p=0.031) and a moderate positive correlation was present between respiratory distress (r=0.372, p=0.006) and NICU admission was found. While PATET values were correlated with gestational age at birth, there was no correlation with respiratory distress and NICU admission.

Discussion

In the present study, significantly higher values of PATET were found in the fetuses whose mothers' pregnancies were complicated by IHCP compared to fetuses of mothers with healthy pregnancies. Although NICU admission and respiratory distress were more frequent in the IHCP group, these were not correlated with PATET. Gestational age at birth and APGAR

Table 1. Maternal characteristics of intrahepatic cholestasis and control groups

Maternal characteristics	Intrahepatic cholestasis group, (n=18)	Control group, (n=37)	p
Age, years	27.4±6.1	27.6±5.6	0.905
Gravidity, (n)	1.5±1.1	2.2±1.1	0.064
Parity, (n)	0.3±0.8	0.9±1.1	0.020
Miscarriage, (n)	0.2±0.4	0.2±0.5	0.710
Living child, (n)	0.3±0.8	0.9±1.1	0.119
Body mass index (k/m^2)	28.6±3.9	29.6±4.5	0.441

score at the fifth minute were the most important determinants of the NICU admission and respiratory complications.

Many studies have focused on the relationship between PATET and respiratory complications, but conflicting results have been reported. Pulmonary artery AT and right ventricle ET were first assessed by Kitabatake et al. (14), and they reported that decreased values of both measurements were present in patients with pulmonary arterial hypertension. Fuke et al. (15), showed that AT/ET ratio of the branches of pulmonary artery appeared to be an accurate parameter with which to predict pulmonary hypoplasia. To date, PATET has been investigated to predict RDS, especially in premature fetuses (12-16). Few studies have investigated PATET values in late term and term fetuses and these showed an

Table 2. Comparison of main pulmonary artery, umbilical and middle cerebral artery Doppler flow indices between intrahepatic cholestasis group and control group

	Intrahepatic cholestasis group, (n=18)	Control group, (n=37)	p
MPA acceleration time milisec, ms	0.0462±0.007	0.035±0.004	<0.001
MPA ejection time milisec, ms	0.214±0.030	0.195±0.015	0.024
PATET	0.217±0.029	0.180±0.020	0.003
MPA PI	2.166±0.17	2.12±0.258	0.434
MPA RI	0.856±0.066	0.847±0.05	0.666
MPA systole/diastole	8.087±4.573	7.389±1.56	0.539
MPA PSV (cm/s)	83.1±10.06	70.6±8.95	<0.001
UA PI	0.85±0.11	0.83±0.21	0.648
UA RI	0.57±0.04	0.58±0.08	0.875
MCA PI	1.54±0.32	1.38±0.33	0.099
MCA RI	0.76±0.06	0.72±0.08	0.037

MPA: Main pulmonary artery, PATET: Pulmonary artery acceleration time-ejection time ratio, PI: Pulsatility index, PSV: Peak systolic velocity, RI: Resistance index, UA: Umbilical artery, MCA: Middle cerebral artery

Table 3. Comparisons of birth characteristics, umbilical cord venous blood gas analysis and NICU admission between intrahepatic cholestasis and control group

	Intrahepatic cholestasis group, (n=18)	Control group, (n=37)	p
Gestational age at birth, weeks	36.6±1.0	38.4±0.9	0.001
Antenatal corticosteroid, (n)	4	2	0.185
Type of delivery, (n)			
Vaginal birth	5	3	0.230
Ceaserean section	13	34	
Birthweight, (g)	2,973±422	3,221±275	0.034
APGAR 1. minute	7.1±0.6	7.5±0.5	0.070
APGAR 5. minute	8.6±0.6	8.9±0.4	0.108
Umbilical venous blood			
pH	7.29±0.05	7.33±0.06	0.016
pO_2 (mmHg)	24.3±10.4	27.1±9.7	0.359
pCO_2 (mmHg)	45.6±7.5	38.2±6.9	0.002
HCO_3 (mEq/L)	21.3±1.9	20.5±2.5	0.234
Lactate (mmol/L)	2.7±1.1	2.2±0.8	0.106
Base excess (mmol/L)	-4.3±3.7	-5.4±2.3	0.273
FO_2Hb (%)	34.8±21.6	45.8±19.9	0.111
Respiratory distress, (n)	5	3	0.096
NICU admission, (n)	8	3	0.012

NICU: Neonatal intensive care unit

inverse correlation between fetal PATET value and transient tachypnea of newborns (10,17).

In 2010, Azpurua et al. (13), reported that the AT/ET in the main pulmonary artery waveform correlated inversely with the lecithin/sphingomyelin ratio. In addition, in 2013, Kim et al. (12), demonstrated that an elevated AT/ET ratio in the fetal pulmonary artery was associated with RDS, further supporting the findings of Azpurua et al (13). Our findings are in keeping with those of Kim et al. (12) and Azpurua et al. (13) in terms of the relationship between elevated PATET and lung immaturity but contrast with many earlier studies. A possible explanation for this relationship is that fetal lung surfactant production is lower in IHCP than healthy fetuses and thus lung damage may be more likely in cases with elevated PATET.

In human fetuses the immunological response to tissue injury or microbial invasion involves both pro-inflammatory and anti-inflammatory responses. It has been shown that newborns exposed to systemic inflammation in utero have a higher frequency of neonatal morbidity, as a result of fetal inflammatory response syndrome, and is associated with multisystemic involvement (18). Fetal lung inflammation is characterized by expression of many different cytokines and the effect of inflammation is usually to stimulate surfactant production. In the literature, there are studies investigating this inflammatory process in order to clarify the etiology of IHCP and the pathophysiological pathways of bile acid-induced inflammation affecting fetal and neonatal outcomes (19-21). Herraez et al. (7) reported that accumulation of maternal bileacids triggered an inflammatory response in maternal and fetal lungs and highlighted the importance of released macrophage associated phospholipase A2 in RDS developmen.

Previous studies demonstrated that the RDS rate was approximately three times higher among the newborns whose mothers' pregnancies were complicated by IHCP (22,23). Arthuis et al. (22), also found a significant difference in intensive care unit admission rates and reported elevated biliary acid levels in this group. The NICU admission rate was higher in our study group, which is consistent with previous studies. Although respiratory distress rate (5/18) was higher in our study group, it was not different from the rate in the control group (3/37). This may be because all NICU admissions in the control group were due to respiratory distress and a lower rate of respiratory distress in all NICU admission in the study group.

To the best of our knowledge, this is the first study to evaluate PATET in fetuses whose mothers' pregnancies were complicated by IHCP. The strength of this study was its prospective nature and good design and being the first study in IHCP. The main limitation was the small sample size, because of the low incidence of IHCP and thus it was not possible to take account of severity of IHCP. Furthermore, the secondary hypothesis of this study was not testable given the results obtained.

Conclusion

Higher values of the main pulmonary artery PATET was present in fetuses whose mothers' pregnancies were complicated by IHCP. This finding may be helpful to understand the etiology of fetal lung damage, secondary to IHCP. Larger prospective studies and possibly more detailed investigation of sub-factors of PATET may further illuminate the prediction of respiratory complications in these newborns.

Ethics Committee Approval: *The study was approved by the Institutional Review Board of University of Health Sciences Turkey, Ankara City Hospital Ethics Committee (approval number: E2-20-89).*

Informed Consent: *After verbal and written information about the study, all eligible and voluntary participants gave informed consent.*

Peer-review: *Externally peer-reviewed.*

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