FETAL PULMONARY ARTERY DOPPLER PARAMETERS IN PREGNANCIES COMPLICATED WITH INTRAHEPATIC CHOLESTASIS OF PREGNANCY: A PROSPECTIVE CASE-CONTROL STUDY

betül yakıştıran[1], Atakan Tanacan[2], Orhan Altınboğa[3], sarkhan elbayiyev[1], emre canpolat[1], and Aykan Yucel[4]

[1]Affiliation not available
[2]Ankara City Hospital
[3]Zekai Tahir Burak Women's Health Training and Research Hospital
[4]Etlik Zubeyde Hanim Kadin Hastaliklari Egitim ve Arastirma Hastanesi

March 07, 2024

Abstract

ABSTRACT Objective: The primary aim of this study was to determine whether PATET was altered in the fetuses whose mothers were complicated by 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. Methods: This prospective case control study was conducted in a tertiary perinatal-neonatal center. A total of 18 fetuses whose mothers were complicated by IHCP were set as the study group and a total of 37 fetuses whose mothers were healthy were selected as the control group. Fetal pulmonary artery Doppler parameters (acceleration time -AT; ejection time -ET; AT/ET ratio) were assessed and neonatal outcomes were evaluated. Results: Mean pulmonary artery AT, ET, PATET were statistically significant 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 (p=0,003). While PATET values were correlated with gestational age at birth, respiratory distress and NICU admission were not correlated with PATET. Conclusions: Higher values of PATET may be helpful to understand fetal lung damage secondary to IHCP. Keywords: acceleration time; ejection time; intrahepatic cholestasis; pulmonary artery

INTRODUCTION

Intrahepatic cholestasis of pregnancy (IHCP) is the most common hepatobiliary system disease of pregnancy that generally occurs in the late second and third trimesters, with the variable incidence between 0,4% and 5% [1]. It is diagnosed with new-onset pruritus particularly in palms and soles of the feet and elevated maternal serum bile acids and/or liver function enzymes. Even though IHCP is known as a usually benign disease that is resolved in two or three weeks after delivery, it is associated with adverse perinatal and neonatal outcomes [2-4]. Due to the severity of the disease, higher incidence of obstetric complications such as preterm delivery, meconium staining of amniotic fluid, respiratory distress, fetal bradyarrhythmia and fetal demise has been observed[1,2]. The underlying pathophysiological mechanism to explain these complications has been associated with raised bile acids in fetal tissues [5]. As in bile acid accumulation in fetal myocardium, chronic exposure to bile acids disrupts fetal pulmonary development and function by blocking surfactant production[1,5]. Moreover, in literature, it has been explained that the higher bile acid concentration is detected in cord blood and

amniotic fluid, the lower level of pulmonary surfactant is produced and respiratory distress syndrome (RDS) may be observed more often in those newborns [6,7].

Respiratory distress syndrome that may complicate newborns even after term deliveries, still remains the major cause of neonatal intensive care unit (NICU) admissions, neonatal morbidity and mortality[8]. Due to its importance, to predict respiratory complications before delivery, some different invasive techniques have been described such as assessment of lecithin/sphingomyelin ratio of amniotic fluid. However in the last decade, pulmonary artery acceleration time (AT) to ejection time (ET) ratio (PATET) has been studied as a non-invasive method evaluating pulmonary lung maturation[8-11]. It has been reported that low PATET ratio has been a reliable ultrasonographic parameter that give tips on fetal lung immaturity particularly has been studied on preterm, small-for-gestational age fetuses [8,9].

Based on previous studies, we hypothesized that effect of IHCP on fetal lung maturation might be detected as evaluating the impact of IHCP on fetal pulmonary artery Doppler parameters. The primary aim of this study was to determine whether PATET was altered in the fetuses whose mothers were complicated by IHCP. The secondary aim was to investigate the association between fetal pulmonary artery Doppler parameters with neonatal outcomes in pregnancies complicated by IHCP.

MATERIAL-METHOD

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 Ankara City Hospital Ethics Committee. The research related to human use has been complied with all the relevant national regulations, institutional policies and in accordance the tenets of the Helsinki Declaration, and has been approved by the authors' institutional review board or equivalent committee (E2-20-89). 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 IHCP. Exclusion criteria included multiple pregnancies, preexisting maternal systemic disease (eg, diabetes mellitus, chronic liver disease, hepatitis, chronic renal failure, rheumatological disease), 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, pregnancy-induced hypertension were excluded.

The gestational age was determined according to crown-lump length (CRL) measurement between 11th and 14th gestational weeks. The medical records of every eligible cases were reviewed the following variables were recorded to dataset: maternal demographic characteristics (age, body mass indices (kg/m2)), obstetric histories (gravidity, parity, miscarriage, living child), pregnancy associated plasma protein A (PAPP-A) MoM values that were obtained in the first trimester aneuploidy screening, maternal liver function enzymes (aspartate aminotransferase -AST (U/L), alanine aminotransferase - ALT (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, the APGAR scores 1. and 5. minutes), NICU admission and the parameters of umbilical cord venous blood samples to determine acid-base status of the newborns were recorded also. 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), multifrequency convex transducer at 3-9 mHz. After admission of participants for delivery, fetal biometric measurements (biparietal diameter, head circumference, abdominal circumference, femur lenght, 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 provider (BY).

A standardized measurement technique that was previously described by Azpurua et al. [11], was used for

fetal main pulmonary artery flow waveforms. After obtaining four-chamber view of the fetal heart, a slight probe rotation was performed to maintain the short axes view that reveals 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 kept under 20 degrees. The time interval between the beginning of the ventriculary systole and the first peak was defined as acceleration time (AT). The time interval of ventricular systole was defined as ejection time (ET) (Figure 1). These measurements were repeated three times and mean values were recorded. The PATET ratio was obtained by dividing the acceleration time to the ejection time (ET). By using the same flow-trace the main pulmonary artery pulsatility and resistance indices were calculated.

Immediately after delivery, umbilical cord was clamped bilaterally and umbilical venous blood samples from 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, base excess (BE) were recorded.

Statistical analysis

The statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS 22, IBM SPSS Statistics for Windows®, Version 22.0 Armonk, NY:IBM Corp). The normality of distribution was evaluated with histograms, probability plots and Kolmogrov Simirnov test. The quantitative data were summarized as mean ± standard deviation. Parametric comparisons were made by using theStudent T test. For all statistical analysis, p-value <0,05 with a 95%CI was considered significant. Correlation analysis was conducted using Pearson analysis.

RESULTS

This study consisted of 55 cases (18 IHCP and 37 control). Comparison of demographic features was summarized in Table 1. There was no statistically significant difference between IHCP and control group in terms of maternal demographic characteristics and obstetric history except parity (p=0,02).

Umbilical artery, middle cerebral artery and pulmonary artery Doppler flow indices were summarized in Table 2. Regarding the Doppler findings, mean pulmonary artery AT, ET, PATET and peak systolic velocity values were statistically significant 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 (p=0,003). Mean maternal serum bile acid value was 27,8 ± 16,3 mmol/L.

In Table 3, birth characteristics, umbilical venous blood gas analysis, NICU admission and respiratory distress values were compared. The comparisons regarding to type of delivery, administration of antenatal corticosteroid, APGAR scores at the first and fifth minutes and respiratory distress were not statistically significant, but gestational age at birth and birthweight were different (p=0,001 and p:0,034). As statistically different, lower pH values and higher pCO_2values were detected in the IHC group. Acidemia was not detected in any of them.

In the IHCP group, 8 (44,4%) newborns admitted to NICU and 5 (27,7%) of them had respiratory distress. Besides, 3(8%) newborns in the control group admitted to NICU due to respiratory distress. When NICU admission and respiratory distress values were compared, NICU admission was significantly different but respiratory distress was not found (p:0,012 and p:0,096, respectively). APGAR score at fifth minutes, gestational age at birth and respiratory distress were significantly correlated with NICU admission. Moderate negative correlations between gestational age at birth (r=-.471 p=0,001) , APGAR score at fifth minutes (r=-.294 p=0,031) and NICU admission were found. A moderate correlation between respiratory distress (r=,372 p:0,006) and NICU admission was found. While PATET values were correlated with gestational age at birth, respiratory distress and NICU admission were not correlated with PATET.

DISCUSSION

In this present study, significantly higher values of the pulmonary artery acceleration to ejection time (PA-TET) were found in the fetuses whose mothers were complicated by IHCP. Notwithstanding detection of

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frequent NICU admission and respiratory distress in the IHCP group, these were not correlated with PATET. Gestational age at birth and APGAR score at fifth minutes were the most important determinants of the NICU admission and respiratory complications.

In literature, although many studies that were focused on the relationship between PATET and respiratory complications, conflicting results have been reported. Pulmonary artery acceleration time and right ventricle ejection time were first assessed by Kitabatake et al, and they reported that decreased values of both measurements have been found in pulmonary arterial hypertension [12]. Fuke et al, showed that AT/ET ratio of the branches of pulmonary artery appeared to be an accurate parameter with which to predict pulmonary hypoplasia[13]. To date, the PATET has been investigated to predict RDS especially premature fetuses [10-14]. Few studies that were focused on PATET values of late term and term fetuses showed that inverse correlation between fetal PATET value and transient tachypnea of newborns [8,15].

However, in 2010, Azpurua et al, reported that the At/Et in the main pulmonary artery waveform correlated inversely with the lecithin/sphingomyeline ratio [11]. In 2013, Kim et al, demonstrated that an elevated At/Et ratio in the fetal pulmonary artery was associated with RDS as supporting Azpurua [10]. The other studies that were referred above, showed contrast findings from Azpurua's study and this study. The findings of both studies observations are similar to our study results in terms of the relationship between elevated PATET and lung immaturity. Possible explanation of it, fetal lung surfactant production is lower in IHCP than healthy fetuses and possible lung damage has been with elevated PATET.

The immunological response to tissue injury or microbial invasion involves pro inflammatory and anti-inflammatory responses in human fetuses. It has been showed that the newborns exposed to systemic inflammation in utero were with higher frequency of neonatal morbidity as a result of fetal inflammatory response syndrome that is associated with multi systemic involvement [16]. Fetal lung inflammation is characterized by expression of many different cytokines and the effect of inflammation results as stimulated surfactant production. In literature, there are studies investigating inflammatory process intended for clarifying the etiology of IHCP and the pathophysiological pathways of bile acid induced inflammation affecting fetal and neonatal outcomes [17-19]. Herraez et al, reported that accumulation of maternal bile-acids triggered an inflammatory response in maternal and fetal lungs and the importance of released macrophage associated phospholipase A2 in RDS development[5].

Previous studies demonstrated that the RDS rate was approximately three times higher among the newborns whose mothers were complicated by IHCP[20,21]. Arthuis et al, also found significant difference for intensive care unit admission rates and they reported that higher biliary acid levels were in this group [20]. NICU admission rate was found higher in our study group which is consistent with the previous studies. Although, respiratory distress rate (5/18) was higher in our study group, it couldn't be found statistically significant when compare to the control group (3/37). That may be explained as all NICU admissions in the control group due to respiratory distress and lower ratio of respiratory distress in all NICU admission for the study group.

To the best of our knowledge, this is the first study that evaluates PATET in fetuses whose mothers were complicated by IHCP. The strength of this study was its prospective and well-designed and being the first study in IHCP as mentioned above. On the contrary, the main limitation was the small sample size depending on the lower incidence of IHCP and couldn't have been categorized based on severity of the disease. Additionally, the secondary hypothesis of this study couldn't be documented with these results.

In conclusion, higher values of the main pulmonary artery acceleration to ejection time that were detected in fetuses whose mothers were complicated by IHCP may be helpful to understand fetal lung damage secondary to IHCP. Larger prospective studies or evaluation of branches PATET values may be enlighten the prediction of respiratory complications of these newborns.

References

Zhang Y, Fei L, Wang Y., et al. Maternal bile acid transporter deficiency promotes neonatal demise. Nat

Commun 2015;6:8186.

Williamson C, Geenes V. Intrahepatic cholestasis of pregnancy. Obstet Gynecol 2014;124(1):120-33

Ovadia C, Williamson C. Intrahepatic cholestasis of pregnancy: Recent advances. Clin Dermatol. 2016;34(3):327-34.

Geenes V, Williamson C. Intrahepatic cholestasis of pregnancy. World J Gastroenterol 2009; 15(17):2049-66

Herraez E, Lozano E, Poli E, et al. Role of macrophages in bile-acid induced inflammatory response of fetal lung during maternal cholestasis. J Mol Med (Ber). 2014; 92(4):359-72

Zecca E, De Luca D, Marras M, et al. Intrahepatic cholestasis of pregnancy and neonatal respiratory distress syndrome Pediatrics 2006;117(5):1669-72

Yu L, Ding YL, Wang CX. Relationship between total bile acid concentration and fetal pulmonary surfactant in intrahepatic cholestasis of pregnancy. Zhonghua Fu Chan Ke Za Zhi. 2011;46(5):324-8

Eraslan SM, Col Madendag I, Sahin E,et al. Fetal pulmonary artery acceleration/ejection ratio for transient tachypnea of the newborn in uncomplicated term small for gestational age fetuses. Eur J Obstet Gynecol Reprod Biol 2020;247:116-120

Büke B, Destegül E, Akkaya H, et al. Prediction of neonatal respiratory distress syndrome via pulmonary artery Doppler examination. J Matern Fetal Neonatal Med 2019;32(10):1640-1645

Kim SM, Park JS, Norwitz ER, et al. Acceleration time-to-ejection time ratio in fetal pulmonary artery predicts the development of neonatal respiratory distress syndrome: a prospective cohort study. Am J Perinatal 2013;30(10);805-12.

Azpurua H, Norwitz ER, Campbell KH, et al. Acceleration/ejection time ratio in the fetal pulmonary artery predicts fetal lung maturity. Am J Obstet Gynecol 2010;203(1):40.e1-8

Kitabatake A, Inoue M, Asao M, et al. Noninvasive evaluation of pulmonary hypertension by a pulsed Doppler technique. Circulation 1983;68(2):302-9

Fuke S, Kanzaki T, Mu J, et al. Antenatal prediction of pulmonary hypoplasia by acceleration time/ejection time ratio of fetal pulmonary arteries by Doppler blood flow velocity. Am J Obstet Gynecol 2003;188(1):228-33

Duncan JR, Tobiasz AM, Dorsett KM, et al. Fetal pulmonary artery acceleration/ejection time prognostic accuracy for respiratory complications in preterm prelabor rupture of membranes. J Maternal Fetal Perinat Med 2020;33(12):2054-58

Büke B, Akkaya H. A non-invasive method to rule out transient tachypnea of the newborn (TTN): fetal pulmonary artery acceleration to ejection time ratio. J Perinat Med. 2018;46(2):219-224.

Jung E, Romero R, Yeo L, et al. The fetal inflammatory response syndrome: the origins of a concept, pathophysiology, diagnosis and obstetrical implications. Seminars in Fetal and Neonat Med. 2020;25:101146

Ozler A, Ucmak D, Evsen MS, et al. Immune mechanisms and the role of oxidative stress in intrahepatic cholestasis of pregnancy. Cent Eur J Immunol 2014;39(2):198-202

Biberoglu E, Kirbas A, Daglar K, et al. Role of inflammation in intrahepatic cholestasisof pregnancy. J Obstst Gynaecol Res. 2016;42(3):252-7

Zhang Y, Pan Y, Lin C, et al. Bile acids evoke placental inflammation by activating Gpbar1/NF-κB pathway in intrahepatic cholestasis of pregnancy. J Mol Cell Biol 2016;8(6):530-541

Arthuis C, Diguisto C, Lorphelin H, et al. Perinatal outcomes of intrahepatic cholestasis during pregnancy: an 8-year case-control study PLoS One 2020;15(2):e0228213

Zecca E, De Luca D, Baroni S, et al. Bile acid induced injury in newborn infants: a bronchoalveolar lavage fluid study. Pediatrics 2008;121(1):e146-149

Figure 1:Fetal main pulmonary artery Doppler flow-trace