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Correlation between Mitral (E/A), Pulmonary (At/Et) Ratios in Doppler Mode and the Biological Marker of Fetal Lung Maturity (Lecithin/Sphingomyelin Ratio)

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Abstract

Objective: To analyse the correlation between Doppler fetal heart indicators such as mitral ratio (E/A), acceleration time/ejection time (AT/ET) ratio in the main of pulmonary artery to the lecithin/sphingomyelin ratio (L/S) dosed in the amniotic fluid.

Material and Methods: Prospective study including singletons between 24 and 39 weeks of gestation, for whom caesarean delivery was planned. E/A and AT/ET ratios were realised during the 24 hours before birth. The L/S ratio was assayed by thin-layer chromatography, from samples of amniotic fluid.

Results: Thirty fetus were included, for a median (IQR) gestational age of 37 weeks (33.8-38.7) and a median weight birth of 2600 g (1888-3140). The correlation between the E/A and L/S ratios was positive: r = 0.56 (95% CI [0.24–0.76], p<0.01) while the correlation between AT/ET and L/S ratios was negative: r = - 0.44 (95% CI [(-0.69) – (-0.10)], p<0.01). The median E/A ratio in the hyaline membrane disease group was lower than in the group without (0.55 vs. 0.78, p< 0.01), while the median AT/ET ratio was higher (0.31 vs. 0.21, p= 0.011).

Conclusion: The E/A, AT/ET, and L/S ratios are correlated. Further studies are necessary to confirm the interest of these Doppler heart indicators to assess the fetal lung maturity.

Keywords: Mitral ratio; Acceleration time/ejection time ratio of the main of pulmonary artery; Lecithin/sphingomyelin ratio; Fetal lung maturity

Introduction

Neonatal acute respiratory distress syndrome is one of the principal causes of neonatal morbidity and mortality. The principal cause of neonatal respiratory distress is Hyaline Membrane Disease (HMD) [1]. This involves a functional deficiency of surfactant, composed of phospholipids that create a surface-active film to prevent alveolar collapse [2]. The incidence of HMD is inversely correlated with gestational age [3,4]. Nonetheless, the correlation is not absolute and some children born near term develop HMD while some preterm babies do not. Antenatal corticosteroid therapy, administered between 24 and 33 Weeks (+6 days) of Gestation (WG), reduces its incidence [5]. The indications for this therapy between 34 and 36 weeks remain controversial. In the absence of ultrasound criteria identifying fetuses at risk of HMD, some hospitals perform amniocentesis to determine the lecithin/sphingomyelin (L/S) ratio.

A Doppler study of the heart makes it possible to assess the fetal cardiocirculatory function, especially by Doppler measurements of the mitral ratio (E/A) and of the pulmonary artery acceleration time/ejection time ratio (AT/ET). The E/A ratio assesses myocardial maturity and the AT/ET ratio pulmonary vascular resistance [6-8]. The objective of our study was to analyse the correlation between Doppler fetal heart indicators (E/A and AT/ET) and the L/S ratio in the amniotic fluid, a reflection of lung maturity in children for whom caesarean delivery is planned.

Materials and Methods

This prospective study took place from January through April 2013. The institutional review committee approved the study, and each patient provided written consent. The study included singletons delivered by planned caesareans from 24 to 39 WG. The exclusion criteria were: premature rupture of the membranes before 24 WG, anamnios, a cardiac anomaly, one or more congenital malformations or an interval of fewer than 12 hours between corticosteroid administration and birth. Gestational age was determined by measurement of crown-rump length during the first trimester ultrasound [9]. We collected and analysed the following

maternal and neonatal characteristics: mother's age, any pre-existing or pregnancy-related diseases, antenatal corticosteroid therapy, indication for caesarean delivery, birth weight, and HMD. HMD was confirmed after exclude an organic pathology and when at least two of the following three criteria were present: clinical signs of respiratory distress and need for oxygen therapy for more than 24 hours, administration of exogenous surfactant, and/or radiographic signs suggestive of HMD. New-borns who did not require transfer to the neonatology department were considered to not have HMD.

Fetal ultrasounds were performed with a Voluson E8 Expert Ultrasound system (General Electric Medical Systems, Milwaukee, WI), equipped with an abdominal probe with a frequency from 3 to 5 MHZ. The initial cardiac morphology analysis began with the four-chamber view and then the great-vessel (or three-vessel) view [10]. All the Doppler measurements were taken in the 24 hours before birth and at least 12 hours after the last corticosteroid injection. Three velocimetric measurements were obtained for each indicator, at different times and always in the absence of respiratory or fetal movements. The three Doppler measurements for each indicator were averaged. Two different operators took these measurements. Their intra-observer and inter-observer variability were calculated for 10 patients.

Technique for measuring the mitral E/A ratio

The mitral E/A ratio was obtained by a four-chamber view taken in a pulsed Doppler mode. The sampling window must be placed at the level of the mitral valve in the highest coloured area. The ultrasound angle of incidence must be less than 20 degrees, to the presumed orientation of blood flow. Two successive velocimetric peaks illustrate the Doppler spectrum of the E/A ratio: the E wave represents the early filling of the ventricle, and the A wave its active filling during atrial systole [6,7]. The mitral ratio was obtained by measuring each peak velocity (i.e. E and A).

Technique for measuring the ratio of acceleration time to ejection time of the pulmonary artery

The AT/ET ratio was obtained with pulsed Doppler of a three-vessel section. The three-vessel view is obtained by sweeping cephalad in serial transverse planes from the four-chamber view [10]. The pulmonary artery, the ascending aorta and the superior vena cava must each be identified. The sampling window is positioned relative to the mid-portion of the pulmonary artery, at an insonation angle less than 20 degrees. The spectrum obtained is characterised by two systolic peaks followed by a diastolic notch [8]. The acceleration time is the interval between the beginning of the systole and its peak, and the ejection time the interval between its beginning and its end.

Technique for assaying the L/S ratio

The L/S ratio was assayed by thin-layer chromatography, from non-bloody samples of amniotic fluid before the amniotomy during the caesarean delivery. The result was obtained by comparing the ratio to a known control value of 2. Values range from 1 to 5. An L/S ratio ≥ 2 is the threshold value for fetal lung maturity [11].

Statistical analysis

The statistical analysis was performed with R software (Foundation for Statistical Computing, Vienna, Austria, ISBN 3-900051-07-0, URL http://www.R-<project.org/). The quantitative variables were expressed as their medians and interquartile ranges (IQR). The correlation between the Doppler measurements and the L/S ratio was calculated by Pearson's test. Wilcoxon's test was used to compare the maternal, neonatal and ultrasound characteristics according to neonatal outcome. The difference was considered significant when $p < 0.05$.

Results

Thirty patients were included. Maternal characteristics, neonatal outcome and Doppler measurements are reported Table 1.

The analysis showed a significant correlation between the E/A, AT/ET, and L/S ratios. The correlation between the E/A and L/S ratios was positive: r = 0.56 (95% CI [0.24-0.76], p<0.01). The correlation between AT/ET and L/S ratios was negative: r = 0.44 (95% CI [0.69–0.10], p=0.01) (Figure 1). The association with the AT/ET ratio was weaker.

Six new-borns developed HMD (median WG at birth: 28.4 vs 38.1 in the group without HMD, p<0.001). In this group, three neonates were born between 28 and 32 WG, and three neonates were born between 25 and 28 WG. The median E/A ratio was significantly lower and the median AT/ET ratio significantly higher in the group of neonates with HMD, respectively 0.55 vs. 0.78, (p = 0.01) and 0.31 vs. 0.21 (p = 0.011).

With a cut-off value of 0.62, the E/A ratio had 100% (95% CI [0.57-1]) sensitivity and 88% (95% CI [0.7-0.96]) specificity. For the AT/ET ratio, a cut-off value of 0.29 had 80% (95% CI [0-0.96]) and 88% (95% CI [0.7, 0.96]) specificity.

Maternal age (year)	30.5 (28-32)
Indication of C-section	
Breech presentation (n)	10 (33.3)
Uterin scar (n)	12 (40)
Preeclampsia (n)	4 (13.3)
Fetal growth restriction (n)	2 (6.7)
PPROM[a] (n)	2 (6.7)
Antenatal corticosteroids (n)	11 (36.7)
Neonatal HMD (n)	6 (100)
No neonatal HMD (n)	5 (36)
Gestational age at delivery (WG)	37 (33.7-38.7)
Birht weight (g)	2660 (1880-3140)
HMD† (n)	6 (20)
Mitral ratio	0.77 (0.63-0.84)
AT/ET ratio	0.23 (0.19-0.29)
L/S ratio	3 (2.6-4)

Table 1: Population characteristics and Doppler results

PPROM*: Preterm Premature Rupture of Membranes; HMD†: Hyaline Membrane Disease. Variables are expressed as median (interquartile ranges) or n (%).

The intra-observer coefficient was 3.6% for the E/A ratio, and 9% for the AT/ET, and the inter-observer coefficients of variability 6.1% and 15%, respectively.

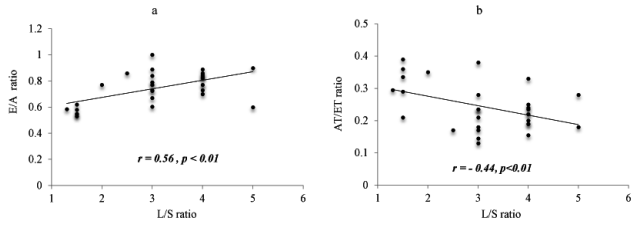

Figure 1: Correlation analysis **a)** Correlation between mitral ratio (E/A) and L/S ratio (n=30). **b)** Correlation between pulmonary ratio (AT/ET) and L/S ratio (n=30).

Discussion

Our study shows that the ultrasound indicators of cardiocirculatory maturity (E/A and AT/ET ratios) correlate well with the laboratory indicators of lung maturity (L/S).

The AT/ET ratio in the pulmonary artery allows pulmonary vascular resistance to be assessed [8]. The associations between lung vascularisation and lung development are well established. In animals, in utero ligation of the pulmonary artery is associated with pulmonary hypoplasia on the same side, and a Doppler of the pulmonary arteries helps to establish this diagnosis and determine its prognosis [12-15]. In particular, HMD is associated with increased pulmonary vascular pressure, which is corrected after administration of surfactant; the corticosteroid therapy itself reduces the AT/ET ratio in utero during the seven days following the injection [16-18]. This finding suggests a reduction in resistance. Our results show a higher AT/ET ratio in neonates with HMD and a significant correlation between the AT/ET ratio and the L/S ratio; both of these suggest better lung maturity. In a recent study, Azprupra et al. observed similar results in a population of 29 fetuses with a still closer correlation between the L/S and AT/ET ratios (r=-0.71) [19].

Similarly there was a significant correlation between the mitral E/A ratio and the L/S ratio. In addition, the mitral E/A ratio were significantly lower when neonates developed HMD. The utility of the E/A ratio lies in its association with lung maturity, stronger than that of the pulmonary AT/ET ratio, and also in its better intra-observer and especially inter-observer variability, clearly below 10%. The greater variability in the measurement of the AT/ET ratio is probably linked to the difficulty of Doppler measurements in the pulmonary artery axis, while the E/A wave measurement is often easier to obtain at the mitral level, even though an ultrasound angle incidence less than 20 degrees is required. The E/A ratio assess myocardial maturity. The increased E/A ratio characterises a more mature myocardium with greater compliance. Our results thus suggest that myocardial maturity and lung maturity develop in parallel. No study has previously assessed the correlation between the E/A and L/S ratios.

In our study the use of a semi-quantitative chromatography assay technique for the L/S ratio might have affected the analysis of the correlation. We think nonetheless that the correlation would be still higher had we used the polarised fluorescence quantitative surfactant assay technique (TDx-FLM), which would have provided continuous numeric values [20]. In any case, the L/S assays to assess pulmonary maturation in amniotic fluid can be performed by either chromatography or polarised fluorescence [21]. Moreover, consistent with the usual findings, no child with a L/S ratio >2 developed HMD. We recognize that the gestational age represents the best predictor of nenonatal HMD. Statistical analysis using logistic regression was not applied in our study because of the small number of neonates with HMD. Further studies are necessary to assess the predictive value of the Doppler heart indicators in predicting the possibility of HMD following birth.

HMD is a frequent complication in preterm neonates. Antenatal corticosteroid therapy administered before 34 WG reduces the risk of HMD. The value of antenatal corticosteroid therapy is currently debated for the gestational ages from 34 to 36 WG. Stutchfield et al. have demonstrated that corticosteroid therapy is useful when a caesarean is indicated between 34 and 39 WG [22]. Recently, Feitosa Porto et al. showed that corticosteroid therapy between 34 and 36 WG did not reduce the incidence of HMD [23]. Because of the disparities in these results, the US National Institute of Child Health and Human Development (NICHD) is conducting a randomised study on corticosteroid therapy for these borderline gestational ages (http://clinicaltrials.gov//ct2/show/NCT01222247). In the absence of consensus about the benefits of this therapy after 34 WG, some teams determine the L/S ratio by amniocentesis, an invasive technique that can result in pregnancy loss. Ultrasound evaluation could provide for these fetuses a risk-free method to assess the risk of HMD. Nevertheless, the results in our study are limited by the small number of HMD (20%). The median term at birth (37 WG) and the administration of corticosteroids in our series could explain this low rate.

The interest of the ultrasound approach lies in the non-invasive nature of its assessment. Numerous ultrasound indicators (including placental maturity, ossification centres, biometry, intestinal echogenicity, respiratory movements, and nasal Doppler) have been studied [24-30]. These indicators, however, are based on qualitative criteria, they are not reproducible and they are unusable in everyday practice. There are no known specific and direct ultrasound indicators of lung maturity. Pulsed Doppler measurements of mitral flow (E/A ratio) and pulmonary flow (AT/ET ratio) should be performed to limit the use of amniocentesis.

Conclusion

The E/A, AT/ET, and L/S ratios are significantly correlated. The E/A and AT/ET ratios could thus allow a non-invasive assessment of lung maturity. Other studies are necessary to confirm the predictive value of these Doppler measurements for the risk of HMD.

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