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Monitoring of fetuses with intrauterine growth restriction: longitudinal changes in ductus venosus and aortic isthmus flow

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KEYWORDS: aortic isthmus; ductus venosus; growth restriction

ABSTRACT

Objectives *To explore in growth-restricted fetuses the sequence of changes in aortic isthmus and ductus venosus blood flow in relation to other arterial Doppler parameters commonly used to evaluate fetal wellbeing.*

Methods *Umbilical and middle cerebral arteries, ductus venosus and aortic isthmus were explored serially by means of pulsed Doppler in a cohort of singleton small-for-gestational age fetuses requiring delivery before 34 weeks. Longitudinal changes in the last 30 days before delivery were modeled by multilevel analysis. Individual regression lines for each variable were calculated for each fetus and from these the regression lines for the whole group were derived, in order to estimate the mean time point at which each Doppler parameter became abnormal (outside the 5^{th}–95^{th} centile range). A survival analysis was performed during the monitoring period, in which the endpoint was an abnormal Doppler pulsatility index.*

Results *A total of 162 observations were performed on 46 fetuses (median, 3; range, 2–10). The median gestational age at inclusion was 28.9 (range, 23.6–33.4) weeks and delivery occurred at a median gestational age of 30.5 (range, 25.9–33.9) weeks. Six (13%) cases of perinatal mortality occurred. Umbilical and middle cerebral artery Doppler showed an almost linear deterioration throughout monitoring, becoming abnormal on average 24 days and 20 days before delivery, respectively. Aortic isthmus Doppler became abnormal on average 13 days before delivery, while ductus venosus Doppler did so within the last week before delivery.*

Conclusions *In preterm growth-restricted fetuses, aortic isthmus blood flow becomes abnormal on average 1 week earlier than does that in the ductus venosus. This could provide a sound basis to better define management protocols aimed to improve intact fetal survival. Copyright © 2008 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Intrauterine growth restriction (IUGR) is an important indicator of increased risk of adverse pregnancy outcome. It is associated with stillbirth, perinatal morbidity, neonatal mortality and cerebral palsy and there can be delayed effects into adolescence and adulthood[1–3]. Since there is no effective fetal therapy for IUGR, timing of delivery is a key issue in the management of affected fetuses.

Monitoring trends of variables can give reliable and valuable information as to the optimal time for delivery, and some studies have addressed the sequence of changes that occurs in Doppler parameters in IUGR fetuses[4–7]. Although this sequence has not been fully delineated, there is substantial agreement about classifying abnormal Doppler parameters into early and late signs according to their trends over the days before delivery. Umbilical and cerebral Doppler findings seem to become abnormal in the early stages of placental insufficiency, after which progressive deterioration occurs. In contrast, ductus venosus (DV) flow abnormalities have been described as a late marker, since this occurs within the last week before delivery[4–7], apparently reflecting acute myocardial impaired relaxation and acidemia[8], which is a major contributor to adverse perinatal outcome and neurological

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damage. However, there is a gap of some weeks between early and late signs, during which new parameters are needed to better document the progression of fetal deterioration. This could help to identify those fetuses whose defense mechanisms against acidemia and severe hypoxemia are about to fail.

The aortic isthmus (AoI) is the only arterial connection between the right ventricle, which supplies mainly the systemic and placental circulations, and the left ventricle, which supplies essentially the cerebral vascular network[9]. Consequently, its blood flow pattern reflects the balance between ventricular outputs and the existence of differences in vascular impedance in either vascular system[10,11]. This has led to suggestions of its potential role as a reliable indicator of the progression of fetal hemodynamic deterioration in IUGR and particularly as a marker of adverse perinatal and neurological outcome. However, no studies have evaluated longitudinally the sequence of changes in the AoI in relation to other arterial and venous Doppler parameters.

This study, therefore, aimed to explore in severe IUGR fetuses the temporal relationship between AoI and DV Doppler findings and those of the other arterial Doppler parameters commonly used to evaluate fetal wellbeing.

METHODS

A cohort was created of all pregnancies with antenatal diagnosis of small-for-gestational age fetus (estimated fetal weight $< 10^{th}$ centile according to local standards[12]) requiring delivery before 34 weeks in our institution between January 2003 and December 2006. Only cases with two or more Doppler assessments from diagnosis to delivery were included. Cases with reversed end-diastolic velocities in the umbilical artery (UA) or DV at admission were excluded. Multiple pregnancies and cases with congenital malformations or chromosomopathies were also excluded. During the study period there were 11 544 singleton deliveries at our institution. Of these, 465 were diagnosed prenatally with IUGR and 102 required delivery before 34 weeks. Six cases were excluded for meeting delivery criteria at admission and in 50, fewer than two measurements were available, leaving a total of 46 cases for analysis.

The study was approved by the local ethics committee and all women gave their informed consent to participate. Gestational age was determined by first-trimester crown–rump length[13]. From diagnosis to delivery or fetal death, biometry was assessed every 2 weeks and the following pulsatility indices (PIs), calculated from three or more consecutive waveforms obtained during minimal fetal activity and the absence of fetal breathing, at insonation angles $< 30°$, were assessed every 48–72 hours: (i) UA-PI, obtained from a free-floating portion of the umbilical cord; (ii) middle cerebral artery (MCA)-PI measured in a similar fashion, distal to the junction with the internal carotid artery; (iii) DV-PI, investigated in a midsagittal or transverse section of the fetal abdomen, positioning the Doppler gate at its isthmic portion; (iv) AoI-PI, measured either in the longitudinal aortic arch view, placing the gate a few millimeters beyond the origin of the left subclavian artery, or in the three vessels and trachea view, placing the gate just before the convergence of the AoI and the arterial duct[14]. Two experienced operators (A.B. and M.D.R.) performed all the Doppler measurements.

Betamethasone was given in all cases for pulmonary maturation. Cases with pre-eclampsia were managed according to standard guidelines[15]. Delivery was indicated by any of the following criteria: (i) reversed end-diastolic velocity in the DV or decelerative cardiotocography (at least six decreases > 30 beats in 60 min) beyond 26 weeks ($n = 13$); (ii) reversed end-diastolic velocity in the UA, absent end-diastolic velocity in the DV or persistent biophysical profile[16] < 6 on two occasions > 8h apart beyond 28 weeks ($n = 24$); (iii) maternal complications secondary to pre-eclampsia[15] ($n = 9$).

All values were converted to *Z*-scores according to published normal reference ranges[17–19]. Longitudinal changes in Doppler parameters in the last 30 days before delivery or fetal death were modeled by multilevel analysis, fitting to second-degree polynomials: $\alpha + \beta t + \gamma t^2$, where α, β and γ are the parameters characterizing the individual fetus and t is the number of days before delivery. These parameters were calculated assuming their randomly normal distribution in the population (random effect model), which allowed the assumption that both the individuals and the number of days from delivery at which the examination was performed were random samples of their respective populations. The software MLwiN 2.1 (Centre for Multilevel Modelling, University of Bristol, Bristol, UK) was used for parameter estimation. Repeated measurements at different time points (days before delivery) in the same fetus comprised Level 1 and those in different fetuses comprised Level 2. Individual regression lines for each variable were calculated for each fetus and from these, the regression lines for the whole group were derived[20]. Regression lines were plotted for the monitoring period against the 5^{th} (*Z*-score $= -1.645$) and 95^{th} (*Z*-score $= 1.645$) centile normal ranges.

For the AoI and the DV, a survival analysis was performed during the monitoring period, in which the 'event' was defined as an abnormal Doppler PI value ($> 95^{th}$ centile). For each Doppler parameter, a comparison was made between cases with and those without pre-eclampsia by means of a Breslow (Generalized Wilconox) test. The software package SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used for the survival analysis.

RESULTS

A total of 162 observations were performed on 46 fetuses (median, 3; range, 2–10). Twenty (44%) women had only two examinations. In 131 explorations, the AoI was insonated in the longitudinal aortic arch view, and in 31 it was insonated in the three vessels and

trachea view. UA, MCA and DV were successfully obtained in all examinations, while AoI could not be obtained in two examinations. The median gestational age at inclusion was 28.9 (interquartile range (IQR), 26.8–31.0; range, 23.6–33.4) weeks. Delivery occurred at a median gestational age of 30.5 (IQR, 28.3–32.7; range, 25.9–33.9) weeks. Seventeen (37%) women delivered before 30 weeks. The median interval from inclusion to delivery was 8 (IQR, 8; range, 2–29) days. Table 1 gives the antenatal characteristics and perinatal outcomes of our population. Apart from four still births, all cases were delivered by Cesarean section. There were two cases of neonatal death: one at 4 days with Grade IV intraventricular hemorrhage and one at 6 days for complicated necrotizing enterocolitis.

Table 2 depicts the Doppler parameters at inclusion and at last examination. Remarkably, at inclusion, eight (17.4%) cases had absent ($n = 4$) or reversed ($n = 4$) end-diastolic flow in the AoI, whereas 17 (37%) cases had absent ($n = 9$) or reversed ($n = 8$) flow at delivery ($P = 0.035$). Similarly, at inclusion, four (8.7%) cases had absent end-diastolic velocities in the DV, while at delivery a total of 12 (26.1%) cases had absent ($n = 5$) or reversed ($n = 7$) end-diastolic velocities ($P = 0.028$).

Table 1 Antenatal characteristics and perinatal outcomes of the study population

Characteristic/ outcome	*Mean (SD) [range] or* n *(%)*
Gestational age at delivery (weeks)	30.5 (2.5) [25.9–33.9]
Birth weight (g)	1003 (263) [480–1510]
Umbilical artery pH	7.24 (0.007) [6.9–7.33]
Umbilical artery pH < 7.15	5/39 (12.8)
5-min Apgar score < 7	2/42 (4.8)
Pre-eclampsia	27/46 (58.7)
Perinatal mortality	6/46 (13)

Table 2 Doppler parameters at entry into the study and at the last examination

Parameter	*First examination*	*Last examination*	P*
UA-PI > 95th centile	28 (60.9)	36 (78.3)	0.07
UA-AREDV	10 (21.7)	17 (37)	0.1
MCA < 5th centile	25 (54.3)	36 (78.3)	0.01
DV-PI > 95th centile	11 (23.9)	20 (43.5)	0.047
DV-AREDV	4 (8.7)	12 (26.1)	0.028
AoI-PI > 95th centile	13 (28.3)	23 (50)	0.033
AoI-AREDV	8 (17.4)	17 (37)	0.035

Values are given as *n* (%). *Pearson chi-square test. AoI, aortic isthmus; AREDV, absent or reversed end-diastolic velocities; DV, ductus venosus; MCA, middle cerebral artery; PI, pulsatility index; UA, umbilical artery.

The results of the multilevel analysis and regression lines indicating trends over time before delivery are shown in Figure 1. Of note, UA-PI and MCA-PI showed an almost linear deterioration throughout monitoring, becoming abnormal (outside the 5th–95th centile range) on average 24 and 20 days before delivery, respectively. AoI-PI became abnormal on average 13 days before delivery, while DV-PI did so within the last week before delivery.

Figure 2 shows the survival of normal AoI and DV (within the 5–95th centile) throughout the study period, plotted against days from inclusion. While the median survival time, i.e. when 50% of the events (abnormal Doppler PI value) had occurred, was 14 days from inclusion for the AoI, it was 7 days for the DV. Stratified analysis for pre-eclampsia showed no significant differences between cases with and without pre-eclampsia in the survival rate of AoI (median, 12 vs. 8 days from

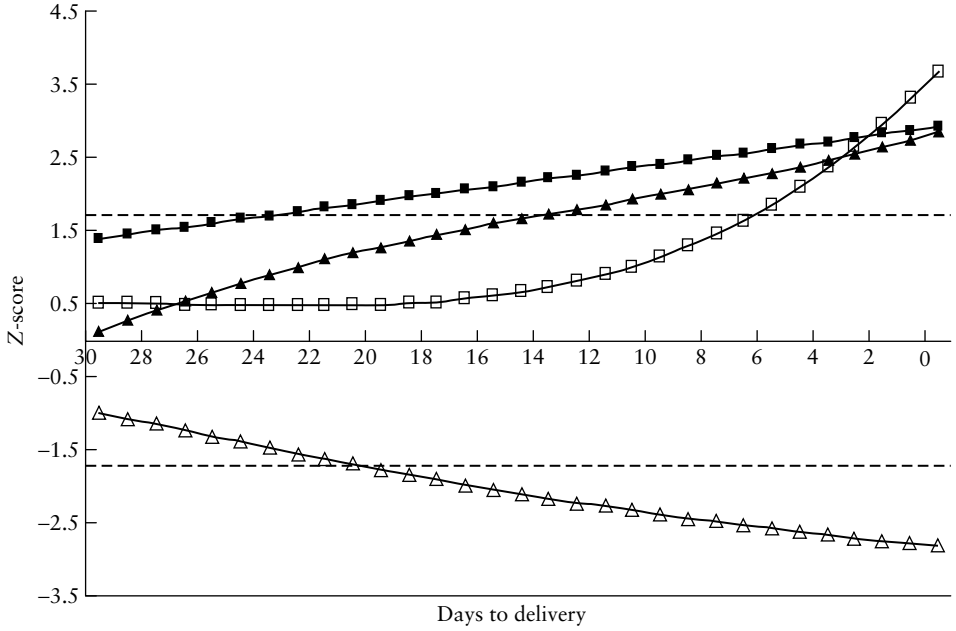

Figure 1 Regression lines indicating trends over time of pulsatility indices in the aortic isthmus (▲), ductus venosus (□), umbilical artery (■) and middle cerebral artery (△) before delivery: horizontal dashed lines indicate the 5th and 95th centiles.

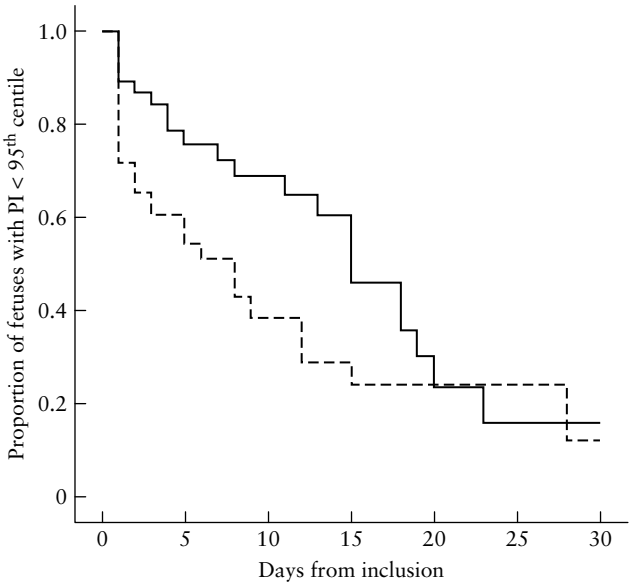

Figure 2 Kaplan–Meier plot showing the proportion of fetuses with normal Doppler findings in the ductus venosus (———) and aortic isthmus (– – –) against the number of days from inclusion.

inclusion; Breslow $P = 0.1$) or DV (median, 7.4 vs. 7.1 days from inclusion; Breslow $P = 0.6$).

DISCUSSION

No studies so far have evaluated longitudinally the sequence of changes in the AoI in relation to other arterial and venous Doppler parameters. Our results, showing that abnormal AoI-PI is an intermediate step between placental insufficiency-hypoxemia and cardiac decompensation, have interesting pathophysiological and clinical implications.

Initial experimental[21] and clinical[22] studies performed in chronic hypoxic models suggested that retrograde flow in the AoI might be an early event, occurring even before deterioration of the UA flow in cases with placental insufficiency. In line with this, Mäkikallio *et al.*[23] also reported no difference in UA Doppler indices between fetuses with retrograde and those with antegrade AoI flow. Contrary to these results, other studies[24–26] have reported that retrograde blood flow in the AoI is consistently associated with the presence of Doppler patterns in the UA suggestive of advanced placental insufficiency. Our longitudinal observations are in agreement with these later studies, since we found that abnormal AoI flow occurs on average 1–2 weeks after abnormal UA flow is observed. We cannot find an explanation for this inconsistency between studies other than different selection criteria. We also found that MCA vasodilatation precedes AoI flow abnormalization. This supports the notion that a decrease in cerebral resistance secondary to hypoxia plays a major role in determining the net AoI diastolic flow[9]. The finding of onset of abnormal AoI flow occurring 1–2 weeks after that of abnormal UA and MCA flow is inconsistent with the concept that blood flow pattern through the AoI simply reflects the balance between ventricular outputs and the existence of differences in the vascular impedance in either vascular system. We hypothesize that an active role of the foramen ovale and the DV in increasing the left stroke volume in these initial phases of hypoxia may initially overcome the effect of different vascular resistance on the AoI-PI.

Our study also provides insight into the pathophysiological events leading to cardiac decompensation. There is a marked association between abnormal AoI and abnormal DV flow: Mäkikallio *et al.*[23] reported that most (6/11) fetuses with net retrograde blood flow had a DV-PI > 1, whereas only a third of those with net antegrade AoI flow had a DV above this cut-off. In our recent cross-sectional study[26], we also found a strong correlation between AoI and DV indices. It could be hypothesized that when there is abnormal AoI blood flow, the left ventricle afterload is increased, leading to a reduction of well-oxygenated blood flow through the foramen ovale. It has been shown that in cases with net retrograde AoI blood flow, there is a reduction of blood flow through the foramen ovale[11]. This could explain the high right atrial pressure signs observed in IUGR fetuses with abnormal AoI blood flow[11], and, secondarily, contribute to the increase in DV pulsatility. Our results, showing that AoI flow abnormalities precede those of the DV, are in line with this hypothesis.

AoI evaluation has been proposed as a potential monitoring tool for IUGR fetuses, since it could indicate the point at which the defense mechanisms against brain hypoxia are overwhelmed[9]. In severe cases of IUGR, a reversed flow could occur through the isthmus, and experimental models found that this feature corresponds with a sharp drop in the amount of oxygen delivered to the brain[10]. Consistently, suboptimal neurological development was found among children who had had net reversed diastolic flow in the AoI antenatally[24]. This opens up the possibility of using the AoI clinically for prevention of neurological damage. Nevertheless, it could be argued that, at least at certain gestational ages, retrograde flow in the AoI is too late an indication for delivery. AoI-PI has the advantage of being a continuous variable so different cut-offs could be used at different gestational ages. Our study has shown that AoI-PI becomes abnormal on average 1 week before abnormal DV flow is evident, the latter reflecting heart failure to manage the increased central venous pressure. We have demonstrated previously that AoI-PI and DV-PI independently predict adverse outcome[26], but their contribution as independent predictors of perinatal mortality and poor neurological outcome remains uncertain. Whether AoI Doppler evaluation should be incorporated into the clinical management of IUGR fetuses has to be addressed by further studies taking into account gestational age and possibly other parameters. Such studies are underway.

This study has some limitations. It was designed not as a management study, but as an observational one. Therefore, conclusions on when to deliver a fetus could not be drawn directly from our findings and there is a need for further evidence from other studies

designed with such an objective. Despite the fact that this study is the first attempt made to describe the temporal relationship between AoI Doppler findings and the other arterial and venous Doppler parameters commonly used to evaluate fetal wellbeing, the relatively small number of observations per fetus and the fact that a sizable group of fetuses had only two examinations reduce the strength of this longitudinal study.

In conclusion, we found that in preterm growth-restricted fetuses, AoI blood flow becomes abnormal on average 1 week before DV blood flow does. This could be used to improve current algorithms for the prediction of mortality and long-term neurodevelopmental deficits.

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