Doppler velocimetry of ductus venous in preterm fetuses with brain sparing effect: neonatal outcome

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Summary

Objective: **to evaluate the relationship between ductus venous (DV) and Doppler velocimetry in neonatal outcome in severe compromised preterm fetuses.**
Methods: **the study was designed as an observational and cross-sectional study with 52 premature neonates with brain sparing effect. The criteria of neonatal severe morbidity were: severe intraventricular hemorrhage (grades 3 or 4), retinopathy of prematurity (grade 3 or 4), cystic periventricular leukomalatia, bronchopneumo dysplasia and neonatal mortality. The fetuses were divided in two groups: group 0 - all the fetuses with ventricular systole/atrial contraction (S/A) in DV ratio values less them 3.4; group 1 - fetuses with values of S/A ratio greater than 3.4.**
Results: **42% of fetuses showed abnormal S/A ratio in DV and 48% showed birth weight below percentile 3 for gestational age. There was no statistical significance comparing the 02 groups according to bronchopneumo dysplasia, retinopathy of prematurity (grade 3 or 4) and intraventricular hemorrhage (grade 3 or 4). Only one fetus presented cystic periventricular leukomalatia. We found statistically significant association between abnormal DV S/A ratio and neonatal mortality (CI 95%, 1.28 - 38.22, p< 0.002).**
Conclusions: **our results suggest that abnormal DV blood flow detected by Doppler examination isn't associated with severe neonatal morbidity but with neonatal mortality.**

Key words: fetus, Doppler, ductus venosus, brain sparing effect, morbidity, mortality.

Introduction

An adequate placental perfusion is crucial for the normal growth and wellbeing of the fetus and newborn. Placenta blood flow can be compromised in a variety of clinical situations, always causing important damage to the gestation. Placental insufficiency promotes compensatory hemodynamic fetal changes including blood flow redistribution towards essential fetal organs, at the expense of others (1). This fetal compensation response causes an increase in the blood flow to the brain, which is called "brain sparing effect" (2,3). The features observed in the fetus are decreased growth, liver volume and adipose deposits (3). As the placental dysfunction progresses, the fetus will have problems in maintaining its vital functions, leading to severe changes in acid-base balance and finally death. The Doppler velocimetry analysis, mainly of the umbilical artery (UA) indexes, shows a mal functioning of the placenta. The magnitude of the changes detected by the Doppler are proportional to fetal compromise. The assessment of fetal wellbeing through arterial Doppler is not absolute, and additional information is necessary to conduct an accurate assessment (4).
Several studies showed adverse perinatal outcomes with statistically significant associations between abnormal waves in the arterial Doppler and gravidic complications (4,5). In the last decade, Kiserud et al. (6) introduced the study of venous circulation, its adaptive phenomena and their association with perinatal outcomes. Rizzo et al. (7) noted that hypoxemia and adverse perinatal outcomes could be predicted non-invasively through the S/A ratio (ventricular systole/atrial systole) of the ductus venous (DV). Therefore, this parameter can become an important tool in the attempt to reduce neonatal morbidity in extreme prematurity (7-9). The challenge of monitoring complicated gestations through placental insufficiency remains because no diagnosis method is complete. Even though the density of fetal compromise can be assessed through arterial (10) and venous Doppler ve-

locimetry (4), currently there is no effective treatment to reverse the placental insufficiency process except to interrupt the gestation. This makes the decision regarding the best time for delivery crucial in assessing the risk benefit of prematurity and fetal risk (10).
The best time for delivery would be when fetal hypoxia has become severe enough so that the risks of intrauterine permanence are higher than those of prematurity. That is the main justification for research in this field (4). The goal of this study is to assess the relationship between DV Doppler velocimetry and the severe adverse neonatal outcomes in fetuses with brain sparing effect.

Methods

Pregnant women from different public and private health institutions were sent to the Pre-Natal Diagnosis and Treatment Center of Perinatal Clinic of Laranjeiras to participate in a cross-sectional observational study that took place between November 2002 and March 2009. This study was part of a line of research developed at Perinatal Clinic of Laranjeiras since 2001, a study protocol that was approved by the Research Ethics Committee of the São Paulo Federal University (UNIFESP) under number 0370/06. The pregnant women that participated in the study did so voluntarily and signed an informed consent.
The population studied was of 52 pregnant women, screened with arterial and venous Doppler, with fetuses presenting centralization of blood flow between 25 to 33 weeks of gestation. The inclusion criteria were: 1 – single pregnancy (regardless of whether or not to use drugs); 2- lack of apparent fetal malformation, confirmed by ultrasound 3- gestational age between 25 to 33 weeks calculated by the date of last menstrual period and confirmed by first trimester ultrasound (11); 4- brain sparing effect diagnosis, pulsatility index (PI) of umbilical artery above the 95th percentile for gestational age (12) in the last Doppler done at least 24 hours before the resolution of the pregnancy and PI MCA / PI UA ≥ 1 (13) ratio; 5- pregnant women submitted to Cesarean section, in the absence of labor. The exclusion criteria were: 1-non-obtention of delivery data and immediate neonatal assistance; 2- data records from medical charts of the newborn incomplete or inaccessible.
The ultrasound exams were done in a Voluson 730 Pro (GE Medical Systems, Milwaukee, WI, USA), using a convex 2-5 MHz transducer. The high frequency filter was adjusted to the sensitivity of 100 Hz. The UA sonogram was obtained through the insonation of three segments of the umbilical cord: next to the abdominal insertion, free cord segment and close to the placental insertion; the arithmetic mean of these three segments was the number used for the purpose of the study. The MCA sonogram was obtained through a cross-sectional section of the fetal brain in a parallel plan more caudal than the plan used to obtain biparietal diameter, including thalamus and cavum of the pellucid septum (usual section plan to measure the biparietal diameter). With the use of color Doppler the Willis polygon was identified and its branches where in close proximity to the greater wings of the sphenoid. The sampling spot was 1.0 cm after its end point in the Willis polygon (14).
The DV Doppler velocimetry was obtained with the pregnant woman in semi-Fowler position and in a time when the fetus was in complete rest. The insonation was done at the starting point of the vessel, once the sinus portal in the cross-sectional or midsagittal abdomen section was identified through the sonogram and color Doppler (15). The Doppler image was registered when at least five flow speed waves with the peculiar DV standard and constant signal were found. This approach guarantees a variation coefficient lower than 10% (15). The peak speed during ventricular systole (S) and the speed corresponding to atrial contraction (A) were measured and then the S/A ratio was calculated. All fetuses had the last DV insonation done at least 24 hours before delivery. The DV Doppler velocimetry was considered abnormal when the S/A ratio was higher than the inflection point on the ROC curve, as a cut point established for the Brazilian population (S/A ratio> 3.4) (16). The assisting physician decided whether or not to interrupt the gestation. This decision was influenced by maternal illness (severe pre-eclampsia, HELLP syndrome) or fetal well-being deterioration.
The stratification in two groups to compare the results in normal and abnormal DV S/A is important; because the best cut-off point of the S/A ratio (where the ROC curves bent) was 3.4. Fetal acidemia in preterm fetuses with brain sparing effect may be noninvasively identified by Doppler measurement of the ductus venous when the S/A rises above 3.4 (16). Previous or similar studies about the relationship between arterial and venous Doppler and perinatal outcome the DV cut-off ratio was the abnormal S/A relationship or PI > 2 standard deviation above the gestational age, but we decided to continue our line of research using the S/A relationship.
In Perinatal Clinic of Laranjeiras, Rio de Janeiro, and other reference centers of Fetal Medicine in Brazil, we use the DV Doppler like an important parameter to predict mortality in fetuses with brain sparing effect and help to determinate the best timing of intervention.
The fetuses were divided in two groups. Group 0 was comprised of fetuses without alterations in the DV S/A ratio and group 1 was comprised of fetuses that showed alterations in the DV S/A ratio. The variables related to the newborns were diagnosed by the neonatal team, using the classification of the world network of standardization of protocols and conduct in neonatology, Vermont Oxford Network 2009, release-13.2 (Manual of Operations for Infants Born 2009). This analysis was based on the clinical exam, laboratory results and imaging methods of newborns examined in the neonatal intensive care (17). Neonatal data from medical charts until the 28th day after delivery or at the time of discharge were collected by the main author of this article (YCC), these included:

1. Vitality: born alive or stillborn (absence of vital signs at birth); if stillborn, the cause of death was stated;
2. Gestational age at the time of the blood flow centralization diagnosis;
3. Gestational age at the time of interruption;
4. Fetal weight in grams at birth and at medical discharge;

5. Ballard (18);
6. Apgar (19);
7. Severe morbidity (20) neonatal sequelae were classified as:
   7.1 - Severe intraventricular hemorrhage: special attention to grades 3 and 4 and those diagnosed by transfontanelle sonogram (21);
   7.2 - Retinopathy of prematurity: retina vasoproliferative disorder observed during ophthalmological exam done in neonatal ICU, generally because of the long-term use of oxygen; grades 3 and 4 are considered severe sequelae according to the International Classification of ROP, 1987 (22);
   7.3 - Cystic periventricular leukomalatia (CPD): diagnosed by transfontalle sonogram and/or magnetic resonance of the skull. To be diagnosed as CPD, multiple periventricular small cysts caused by degeneration of white substance adjacent to the brain ventricle have to be found, followed by hypoxia and probable paralisis (23);
   7.4 - Bronchopulmonary dysplasia (BPD): severe sequelae of breathing discomfort syndrome caused by the use of supplementary oxygen and mechanical ventilation (24) in newborns at 36 weeks of corrected gestational age. BPD can be diagnosed through a chest x-ray and/or helical high resolution computerized tomography.

S-Plus 8.0 (Insightful Corp., Seattle, WA, USA) was the program used for statistical analysis. The t-Student tests and Wilcoxon signaled posts were used to compare the number variables. The Chi square tests (x^2) and Fisher exact were used to compare frequencies and independence of categorical variables. The sampling power used was of 0.0679 (6.79%) to detect discrepancies of up to 5% in the DV prevalence. The significance level used was $(p) < 0.05$.

Results

52 fetuses met the inclusion and exclusion criteria and were used in the final statistical analysis. Group 0 was comprised of 31 fetuses (59.6%) with normal DV S/A ratio and group 1 was comprised of 21 fetuses (40.3%) with altered DV S/A ratio.

The average maternal age was 31.9, and it is not changed the outcome neonatal analyses ($p>0.05$). The average gestational age at the time of diagnosis was of 28 weeks and 28.2 weeks at the time of birth. The average interval between the Doppler and the Cesarean section was of 24 hours. Table 1 shows the descriptive analysis of women pregnant with fetuses with brain sparing effect to the Doppler. The weight of the newborns for gestational age was inversely proportional to the Doppler compromise. In group 0 the average weight was 964 grams and in group 1 it was of 662 grams ($p <0.0028$). Considering the Apgar score at 1 minute: 23 newborns (44.2%) presented a score lower than 7, while 29 of them (55.8 %) presented an Apgar score higher than 7. In the 5th minute, 4 (8%) of the newborns had an Apgar score lower than 7, while 48 of them (92%) had a score higher than 7. Absent or reverse flow of the UA was diagnosed in 23 fetuses (44%); 21 fetuses (40%) presented an abnormal DV S/A ratio and 25 fetuses (48%) presented fetal weight under percentile 3 for their gestational age. In the UA a positive final diastolic flow was observed in 27 fetuses (30%), zero diastole in 23 fetuses (44.4 %) and reverse diastole in 13 fetuses (25%). Table 2 shows the analysis of fetuses with brain sparing effect in groups 0 and 1.

A survival rate of 85% until the 28th day of life and death in 9 (17.3%) of the cases was observed. The causes were as follows: three cases with extreme prematurity, three cases of respiratory failure and three cases of multiple organ and systems failure. In this study there was an important correlation between mortality and altered DV, i.e. 7 of the 9 neonatal deaths were in Group 1 ($p< 0.002$). The premature fetuses with brain sparing effect presenting DV abnormal blood flow showed a greater possibility of mortality when compared to those that presented normal flow (CI 95%: 1.28 - 38.22). The analysis of the DV S/A ratio (altered = S/A> 3.4) was considered abnormal in 12 patients (23%) and the wave was reverse in 5 patients (9.6%). A statistically significant association was found between the altered DV and neonatal mortality ($p< 0.05$) (Tab. 3). As to neonatal morbidity, there were 7 cases of IH grades 3 and 4 found; 8 cases of ROP; one case of CPD and 26 cases of BPD; there was no statistically significant difference between both groups as to morbidity ($p> 0.05$) (Tab. 3).

Discussion

In the past decades, there was a development in the understanding of placental insufficiency physiopathology and its neonatal repercussions. Fetal wellbeing was previously assessed by biophysical parameters that became altered once acidemia was installed. With the Doppler, there was progress in the assessment of the fetal hemodynamic state prior to severe fetal compromise.

Even though there is no intrauterine treatment for fetal suffering, it is left to physicians to decide the best time for delivery. The characteristics of high risk gestation are determined by gestational age and the level of placental compromise. The medical conduct between 25 to 33 weeks is of specific importance when the risks of keeping the gestation have to be analyzed and compared to the mortality risks, assessing the possibility of severe neonatal sequelae, including cerebral paralysis. Therefore, the purpose is not only to reduce mortality, but also morbidity.

Trudinger et al. (25) presented the first systematic study on UA Doppler and the association with the increase of vessel resistance and adverse fetal outcomes. The Doppler velocimetry standards were then compared with the anatomic findings of placental circulation and a reduction of the arterioles of the placenta was observed. The main consequences of this change to the fetus were growth restriction, intrauterine death and intra-partum fetal suffering. DV has since become relevant in predicting adverse neonatal outcomes and evaluating

Table 1. Descriptive analysis of pregnant with fetuses presenting the brain sparing effect by ductus venous Doppler.

Number of patients	**52**
Maternal age (years)	
Mean ± standard deviation	31.92 ± 5.65
Median	32
Minimum - Maximum	19 - 43
Gestational age at diagnosis (weeks)	
Mean ± standard deviation	27.98 ± 2.56
Median	27.71
Minimum - Maximum	25 - 33
Gestational age at interruption (weeks)	
Mean ± standard deviation	28.31 ± 2.41
Median	28.24
Minimum - Maximum	25 - 33
Time taken for delivery (hours)	
Mean ± standard deviation	69 ± 7.24
Median	48
Minimum - Maximum	2 - 288
Weight of newborn (grams)	
Mean ± standard deviation	842.69 ± 369.30
Median	805
Minimum - Maximum	315 - 1,670
BALLARD (days)	
Mean ± standard deviation	200.65 ± 17.62
Median	200
Minimum - Maximum	161 - 235
Apgar 1st	
Mean ± standard deviation	5.71 ± 2.35
Median	7
Apgar 5th	
Mean ± standard deviation	7.98 ± 1.54
Median	8
Minimum - Maximum	1 - 10
Clinical and obstetric pathology	
Mean ± standard deviation	9.0 ± 6.51
Corticoid	
Mean ± standard deviation	9.0 ± 4.52

Table 2. Descriptive analysis of groups of fetuses with fetuses presenting the brain sparing effect by ductus venous Doppler.

	Ductus Venous		
	Normal Ductus (Group 0)	**Amended Ductus (Group 1)**	**p**
Age	33.39 ± 5.28	29.76 ± 5.58	0.0215
Gestational age at diagnosis (weeks)	28.76 ± 2.43	26.83 ± 2.36	0.0064*
Gestational age at interruption (weeks)	29.09 ± 2.27	27.16 ± 2.18	0.0036*
Weight of newborn (grams)	964.84 ± 364.48	662.38 ± 302.06	0.0028*
BALLARD	206.61 ± 14.00	191.40 ± 18.96	0.0018*
APGAR 1st	6.61 ± 1.75	4.38 ± 2.54	0.0216
APGAR 5th	8.55 ± 0.89	7.14 ± 1.90	0.0222
APGAR 1st < 7			0.1146
0	21	7	
1	10	14	
APGAR 5th < 7			0.1446
0	30	17	
1	1	4	
Clinical and obstetric pathology	5	47	0.0027*
Corticoid			0.1446
0	1	4	
1	30	17	

* Chi square test (x^2)

Table 3. Descriptive analysis of fetuses groups presenting the brain sparing effect by ductus venous Doppler in relation to morbidity and mortality.

	Normal Ductus venous (Group 0)	**Amended Ductus venous (Group 1)**	**p**
Intraventricular hemorrhage			**0.4205**
0	28	17	
1	3	4	
Retinopathy of prematurity			**0.6997**
0	27	17	
1	4	4	
Periventricular leukomalatia			**0.4038**
0	31	20	
1	0	1	
Bronchopulmonary dysplasia			**0.5090**
0	21	5	
1	10	16	
Neonatal mortality			**0.0234 ***
0	29	14	
1	2	7	

*Chi square test (x^2)

the wellbeing of premature fetuses with growth restriction and change in the blood flow found in arterial Doppler velocimetry (26).

In the present study there was homogeneity between both groups for gestational age at birth and Apgar score< 7 on the 5th minute. However there was a significant statistical difference between the groups with respect to abnormal S/A ratio, which was more associated with an increase of neonatal mortality. This can be due to the higher risk found in the blood flow distribution in these cases. This indicated that mortality with altered DV can be related to the extreme low weight of these newborns, who are in the threshold of feasibility. Significant association was not found between DV altered S/A ratio and the other variable studied.

This article is different when compared to others in literature because it exclusively correlates DV alterations with neonatal parameters of bad prognosis. The study shows the importance of the DV S/A ratio with studied results; since there is no longitudinal follow up of gestation until changes in other parameters considered late for pregnancy interruption such as fetal biophysical profile and cardiotocography (27) are observed. Birth took place in a maximum period of 24 hours after DV evaluation. The Doppler analysis of fetal venous vessels does not show a consistent pattern. Fetal response to placental insufficiency and its development during the gestation varies and there is no consensus as to the ability to predict fetal mortality and morbidity by Doppler velocimetry parameters.

Müller et al. (28) considered the DV assessment in gestations of fetuses of zero or reverse diastole as an additional parameter to determine gestation interruption and prediction of early neonatal outcomes. They conducted a multicentre study with 70 fetuses that had early fetal growth restrictions with gestational age between 26 to 33 weeks and found correlation between altered DV ratios and adverse perinatal outcomes such as perinatal mortality, HIV and DBP. In another study, Carvalho et al. (29) assessed perinatal repercussions of DV abnormality and observed that the fetal group with abnormal S/A ratio had a greater association with the increase of neonatal mortality, however this association presented a limit value, possibly by the small size of the sample, requiring further studies.

The selection of our populational group was based upon rigid criteria of gestational age, and all fetuses were preterm and diagnosed with brain sparing effect. This strict selection aimed at restricting the use of the method previously described to situations of real importance to the obstetrics practice. As seen in literature (28,30), our results suggest that the fetuses that present abnormality in the DV S/A ratio have a greater possibility of neonatal death. Therefore we understand that the DV study can be used as an additional factor to be considered in scheduling the interruption of gestations of fetuses with brain sparing effect, possibly with a low risk of severe neonatal morbidity (28,30). Therefore, the fetuses that show changes in arterial Doppler can benefit from a longer intrauterine permanence, if they have a normal DV Doppler velocimetry. This conduct can postpone the birth in a week or more, reducing the preterm complications in early gestation ages.

Conclusion

In summary, this study has shown that DV Doppler is an important parameter to predict mortality in fetuses with brain sparing effect.

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