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The relationship between an aortic isthmus blood flow velocity index and the postnatal neurodevelopmental status of fetuses with placental circulatory insufficiency

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Doppler measurement
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Objective: The purpose of this study was to evaluate the association between an abnormal aortic isthmus blood flow index and postnatal neurodevelopmental outcome in fetuses with placental circulatory insufficiency.

Study design: Forty-eight children who were born between 1991 and 1999 were included in this study on the basis of abnormal umbilical artery Doppler velocimetry. Prenatal isthmus blood flow index was obtained by dividing the sum of the systolic and diastolic Doppler blood flow velocity integrals by the systolic blood flow integrals.

Neurodevelopmental outcome between 2 and 5 years was classified as optimal, when neurologic assessment and developmental quotient were within normal limits and as nonoptimal when abnormal neurologic findings and/or a nonoptimal developmental quotient was present. Neurodevelopmental outcome was analyzed in relation to isthmus flow index and pulsatility indices in the umbilical artery.

Results: The mean gestational age at delivery was 33.0 $\pm$ 2 weeks. Nonoptimal neurodevelopmental outcome was found in 60.4% of the children (29/48). An inverse correlation was found between the isthmus blood flow index and postnatal neurodevelopmental outcome. All 13 children with an isthmus blood flow index of <0.5 were in the nonoptimal group. All 19 children with an optimal outcome had an isthmus blood flow index of >0.5, but this was also the case for 16 other children with nonoptimal neurodevelopmental outcome. An isthmus blood flow index cut-off value of 0.70 was associated with the highest overall positive and negative predictive

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values. The pulsatility index in the umbilical artery did not provide any significant contribution in the explanation of the outcome.
Conclusion: The isthmic blood flow index can help to identify a subgroup of fetuses with placental circulatory insufficiency that might benefit from early delivery.

Both experimental[1,2] and clinical[3-5] investigations have demonstrated that placental circulatory insufficiency causes fetal hypoxemia by reducing umbilical blood flow. In these circumstances, the fetus can still maintain adequate cerebral oxygenation, because of many adaptive mechanisms among them, blood flow redistribution towards essential fetal organs (such as the brain, heart, and adrenal glands).[6] In severe cases, however, this defense system is overwhelmed, and decompensation occurs that results in metabolic acidemia and cerebral hypoxia.[6-8] In clinical practice, growth-restricted fetuses with placental circulatory insufficiency are being delivered on the basis of signs that reflect neurocirculatory decompensation.[9] Not surprisingly, the incidence of neurodevelopmental disorders among intrauterine growth restriction (IUGR) survivors has been found to be as high as 50%.[10]

Ideally, to prevent postnatal sequellae of fetal cerebral hypoxia, delivery should be induced just before decompensation. Abnormal ductus venosus Doppler waveforms have been suggested as a useful parameter to identify such fetuses.[11] However, these venous changes are also often late signs of fetal compromise and frequently are associated with metabolic acidemia, myocardial cell destruction,[12] and higher likelihood of perinatal death.[8,13] Acute experiments in the ovine fetus have shown that a stepwise increase in resistance to placental blood flow causes a fall in oxygen delivery to the brain when a predominant reverse diastolic blood flow is observed through the aortic isthmus.[1] In the human fetus, predominant diastolic reverse blood flow through the aortic isthmus is associated with nonoptimal postnatal neurodevelopmental outcome[14] and impairment of the venous Doppler waveforms.[15] However, although a predominant diastolic reverse blood flow in the fetal aortic isthmus appears to be a highly specific sign of decompensation, it has a relatively poor sensitivity. Indeed, close to 50% of previous IUGR children with nonoptimal neurodevelopmental outcome did not have a predominant reverse isthmic blood flow in their prenatal life.[14] To better correlate the blood flow pattern through the fetal aortic isthmus with impending decompensation and acidemia, we developed an index that takes into account the amount and the direction of the isthmus blood flow on a continuous scale.[16] The objective of this study was to investigate the association between changes in this aortic isthmus blood flow index (IFI) and the postnatal neurodevelopmental outcome of fetuses with placental circulatory insufficiency.

Material and methods

The protocol of the investigation was approved by the ethics committee on human research of our institution, and informed consent was signed by all participants.

Studied population

This study was part of a larger study that attempted to document the usefulness of different pre- and perinatal parameters to predict neurodevelopmental outcome. To be eligible, all fetuses had to show an abnormal umbilical Doppler velocity waveform (pulsatility index at the fetal end of the cord >95th percentile),[17] and delivery had to occur after 28 weeks of pregnancy to avoid the potential confounding effects of extreme prematurity. Exclusion criteria included residence outside the Montreal metropolitan area, families who did not speak French at home (to exclude bias in the developmental assessments that were carried out in French), chromosome abnormalities, congenital malformations, and evidence of sociofamilial problems (such as drugs addiction, alcoholism, mental illness, consanguinity, welfare beneficiary, and history of battered children). The Doppler findings at the level of the isthmus were never disclosed to the attending staff. The timing of delivery was decided on the basis of conventional criteria that were classified in 2 categories: fetal (absence of weight gain, abnormal biophysical profile score,[18] reverse diastolic blood flow in the umbilical artery) or maternal (severe preeclampsia). The initial cohort included 124 subjects, among which 55 subjects were twins. For the purpose of the current study, however, only the singleton infants with an adequate Doppler tracing of the aortic isthmus blood flow, which was recorded no >7 days before delivery, and with a neurodevelopmental assessment that was completed between the age of 2 and 5 years were retained. IUGR was defined as birth weight below the third percentile for gestational age.[19]

Doppler investigation

The technique of Doppler investigation of the fetal aortic isthmus has been described previously.[14] Briefly,

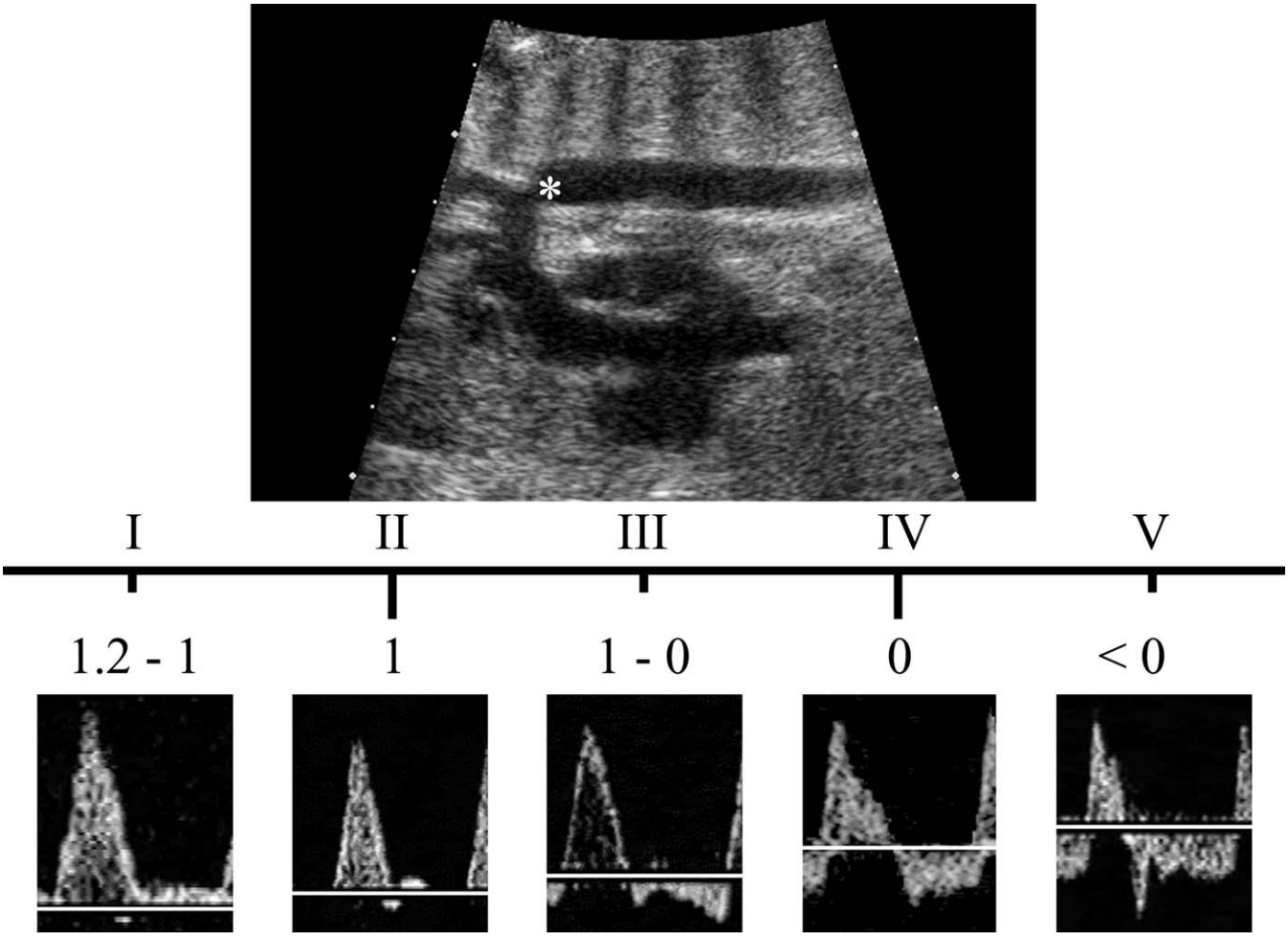

Figure 1 **Top**, Real-time echographic imaging of the aortic arch. The *asterisk* identifies the localization of the sample volume for Doppler interrogation in the isthmus. **Bottom**, Examples of isthmic Doppler blood flow velocity waveforms that were recorded in fetuses with various degrees of placental circulatory insufficiency. Above these tracings, 5 types (in roman numbers) with their corresponding IFI values (in Arabic numbers) relate to the increasing severity of the condition. *Type I*, Forward blood flow is observed in diastole; the IFI is >1 but lower than normal. *Type II*, No isthmic diastolic velocities are recorded. *Type III*, Reverse diastolic blood flow is present, but with predominant antegrade blood flow in systole. *Type IV*, Antegrade systolic are equal to the retrograde diastolic velocities. *Type V*, The reverse diastolic blood flow is dominant and net blood flow through the isthmus is retrograde. Values of IFI are then negative, <0.

from a horizontal 4-chamber view of the fetal heart, a 90-degree rotation of the transducer provides a saggital view of the fetus on which the aortic arch can be observed. The isthmus is then identified between the origin of the left subclavian artery and the aortic end of the ductus arteriosus. Only recordings obtained during nonbreathing and a quiet fetal state were kept for further calculations. The proposed index was obtained by dividing the sum of the systolic (S) and diastolic (D) Doppler blood flow velocity integrals by the systolic blood flow integral (IFI = S + D/S).[16]

Positive and negative signs are assigned to antegrade and retrograde velocity values, respectively. Figure 1 shows a real-time ultrasound picture of the aortic arch and the location of the Doppler sample volume in the isthmus and shows the types of isthmic Doppler patterns that can be observed in fetuses with abnormal increase in placental vascular resistance. The actual IFI values that correspond to these 5 types are also shown.

Neurodevelopmental assessment

Neurodevelopmental outcome was established according to the results obtained from 2 assessments that were administered by independent examiners who were unaware of the Doppler results. The first assessment was a standardized neurologic evaluation that evaluated passive and active tone, deep tendon reflexes, primitive reflexes, head circumference measurement, and cranial suture status.[20] Results of this assessment were classified

Table I Perinatal and sociodemographic characteristics of the subjects, according to neurodevelopmental outcome

Characteristic	Optimal (n = 19)	Nonoptimal (n = 29)	*P* value
Interval between last Doppler and delivery (d)*	1.7 ± 1.6	2.0 ± 2.2	.509
Gestation (wk)*	32.7 ± 2.3	33.4 ± 2.2	.272
Delivery indications: Fetal (n)	13 (68.4%)	20 (69.0%)	.968
Birth weight (g)*	1484 ± 398	1443 ± 441	.745
Days in neonatal intensive care unit*	1.3 ± 1.9	3.1 ± 5.7	.063
Male (n)	11 (57.9 %)	13 (44.8%)	.376
IUGR (n)	10 (52.6%)	19 (65.5%)	.372
Respiratory distress syndrome (n)	3 (15.8%)	5 (17.2 %)	.895
Assisted ventilation (n)	4 (21.1%)	4 (14.0%)	.509
Maternal education (high school level) (n)	8 (42.1%)	9 (31.0 %)	.549
Family income <$30000 (n)	1 (5.2%)	3 (10.3%)	.533
Age at neurodevelopmental assessment (y)*	4.2 ± 1.1	4.4 ± 0.9	.764

* Data are given as mean ± SD.

Table II Comparison of Doppler velocimetric indices and their eta-squared coefficients in relation to neurodevelopmental outcome

Indices	Sample size	Nonoptimal (mean ± SD)	Optimal (mean ± SD)	*P* value	Eta
Umbilical artery pulsatility index	48	2.22 ± 0.81	2.06 ± 0.83	.524	0.869
IFI	48	0.44 ± 0.80	1.02 ± 0.22	.001	0.899

in 2 categories: (1) optimal neurologic function, when either 1 isolated abnormal sign was found or none; (2) nonoptimal neurologic function, when severe or moderate neuromotor impairment was present that resulted in the diagnosis of cerebral palsy or milder signs that were compatible with independent walk by the corrected age of 2 years.

Concomitantly, the Griffiths Mental Developmental Scales were used to assess developmental performances.[21] The general developmental quotient (DQ) was obtained by the averaging of scores from 6 different subscales. This DQ was initially defined on a continuous scale (100 ± 12.67) and subsequently dichotomized into 2 categories according to the work of Bowen et al[22] and Ley et al[23]: optimal when the score was ≥87; nonoptimal when the score was <87.

The neurodevelopmental outcome was then defined as a combination of the results of both assessments: optimal, when neurologic assessment and DQ were within normal limits; nonoptimal, when abnormal neurologic findings and/or nonoptimal DQ were present.

Statistical analysis

Descriptive statistics were computed for all the variables that were considered in this study. The comparability of the 2 outcome groups (optimal and nonoptimal) was investigated through *t*-tests (numeric variables) and chi-squared tests (categoric variables) on various perinatal and sociodemographic variables. To compare the criterion that had predictive validity of the umbilical artery pulsatility index with that of the IFI, the eta-squared coefficient was computed. Eta coefficient is a directional correlation that measures the association between the numeric indices (independent) and the dichotomic outcome (dependent). When eta is squared, the result is a correlation ratio that can be interpreted as a percentage of explained variation.[24] Then, the predictive validity of IFI was assessed through the estimation of sensitivity, specificity, predictive values, and likelihood ratios at 4 different cut-off points.[25] All hypotheses testing was done at the .05 level of significance. Finally, a forced entry logistic regression analysis was carried out with the score of the IFI index as the independent predictor and neurodevelopmental outcome as a binary outcome variable. Odds ratios and 95% confidence intervals were estimated. Two models were tested: a simple model that included only the index; the other model adjusted for birth weight, gestational age, and maternal level of schooling. Predicted probabilities were computed from the former model to create an expectancy table. A third model, a backward stepwise ($P < .05$ to enter; $P < .06$ to remove any variable) logistic regression model, was tested to determine the relationship between umbilical artery velocimetric indices and the outcome.

Results

Of the 69 singleton fetuses who were part of the initial cohort, 56 fetuses fulfilled the selection criteria. Eight families could not be located. The final study group

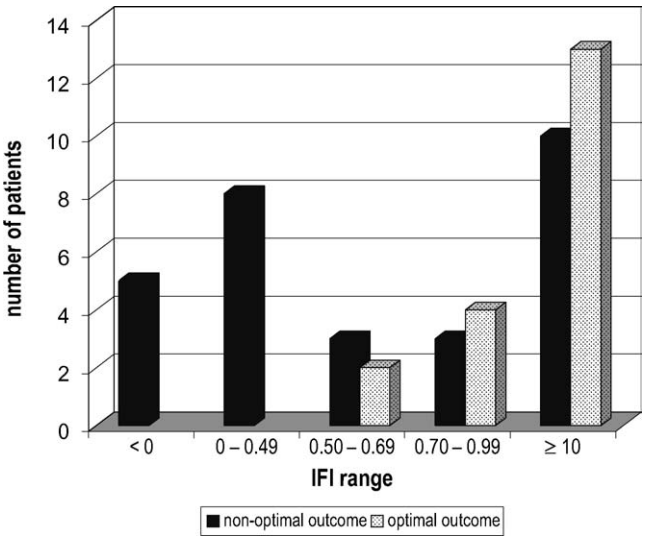

Figure 2 Breakdown of children with optimal and nonoptimal neurodevelopment outcomes, according to their isthmic blood flow index.

included 48 children who were born between 1991 and 1999. The perinatal and sociodemographic characteristics of the subjects according to their neurodevelopmental outcome are presented in Table I. No significant difference was found between the 2 groups. No grade III or IV intraventricular hemorrhage has been observed on ultrasound or computed tomography scan during the neonatal period. Steroids were administered to only 1 subject, which prevented any between group comparisons.

The Doppler velocimetric indices are presented in Table II. A significant difference between the 2 outcome groups was observed for the IFI values, which were lower for children in the nonoptimal group. On the other hand, no significant difference was found for the umbilical artery pulsatility indices. Table II gives the eta-squared coefficients for velocimetric indices in relation to the neurodevelopmental outcome. As evident in this table, eta-squared coefficients are high.

The distribution of the fetuses according to their IFI and their neurodevelopmental outcome are presented in Figure 2. A nonoptimal development was found in 29 children, which represented 60% of the population. It is apparent from Figure 2 that all 13 fetuses with an IFI of <0.5 were in this nonoptimal group. On the other hand, all 19 cases with an optimal outcome had an IFI of >0.5, but this was also the case for 16 other children with nonoptimal development. Table III gives predictive validity indices for 4 cut-off values of the IFI. With respect to the IFI value below which a fetus was at a greater risk of presenting with abnormal neurodevelopment, a cut-off value of 0.70 was associated with the highest overall positive and negative predictive values. It was also associated with a sensitivity of 0.55 and a specificity of 0.89.

Table III Estimation of sensitivity, specificity, predictive values, and likelihood ratios of different IFI cut-off values to predict abnormal neurodevelopmental status

IFI cutoff value	≤0	≤0.5	≤0.7	≤1.0
True positive	5	13	16	21
True negative	19	19	17	12
False positive	0	0	2	7
False negative	24	16	13	8
Sensitivity	0.17	0.45	0.55	0.72
Specificity	1.00	1.00	0.89	0.63
Positive predictive value	1.00	1.00	0.89	0.75
Negative predictive value	0.44	0.54	0.57	0.60
Likelihood ratio (+)*	†	†	5	1.95
Likelihood ratio (−)‡	0.83	0.55	0.51	0.44

* Sensitivity/1–specificity.
† Denominator = 0.
‡ 1-Sensitivity/specificity.

In the simple logistic regression model that used the IFI as the independent variable, an inverse correlation was found between the isthmic blood flow velocity index and the postnatal neurodevelopmental outcome. Clinically speaking, as the IFI diminishes, the probability of having a nonoptimal outcome increases. The estimate for the regression coefficient and its standard error was -3.12 ± 1.15 ($P = .007$). The 95% confidence interval for this coefficient indicates that, for each unit decrease in IFI, the probability of a nonoptimal outcome would be between 2.4 and 200 times greater. The average probabilities of nonoptimal outcome, as predicted by the logistic regression model for 5 subgroups of IFI, are as follows: IFI <0: 0.985 (95% CI, 0.96-1.00); from 0 to 0.49: 0.902 (95% CI, 0.86-0.95); from 0.5 to 0.69: 0.765 (95% CI, 0.73-0.80); from 0.7 to 0.99: 0.597 (95% CI, 0.53-0.66); and >1: 0.385 (95% CI, 0.35-0.42).

The backward stepwise model indicated that umbilical pulsatility index did not show any significant contribution in the explanation of the outcome.

Comment

In this study, a significant negative correlation was found between the isthmic blood flow velocity index and postnatal neurodevelopmental outcome, which added to the demonstration of predictive validity for the IFI. This observation can be explained by the unique position of the isthmus between the 2 fetal arterial systems disposed in parallel.[26] In the presence of a placental circulatory insufficiency, the increase in placental vascular resistance, coupled with the hypoxemic cerebral vasodilation, cause a decrease in the forward diastolic blood flow through the isthmus; with further deterioration, the diastolic isthmic blood flow disappears and, in very severe cases, could become markedly retrograde. When reverse blood flow occurs in the aortic isthmus, blood coming from the

pulmonary artery and descending aorta is being diverted from its normal destination, mainly the placenta; the brain then is perfused partly by blood that is deprived of substrates, placental or maternal, that are essential for fetal development[27] and, at the same time, by red cells very poorly saturated in oxygen.[1-5] The greater the reverse isthmic blood flow, the lower the IFI and the higher should be the risk of prenatal cerebral damage. The results of the logistic regression model point in that conceptual direction.

According to this concept, all fetuses with a forward systolic and diastolic isthmic blood flow (IFI, >1) would be in a "safe zone," protected from cerebral hypoxia. However, approximately 40% of the 23 fetuses who were in this "safe zone" in our sample had a neurodevelopmental impairment. This observation confirms that other factors besides the degree of prenatal hypoxia participate in the development of unfavorable postnatal outcome. Perinatal events and manipulations in the neonatal intensive care unit could be responsible for this finding. However, the review of the charts did not disclose any adverse major postnatal events (such as ventricular hemorrhage or periventricular leukomalacia). Furthermore, the demographic variables that are presented in Table I were comparable in both groups. The evidence of different neurodevelopmental outcomes in children who had presumably the same level of hypoxic stress in utero could also suggest individual differences in cerebral sensitivity. The mechanisms underlying brain injury that is associated with uteroplacental insufficiency are, for the most part, unknown. Proteomic and genomic profiling of cells and tissues only recently has begun to be explored in the mature subject after focal cerebral ischemia.[28] Individual genetic polymorphism or differences in placental and cerebral gene expression in the presence of hypoxemia are speculative explanations that are worth investigating.

Neurodevelopmental status was chosen as the outcome measure in this study because contemporary improvement in postnatal care allows survival of most IUGR fetuses who are delivered at >29 weeks of pregnancy. Rate of survival alone is therefore an insufficient criterion for the assessment of prenatal management in this context. Furthermore, the search for a marker that would allow clinicians to identify IUGR fetuses who must be delivered before evidence of cerebral hypoxia must fulfill at least 2 major requirements: first, ensure the highest possible rate of detection of fetuses at risk; second, avoid any significant increase of unnecessary preterm deliveries. Our results reveal that the IFI values that come closer to these criteria are in the type III range, more precisely between 0.5 and 1. In this sample, the sensitivity of the cut-off at 0.7 is approximately 3.5 times that of a cut-off at 0 (0.17).

In conclusion, this preliminary report concerning an ongoing investigation demonstrates that traditional criteria that are used for timing delivery in cases of placental circulatory insufficiency are associated with an elevated risk of nonoptimal postnatal neurodevelopment. It also shows a good negative relationship between fetal isthmic blood flow velocity index and the incidence of postnatal neurodevelopmental outcome. A greater number of patients who come from >1 center need to be investigated to establish with confidence the IFI level at which delivery of an IUGR fetus would be indicated rationally. It will then become necessary to position this "cut-off level" in relation to other more readily available testing modalities and to set up randomized studies to verify that intervention at the "impending-decompensation" stage produces any benefit.

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