Correlation between prenatal velocity waveforms in the aortic isthmus and neurodevelopmental outcome between the ages of 2 and 4 years

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OBJECTIVE: Experimental studies on fetal lambs have shown that during an increase in the resistance to placental flow the delivery of oxygen to the brain is preserved as long as net flow through the aortic isthmus is antegrade. Our purpose was to determine whether the same changes in aortic isthmus flow in human subjects have any impact on neurodevelopmental outcome.

STUDY DESIGN: Forty-four fetuses were retrospectively included in this study on the basis of an abnormal Doppler velocity in the umbilical artery. Mean gestational age at delivery was 33.0 ± 2.0 weeks and mean birth weight 1386 ± 435 g. The neurodevelopmental condition was assessed between the ages of 2 and 4 years. The developmental score was analyzed in relation to the flow patterns in the fetal aortic isthmus, which were classified as follows: group A, net isthmic flow antegrade (defined as the ratio of the systolic antegrade to the diastolic retrograde velocity integrals) (n = 39); group B, net isthmic flow retrograde (n = 5).

RESULTS: Nonoptimal neurodevelopment was observed in 19 (49%) of 39 fetuses in group A and in all 5 fetuses (100%) in group B. This difference is significant and leads to a relative risk of 2.05 (95% confidence interval, 1.49-2.83) for neurodevelopmental deficit when predominantly retrograde flow is observed in the fetal aortic isthmus before birth.

CONCLUSION: Measuring the ratio of antegrade to retrograde velocity integrals in the aortic isthmus could help in the indirect assessment of cerebral oxygenation during placental circulatory insufficiency. (Am J Obstet Gynecol 2001;184:630-6.)

Key words: Aortic isthmus, Doppler, neurodevelopment, placental insufficiency

Placental circulatory insufficiency is associated with an increase in placental resistance, which causes a fall in umbilical flow and secondary hypoxemia.[1-3] Many defense mechanisms are known to help the fetus maintain adequate cerebral oxygenation despite this hypoxemic stress.[4] During the compensated stage, diastolic flow in the umbilical artery is reduced or absent, but the biophysical profile remains mostly undisturbed. On the other hand, signs associated with failure of the defense system include alteration in the biophysical profile and a marked retrograde diastolic component in the Doppler flow velocity waveforms of the umbilical artery. At this

stage severe hypoxemia and acidemia are known to be present.[5] There are, however, no existing criteria that allow accurate identification of fetuses on the verge of deterioration. In our present state of knowledge, the real clinical challenge is no longer to identify the conditions of compensated or decompensated hypoxemia but to recognize fetuses in the critical stage of impending cerebral hypoxia.

Previous experimental studies on lamb fetuses led us to believe that Doppler investigation of the flow patterns in the fetal aortic isthmus could help in this discriminating process.[6] These experiments demonstrated that, in the presence of a stepwise increase in placental vascular resistance, the normal isthmic antegrade diastolic flow decreases early and becomes rapidly retrograde; delivery of oxygen to the brain is, however, preserved as long as the net flow through the isthmus is antegrade.[6] When the net isthmic flow becomes retrograde, there is marked contamination of the blood ejected by the left ventricle toward the brain by poorly oxygenated blood coming from the pulmonary artery.

This study is a first attempt to determine whether these experimental observations have any clinical significance. Our specific goal is to demonstrate possible correlations

Table I. Perinatal potential confounders

Prenatal	Perinatal	Postnatal
Parity	Birthplace (outborn)	Bronchopulmonary dysplasia
Multiple pregnancy	Urgent delivery	Neonatal intensive care unit stay (d)
Smoking	Apgar score <6 at 5 min	Postnatal neurologic problems
Toxemia	Male sex	Maternal education (y)
Chronic hypertension	Birth weight	
Maternal chronic disease	Head circumference	
Placental anomalies*	Assisted ventilation (d)	
Breech presentation	Neurologic problems	
	Pulmonary problems	
	Cardiovascular problems	
	Renal problems	
	Metabolic problems	

*Other than the increase in vascular resistance.

between prenatal changes in the aortic isthmus velocity waveform and neurodevelopmental outcome between the ages of 2 and 4 years. Clinical confirmation of our experimental findings could lead to the identification of a valid marker of the impending failure of fetal adaptive mechanisms.

Material and methods

All patients seen in our fetal cardiology unit from January 1991 to December 1996 whose computerized chart mentioned an abnormal umbilical Doppler velocity waveform (pulsatility index >95th percentile)[7] were retrospectively considered admissible for the study. They were ultimately enrolled if adequate Doppler flow velocimetry in the fetal aortic isthmus was also available on the videotape recordings. Neither the treating obstetricians nor those responsible for the neurologic and developmental assessments were aware of the Doppler findings in the isthmus.

The exclusion criteria were a gestational age <29 weeks at birth, residence outside the Montreal metropolitan area, families that did not speak French at home (to exclude bias in the developmental assessments, which were carried out in French), chromosome disorders, congenital malformations, and evidence of sociofamilial problems such as drug addiction, alcoholism, mental illness, consanguinity, welfare beneficiary, and history of battered children. The last ultrasonographic studies had to be recorded within 2 weeks of delivery. Both singleton and multiple births were included. All clinical charts were reviewed for the presence of prenatal and postnatal risk factors listed in Table I. The protocol of the investigation was approved by the ethics committee on human research of our institution, and an informed consent form was signed by all participants.

Doppler investigation. The technique of Doppler investigation in the fetal aortic isthmus was described previously.[8] Briefly, a 4-chamber view is first obtained from a transverse thoracic approach with the heart in a horizontal position, the spine being at the top or preferably at the bottom of the picture. Then a 90° rotation of the transducer provides a sagittal view of the fetus and of the aortic arch. The sample volume was placed a few millimeters beyond the origin of the subclavian artery (Fig 1). All videotape recordings were reviewed by the same investigator (Jean-Claude Fouron).

The subjects were initially subdivided into 4 groups according to the following flow patterns in the aortic isthmus: group 1, decreased antegrade diastolic velocities; group 2, absent diastolic velocities; group 3, slight retrograde diastolic velocities (in this group the net velocities [defined as the ratio of the systolic antegrade to the diastolic retrograde velocity integrals] were still antegrade, resulting in a ratio >1); group 4, marked diastolic retrograde velocities and net velocities that were retrograde and resulted in a ratio <1. Fig 2 shows an example of the flow waveforms observed in groups 2, 3, and 4. For each group the corresponding Doppler velocity waveforms in the umbilical artery were also recorded and classified according to 1 of 3 diastolic velocity patterns—decreased, absent, or retrograde.

Growth characteristics at birth. The United Kingdom cross-sectional reference data charts were chosen as the reference for growth charts.[9] These curves have the two main advantages of taking into account the degree of prematurity and of being usable from birth until the age of 18 years. Fetal growth was considered symmetric or proportionate when birth weight and head circumference at birth were <2 SD apart. Fetal growth was considered asymmetric or disproportionate when head circumference at birth was greater than birth weight (≥2 SD on the growth chart). Intrauterine growth restriction (IUGR) was defined by birth weight ≤2 SD (2nd percentile) for gestation.

Neurologic assessment. A standardized neurologic evaluation was used,[10] including passive and active tone, deep tendon reflexes, primitive reflexes, head circumference measurement, and suture status; each of these responses or measurements evolves with age, and therefore the coding system is age dependent. Any neurologic impairment

Fig 1. A, Sagittal view of fetus, showing aortic arch. *Arrow* identifies isthmus and location for Doppler flow velocity recordings. **B,** Normal Doppler velocity waveforms in isthmus of 26-week fetus.

present at or after 2 years is considered permanent, as opposed to resulting motor dysfunction, which is age dependent. An occupational therapist and a neonatologist were involved in the data collection. Both had previously been trained by Claudine Amiel-Tison.

The interpretation of the neurologic assessment is based on the association of signs. At a corrected age of 2 years the data are classified into the following 2 categories: (1) optimal neurologic function, when no sign or only one isolated abnormal sign is found, and (2) nonoptimal neurologic function, when severe or moderate neuromotor impairment is present, resulting in the diagnosis of cerebral palsy, or when milder signs, compatible with independent walking by a corrected age of 2 years, are present. Two signs have proved particularly helpful in revealing impairment of the pyramidal system—phasic stretch in the triceps surae muscle and imbalance of passive axial tone, with predominance of extensor tone. In addition, a ridge over the squamous suture implies a deceleration in hemispheric growth after the perinatal insult. This ridge may be permanent or regressive after the age of 2 years. These 3 signs are usually associated; when

only 2 signs are present, the abnormal stretch must be in one of them to classify the subject in the nonoptimal group.[11]

Developmental assessment. The Griffiths Mental Developmental Scales[12] were completed at the corrected age of 2 years or afterward. These scales assess the following 6 areas of development: locomotor, eye-hand coordination, personal-social, hearing and speech, performance, and practical reasoning. Subscale quotients for each area can be calculated independently, and the general developmental quotient (DQ) is obtained by averaging scores from all subclasses (mean ± SD, 100 ± 12.76). Only the last general DQ has been considered for analysis. The categorization in 2 levels of DQ, which represent conservative normal limits, was based on the recent work of Bowen et al[13] and Ley et al[14]: (1) the optimal level, within normal limits of ≥87 DQ; (2) the nonoptimal level, with intellectual functioning at <87 DQ (100 − 1 SD). For the final categorization of the neurodevelopmental outcome between the ages of 2 and 4 years, the optimal level was achieved when findings of normal neurologic assessment and the DQ were within normal limits, and the nonopti-

mal level was characterized by either abnormal neurologic findings or a nonoptimal DQ or both of these.

Statistical analysis. Groups 1, 2, and 3, which have in common a net antegrade isthmic flow, were first analyzed to confirm the absence of any intergroup differences concerning both neurodevelopmental outcome and perinatal characteristics. Analysis of variance and χ^2 tests were used. The subsequent analyses were performed on 2 groups as follows: group A, consisting of all fetuses with net antegrade isthmic flow; group B, formed by those with net retrograde isthmic flow. The χ^2 test was used to compare the incidence of nonoptimal neurodevelopmental outcome in each group, and relative risk with a 95% confidence interval was also estimated.

Results

On the basis of our selection criteria, the children of 82 women were admissible. Twenty-six women were not located, and 15 refused to participate. The final cohort comprised 44 survivors born between 1991 and 1996, including 3 pairs of twins. The mean age at follow-up was 3 years 3 months (range, 2-4 years). The perinatal characteristics of the subjects for each group are presented in Table II. There were no significant differences between groups in regard to prenatal variables. Only a few perinatal and postnatal complications did not allow any multivariate analysis (2 cases of respiratory acidosis, 3 cases of pulmonary bronchodysplasia, 2 cases of necrotizing enterocolitis, and 2 cases of grade 2 intraventricular hemorrhage). However, there was a slight trend toward a lower gestational age for the group with a net retrograde isthmic flow. This difference was not statistically significant.

Evidence of IUGR was present in 30 of the 44 children, with a majority (27/30) having proportionate IUGR (Table III). There appeared to be a slight trend toward an increase in nonoptimal outcome when proportionate IUGR was present.

Table IV shows the relationship between the echocardiographic Doppler findings and the results of the neurodevelopmental assessments. Twenty children had an optimal neurodevelopmental outcome, whereas 24 had a nonoptimal outcome. Six children were classified as having a nonoptimal outcome on the basis of both a low DQ (<87) and moderate neurologic signs; 3 children had a low DQ (<87) but their neurologic examination showed only isolated neurologic findings. Finally, 15 children had moderate neurologic signs with a DQ of ≥87. No case of cerebral palsy was detected. Of the 39 subjects with a net antegrade isthmic flow, 15 had a decreased diastolic isthmic flow (10 with nonoptimal neurodevelopmental outcome), 16 had no diastolic isthmic flow (5 with a nonoptimal neurodevelopmental outcome), and 8 had a retrograde diastolic isthmic flow (4 with a nonoptimal neurodevelopmental outcome).
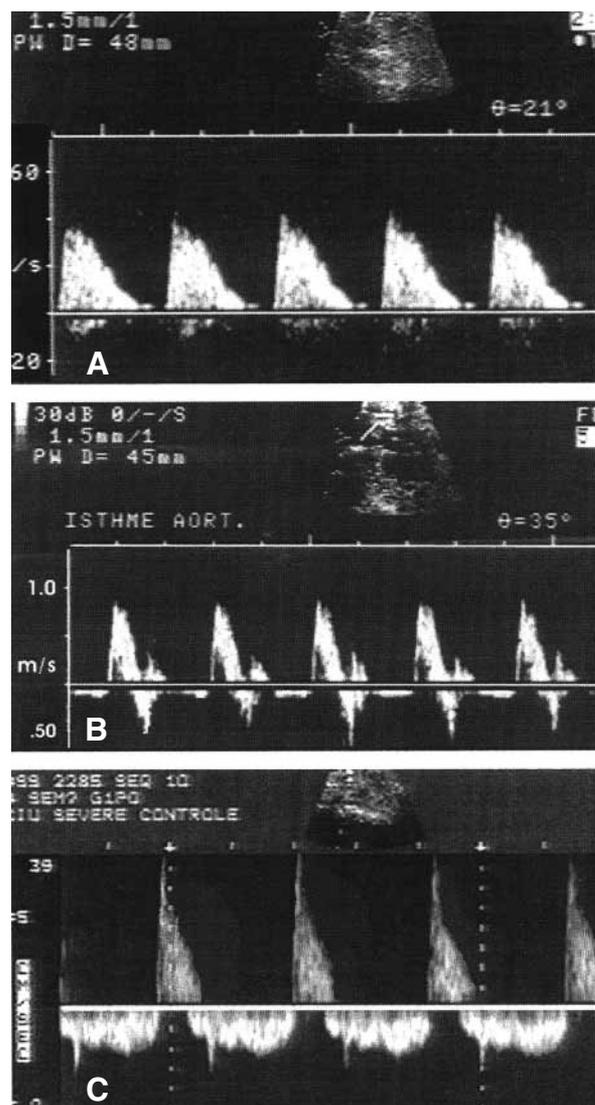
All 5 children with a net retrograde isthmic flow

Fig 2. Examples of flow velocity waveforms in aortic isthmus of fetuses in group 2 (**A,** absent diastolic flow), group 3 (**B,** slightly retrograde diastolic flow), and group 4 (**C,** marked retrograde diastolic flow). In groups 2 and 3 the net velocities are still antegrade and the ratio of systolic antegrade to diastolic retrograde velocity integrals are >1. In group 4 the net velocities are retrograde and the ratio is <1. In the interest of space, waveforms of group 1 were omitted.

(group B) showed a nonoptimal neurodevelopmental outcome. This distribution is illustrated in Fig 3. From Table IV, we carried out a comparison for which data were collapsed over the umbilical artery variable, thus contrasting the groups defined respectively by net antegrade and net retrograde isthmic flows. The comparison was statistically significant ($\chi^2 = 4.70$; $P = .03$). The relative risk was 2.05 (95% confidence interval, 1.49-2.83). It has to be mentioned that the umbilical artery flows for 2 of these 5 children were not yet retrograde but were absent.

Table II. Perinatal characteristics of subjects

		Isthmic flow			
Characteristic	Total (n = 44)	Decreased (n = 15)	Absent (n = 16)	Retrograde (n = 8)	Net retrograde (n = 5)
Time interval between last Doppler delivery (d, mean ± SD)	4.7 ± 3.9	4.8 ± 2.8	5.7 ± 5.0	4.1 ± 3.6	2.2 ± 2.2
Gestational age (wk, mean ± SD)	33.0 ± 2.0	33.0 ± 2.3	32.9 ± 2.1	33.6 ± 1.3	31.8 ± 1.3
Birth weight (g, mean ± SD)	1386 ± 435	1449 ± 429	1331 ± 389	1421 ± 619	1301 ± 297
Head circumference (cm, mean ± SD)	29.2 ± 2.2	29.3 ± 2.4	29.1 ± 2.2	29.1 ± 2.6	29.1 ± 2.7
Intensive care (d, mean ± SD)	5.8 ± 13.6	2.7 ± 8.8	7.3 ± 16.3	8.0 ± 17.7	6.8 ± 13.5
Transferred from community hospital (No.)	2 (5%)	1 (7%)	1 (6%)	—	—
Reason for delivery (No.)					
Urgent cesarean delivery					
Maternal reasons	9	4	2	1	2
Fetal reasons	5	1	2	1	1
Elective cesarean delivery					
Severe IUGR	17	3	2	5	2
IUGR with gestational age >35 wk	3	2	—	—	—
Induced vaginal delivery	10	5	—	1	—
Reanimation at birth (No.)	6 (14%)	1 (7%)	2 (13%)	2 (25%)	1 (20%)
Male (No.)	24 (55%)	8 (53%)	8 (50%)	6 (75%)	2 (40%)
Hyperbilirubinemia (bilirubin >120 μmol/L, No.)	32 (73%)	10 (67%)	13 (81%)	5 (63%)	4 (80%)
Anemia (No.)	11 (25%)	2 (13%)	4 (25%)	2 (25%)	3 (60%)

Table III. Growth characteristics at birth and neurodevelopmental outcome

	Neurodevelopmental outcome	
Intrauterine growth	Optimal	Nonoptimal
Proportionate IUGR	11	16
Disproportionate IUGR	2	1
Proportionate without IUGR	2	2
Disproportionate without IUGR	5	5

Table IV. Doppler velocimetry and neurodevelopmental outcome

		Neurodevelopmental outcome	
Umbilical arteries	Aortic isthmus	Optimal	Nonoptimal
Decreased	Net antegrade	13	16
	Net retrograde	—	—
Absent	Net antegrade	6	2
	Net retrograde	—	2
Retrograde	Net antegrade	1	1
	Net retrograde	—	3
TOTAL	Net antegrade	20	19
	Net retrograde	—	5

Of the 24 children who had a second developmental assessment as part of the follow-up, 15 lost at least 5 points (and up to 29 points) on the DQ. Apart from the 7 children already scoring <87, 15 other children scored between 87 and 100; 9 of them also had associated neurologic signs.

Comment

The incidence of nonoptimal outcome, defined by a low DQ (<87) or the association of at least 2 minor neurologic signs, was relatively elevated (24 out of 44 subjects in our studied population). The same observation has been reported by others.[15] This finding, even in the low-risk groups (groups 1, 2, and 3), could be in part a result of the retrospective nature of the study, especially in relation to the time of the last echocardiographic Doppler study, making it possible for further fetal hemodynamic deterioration to occur before birth. Another explanation for this finding could be the multifactorial origin of brain injuries occurring during the prenatal and postnatal periods. In the current study, to minimize the effects of extreme prematurity and low birth weight, we included only infants born after 29 weeks' gestation. The fact that the great majority of our children (27/44) showed proportionate IUGR at birth strongly favors the likelihood that an early placental insufficiency caused impairment in brain development, rather than hypoxic injuries.[16] Furthermore, it should be kept in mind that the developmental assessments were completed when the children were between the ages of 2 and 4 years. A recent study[13] demonstrated a trend toward a decrease in the DQ between the ages of 3 and 5 years. Although none of the children studied had reached school age, it can be concluded, on the basis of previous observations, that the risk of school failure or other difficulties could be expected to be as high as 54% (24 cases).[11]

To the best of our knowledge, our study is the first attempt to correlate circulatory changes in the aortic isthmus with developmental outcome in human fetuses with evidence of an increase in placental vascular resistance. The observation that all 5 fetuses with net retrograde flow

in the aortic isthmus showed evidence of abnormal developmental outcome is in accordance with previous experimental findings showing a fall in oxygen delivery to the brain in this situation.[6] It is of interest that velocities in the umbilical artery of these 5 fetuses were variable, with a retrograde diastolic velocity in 3 fetuses but absent velocity in 2 of them. Previous reports that have demonstrated a relationship between abnormal Doppler velocities in the descending aorta and umbilical artery and postnatal morbidity have also shown that adverse neurologic sequelae could occur with either absent or reversed diastolic flow velocity waveforms.[14, 17-21] Others have found little relationship between antenatal cerebral Doppler findings and neurologic outcome in very preterm infants.[22] This discrepancy between the umbilical artery and the fetal aortic isthmus is, in all likelihood, caused by the differences in circulatory dynamics of these two arterial segments. The downstream resistances that alter the flow pattern in the umbilical artery are exclusively made of the placental vascular network. Furthermore, although abnormal development of the placental vessels interferes with maternal-fetal oxygen exchange, hypoxemia per se does not influence the resistance of the placental vascular bed, which is known for its lack of reactivity; consequently, Doppler flow velocity in the umbilical artery is not influenced by fetal blood oxygenation.[23] The situation differs for the aortic isthmus. This vascular segment, localized between, on the one hand, the emergence of the left subclavian artery (perfused by the left ventricle) and, on the other hand, the aortic end of the ductus arteriosus and the subdiaphragmatic circulation (perfused by the right ventricle) represents, in the fetus, the only link between the two parallel ventriculoarterial systems. Because of this unique anatomic position, the isthmic flow velocity waveforms are therefore influenced not only by the downstream impedance in the subdiaphragmatic circulation but also by changes in the arterial tone in the upper part of the body, especially the brain. Both vascular networks are influenced by hypoxemia and, more important, in an opposite fashion. Hypoxemia causes a marked vasoconstriction in major parts of the subdiaphragmatic circulation while causing cerebral vasodilatation, consistent with the redistribution of blood flow described in fetuses with IUGR.[24] It must be realized that the increase in placental vascular resistance, which normally characterizes the disease, further increases the rise in subdiaphragmatic vascular resistance initiated by hypoxemia in other major vascular beds, such as the mesenteric arteries. Both experimental[25] and clinical[26] investigations have confirmed that during placental circulatory insufficiency these concomitant changes markedly alter the isthmic flow pattern; its normal diastolic antegrade flow decreases early and becomes rapidly retrograde at a stage where it is only absent or simply decreased in the umbilical artery. With the appearance of a
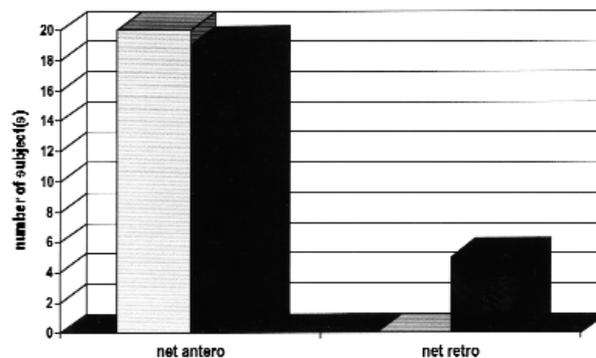

Fig 3. Distribution of neurodevelopmental outcome according to isthmic flow alone. All 5 children who had a net retrograde isthmic flow during their fetal life showed a nonoptimal outcome (*filled bar*). The numbers of children with an optimal outcome (*open bar*) and those with a nonoptimal outcome (*filled bar*) after net antegrade isthmic flow are also shown.

net retrograde flow through the isthmus, blood with very low oxygen content, which comes from the pulmonary circulation and is destined for the placenta, is reoriented toward the brain. This causes a major negative impact on oxygen delivery to the brain despite maintenance of carotid artery blood flow.[6]

Our findings raise the question of considering prenatal monitoring of the flow velocity waveforms in the aortic isthmus as a means of preventing hypoxic prenatal brain injury. These retrospective data show that 5 (20%) of 24 children with an unfavorable neurodevelopmental outcome had a net reverse flow in the isthmus and, in all likelihood, had hypoxic brain injury. On the basis of these data, one can speculate that extraction of these 5 fetuses before the occurrence of the net retrograde isthmic flow could have, at least in part, reduced the number of cases of brain injury. Furthermore, relying on net inversion of isthmic flow to decide the time of delivery of a fetus with IUGR could also help to prolong the pregnancy safely and therefore reduce the additional risk of great prematurity. In practice, the simple measurement of the ratio of antegrade to retrograde velocity integrals in the aortic isthmus could directly inform the clinician regarding the hemodynamic condition of a fetus with placental vascular insufficiency. This would represent for the first time a simple quantitative, indirect index of cerebral oxygenation. Obviously, a prospective longitudinal study involving a greater number of cases with sequential ultrasonographic monitoring is mandatory to determine the index value beyond which a turning point is reached and fetuses with IUGR are at significant risk of having cerebral hypoxic damage.

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