Dear colleagues,

I would like to thank you very sincerely for agreeing to participate in our multicentre study on the clinical significance of recording fetal aortic isthmus flow during placental circulatory insufficiency.

The primary objective of this project is to identify the threshold value of the isthmic flow index (IFI) below which a fetus suffering placental insufficiency is at risk of intrauterine cerebral hypoxic injury.

The project will be undertaken in three phases. The first phase is designed to ensure uniformity in all centres for Doppler recording techniques in all vascular sites included in the study. The second phase is the collection of obstetrical and neonatal data and, the final phase involves the assessment of neurodevelopment at 2 years of age.

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<th>Phase</th>
<th>YEAR 1</th>
<th>YEAR 2</th>
<th>YEAR 3</th>
<th>YEAR 4</th>
<th>YEAR 5</th>
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<tr>
<td>Phase I</td>
<td>Knowledge transfer</td>
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<td>Phase II</td>
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<td>Obstetrical and Neonatal follow-up</td>
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<td>Phase III</td>
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<td>Neurodevelopment follow-up</td>
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The internet site that you are currently viewing was designed primarily to facilitate phase I, which is the knowledge transfer phase. Prior to that, it seemed necessary to justify our working theory concerning the isthmus. A physiological review is first required for this purpose.
Why the fetal aortic isthmus?

Two basic elements characterize fetal circulatory dynamics: first, the parallel arrangement of the two ventricles and their arterial outlet and, second, the presence of shunts.

The parallel arrangement of the fetal ventricles, well demonstrated experimentally, is observed daily in any Fetal Cardiology unit where we can see the two cardiac pumps perfusing the systemic circulation in parallel, the left ventricle via the aortic arch and the right ventricle via the pulmonary arch made up of the main pulmonary trunk and arterial duct.

By definition, a shunt diverts a portion of blood flow from its normal trajectory to a circuit with less resistance.

In the fetus, the ductus venosus corresponds very well to the definition of a shunt since the umbilical vein normally drains into the portal system. Part of the umbilical venous
blood, which should make it to the liver, is diverted towards the inferior vena cava through the ductus venosus. This is also true for the foramen ovale which allows the passage of blood from the right to the left atrium, whereas normally it should go to the right ventricle.

However, the concept of a fetal circulation with two cardiac pumps, left and right, arranged in parallel is incompatible with identification of the arterial duct as a shunt. Indeed, describing a right to left shunt between the pulmonary artery and the thoracic aorta logically means that the normal destination of blood, ejected by the right ventricle in the fetal pulmonary artery, would be the lungs and, subsequently, this blood would go to the left heart. In other words, it would be a circulation in series, as described classically in the postnatal period. Therefore, it is totally irrational to affirm that the two cardiac pumps and their respective outlet are arranged in parallel during the fetal period, and describe, in the same breath, the flow to the arterial duct as a right to left shunt.

According to the next figure, we can very easily understand that the aortic arch and the pulmonary arch are perfusing the systemic circulation in parallel. Considering this figure, the right and left pulmonary arteries during fetal life are branches of the pulmonary arch in the same way as carotid and left subclavian arteries are branches of the aortic arch. We can also easily conclude from this figure that the isthmus, not the arterial duct, is the sole arterial shunt in the fetal circulation connecting the two parallel arterial arches.
In systole, the orientation of the isthmic shunt to the head or to the feet will depend both on left ventricular function which has an antegrade influence on the shunt, and on right ventricular function which influences the isthmic shunt in a retrograde manner. There are several examples of malformations that demonstrate this phenomenon very well.

In diastole, while the pulmonary and aortic valves are closed, the orientation of the shunt will essentially depend on balance between the supradiaphragmatic circulation, excluding that of the lungs, and the infradiaphragmatic circulations.

Since cerebrovascular resistance decreases while a plateau is observed at the level of placental resistance from the second trimester to the end of the pregnancy, we observe a progressive diminution of isthmic antegrade diastolic flow. It is important to note, on velocity Doppler curves in the isthmus, that we encounter a retrograde telesystolic incisure that gradually increases from the beginning of the third trimester to the end of the pregnancy. It is a physiological phenomenon related to the increasing preponderance of right ventricular stroke volume which at the very end of systole
Influences the isthmic flow in a retrograde manner. The fact that this brief retrograde flow occurs during systole is well illustrated by simultaneous recording of flows in the isthmus and arterial duct. We can see that the left ventricular antegrade influence stops just before the end of systole and leaves room for the right ventricular influence through the arterial duct. This point is very important in the interpretation of pathological Doppler tracings.

Simultaneous recording of the aortic isthmus flow and the arterial duct flow

In the presence of increased placental resistance, as this is the case in placental insufficiency, we note the disappearance of the diastolic flow in the umbilical artery, and then very quickly, a retrograde flow arises, first telediastolic and subsequently holodiastolic in the more severe cases.

Those changes in the Doppler waveforms observed at the level of the umbilical artery can also be recorded at the level of the aortic isthmus.
Aortic isthmus flow recording

1) Normal case, antegrade diastole, 2) Absent diastole, 3) Retrograde diastole, 4) Severe case, dominant retrograde diastole

An isthmic flow index has been proposed, based on the ratio of integral systolic and diastolic velocities, and corrected for systolic velocities. In normal cases, the IFI is always above 1.2 regardless of gestational age.

Five types of IFIs changes occur in the presence of increased placental resistance:
- Type I: IFI > 1, antegrade diastolic flow is still present, but reduced;
- Type II: IFI = 1, diastolic flow is absent;
- Type III: IFI is a fraction of 1 but greater than 0, which reflects the appearance of a diastolic retrograde flow, but with a dominant antegrade flow;
- Type IV: IFI = 0, antegrade and retrograde isthmic flows are equal, which is equivalent to an absence of flow in the isthmus;
- Type V: IFI < 0, retrograde diastolic flow is predominant, the index being negative.
“IFI”

Interpretation chart

<table>
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<tr>
<th>Dominant Retrograde Diastole</th>
<th>Retrograde Diastole ≤ Antegrade Systole</th>
<th>Antegrade Diastole</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Type V</td>
<td>Type IV</td>
<td>Type II</td>
</tr>
<tr>
<td>Type III</td>
<td></td>
<td>Type I</td>
</tr>
</tbody>
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In closing, it is important to remember the limits of various Doppler tracings currently used to decide whether to deliver a fetus with growth restriction due to placental circulatory insufficiency. These limits are well illustrated in this figure taken from the publication of Hecher and coworkers.

**Pulsatility indices (umbilical artery, ductus venosus, descending aorta, inferior vena cava, middle cerebral artery), amniotic fluid index and, short-term variations**

![Graph showing trends over time of variables in relation to time before delivery and reference ranges (±2 SD) for Group 1 (fetuses delivered before or at 32 weeks of gestation).](image)

Hecher K *et al.* Ultrasound Obstet Gynecol 2001; 18: 564-570
The values of standard deviations of different parameters are on the y-axis. All values between +2 and -2 standard deviations are considered to be within the limits of normal. The days that precede childbirth are on the x-axis, the date of delivery corresponding to day 0. These fetuses have been followed for more than a month before delivery.

It is very easy to see, from the onset, that the umbilical artery is abnormal. It has indeed been well demonstrated that the degree of hypoxemia cannot be evaluated by the pulsatility index at the level of the umbilical artery. This index informs us only about the degree of resistance of a single vascular bed, the placenta, without telling us what is happening throughout the fetal body. It is noteworthy that the dominant retrograde flow observed at the level of the aortic isthmus in a fetus with restricted growth is never observed in the umbilical artery since it is obviously incompatible with fetal life. Doppler recording in the abdominal aorta and the amniotic fluid volume index are also abnormal very early. This is also the case for the pulsatility index of the middle cerebral artery, reflecting a compensatory phenomenon in response to hypoxemia ensuring adequate cerebral oxygenation. During a major part of the observation period, the flows in the ductus venosus and inferior vena cava as well as short-term variations in cardiac rate remain within the limits of normal. It is only five to six days before the expected date of delivery that these variables became abnormal. We know now that the appearance of changes at the level of the ductus venosus or vena cava corresponds to a state of severe hypoxia which leads to myocardial diastolic dysfunction. The myocardium is by far more resistant to hypoxia than the brain, which allows us to anticipate at this stage a central nervous system injury of hypoxic origin. It is not surprising to observe also that venous flow anomalies are associated almost simultaneously with the deterioration and loss of short-term normal variation of fetal cardiac heart beats. We know indeed that this variation is normally under the influence of the central nervous system.

In other words, most of the current criteria presently used to decide the delivery of a fetus suffering from IUGR are based on signs of cardiocirculatory decompensation and central nervous system dysfunction. That is what we want to avoid in our study, indeed. Obviously, the ideal criterion is one that would allow the delivery of these fetuses just before the appearance of decompensation.
This last figure illustrates why the isthmus appears to be potentially the ideal site for evaluating the degree of secondary fetal hypoxemia.

Indeed, in the presence of increased placental circulatory resistance, hypoxemia causes cerebral and coronary vasodilatation decreasing vascular impedance in the supradiaphragmatic circulation. In the infradiaphragmatic circulation of IUGR fetuses, the elevated vascular resistance is not only due to the changes in placental resistance but also to the intense hypoxic vasoconstriction observed in the mesenteric artery network. The balance between supradiaphragmatic and infradiaphragmatic resistances is then disrupted and the isthmus flow becomes abnormal. This pattern of changes which reflects the degree of hypoxemia should be reliably expressed by the wide range of possible alterations previously shown in the isthmus flow index.

Noteworthy, a dominant retrograde diastolic aortic flow can be observed at the level of the aortic isthmus in a fetus with severe IUGR, of course at the level of the umbilical artery such a flow pattern would be incompatible with fetal life.

On behalf of my colleagues and the entire technical staff who participate in preparing this Internet site, I want to thank you all for your attention.