DOPPLER VELOCIMETRY WITH EMPHASIS ON THE FETAL CEREBRAL CIRCULATION

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DOPPLER VELOCIMETRY WITH EMPHASIS ON THE FETAL CEREBRAL CIRCULATION

Doppler bloedstroomsnelheidsmetingen met nadruk op de foetale cerebrale circulatie

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CONTENTS

Chapter 1

INTRODUCTION AND DEFINITION OF STUDY OBJECTIVES

1.1 Introductory remarks

Despite its limitations, most centres still consider fetal heart rate monitoring (CTG) as the method of choice in the antepartum assessment of fetal well-being. Another antepartum test that has gained widespread acceptance is the biophysical profile (Manning et al, 1980), originally consisting of a nonstress test (CTG), fetal breathing movements, fetal limb or body movements, fetal tone and amount of amniotic fluid volume.

Doppler blood flow examinations can be a useful tool in the evaluation of fetal condition and in the prediction of fetal distress and neonatal outcome (Reuwer et al, 1987; Marsal and Persson, 1988; Groenenberg et al, 1993).

Impaired placental perfusion is associated with reduced transfer of oxygen and nutrients from the mother to the fetus. Consequently, fetal growth and oxygenation are reduced resulting in intrauterine growth retardation (IUGR) and fetal hypoxaemic hypoxia. In the presence of IUGR compensatory mechanisms may result in normal head growth or brain-sparing.

Most information on regulation of fetal cerebral blood flow originates from animal experiments. The fetal cerebral circulation is capable of responding to changes in the fetal environment, the most striking change caused by hypoxia. Peeters et al (1979) demonstrated that fetal hypoxaemia is associated with increased blood flow to the heart, adrenal glands and brain and decreased blood flow to the visceral organs as digestive tract, kidneys and lungs.

In order to study possible mechanisms of hemodynamic redistribution associated with utero-placental insufficiency in the human fetus, insight in normal cerebral blood flow is necessary.

In the human fetus Doppler cerebral flow velocity waveforms were first obtained in the common carotid artery (Marsal et al, 1984) and in the internal carotid artery (Wladimiroff et al, 1986). Lately, cerebral flow velocity waveforms have been obtained as early as 10-11 weeks of gestation (Wladimiroff et al, 1991; 1992).

The question of whether the growth-retarded human fetus has the ability to redistribute blood flow preferentially to the brain has been addressed by several groups of investigators using similar methods (Wladimiroff et al, 1986; Woo et al, 1987; Vyas et al, 1990).

Like in all other fetal vessels, fetal cerebral flow velocity waveforms are subject to both internal and external variables, like fetal breathing movements (Wladimiroff and van Bel, 1987), fetal heart rate (van den Wijngaard et al, 1988; Mari et al, 1991), fetal behavioural states (van Eyck et al, 1987), maternal plasma glucose concentration (Degani et al, 1991), Braxton-Hicks contractions (Oosterhof et al, 1992), changes in oxygenpressure (Arduini et al, 1988), etc. Also drugs can influence fetal (cerebral) blood flow (Mari et al, 1989; Belfort et al, 1994).

1.2 Definition of objectives

In this thesis the following questions were addressed:

1. Are changes in placental vascular resistance associated with alterations in arterial down stream impedance at fetal level?

To this purpose placental embolization was carried-out in the fetal lamb with subsequent Doppler velocimetry in the fetal descending aorta (chapter 2).

2. What happens to the human fetal cerebral circulation relative to normal and raised umbilical placental resistance?

To answer this question, the human fetal cerebral and umbilical artery were studied under physiological (chapter 3) and pathological conditions (chapter 4) using traditional 2-D real-time and Doppler techniques as well as colour-coded Doppler.

3. Which internal and external variables affect the human fetal cerebral circulation?

Here, distinction should be made between breathing movements (chapter 3), behavioural states (chapter 5) and maternal drug administration, with emphasis on indomethacin (chapter 6).

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Chapter 2

CHANGES IN PERIPHERAL VASCULAR RESISTANCE; IMPACT ON THE FETAL CIRCULATION

2.1 Literature review

In the fetus the systemic, pulmonary and umbilical circulation are connected by several shunts. The umbilical placental circulation is an extra-corporal circulatory system essential for fetal survival and growth, which is discarded at birth. Quantitative information on the fetal circulation is almost entirely obtained in the last trimester of pregnancy in the fetal lamb.

In contrast to the adult situation another unique aspect of the fetal circulation is the relatively high cardiac output, high fetal heart rate and low arterial pressure. Fetal cardiac output is almost exclusively altered by changes in heart rate, since the fetus has little capacity to alter its stroke volume (Rudolph and Heymann, 1974). The fetal heart has been shown to work close to the top of its Frank-Starling curve (Gilbert, 1980). Apart from the high heart rate, blood flow to the fetal tissues and placenta will also be dependent on alterations in perfusion pressure and resistance in the various vascular beds (Dawes, 1962; Berman et al, 1976).

Pressure measurements in the vessels of the umbilical circulation in fetal lambs from the distal aorta to the inferior vena cava indicate that the major pressure gradient is constituted in the placental microvasculature which is considered a low resistance pool (Dawes, 1962). In the fetal lamb from 90 to 115 days of gestation placental vascular resistance decreases, while umbilical blood flow per kg fetal weight increases. From 115 days of gestation onwards placental vascular resistance does not significantly alter. The increase in umbilical blood flow, in order to match fetal growth, is subsequently caused by a gradual rise in blood pressure (Dawes, 1962). Newnham et al reported a fall in umbilical artery A/B ratio from 66 to 109 days of gestation, with no alterations in A/B ratio from 109 to 136 days for the fetal lamb (Newnham et al, 1987). These observations suggest an association between placental resistance and Doppler flow velocity waveform indices.

The introduction of transvaginal pulsed Doppler systems has allowed the possibility of studying human fetal flow velocity waveforms as early as 10 weeks' gestation. Preliminary data have shown that in the late first trimester of pregnancy, end-diastolic velocities in the fetal descending aorta and umbilical artery are nearly always absent, suggesting a high fetal placental vascular resistance (Wladimiroff et al, 1992). Previous Doppler studies have detected end-diastolic flow velocities in the fetal descending aorta and umbilical artery as early as 16-18 weeks (Trudinger et al, 1985; van Vugt et al, 1987a and 1987b). During the late first and early second trimesters of normal pregnancy the pulsatility indices of the fetal descending aorta and umbilical artery are decreasing with advancing gestational age, suggesting a reduction in fetal and umbilical placental vascular resistance (Wladimiroff et al, 1991). Of interest at this point is the secondary trophoblast invasion of the spiral arteries during the early second trimester of pregnancy, resulting in low-resistance uteroplacental vessels (Brosens et al, 1967; de Wolf et al, 1973). This ensures optimal placental perfusion, which is necessary to accommodate the increased blood flow to the developing fetus. Uncomplicated third trimester pregnancies are also characterized by forward end-diastolic flow velocities in umbilical and fetal arterial vessels reflecting the presence of a low resistance feto-placental unit (Trudinger et al, 1985).

Calculation of placental vascular resistance is based on the Poisseuille equation: placental vascular resistance = mean arterial pressure minus mean umbilical venous pressure divided by umbilical blood flow. The formula is not applicable in case of variations in heart rate (Rudolph, 1976), and may be unreliable in a pulsatile flow system (Milnor, 1972). Pulsatile flow and pressure are generated by cardiac contraction and the pulsatility in the vascular bed depend largely upon the elasticity of the vessel walls (McDonald, 1974). Apart from resistance, the reactance of the vascular bed has to be taken into account, which is enclosed in the calculation of vascular impedance. Vascular impedance is the ratio of pulsatile pressure and pulsatile flow and does not have to be the same for all pulse frequencies (Milnor, 1972).

With regard to placental vascular resistance calculation the site of measurement of the arterial and venous pressure in the fetal lamb is important. Mean arterial pressure is commonly measured in the distal abdominal aorta, which is representative of umbilical arterial pressure (Dawes, 1962).

Most animal studies involve acute experiments, whereas intrauterine growth retardation is a chronic condition. In understanding the pathophysiological mechanisms operating in intrauterine growth retardation, experiments assessing the fetal response to hypoxia are of interest because the chronically impaired placental function may be associated with fetal hypoxia (Sheppard and Bonnar, 1976; De Wolf et al, 1980). This assumption is supported by a study by Creasy et al: embolization of the uterine vascular bed in the fetal lamb resulting in intrauterine growth retardation, is associated with a decrease in fetal pO2 (Creasy et al, 1972). In chronically instrumented pregnant sheep in the last third part of pregnancy selective occlusion of the umbilical veins causes a decrease in uterine blood flow, increase of uterine perfusion pressure (uterine arterial pressure - uterine venous pressure) and increase of calculated uterine vascular resistance (Poiseuille equation). Occlusion of the umbilical arteries on the other hand results in a small increase in uterine blood flow, while uterine perfusion pressure and uterine vascular resistance does not change. Total cord occlusion results in a decrease in uterine blood flow; however, uterine perfusion pressure and uterine vascular resistance does not change (Hasaart, 1988). Applying a radionuclide microsphere technique in fetal lambs, a 50% reduction in umbilical blood flow appears to be associated with an increase in the fraction of fetal cardiac output distributed to the brain, heart, carcass, kidneys, and gastrointestinal tract. There is a fall in pulmonary blood flow. Oxygen delivery to the brain and myocardium is maintained, but is reduced in the peripheral, renal, and gastrointestinal circulations. Hepatic blood flow decreases and oxygen delivery shows a 75% drop. The proportion of venous return enhances, thus increasing cardiac output and maintaining systemic oxygen delivery during hypoxemia in the fetal lamb (Itskovitz, 1987). Embolization of the uteroplacental vascular bed results in lower fetal arterial pO_2 and umbilical perfusion, while perfusion of the adrenal glands, brain, and heart is significantly higher. During imposed acute hypoxemia there is preferential perfusion of vital organs, more pronounced in embolized animals than in control fetuses (Block et al, 1984; Block et al, 1989). The impact on the fetal cerebral circulation will be further discussed in chapter 3.

Umbilical artery flow velocity waveforms in fetal sheep do not change during a period of hypoxemia. It can therefore be concluded that normal Doppler waveforms in the umbilical artery do not necessarily imply fetal normoxemia in

sheep, and fetuses with abnormal umbilical artery waveforms are not necessarily hypoxemic (Morrow et al, 1990). Flow velocity waveforms in the fetal descending aorta and umbilical artery have been related to fetal acid-base status and oxygen tension prenatally and at delivery (Laurin et al, 1987b; McCowan et al, 1987; Ferrazzi et al, 1988; Nicolaides et al, 1988; Wladimiroff et al, 1988; Brar et al, 1989; Tyrrell et al, 1989). Contradictory results have been reported in pregnancies with small-for-gestational age fetus: Wladimiroff et al (1988) and Ferrazzi et al (1988) have found a correlation between pH at delivery and PI in the umbilical artery, wheras McCowan et al (1987) did not. No significant relationship has been reported between the PI in the fetal thoracic descending aorta and pH (Laurin et al, 1987b). Groenenberg et al (1991) found that the correlation between the PI of the umbilical artery and the pH is mainly determined by gestational age. A relationship between flow velocity waveforms in the umbilical artery (Nicolaides et al, 1988) and in thoracic descending aorta (Soothill et al, 1986) and fetal pO_2 and pH has been established in cordocentesis studies. The positive correlation between time-average velocities in the ascending aorta and umbilical artery pO_2 may be explained by differences in placental vascular impedance (Groenenberg et al, 1991). Since Doppler data from the umbilical artery and pulmonary artery were not related to umbilical artery pO_2, the meaning of this relationship is not clearly understood.

In fetal lamb embolization of the umbilical placental circulation, whereby increasing the peripheral vascular resistance, is associated with an increase in RI (resistance index), S/D (systolic/diastolic ratio), and PI (pulsatility index) and a decrease in D/S (diastolic/systolic ratio) in the umbilical artery (Trudinger et al, 1987; Adamson et al, 1990; Morrow et al, 1989). Muysers et al (1991) found a linear correlation between umbilical PI and umbilical vascular resistance after selective umbilical embolization. We have studied the Doppler flow velocity waveforms from the fetal descending aorta in an acute experiment in ewes, while increasing peripheral vascular resistance by stepwise embolization by microspheres (see chapter 2.2). For the completeness of the discussion above also literature after 1987 is incorporated.

It can be concluded from animal experiments that fetal hypoxia resulting from chronic placental "insufficiency" is associated with cardiovascular adaptations in the fetus, including changes in both the arterial and venous systems. Doppler

studies of the human circulation report a redistribution in the arterial circulation with increased impedance to flow in the descending aorta and decreased impedance in the cerebral circulation in case of fetal hypoxia (see chapter 4). Recent animal experiments are focussed on fetal endocrine reactions rather than fetal cardiovascular adaptations in an attempt to understand maintainance of fetal homeostasis during the development of placental insufficiency, e.g. an increased production of prostaglandin E_2 (Murotsuki et al, 1995).

2.2 Fetal blood flow velocity waveforms in relation to changing peripheral vascular resistance

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INTRODUCTION

Several clinical studies, in which pulsed Doppler Ultrasound equipment was used, suggest that an increase in peripheral vascular resistance (PVR) at the level of the placenta results in characteristic changes in the blood flow velocity waveform in the descending aorta of the human fetus (Griffin et al, 1984; Jouppila et al, 1984; Tonge et al, 1986). These changes are a lowering or absence of the end-diastolic velocity (EDV) and an elevation of the Pulsatility Index (PI). Although lowering or absence of the EDV in the umbilical artery has been closely associated with obliteration of small muscular arteries in the tertiary stem villi of the placenta (Giles et al, 1985), the assumption that these flow changes reflect largely an increase in PVR has not been validated. For obvious ethical and technical reasons PVR can neither be experimentally modified nor calculated in the human fetus.
In an effort to attribute some experimental evidence, we studied the effect of

increased PVR by acute stepwise embolization of the lower body vascular bed on the blood flow velocity waveform in the fetal lamb descending aorta.

MATERIAL AND METHODS

Animals

Five Texel ewes with singleton pregnancies were studied at 120-135 days of gestation (term 147 days). At autopsy mean total fetal weight was 2.9 $\pm$ 0.8 kg. All animals appeared healthy and unstressed at the onset of the experiments.

Surgery

After induction of anaesthesia with Ketamine hydrochloride (1000 mg), atropin (0.5 mg) and phenobarbital sodium (300 mg) intravenously, the ewes were intubated. Throughout surgery they were ventilated with a mixture of nitrous oxide (4:1) and oxygen (2:1) supplemented by enflurane (0.5-2 vol.%). Following laparotomy and hysterotomy, one catheter was inserted into the fetal descending aorta and one into the inferior vena cava via vessels in the hind limbs. Through an incision in the fetal flank, a precalibrated right-angled electromagnetic flow probe (Skalar instruments, Delft, The Netherlands) of appropriate size (5-7 mm i.d.) was placed around the fetal descending aorta, 1 cm above the bifurcation. The incisions in the fetus, the membranes and the uterus were closed.

EXPERIMENTS

The experiments were commenced 15-30 min following closure of the uterus. No bloodgas samples were taken. Descending aortic blood flow was measured continuously from the electromagnetic flow probe and blood pressure recordings were taken from the descending aorta and inferior vena cava. PVR (mm Hg/ml/kg/s) was calculated from the perfusion pressure (mm Hg) divided by blood flow volume (ml/kg/s) and averaged over a period of 5 s using a computer (Digital PDP 11/70 BMDP).

A combined linear-array real-time scanner and pulsed Doppler system (Eik-Nes et al, 1980) was used for the recording of the blood flow velocity in the fetal descending aorta immediately above the electromagnetic flow meter, which could

be visualized on the 2D real-time image. The blood flow velocity waveform was recorded during fetal apnoea, over a 5-s period, which included an average of 15-20 consecutive cardiac cycles. In each flow velocity recording at least ten optimal cardiac cycles were selected and the mean value for the peak velocity (PV, cm/s), time-averaged velocity (AV, cm/s), end-diastolic velocity (EDV, cm/s) and instantaneous fetal heart rate (FHR) was calculated using an Apple microcomputer. The PI was calculated according to Gossling and King (1975).

Embolization of the placental circulation was achieved by repeated bolus injections of Sephadex G-25 microspheres (particle size, 20 μm), 12.5 mg suspended in 1 ml 0.9% saline solution (Stam et al 1977) via the pressure catheter situated in the descending aorta. The time interval between subsequent Sephadex administrations was determined by the return of a steady state situation for all measured parameters over a period of at least 15 min following a bolus Sephadex injection. During this steady state period a maximum of four pressure and flow recordings for further analysis was obtained.

RESULTS

Tables I and II present for each fetal lamb the control and final data for all measured variables. Control values showed a wide variation between individual lambs for all blood flow velocity parameters, perfusion pressure and flow and therefore PVR. Stepwise placental embolization resulted in a gradual increase in PVR, because perfusion pressure increased and aortic volume flow decreased. Of the flow velocity waveforms, PV, AV, and EDV showed gradual reductions, while PI increased.

Figures 1-4 depict for each fetal lamb the actual data and calculated regression line for the correlation PV/PVR (Fig. 1); EDV/PVR (Fig. 2); PI/PVR (Fig. 3) and the correlation PI/volume flow (VF) (Fig. 4). In each fetal lamb PVR displays a negative correlation with PV ($p<0.01$) and EDV ($p<0.001$) and a positive correlation with PI ($p<0.01$). A negative correlation ($p<0.01$) was found between PI and VF.

Table I *PVR before and after repeated embolizations of the peripheral vascular bed.*

Lamb no.	No. of Sepha-dex admin.	No. of flow meas.	Fetal wt. (kg)	Perfusion pressure (mm Hg)		Aortic volume flow (ml/kg/s)		PVR (mm Hg/ml/kg/s)	
				control	final	control	final	control	final
1	3	8	3.7	68	89	2.3	1.1	7.9	21.7
2	3	10	2.7	54	65	3.3	3.0	6.1	7.9
3	7	18	3.8	40	55	4.6	2.8	2.3	5.2
4	12	35	2.2	51	51	2.4	1.0	9.6	24.3
5	9	26	2.2	71	79	2.2	1.4	14.5	25.5

PVR=peripheral vascular resistance.

Table II *Flow velocity waveform characteristics before and after repeated embolizations of the peripheral vascular bed.*

Lamb no.	PV (cm/s)		EDV (cm/s)		AV (cm/s)		PI	
	control	final	control	final	control	final	control	final
1	66	48	7	-10	25	10	2.4	5.8
2	70	56	14	-1	30	22	1.9	2.6
3	57	35	15	2	31	15	1.4	2.2
4	41	32	4	-3	16	8	2.3	4.4
5	46	30	6	-1	19	3	2.1	10.3

PV=peak velocity; EDV=end-diastolic velocity; AV=time-averaged velocity; PI=pulsatility index.

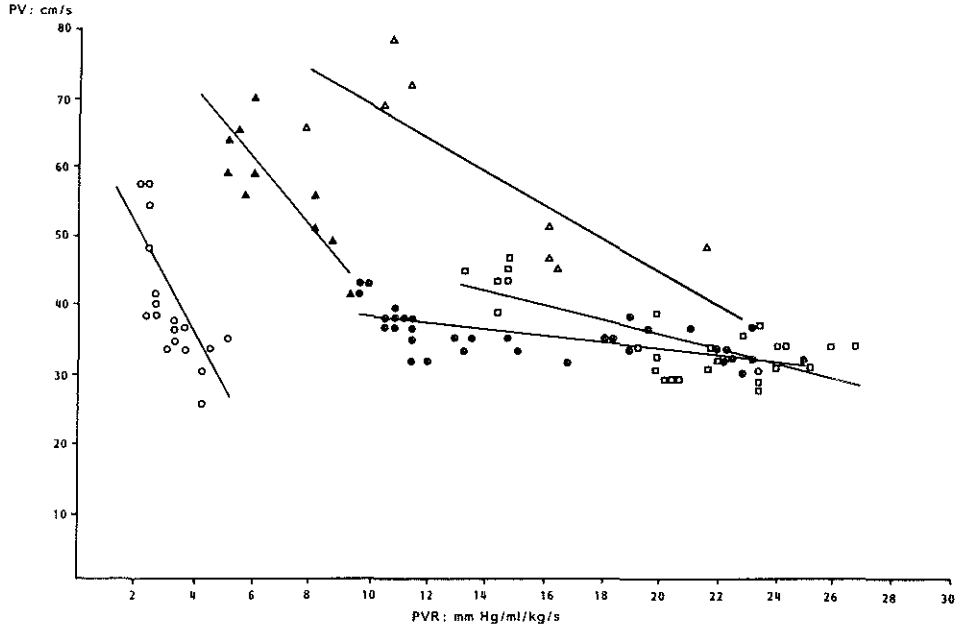

Fig. 1. PV vs. PVR; regression lines for individual lambs. △, lamb 1; ▲, lamb 2; ○, lamb 3; ●, lamb 4; □, lamb 5.

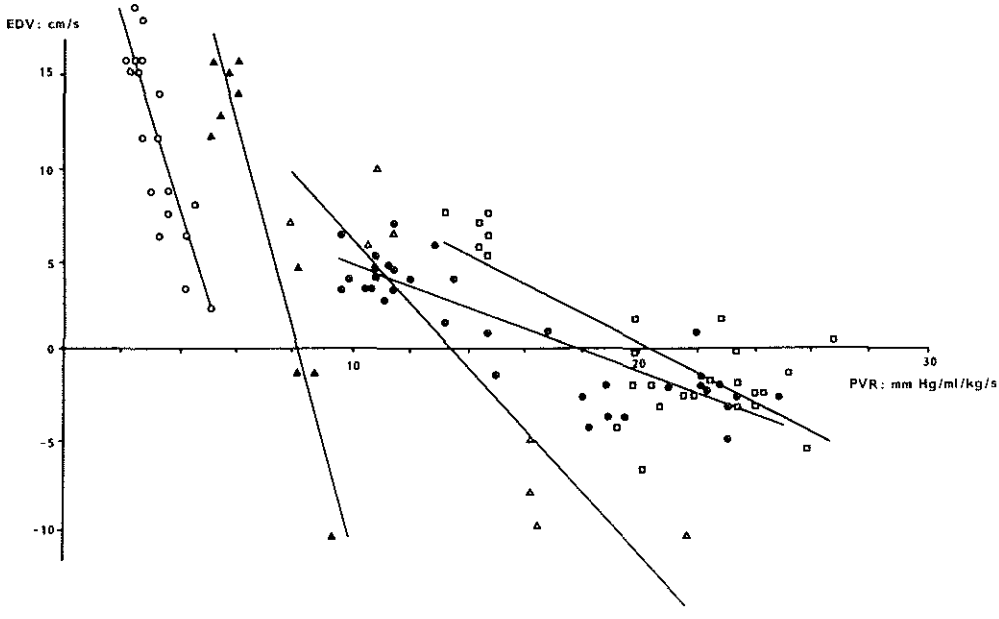

Fig. 2. EDV vs. PVR; regression lines for individual lambs. △, lamb 1; ▲, lamb 2; ○, lamb 3; ●, lamb 4; □, lamb 5.

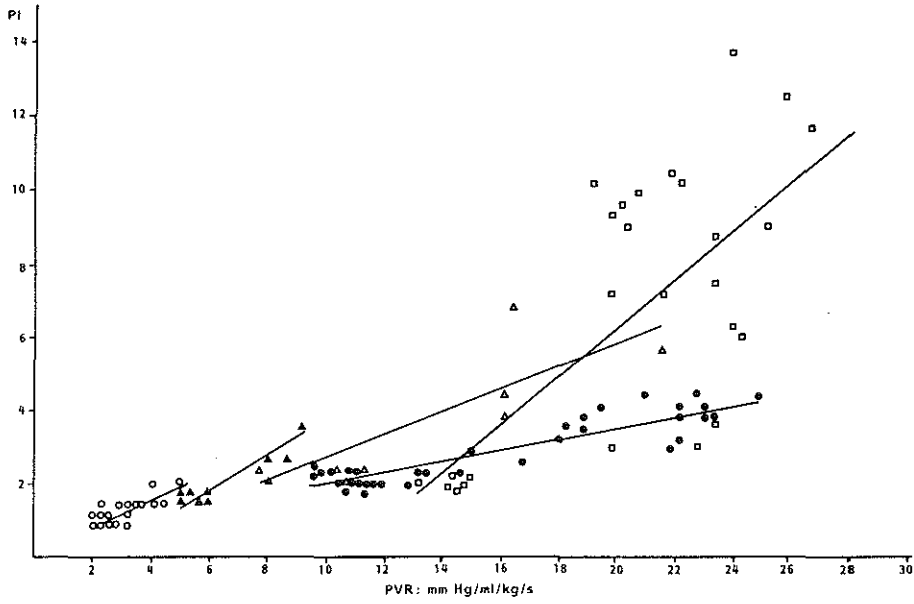

Fig. 3. PI vs. PVR; regression lines for individual lambs. △, lamb 1; ▲, lamb 2; ○, lamb 3; ●, lamb 4; □, lamb 5.

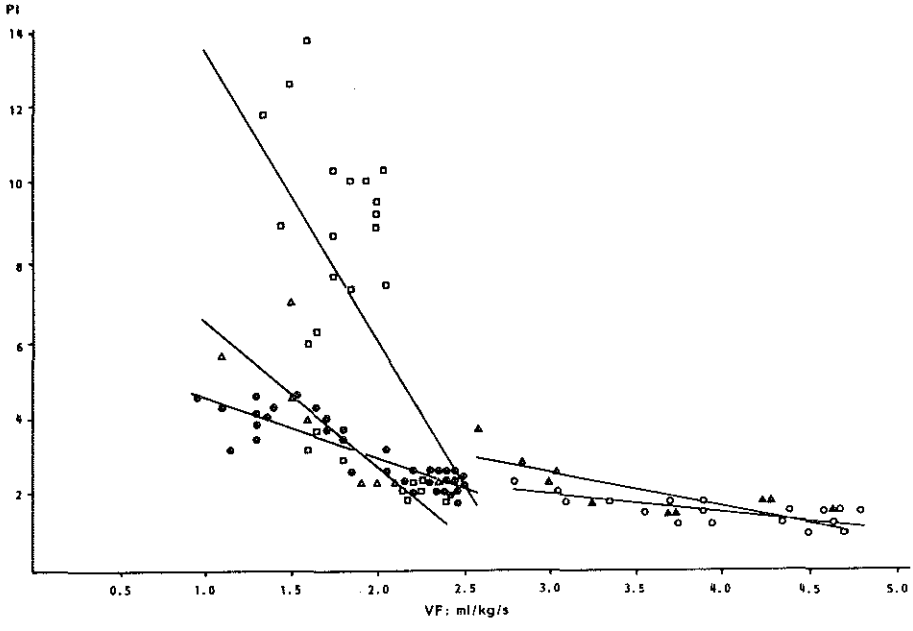

Fig. 4. PI vs. VF; regression lines for individual lambs. △, lamb 1; ▲, lamb 2; ○, lamb 3; ●, lamb 4; □, lamb 5.

DISCUSSION

The need for verification and deeper understanding of non-invasive Doppler ultrasound measurements of human fetal volume flow and arterial flow velocity waveforms has lead to a number of recent animal studies. In an acute experiment on exteriorized fetal lambs (Lingman et al, 1986) cord occlusion was followed by a marked rise in aortic PI. It was demonstrated in a chronic fetal lamb experiment (Trudinger, 1986) that placental embolization over a period of 9 days resulted in an increase in the umbilical artery systolic/diastolic ratio of the velocity waveform. Resistance did not change significantly, which suggests that flow velocity waveform systolic/diastolic ratio measures peripheral wave reflection and outflow only. The shape of the aortic blood flow velocity waveform is thought to be mainly determined by the interaction of the forward pressure wave caused by cardiac systole and reflected waves from the peripheral arteriolar bed (Gosling, 1976). In the fetal descending aorta the indices of PVR are affected by the resistance in the visceral vascular bed, the lower extremities and the placenta. Forward flow during end-diastole has been documented by others, both in the human fetus (Eik-Nes et al, 1980; Griffin et al, 1984; Jouppila et al, 1984; Tonge et al, 1986) and in the fetal lamb (Lingman et al, 1986; Trudinger, 1986). The observed positive EDV (4-15 cm/s) prior to placental embolization in the present study reflects the continuous perfusion which results from low resistance. In the human fetus peak velocity levels below 50-55 cm/s and reverse end-diastolic flow in the lower thoracic part of the fetal descending aorta are generally associated with a poor fetal oucome (Tonge et al, 1986). In two of our fetuses (Nos. 4 and 5) control levels for peak velocity were below 50 cm/s. One might speculate that these two fetal lambs may already have been compromised to some degree at the onset of the study.

As expected, the PI in the fetal descending aorta was inversely related to the volume flow. Volume flow levels below 2.0-3.0 ml/kg/s fetal body weight in three fetuses were associated with a more pronounced rise in PI than was observed in the other two fetuses (Nos. 2 and 3) with higher volume flow levels and lower levels of PVR (Figs. 3 and 4). Although this may suggest that the PI rises more sharply at higher levels of vascular resistance, further studies are needed to substantiate this suggestion.

Our data demonstrate that increased PVR brought about by stepwise placental embolization results in a reduction in peak and EDV and a rise in PI in the fetal descending aorta. This suggests that similar changes in the flow velocity waveform in the human fetal descending aorta in the presence of 'uteroplacental insufficiency' may indeed be determined by raised PVR.

SUMMARY

In an acute experiment in Texel ewes, Doppler flow velocity waveforms from the fetal descending aorta were related to peripheral vascular resistance as calculated from perfusion pressure divided by electromagnetically measured volume flow in the descending aorta. Vascular resistance was increased by stepwise embolization of the peripheral circulation via repeated bolus administration of Sephadex G-25 microspheres. A rise in peripheral vascular resistance was associated with a reduction in peak and end-diastolic flow velocity and an increase in Pulsatility Index. Clinically, if similar changes are observed in growth retarded fetuses, the findings are usually interpreted to represent 'uteroplacental insufficiency'. Present data provide evidence that raised peripheral vascular resistance does indeed produce such waveform changes.

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Chapter 3

THE NORMAL FETAL CEREBRAL CIRCULATION, ANIMAL EXPERIMENTAL AND HUMAN DATA

3.1 Introductory remarks

Increasing interest in the fetal cerebral circulation was aroused in the mid eighties when for the first time it became possible to obtain non-invasive information on human fetal cerebral flow velocity waveforms. Earlier data were collected from animal experimental studies, notably by Peeters et al (1979) who demonstrated that fetal hypoxaemia is associated with increased blood flow to the heart, adrenal glands and brain and decreased blood flow to the digestive tract, kidneys and lungs. Aortic chemoreceptors may play a role in this redistribution of the fetal circulation as they respond to changes in arterial oxygen tension (Dawes et al, 1968,1969; Blanco et al, 1984; Jensen and Lang, 1987). Radioactively labelled microsphere studies in fetal sheep have shown that induced hypoxaemia initially is associated with marginally decreased oxygen consumption and increased cerebral blood flow, thus maintaining oxygen delivery coupled to cerebral oxygen consumption (Richardson et al, 1989).

In order to study possible mechanisms of hemodynamic redistribution in the human fetus associated with utero-placental insufficiency, insight in normal cerebral blood flow is necessary. Doppler velocimetry, however, does not allow reliable volume flow measurements. Instead, flow velocity waveforms were investigated with emphasis on resistance indices calculations reflecting downstream impedance. Subsequently, some studies appeared on absolute flow measurements. Recently, colour coded Doppler techniques have made visualization of intracerebral vessels and Doppler measurements in the fetal cerebral circulation easier, more reliable and less time-consuming (Vyas et al, 1990a; Locci et al, 1992; Wladimiroff et al, 1993).

New Doppler imaging techniques are colour velocity imaging and power angiography. This chapter will focus on the normal fetal cerebral circulation which includes a separate sub-chapter on new Doppler imaging developments.

3.2 Regulation of cerebral blood flow during fetal life; animal experimental data

Most studies on the regulation of fetal cerebral blood flow originate from animal experimental work. Initial investigations were carried out on exteriorized fetal lambs (Campbell et al, 1967; Kjellmer et al, 1974). Data from these preparations did not really reflect the true physiological status of the cerebral circulation. More realistic information became available with the introduction of radioactive microsphere techniques (Behrmann and Lees, 1971; Rudolph and Heymann, 1967), allowing the study of fetal cerebral blood flow in a chronic fetal sheep preparation (Makowski et al, 1972).

The question arises as to what extent data from fetal sheep are applicable to the human fetus. The fetal sheep and human fetus are similar in that they are both hypoxaemic (Rosenberg et al, 1986) and mildly hypercapnic (Rosenberg et al, 1986; Soothill et al, 1986) by postnatal standards. Moreover, both species must regulate their cerebral blood flow at an arterial blood pressure which is 40%-50% of the adult level (Koehler et al, 1984; Bucci et al, 1972). The fetal cerebral circulation is capable of responding to changes in the fetal environment, the most striking change being hypoxia. The nature of the response will depend on the maturity of the developing fetal brain, i.e. gestational age. Moreover, it should be realized that at a comparable gestational age fetal sheep are less immature than the human fetus; this also applies to the state of brain development (Jones and Traystman, 1984).

The late gestational sheep fetus is capable of autoregulating its cerebral blood flow (Lou et al, 1979; Tweed et al, 1986). In the fetal lamb an autoregulatory plateau between a fetal blood pressure level of 50 and 80 mmHg has been established (Papile et al, 1985). Both hypercapnia and hypoxic hypoxia may interfere with autoregulation.

Whereas carbondioxide may exert some vasodilatory effect on the fetal cerebrum (Rosenberg et al, 1982), alterations in intravascular pH have no direct effect on cerebral blood flow (Harper and Bell, 1963).

3.2 Human cerebral blood flow velocity waveforms

In the human fetus Doppler cerebral flow velocity waveforms were first obtained in the common carotid artery (Marsal et al, 1984) and in the internal carotid artery (Wladimiroff et al, 1986). High end-diastolic velocities were established as a result of reduced downstream impedance in growth retarded fetuses, suggesting a so-called brainsparing effect (Marsal et al, 1984; Wladimiroff et al, 1986). Similar findings were done in other cerebral arteries, in particular the anterior, middle and posterior cerebral artery (Woo et al, 1987; Kirkinen et al, 1987; Arbeille et al, 1987; Mirro and Gonzalez, 1987; Mari et al, 1989).

3.3.1 Methodology

Most of the intracerebral Doppler studies relate to angle-independent measurements with calculations of the pulsatility index, resistance index or cerebral index (Arbeille et al, 1988). Most measurements were obtained from a transverse cross-section through the fetal brain at the level of the fetal cerebral peduncles, allowing visualization of the circle of Willis with emphasis on the internal carotid artery, anterior, middle and posterior cerebral artery. Absolute measurements of flow velocities are feasible in the common carotid artery (Bilardo et al, 1988) and middle cerebral artery (Lang et al, 1988) with interrogation angles approaching zero degrees. Both are relatively straight vessels. For the middle cerebral artery, the thalamus insula, the sphenoid bone and other landmarks have been proposed (Kirkinen et al, 1987; Woo et al, 1987; Van den Wijngaard et al, 1989; Arduini and Rizzo, 1990;).

Transvaginal scanning of the cerebral circulation was achieved as early as 10 weeks of gestation with the middle cerebral artery being the most accessible vessel in a transverse cross section through the brain (Wladimiroff et al, 1991, 1992). Later in pregnancy a transvaginally obtained coronal section of the fetal brain was recommended (Lewinsky et al, 1991), displaying separate and easily distinguishable images of these arteries, with the internal carotid artery being located medially and inferiorly to the corresponding middle cerebral artery.

When performing flow velocity waveform recordings at cerebral level, a number of technical and methodological criteria have to be met. The sample gate should not

exceed 4 inch, a high pass filter of 50-100 Hz should be employed to demonstrate low frequency signals originate from the vessel wall. Recordings should be collected during fetal apnoea, since high amplitude fetal breathing movements modulate flow velocity waveforms (Marsal et al, 1984).

3.3.2 Normal flow velocity waveform patterns

The circle of Willis is considered to be fully formed at 6-7 weeks of gestation. Flow velocity recordings from the internal carotid and middle cerebral artery during the late first trimester of pregnancy demonstrate absent end-diastolic velocities at 10 weeks but increasing end-diastolic velocities in 50-60% of cases at 11-12 weeks of gestation. Of interest is that end-diastolic velocities in the descending aorta are absent at that time, indicating low cerebral vascular downstream impedance when compared with downstream impedance at fetal trunk level (Wladimiroff et al, 1991; 1992). This observation may also explain the relatively prominent size of the fetal head this early in gestation. Later in pregnancy, particularly during the third trimester, predominantly positive end-diastolic velocities are observed in all cerebral arteries (Kirkinen et al, 1987; Van den Wijngaard et al, 1989). In the common carotid artery, flow velocities are usually absent before 32 weeks of gestation, but demonstrate a progressive increase thereafter (Bilardo et al, 1988). The PI in the middle cerebral artery was found to be higher than in the other cerebral vessels (Mari et al, 1989; Vyas et al, 1990; Lewinsky et al, 1991). Lower velocities were established in the posterior cerebral arteries compared with the anterior and middle cerebral arteries (Hata et al, 1991). However, no difference was found between the anterior and posterior cerebral artery, when calculating the cerebral index (=systolic minus diastolic divided by systolic amplitude) (Arbeille et al, 1990). In one study (Cynober et al, 1992), in which colour coded Doppler was used no difference in downstream impedance as expressed by the end-diastolic/peak systolic ratio was found for all cerebral arteries. It was suggested that the most accessible vessels providing the best signal should be used for determining cerebral downstream impedance. Our own experiences in fetal cerebral flow velocity waveform recordings in normal 3rd trimester pregnancies are presented in chapter 4.2.

When looking at the successrate in obtaining cerebral artery flow velocity

waveforms in general, it was demonstrated that the middle cerebral artery is the most accessible vessel with a successrate of 91%. This was followed by the internal carotid artery (89%), the anterior cerebral artery (64%) and the posterior cerebral artery (58%) (Van den Wijngaard et al, 1989). In one study a successrate of 80% was documented for the anterior cerebral artery (Mirro and Gonzalez, 1987).

When looking at normal cerebral artery waveform patterns, there should be information on the reliability of waveform recordings. However, very little data is available. Proper inter-observer and intra-observer reliability has only been studied for the internal carotid artery PI (Scherjon et al, 1993). It was demonstrated that the reliability for this resistance index is poor, similar to that in the umbilical artery and descending aorta. This gives limitations to the clinical applicability of these fetal flow velocity waveforms.

In general, all cerebral arteries display a rise in resistance index with advancing gestational age with plateauing and subsequent reduction during the last 6-8 weeks of pregnancy (Wladimiroff et al, 1987; Satoh et al, 1988; Vyas et al, 1990a; Ferrazzi et al, 1991), which is most prominent in the common carotid artery (Bilardo et al, 1994). These data suggest a redistribution of blood supply with advancing gestational age with a reduced impedance to flow to the brain.

Mean blood flow velocities in the common carotid artery (Bilardo et al, 1994) and in the middle cerebral artery (Meerman et al, 1990) increases throughout gestation, whereas the mean velocity in the descending aorta plateaus at approximately 32 weeks with a slight fall after 40 weeks, suggesting a rising fraction of the cardiac output being shunted to the fetal brain (De Smedt et al, 1987). Bilardo (1994) pointed out that this discrepancy in mean flow velocity between common carotid artery and descending aorta may suggest a homeostatic readjustment in the human fetal circulation which may be related to changes in blood pO2 and pCO2 levels during this period of pregnancy, as documented by Soothill et al (1986). This view is supported by findings in the baboon fetus in which an increase in blood supply to the fetal head is associated with a fall in pO2 level during late gestation (Paton and Fisher, 1984). During the perinatal period marked changes in cerebral downstream impedance occur: there is a significant increase in resistance index in the anterior cerebral and internal carotid artery between before birth and 8 hours following birth (Connors et al, 1992). This is

followed by a significant decrease below fetal levels by 24 hours after delivery with little change thereafter. It is suggested that in the newborn there is a rise in cerebral vascular resistance and therefore a decrease in cerebral blood flow in response to the increase in arterial oxygenation. The subsequent decrease in cerebral vascular resistance between 8 hours and 24 hours of life cannot be explained by a loss of ductal shunting, but may rather reflect a remodeling of the circulation due to impedance matching (Connors et al, 1992).

Cerebral flow velocities have also been studied during the process of normal labour. A 40% reduction in the middle cerebral artery S/D ratio and resistance index was established during active labour compared with a control group of women without uterine contractions (Yagel et al, 1992). A reduction in downstream impedance during labour was also demonstrated in the anterior cerebral artery, but Doppler indices of blood flow remained constant (Mirro and Gonzalez, 1987). No changes in cerebral (and umbilical artery) downstream impedance was found when comparing the period before, during and after uterine contractions (Maesal et al, 1990; Yagel et al, 1992). Based on their findings, Yagel et al (1992) suggest that relative hypoxaemia may not be the only mechanism involved in the reduction of downstream impedance in the fetal brain. There may be a "brain sparing" process which helps to prevent fetal cerebral hypoxaemia by maintaining stable cerebral blood flow. We believe, however, that whereas a "protective" mechanism may in place during labour, this is subject to changes in cerebral artery pO2. We found that PI values from the internal carotid artery are positively related to pO2 and base excess from fetal blood samples collected following artificial rupture of the membranes in uneventful pregnancies (Simonazzi et al, 1989). It should be added that there is no relationship between these cerebral PI values and pCO2. Fetal lamb studies have demonstrated that although the fetal cerebral circulation is responsive to PCO_2 (Jones et al, 1982; Rosenberg et al, 1982), the degree of vasodilatation is only about half of that seen in the adult (Rosenberg et al, 1982). Relative to oxygen tension, pCO_2 is less effective a regulator of fetal cerebral blood flow (Jones et al, 1982). However, transient maternal breathing of a 3% carbon dioxide gas mixture causes a decrease in the middle cerebral artery peak systolic to end-diastolic velocity ratio, whereas in other fetal vessels, notably the umbilical and renal artery, no changes in downstream impedance could be demonstrated (Veille and Penry, 1992).

3.3.3 Internal and external variables affecting fetal cerebral blood flow velocities

Fetal cerebral flow velocity waveforms, line any other fetal vessel, are subject to both internal and external variables.

Fetal breathing movements modulate cerebral arterial flow velocity waveforms (Wladimiroff and Van Bel, 1987); a quantitated study showed that high amplitude breathing is associated with significantly increased standard deviations for cerebral arterial flow velocity parameters, while the parameters were not different from those observed during apnoea (Burghouwt and Wladimiroff, 1992).

The inverse relationship between cerebral artery PI and fetal heart rate (FHR) has been demonstrated by several workers during FHR-decelerations (Van den Wijngaard et al, 1988; Mari et al, 1991) and tachycardias as a result of maternal ritodrine administration (Rasanen, 1990). This is inherent to the formula used for PI calculations and has consequences for the interpretation of FHR-related changes in PI in clinical studies.

The impact of fetal behavioural states on the fetal cerebral circulation will be discussed in Chapter 5.

A positive relationship exists between maternal plasma glucose concentration and internal carotid artery PI, suggesting a compensatory increase in cerebral downstream impedance during raised glucose levels (Degani et al, 1991).

Cerebral artery flow velocity waveforms have also been examined relative to Braxton Hicks' contractions, which in sheep are associated with a considerable increase in vascular resistance in the uteroplacental circulation (Sunderji et al, 1984; Lange et al, 1986). It has been shown by us (Simonazzi et al, 1989) that flow velocity waveforms in the fetal internal carotid artery respond to changes in pO_2 under normal conditions, suggesting that cerebral downstream impedance dcreases when pO_2 falls. However, it was also revealed that in the internal carotid artery downstream impedance is not significantly altered during Braxton Hicks' contractions, suggesting that these contractions have little or no effect on the cerebral circulation in the normally developing fetus (Oosterhof et al, 1992).

Also, the effect of external interventions such as vibro-acoustic stimulations, maternal oxygen administration and fetal head compression on cerebral artery flow velocity waveforms have been examined.

Vibro-acoustic stimulation during the active sleep state in the healthy term fetus has no measurable effect on cerebral vascular resistance (Wladimiroff and Cheung, 1989).
Whereas in the growth retarded fetus, maternal oxygen administration showed marked temporary hemodynamic modifications as expressed by changes of the PI that increased in the internal carotid artery and decreased in the descending aorta, no such changes were found in the healthy fetus (Arduini et al, 1988).
Fetal head compression will result in increased intracranial pressure and therefore raised cerebral artery PI values, notably in the middle cerebral artery as a result of reduced to reversed diastolic flow (Vyas et al, 1990b).

3.3.4 Recent Doppler imaging developments

Colour coded Doppler ultrasonography is now an established means of visualizing flow direction in the developing fetus. A new development is colour velocity imaging (CVI) which measures flow velocity within vessels using time of flight changes between consecutive pulses (Campbell et al, 1994). A packet of signals from blood cells is identified at short time intervals allowing calculation of the distance travelled by the packet of cells over time. The advantage of this approach is the use of shorter pulse lengths allowing better resolution of the velocity profile.
Lately, colour coded flow information can also be obtained based on amplitude variation rather than frequency shifts. This power Doppler or ultrasound colour angiology approach seems to be more sensitive to low flow velocities than frequency and velocity maps. When only based on the amplitude of the Doppler signal, one can use frame averaging techniques to boost the signal to noise ratio. Moreover, the amplitude estimate of the signal is less noisy than the frequency estimate. Power Doppler can detect the presence of flow and provides information on the perfusion in the scan plane (Campbell et al, 1994). An example is given in figure 2 on page 75 which depicts the circle of Willis in a normal fetus at 32 weeks of gestation.

3.4 References

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Chapter 4

FETAL GROWTH RETARDATION AND INTRACEREBRAL BLOOD FLOW

4.1 Literature review

Chronic fetal hypoxaemia is associated with increased fetal mortality and morbidity. With the advent of fetal Doppler velocimetry a non-invasive tool became available to study fetal circulatory changes during impaired oxygen supply.

4.1.1 Animal experimental work

Invasive animal experiments have shown that fetal cardiovascular adjustments occur in response to hypoxaemia. In pregnant sheep, reduction in oxygen supply led to redistribution of cardiac output with increased blood flow to the heart, brain and adrenals and reduced blood flow in the gut, carcass and kidneys (Peeters et al, 1979). It appears that partial oxygen and carbon dioxide pressures play a role, presumably via the chemoreceptors (Dawes et al, 1969).

The effect of hypoxia on the cerebral circulation

A distinction should be made between hypoxic hypoxia and anaemic hypoxia. In fetal sheep cerebral blood flow has been shown to increase during both types of hypoxia (Ashwal et al, 1984;Bisonette et al, 1984; Johnson et al, 1979; Jones et al, 1978; Fumia et al, 1984). Factors which influence cerebral blood flow are oxygen consumption, blood pressure and arterial pCO_2. As has been said earlier, there is mild hypercapnia by neonatal standards, whereas fetal blood pressure is lower than after birth.

Hypoxic hypoxia

In the fetal lamb, hypoxic hypoxia is associated with a more pronounced increase in cerebral blood flow than during the neonatal and adult stage, this is particularly so when flow is corrected for cerebral oxygen consumption. However, this difference disappears when considered relative to baseline cerebral blood flow. In fact, despite different absolute increases in cerebral blood flow during hypoxia the

relative increase in the fetal and neonatal lamb defined in terms of ability to maintain cerebral oxygen transport, is the same (Jones and Hudak, 1989).

Cerebral oxygen transport in fetal lambs is high relative to cerebral oxygen consumption (Jones et al, 1982) as a result of much higher oxyhemoglobin affinity in the fetus than in the newborn lamb and the adult (Meschia et al, 1961). Changes in oxyhemoglobin affinity will affect cerebral blood flow. A high fetal oxyhemoglobin affinity during fetal life explains why cerebral blood flow is high even in the presence of a low arterial pO_2 and therefore a low fetal fractional oxygen extraction (Jones et al, 1982;Rosenberg et al, 1986).

Data on autoregulation in hypoxia/asphyxia, as determined by cerebral blood flow measurements at different blood pressure levels are subject to some controversy. This may be due to the limited flow measurements performed in the same subject and the different mechanisms (mechanical pressure, blood withdrawal, pharmacologic agents) through which intracerebral pressure is changed (Jones and Hudak, 1989). For instance, in two studies loss of autoregulation in fetal and newborns lambs was based on cerebral blood flow measurements from just two points (Tweed et al, 1983) or on cerebral blood flow measurements at just two levels of blood pressure (Lou et al, 1979). Some studies have failed to show any effect of hypoxic hypoxia on autoregulation in lambs (Borel et al, 1987).

Anaemic hypoxia

In anaemic hypoxia like in hypoxic hypoxia cerebral oxygen consumption and fractional oxygen extraction are maintained (Fan et al, 1980; Jones et al, 1981). Whereas flow responses to hypoxic and anaemic hypoxia are more or less identical, the mechanisms of cerebral blood flow increase must be different. A drop in brain tissue pO_2 will result in an increase in cerebral blood flow (Kontos et al, 1978). In anaemic hypoxia there is no drop in tissue pO_2 (Leniger-Follert, 1985). It is assumed that much of the cerebral blood flow increase is rather the passive result of reduced blood viscosity (Borgstrom et al, 1975; Hudak et al, 1986).

4.1.2 Human data

Following the first description of pulsed Doppler velocimetry in the human fetal carotid artery and the possible changes occurring in relation to fetal growth retardation (Wladimiroff et al, 1986), a host of papers has appeared on this topic. Essential is the reduction in pulsatility indices, suggesting an increase in end-diastolic velocities, in cerebral arteries providing evidence of the brainsparing effect in the presence of fetal hypoxaemia. This increase in end-diastolic velocity has been established in the common carotid, internal carotid, anterior cerebral, middle cerebral and posterior cerebral artery (Arduini et al, 1987; Wladimiroff et al, 1987; Woo et al, 1987; Wijngaard et al, 1989; Bilardo et al, 1990; Vyas et al, 1990a). The vast majority of papers report on angle-independent measurements in intracerebral arteries resulting in calculation of the pulsatility index (PI) or resistance index (RI). Increased end-diastolic flow velocities will result in reduced PI and RI values. Since chronic hypoxaemia effects various regions of the fetal circulation it is understandable that Doppler velocimetry was performed simultaneously in several vessels, notably the umbilical artery or descending aorta in combination with one of the intracerebral arteries with the objective to better predict fetal outcome. Indeed, a better prediction of fetal outcome was achieved when performing these kind of combined measurements. It was demonstrated in our own centre that the predictive value of the internal carotid artery and umbilical artery PI at the 2SD cut-off level was 48% and 60% respectively, whereas for the umbilical artery/internal carotid artery ratio this was 70% (Wladimiroff et al, 1987). The relatively limited predictive value of the internal carotid artery PI may be explained by the degree of hemodynamic redistribution in a particular growth-retarded fetus. This is described in detail in sub-chapter 4.2.

For instance, Veille and Cohen (1990) found, despite a significant difference in fetal weight and systolic/diastolic ratio of the umbilical artery flow velocity waveform between normal weight for gestational age and small for gestational age fetuses, no difference in either the systolic/diastolic ratio or in the Pourcelot index of the middle cerebral artery. This observation may already reflect a protective effect on the cerebral circulation in the small for gestational age fetus. The limited predictive value of intracerebral arterial velocimetry was further emphasized in a multivessel study, involving the internal carotid artery and artery and anterior, middle and posterior cerebral artery (Van den Wijngaard et al, 1989). Whereas for

the posterior cerebral artery a 100% sensitivity was achieved a 40-50% sensitivity was reached for the remaining cerebral arteries. The relatively high sensitivity in the posterior cerebral artery was most probably determined by the limited number of patients included in the study. A better predictive value with respect to fetal outcome based on combined umbilical and cerebral artery Doppler velocimetry than on each vessel alone was also demonstrated by other investigators (Favre et al, 1991; Gramellini et al, 1992; Rudigoz et al, 1992; Arduini and Rizzo, 1992) with sensitivity values ranging between 70% and 90%. An exception is formed by an earlier paper by Rizzo et al (1989) in which it was demonstrated that the pulsatility index from the internal carotid artery obtained immediately prior to caesarean section for severe fetal growth retardation, was a powerful indicator (sensitivity 75%) of the development of neonatal neurological abnormalities.

Umbilical artery/middle cerebral artery PI has also been studied in relation to neurological outcome in very preterm infants (Scherjon et al, 1993). Antenatally raised ratios were associated with poor obstetric outcome (fetal death and fetal growth retardation). However, the incidence of intracranial hemorrhages and ischemic lesions was not different from infants with normal or raised prenatal ratios. The incidence of neurological abnormalities was the same for both ratio groups. The authors conclude that the brainsparing effect is a mechanism to prevent fetal brain hypoxia rather than a sign of impending brain damage.

Cordocentesis allows direct measurement of fetal oxygenation. This created a major opportunity to establish in more detail the role of Doppler velocimetry in determining fetal oxygenation. Bilardo et al (1990) collected Doppler flow velocity waveforms from the common carotid artery and correlated PI and mean blood velocity with umbilical cord blood gases in samples obtained by cordocentesis in both normally developing and growth retarded fetuses. They found significant correlations between PI from the common carotid artery and degree of hypoxaemia and acideamia. The common carotid artery time-averaged velocity was increased in the growth retarded fetus. Also, there was a significant association between the magnitude of this rise in velocity and the severity of hypoxaemia and acidaemia. The limitation of common carotid artery flow velocity waveform recordings is that the waveforms only provide indirect evidence of fetal brainsparing, since they also represent blood flow to the face and neck region. Vyas et al (1990) using colour coded Doppler flow mapping were the first to relate

umbilical cord blood gases to Doppler indices of velocity and impedance to flow in the fetal middle cerebral artery. They studied fetuses with an upper abdominal circumference below the 2.5th centile for gestational age. A significant negative correlation was found between umbilical venous PO_2 and fetal middle cerebral artery time-averaged velocities and a significant positive correlation was established between umbilical venous PO_2 and fetal middle cerebral artery PI. The latter finding suggests vasodilatation of the fetal middle cerebral artery at different levels of fetal hypoxaemia. However, the weak correlation between PI and time-averaged velocity in the middle cerebral artery indicates that the changes in time-averaged velocity are not only determined by downstream impedance but also by cardiac contractility, blood viscosity and vessel compliance. Of interest is their finding that with severe degrees of hypoxaemia usually with associated acidaemia, the drop in PI reaches a maximum, which probably reflects vessel dilatation. This may even be followed by a slight rise in PI, which may be due to increased intracranial pressure and as a result of cerebral oedema (Vyas et al, 1990b). This brings us to the issue of external pressure on the fetal head. Van den Wijngaard et al (1988) was able to demonstrate raised PI values in the internal carotid artery in the presence of severe oligohydramnios. It was proposed that prolonged severe oligohydramnios hampers cerebral blood flow through fetal head compression. According to Vyas et al (1990b) these raised PI values were determined by external pressure applied by the ultrasound transducer during the examination.

Bilardo et al (1990), studying the so-called aortic-carotid index consisting of the aortic time-averaged velocity and common carotid artery PI, found that when this index was abnormal, all fetuses had an asphyxia index (combined umbilical venous blood gases and pH through cordocentesis) above the mean, 89% of the fetuses displayed an asphyxia index one standard deviation above the mean and 60% were more than two standard deviations above the mean. A normal index was always associated with normal blood gasses. It was argued that combined cerebral artery/descending aorta Doppler velocimetry was more representative of hypoxaemia related hemodynamic changes than combined cerebral artery and umbilical artery Doppler flow velocity waveform recordings.

Intracerebral artery flow velocity waveforms have also been studied relative to fetal heart rate in the recognition of fetal compromise. A reduced resistance index was established in the middle cerebral artery in the presence of a non-reactive fetal

heart rate pattern (Satoh et al, 1989). It was suggested that fetal growth retardation perse seems to be attributable to a chronic increase in resistance index in the umbilical artery flow velocity waveform while cerebral vascular resistance seems to decrease when the fetal heart rate pattern is non-reactive or demonstrates acute fetal distress. Chaudran et al (1993) reported that in about half of the hypoxaemic fetuses (umbilical artery PO_2) at delivery of less than 8.9 mmHg), the middle cerebral artery PI became reduced up to four days before any fetal heart rate abnormality. They state that a normal middle cerebral artery PI in a fetus at risk of developing hypoxaemia would be reassuring, while a low value may herald the onset of an abnormal fetal heartrate. In another study the monitoring value of Doppler velocimetry in predicting fetal distress as determined by daily fetal heart rate recordings was assessed in fetal growth retardation. The umbilical artery and internal carotid artery PI were the most predictive parameters for the development of fetal distress as reflected by the fetal cardiotocogram (Groenenberg et al, 1993). Performing middle cerebral artery Doppler velocimetry, Arduini et al (1992) observed a nadir of vasodilatation approximately two weeks before the onset of antepartum late fetal heart rate decelerations. Whereas significant changes in the other peripheral fetal arteries (descending aorta, renal artery) and umbilical artery occurred close to the onset of abnormal fetal heart rate patterns. It was proposed that despite a brainsparing effect, there are further Doppler detectable modifications in the fetal circulation that differ between the cerebral and peripheral vascular beds.

After establishing the nature of the Doppler velocimetry changes in the fetal circulation during fetal hypoxaemia, these changes became instrumental in assessing the impact of maternal hyperoxygenation on the fetal circulation. Contradictory findings were done on fetal cerebral flow velocity waveforms relative to maternal hyperoxygenation. Whereas Arduini et al (1989) established an increase in internal carotid artery PI, Bilardo et al (1991) observed only a small increase in common carotid artery PI in those hypoxaemic fetuses which survived. Different vessels, different duration of maternal oxygen supply, but particularly different gestational age periods may have been responsible for the observed discrepancy. Bilardo et al (1990) suggests that the lack of a significant effect of maternal oxygenation on fetal common carotid artery PI could be beneficial to the fetus. They hypothesize that since hypoxaemic growth retarded fetuses are also

hypoglycaemic (Economidis and Nicolaides, 1989), suppression of the increased cerebral perfusion of the hypoxaemic fetus during maternal hyperoxygenation could result in a reduced glucose supply to the brain.

Relatively little information is available on flow velocity changes at cardiac level relative to the brainsparing effect as expressed by reduced PI or increased flow velocities in the cerebral arteries. A combined cardiac and extracardiac flow velocity waveform study performed in our own centre (Groenenberg et al, 1989) demonstrated in growth retarded fetuses reduced flow velocities in the cardiac outflow tract, i.e. the ascending aorta, pulmonary artery and ductus arteriosus. Reduced cardiac outflow velocities were thought to be secondary to reduced volume flow, increased valve or vessel size or raised afterload. It was further demonstrated that cardiac outflow tract velocities were poor predictors of fetal outcome (Groenenberg et al, 1990).

The literature so far discussed in this chapter relates merely to cross-sectional Doppler studies in one or several fetal vessels. There is no clear consensus on the preferred cerebral artery and flow velocity waveform parameter, although most reports refer to the pulsatility index in the middle cerebral artery.

Doppler velocimetry has now firmly established in the human fetus the presence of so-called brainsparing in hypoxaemia. Various vessel combinations have been suggested to be helpful in predicting fetal outcome, although a clear definition of fetal outcome is sometimes lacking. It was shown that the combination of aortic velocity and common carotid artery PI appropriately reflects the degree of fetal hypoxaemia. Clearly there is a need for serial assessment of fetal hemodynamic performance in the growth retarded fetus in order to better understand the interrelationship between flow velocity waveform changes in different fetal vessels. In such a study (Weiner et al, 1994), it was demonstrated that at fetal cardiac level there is a shift from right ventricular to left ventricular predominance with progressive fetal hypoxaemia. Moreover, there was inverse relationship between left ventricular cardiac output as expressed by the ascending aorta Doppler velocity integral and time-averaged velocity in the middle cerebral artery. Previous reports on a redistribution in the fetal circulation with increased impedance to flow in the descending aorta and decreased impedance in the cerebral circulation were confirmed in case of fetal hypoxemia and acidemia in intrauterine growth retardation (Hecher et al, 1995). Additionally a decrease in flow velocity in the

venous system and across the atrioventricular valves was observed, whereas the pulsatility index of waveforms in the inferior vena cava and ductus venosus was increased (Hecher et al, 1995).

It would also be necessary to obtain more detailed information on absolute values in the various cerebral arteries, if only to establish whether all cerebral arteries react similarly to chronic fetal hypoxaemia or not.

In sub-chapter 4.3, an effort is made to determine the nature of angle independent and angle dependent flow velocity waveform changes in the fetal internal carotid artery as well as the anterior, middle and posterior cerebral artery in the presence of fetal growth retardation.

4.2 Fetal internal carotid and umbilical artery blood flow velocity waveforms as a measure of fetal well-being in intrauterine growth retardation.

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INTRODUCTION

Recently, a Doppler ultrasound method for recording the blood flow velocity waveform in the fetal internal carotid artery was described (Wladimiroff et al, 1986).

Preliminary results suggested that in intrauterine growth retardation (IUGR) due to impaired placental perfusion there was a higher percentage of abnormal pulsatility index (PI) values in the umbilical artery (UA) than in the internal carotid artery (ICA) (Wladimiroff et al, 1987). It was also suggested that the reduction in ICA PI reflects redistribution of blood flow in the fetus with the aim of maintaining optimal oxygen supply to the fetal brain (Wladimiroff et al, 1987). The question arises as to if this redistribution of blood flow reflects a further deterioration in fetal oxygen supply in the presence of IUGR.

The objective of the present study was 3-fold: 1) to establish the normal distribution of UA PI and ICA PI during the third trimester of pregnancy; 2) to determine the degree of abnormality of UA PI and ICA PI during this period of gestation in the presence of IUGR due to impaired placental perfusion; 3) to relate UA PI and ICA PI to fetal well-being as expressed by antenatal fetal heart rate patterns before delivery, Apgar score at 1 min, and umbilical arterial pH.

SUBJECTS AND METHODS

A combined mechanical sector and pulsed Doppler system (Diasonics CV 400) with a carrier frequency of 3.5 and 3 MHz was used for blood flow velocity measurements in the fetal internal carotid artery and umbilical artery. The energy output of the pulsed Doppler transducer was 1.5 mW/cm^2 (spatial peak, temporal average). The maximum flow velocity waveform in the internal carotid artery was obtained at the level of the bifurcation into the middle and anterior cerebral artery (Wladimiroff et al, 1986). The sample size of the Doppler probe, necessary for sampling frequency shifts originating from the moving erythrocytes within a vessel, was 4 mm. This allowed clear signals from the internal carotid artery without interference from other nearby vessels such as the middle and anterior cerebral artery. The maximum flow velocity waveform in the umbilical artery was recorded using the method first described by McCallum et al (1978). All flow velocity waveform records were obtained during fetal apnea to avoid modulation of the waveforms by fetal breathing movements. Therefore, only waveforms without visible changes in the waveform pattern were accepted. The degree of pulsatility of the waveform was quantified by calculating the PI according to the following formula (Gosling and King, 1975): fmax - fmin/fmean, in which fmax is the maximum Doppler frequency shift, fmin is the minimum Doppler frequency shift, and fmean is the mean Doppler frequency shift over the entire cardiac cycle. In both flow velocity waveforms, the PI was calculated by a microcomputer. The mean value over at least four cardiac cycles represented the PI for a particular pregnancy.

A total of 240 normal pregnancies and 44 cases of IUGR participated in the study after oral informed consent was obtained. Gestational age varied between 26 and 39 weeks. Each subject was certain of the onset of the last menstrual period.

Normal pregnancy was defined by a normal biparietal diameter on ultrasound and a birth weight between the 10th and 90th percentile for gestational age, corrected for maternal parity and fetal sex (Kloosterman, 1970). Each subject was included in the study only once. The median maternal age was 27 years (range 17-41 yr), the median parity was 2 (range 1-6).

Acceptable flow velocity waveforms for PI calculations were obtained from the ICA in 205 (85%) and from the UA in 225 (94%) of the 240 normal subjects. IUGR was

defined by: 1) flattening of the growth pattern resulting in a clinical discrepancy of more than 2 weeks on fundal height on two successive appointments combined with an ultrasound finding of the upper abdominal circumference measurement below the 10th percentile in association with a normal or reduced head circumference measurement (Campbell, 1976) and 2) postnatal confirmation by a birth weight below the 10th percentile for gestational age, corrected for maternal parity and fetal sex (Kloosterman, 1970). The lagtime between flow velocity records and delivery in the 44 cases of IUGR ranged between 2 hours and 14 days (median 4 days). Occasionally more than one measurement was done per patient. In such cases the measurement nearest to the date of delivery was chosen for analysis. Median maternal age was 28 years (range 18-40 yr), median parity 2 (range 1-5). In 38 subjects PI values from both vessels were related to the Apgar score at 1 min; in 25 subjects also to UA pH. In 35 cases PI values from both vessels were related to fetal heart rate (FHR) patterns before the onset of labor or elective cesarean section. FHR was recorded using a Doppler ultrasound cardiotocograph (Hewlett Packard 8040A, carrier frequency 1 MHz). A normal FHR pattern was defined as a pattern with a baseline varying between 110-160 beats/min, with good beat to beat variability, periodic accelerations, and no decelerations. An abnormal FHR pattern was one that deviated from this normal definition.

Statistical analysis included investigation of the relations between the pulsatility indices and gestational age by polynomial regression. Differences in the degree of abnormality of UA PI and ICA PI in IUGR were tested by McNemars test. Differences in distributions of PI were tested by use of the Mann-Whitney test in comparing two groups. Correlation coefficients given are according to Spearman.

RESULTS

Table 1 shows the mean PI of both arteries as a function of gestational age, grouped in 2-weeks intervals. The mean of each index varied with gestational age, whereas the SD did not differ significantly between the age groups.

By polynomial regression, it appeared that the mean UA PI could be described by a linear function of gestational age (Fig. 1, *upper panel*). No significant improvement of the curve's fit could be obtained by adding quadratic or cubic components of gestational age.

Table 1 *Means and SD of UA PI and ICA PI according to duration of gestation, grouped in 2-wk intervals for cases with normal pregnancies.*

Gestational age (wks)	UA PI			ICA PI		
	Mean	SD	n	Mean	SD	n
26-27	1.14	0.13	17	1.63	0.19	14
28-29	1.06	0.14	23	1.58	0.15	16
30-31	1.05	0.18	32	1.55	0.20	24
32-33	1.00	0.15	32	1.61	0.21	27
34-35	0.89	0.14	29	1.58	0.21	33
36-37	0.82	0.14	50	1.37	0.27	50
38-39	0.78	0.15	42	1.31	0.21	41

PI=Pulsatility index; UA=umbilical artery; ICA=internal carotid artery.

For the internal carotid artery, the mean PI (ICA PI) could be described by a quadratic function of gestational age (Fig. 1, *lower panel*). Addition of a cubic component of gestational age did not significantly improve the fit of the curve. The SD of the measurements around the fitted curves for the UA PI and the ICA PI were 0.15 and 0.20, respectively. In establishing normal limits according to gestational age, these SD were used by taking estimated means $\pm$ 2 SD.

In Figure 2, these limits are graphed for both PI. Also in Figure 2, the data points are plotted for the 44 cases with IUGR. For the UA PI, the majority of IUGR cases (80%) showed increased (>2 SD) values. For the ICA PI, 45% of IUGR cases showed decreased (>2 SD) measurements.

The percentage of cases of IUGR with an increased UA PI was significantly greater than the percentage with a decreased ICA PI. This applied to the shorter gestational ages as well as to the longer ones (Table 2).

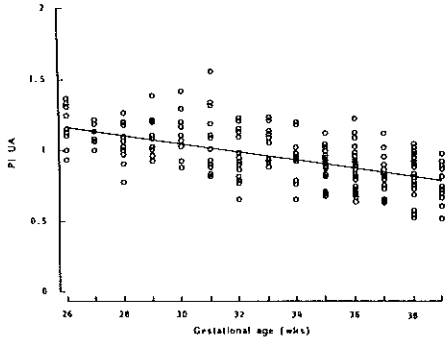

Fig. 1. UA PI and ICA PI of normal subjects. Least squares fitted curves are: UA PI = $1.99 - 0.032^{(1)} \times$ age and ICA PI = $-1.69 + 0.23^{(2)} \times$ age $- 0.004^{(3)} \times$ age square. SE of coefficients: 0.003 for (1), 0.08 for (2) and 0.001 for (3).

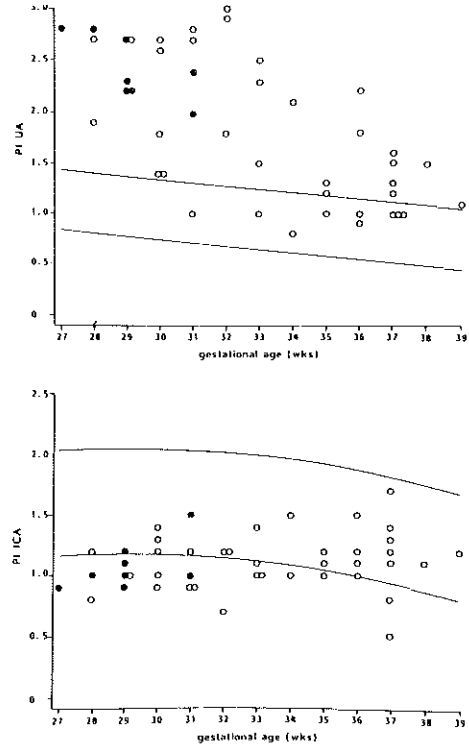

Fig. 2. UA PI and ICA PI for IUGR cases (n = 44) according to gestational age. Plotted curves represent normal limits (means ± 2 SD). Closed circles denote perinatal deaths.

It appears that the measured values of UA PI in IUGR pregnancies at longer gestational ages were generally lower than at shorter ages (r=-0.64; p<0.001) and approached normal values with increasing gestational age. The mean UA PI [1.23 ± 0.25 (SD)] of the seven IUGR cases studied at week 37 was, however, still significantly greater (p<0.001) than the mean index [0.81 ± 0.14 (SD)] of the 19 normal subjects studied at the same age.

Table 2 *Numbers of IUGR cases according to gestational age, UA PI, and ICA PI.*

Gestational age	27-32 wk			33-39 wk		
ICA PI	Decreased	Normal	Total	Decreased	Normal	Total
Increased UA PI	13	8	21 (95%)*	6	8	14 (64%)#
Normal UA PI	0	1	1	1	7	8
Column total	13 (62%)*	9	22	7 (32%)#	15	22

Significantly different: * $p = 0.008$, # $p = 0.04$.

IUGR=intra-uterine growth retardation; PI=Pulsatility index; UA=umbilical artery; ICA=internal carotid artery.

With respect to the ICA PI no significant correlation with gestational age was present in the IUGR cases ($r=0.25$; $p>0.10$). The mean value of the ICA PI at 37 weeks [1.14 ± 0.40 (SD)] for IUGR cases did not differ significantly from the mean [1.30 ± 0.26 (SD)] of the normal subjects studied at the same age.

In Figures 3 to 5, the fetal well-being of the IUGR cases, as reflected by the umbilical arterial pH (Fig. 3), Apgar score at 1 min (Fig. 4) and FHR pattern (Fig. 5) is related to UA PI and ICA PI. All three indicators correlated significantly with UA PI. The mean UA PI in cases with abnormal FHR was significantly higher than at normal FHR. No correlation could be established between the three indicators of fetal well-being and ICA PI. There were eight perinatal deaths, five of which occurred *in utero* and three within 7 days after delivery. All deaths were associated with increased PI values in the UA and five cases were associated with reversed end-diastolic flow. ICA PI was reduced in six of the eight cases.

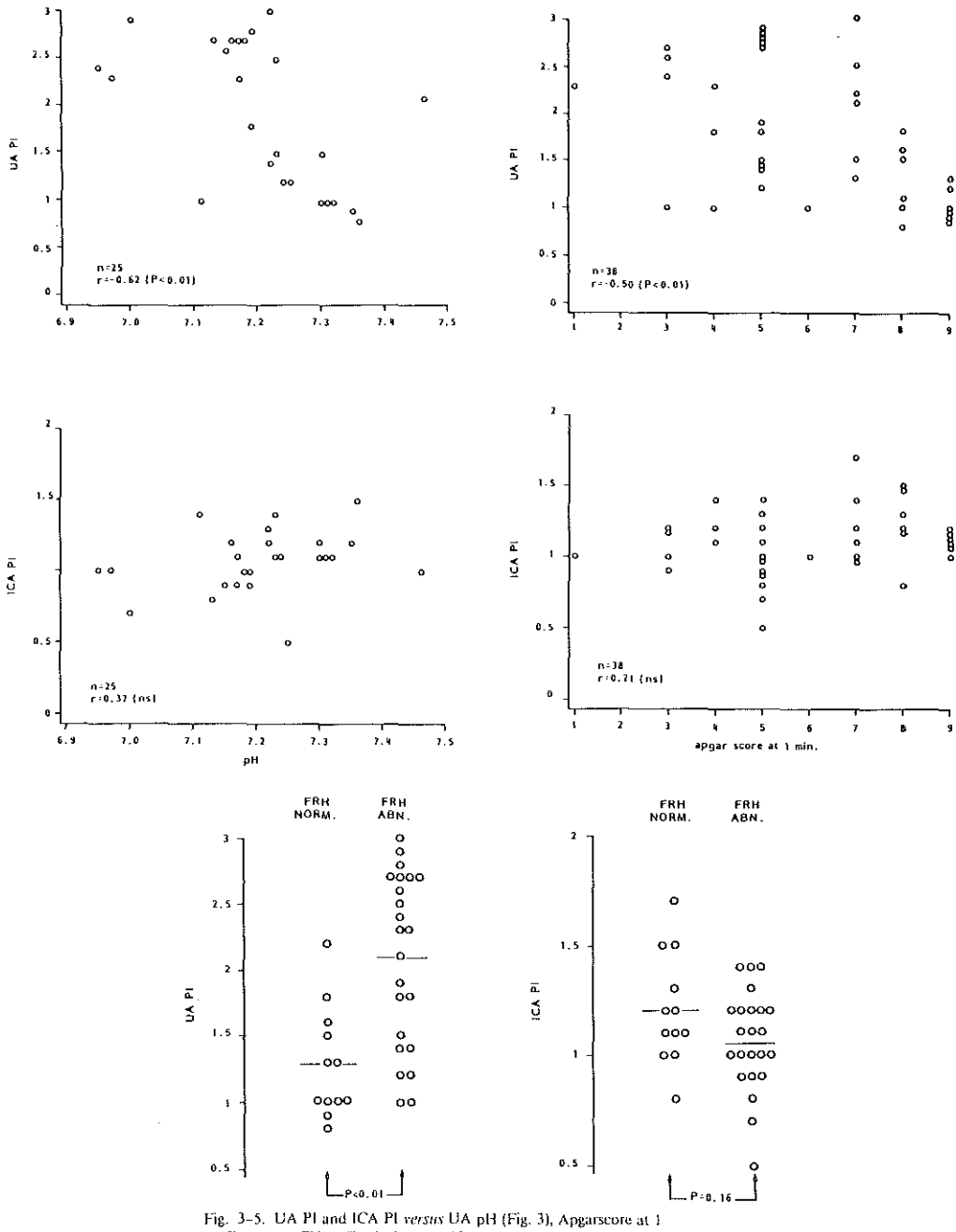

Fig. 3–5. UA PI and ICA PI *versus* UA pH (Fig. 3), Apgarscore at 1 min (Fig. 4) and FHR (Fig. 5) during IUGR.

DISCUSSION

The potential clinical use of flow velocity waveform records from the fetal ICA is demonstrated by the 85% success rate in obtaining such records. Failure to demonstrate the fetal ICA was usually due to excessive fetal movements or maternal obesity. The PI from the UA shows a significant decrease during the third trimester of pregnancy, reflecting a reduction in placental vascular resistance, as has been established by other studies (Stuart et al, 1980; Reuwer et al, 1984; Trudinger et al, 1985; Fleisher et al, 1985). The PI from the fetal ICA shows a fairly constant pattern up to 32-33 weeks of gestation followed by a decrease toward term. Inasmuch as a gradual reduction in fetal pO_2 during the last 4-5 weeks of gestation has been observed (Soothill et al, 1986), this decrease in PI may reflect a relative increase in fetal internal carotid blood flow to maintain cerebral oxygenation. The decrease in PI from the fetal ICA during IUGR is mainly due to changes in end-diastolic flow velocity and confirms earlier data suggesting a redistribution of blood flow favoring oxygen supply to the fetal brain in growth-retarded fetuses (Wladimiroff et al, 1987).

Our study indicates that in IUGR due to impaired placental perfusion, a considerable percentage (55%) of ICA PI values is within the normal range. We suggest that, in the presence of a raised PI from the UA, a normal PI from the ICA may already reflect some kind of redistribution of blood flow. Fetal compromise, as expressed by an abnormal FHR tracing, low umbilical arterial pH, and low Apgar score, correlated well with UA PI, suggesting that this flow variable may be helpful in recognizing fetal compromise. Support for this can be found in a recent comparative study between UA flow velocity waveform and antenatal fetal heart rate monitoring (Trudinger et al, 1986). Fetal compromise was more efficiently recognized by the UA waveforms, with two to three times higher sensitivity and similar positive and negative predictive values. Even more important was the identification of those fetuses at risk of further morbidity, *i.e.* admission to neonatal intensive care.

In our study, no correlation could be documented between the indicators of fetal well-being and ICA PI. Whereas a reduction in ICA PI may reflect blood flow redistribution as a result of chronic fetal hypoxia, the degree of reduction of this variable does not seem to accurately reflect fetal welfare.

It can be concluded that flow velocity measurements in the UA are helpful in predicting fetal well-being, whereas this is not true for flow velocity measurements in the ICA.

4.3 Doppler colour flow imaging of fetal intracerebral arteries and umbilical artery in the small for gestational age fetus

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INTRODUCTION

Fetal intracranial arterial flow velocity waveforms have been mainly studied using combined Doppler and conventional real-time equipment. Most reports discuss angle independent pulsatility index (PI) data originating from the internal carotid artery (Wladimiroff et al, 1986a, 1986b) and middle cerebral artery (Kirkinen et al, 1987) with emphasis on reduction in PI in the small for gestational age (SGA) fetus suggesting "so-called" brain-sparing (Wladimiroff et al, 1987; Arduini et al, 1987). Similar findings were done for the anterior and posterior cerebral arteries (Van den Wijngaard et al, 1989).

Doppler colour flow imaging will allow accurate determination of direction of flow movement (Vyas et al, 1990 a) and therefore angle dependent measurements of absolute flow velocities.

The aim of the present study was: (i) to determine the role of Doppler colour flow imaging in obtaining waveforms from intracranial arterial vessels; (ii) to detect whether changes in absolute flow velocities are present in these vessels in the SGA fetus; (iii) to establish which velocity parameter is most discriminating in this pathologic condition; (iv) to relate this parameter to umbilical artery PI.

MATERIALS AND METHODS

The study was performed in the Department of Obstetrics and Gynaecology of the Academic Hospital Rotterdam-Dijkzigt which serves as a tertiary referral centre for cases of fetal growth retardation.

A SGA fetus was diagnosed in 28 singleton pregnancies at 24 - 38 weeks of gestation (mean 30.8; SD 3.7) when the fetal abdominal circumference was below the 10th percentile for gestational age (Campbell and Wilkin, 1975). In 22 cases the fetal abdominal circumference was equal or below the 5th percentile and in 14 cases equal or below the 2.3rd percentile. The pregnancy duration was determined from the last menstrual period and confirmed by ultrasonic measurement of the fetal biparietal diameter at 14 - 20 weeks. Maternal age ranged between 18 and 37 years (mean 28.3; SD 4.7).

Eighteen women were nulliparous (64%). Two pregnancies were complicated by pregnancy-induced hypertension, while pre-eclampsia was present in nine women. Pregnancy-induced hypertension is defined as a diastolic blood pressure of 90 mm Hg or more in the second half of pregnancy in a previously normotensive woman. In pre-eclampsia, pregnancy-induced hypertension is accompanied by proteinuria of 300 mg/l or more. In one case positive maternal CMV-serology without structural fetal abnormalities was diagnosed.

Caesarean section was performed in 13 women (46 %) because of fetal distress at gestational ages ranging between 28 and 37 weeks (mean 32.4; SD 2.6). The time interval between measurement and delivery ranged between 1 and 39 days (mean 13.1; SD 11.2).

In 27 women fetal birth weight was below the 10th percentile according to Kloosterman's Tables (Kloosterman, 1970) corrected for maternal parity and fetal sex. One fetus displayed catch-up growth, resulting in a birth weight on the 25th percentile. The perinatal mortality rate, which was defined as intrauterine (n=5) or neonatal death (n=2), was 25 %. Delivery was accomplished within three days after intrauterine death occurred.

Twenty-eight normal singleton pregnancies with a fetal abdominal circumference between the 10th and 90th percentile for gestational age served as matched controls. These were selected from outpatients of the Department of Obstetrics and Gynaecology of the Academic Hospital Rotterdam-Dijkzigt. Matching took place with respect to gestational age and maternal age and parity. Gestational age varied between 24 and 39 weeks (mean 30.7; SD 3.6). Maternal age ranged from 18 to 39 years (mean 28.5; SD 5.9).

In the normal control group 26 women delivered vaginally (93%). Caesarean section was performed in two women because of fetal distress at a gestational age

of 40 and 42 weeks, respectively. The time interval between measurement and delivery varied between 12 and 112 days (mean 64.5; SD 25.3). Fetal birth weight was between 10th and 95th percentile, except for one fetus which displayed a birth weight on the 5th percentile. There was no perinatal mortality in the control group.

The number of fetuses studied is sufficient (power>80% at alpha=5%) to detect differences between SGA and controls if the means differ by at least 0.75 standard deviation. The protocol of the study was approved by the Hospital Ethics Committee. All pregnant women consented to participate in the study. Each woman was included in the study only once, the Doppler examinations were performed by one examiner (MJN).

A Toshiba SSA 270 A with a curved-linear 3.75 MHz probe was used. In each woman an attempt was made to document Doppler colour flow patterns in the fetal middle cerebral artery (MCA), internal carotid artery (ICA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA), as well as in the umbilical artery (UA). The technique of colour flow imaging to identify the intracranial vasculature has been described previously (Vyas et al, 1990 a). A transverse scan through the lower part of the fetal cerebrum shows a heart-shaped cross-section of the brain stem with the anterior lobes representing the cerebral peduncles (Wladimiroff et al, 1986a). Anterior to this heart-shaped structure and on either side of the mid-line the anterior cerebral arteries can be seen. The middle cerebral artery can be required as a major branch of the circle of Willis running anterolaterally towards the lateral edge of the orbit. The internal carotid artery is visualised at its bifurcation into the middle and anterior branches. The posterior cerebral arteries can be detected laterally of the cerebral peduncles. Umbilical artery waveforms were obtained from a free floating loop of the umbilical cord (see figure 1, page 75).

Sample volume length ranged between 0.1 and 0.3 cm. The correct position of the pulsed Doppler gate was ensured by two-dimensional ultrasound. Doppler tracings in the intracranial arteries were accepted when the angle between the Doppler cursor and the direction of flow was 10 degrees or less. Peak systolic (PSV, cm/sec), end-diastolic (EDV, cm/sec), and time-averaged (AV, cm/sec) velocities were determined in all four intracerebral vessels. The pulsatility index in these vessels and umbilical artery was calculated according to Gosling and King(1975).

All Doppler studies were performed with the woman in the semirecumbent position

and during periods of fetal apnoea while applying minimal transducer pressure to the maternal abdomen, as fetal head compression is associated with alterations in the fetal intracranial arterial flow velocity waveform (Vyas et al, 1990 b).

All flow velocity waveforms were recorded on hard copies. A microcomputer (Olivetti M24), linked to a graphics tablet was used for analysis of the Doppler recordings. An average of at least three consecutive flow velocity waveforms of optimal quality was used to establish each value.

Statistical analysis of the data consisted of the paired t-test for the univariate comparison of the Doppler data from the SGA fetus with data from the matched control subjects. All Doppler parameters were converted into standard deviations scores (SD-scores). Each SD-score represents the number of standard-deviations the obtained value deviates from the mean of the control group taking into account the gestational age. Multiple logistic regression analysis (Anderson, 1974) was used to simultaneously evaluate the discriminative value of the SD-scores of the various Doppler parameters with regard to the presence of an SGA fetus. Receiver Operating Characteristics (ROC) curves, graphically depicting the sensitivity versus the false positive rate for various SD cut-off levels, were constructed. The level of statistical significance was set at P=0.05 (two-sided).

RESULTS

The success rate in obtaining good quality Doppler flow velocity waveforms was 100% for the UA, MCA and ICA, and 98% and 87.5% for the ACA and PCA, respectively.

Table 1 presents the mean, SD, and range for all vessel parameters in the SGA fetus and controls. For the middle cerebral artery, all four parameters (PSV, AV, EDV and PI) differ significantly between SGA and controls. The same applies to the anterior cerebral artery, except for PSV. For the internal carotid and posterior cerebral artery, a significant difference is only demonstrated for EDV and PI. Also, for the UA PI a significant difference between SGA and control group was established.

Table 1. Umbilical and Cerebral Flow Velocity Waveform Values in Patients with SGA and Normal Control Subjects

	SGA (n=28)			Normal (n=28)			
	Mean	SD	Range	Mean	SD	Range	Significance of difference (P)
Umbilical artery PI	1.84	0.64	0.91- 3.16	1.03	0.20	0.58- 1.47	<0.001
Middle cerebral artery							
PSV (cm/s)	49.5	9.8	31.8 -65.5	44.1	11.0	26.2 -65.1	0.02
AV (cm/s)	26.6	6.8	12.3 -39.8	20.6	6.1	12.0 -36.2	0.001
EDV (cm/s)	12.6	5.5	0.7 -24.5	7.2	4.1	2.8 -19.0	<0.001
PI	1.45	0.40	0.89- 2.53	1.84	0.39	1.18- 2.80	0.001
Internal carotid artery							
PSV (cm/s)	33.6	8.4	20.1 -64.2	35.3	9.8	22.6 -65.9	0.3
AV (cm/s)	19.6	5.2	10.9 -37.7	18.4	5.3	12.8 -32.8	0.3
EDV (cm/s)	10.3	3.7	3.8 -20.8	7.3	3.3	4.1 -16.7	0.003
PI	1.22	0.29	0.71- 1.87	1.55	0.33	0.74- 2.26	0.001
Anterior cerebral artery*							
PSV (cm/s)	32.0	10.1	13.8 -52.0	27.8	8.9	16.3 -44.1	0.1
AV (cm/s)	17.9	6.2	7.4 -32.5	13.7	4.2	8.8 -21.4	0.006
EDV (cm/s)	8.7	4.5	1.1 -20.8	4.8	2.0	1.6 - 9.0	0.001
PI	1.35	0.45	0.80- 2.59	1.70	0.36	1.01- 2.49	0.005
Posterior cerebral artery**							
PSV (cm/s)	16.7	4.7	10.3 -27.9	16.6	6.1	7.3 -35.1	0.5
AV (cm/s)	10.4	3.0	6.0 -19.5	9.4	3.3	4.2 -18.0	0.16
EDV (cm/s)	5.7	2.3	1.1 -13.1	4.1	2.0	0.2 - 8.1	0.02
PI	1.08	0.31	0.70- 1.94	1.36	0.29	0.87- 1.81	0.01

SGA, small-for-gestational age; PSV, peak systolic velocity; AV, time-averaged velocity; EDV, end-diastolic velocity; PI, pulsatility index.

* n = 2 7
**n=24

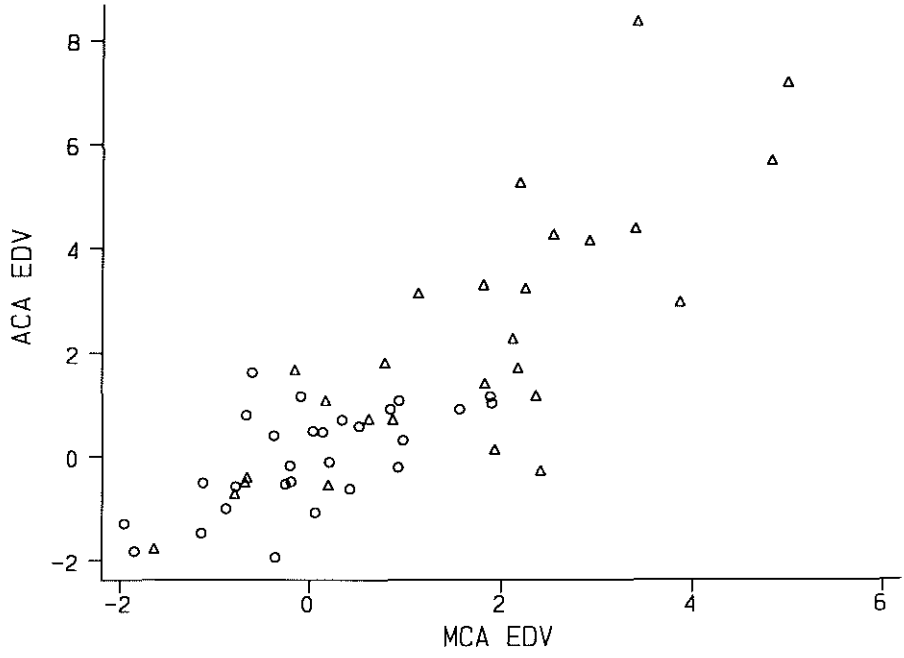

Figure 1: Correlation between the standard deviation (SD) scores of the Middle Cerebral Artery End-diastolic Velocity (MCA EDV) and the Anterior Cerebral Artery End-diastolic Velocity (ACA EDV).

O represents the normal controls, ∩ represents the small for gestational age (SGA) fetuses.

Table 2 displays the regression coefficients for the mean values of the Doppler parameters versus gestational age in control cases. A statistically significant linear relation is observed for UA PI and all intracerebral vessel parameters, except for MCA PI, ACA PI and PCA PI.

Applying multivariable analysis to the cerebral Doppler parameters, each expressed as a SD score, according to the findings given in table 2, it was found that both MCA EDV and ACA EDV are the most sensitive cerebral parameters discriminating between SGA and controls. If either of these parameters is taken into account, none of the other cerebral Doppler parameters significantly contributes to the discrimination between SGA and controls. As shown in figure 1, MCA EDV and ACA EDV are significantly correlated, both for SGA ($r=0.80$, $p<0.01$) and controls ($r=0.63$, $p<0.01$). When both these parameters were evaluated simultaneously with UA PI, it was found that only UA PI remained a significant indicator of SGA. MCA EDV and ACA EDV separately or in combination

Table 2. Relation between Flow Velocity Waveform Values and Gestational Age in Normal Control Subjects (n=28)

	Intercept	Slope	SD	r	P
Umbilical artery PI	1.70	-0.02	0.18	-0.41	0.03
Middle cerebral artery					
PSV (cm/s)	-14.93	1.92	8.67	0.64	<0.001
AV (cm/s)	-14.41	1.14	4.62	0.68	<0.001
EDV (cm/s)	-15.73	0.75	3.15	0.66	<0.001
PI	2.65	-0.03	0.38	-0.25	0.21
Internal carotid artery					
PSV (cm/s)	- 1.83	1.21	8.88	0.45	0.02
AV (cm/s)	- 9.81	0.92	4.25	0.63	<0.001
EDV (cm/s)	-12.31	0.64	2.45	0.70	<0.001
PI	2.72	-0.04	0.30	-0.42	0.02
Anterior cerebral artery					
PSV (cm/s)	- 3.30	1.01	8.26	0.41	0.03
AV (cm/s)	- 2.40	0.52	3.78	0.46	0.01
EDV (cm/s)	- 3.82	0.28	1.77	0.51	0.006
PI	1.96	-0.01	0.36	-0.09	0.65
Posterior cerebral artery*					
PSV (cm/s)	-14.50	1.01	4.81	0.64	<0.001
AV (cm/s)	- 8.94	0.60	2.43	0.69	<0.001
EDV (cm/s)	- 7.80	0.39	1.41	0.73	<0.001
PI	1.94	-0.02	0.29	-0.25	0.24

PSV, peak systolic velocity; AV, time-averaged velocity; EDV, end-diastolic velocity; PI, pulsatility index; SD, standard deviation of residuals; r, correlation coefficient; P, significance of slope. *n=24

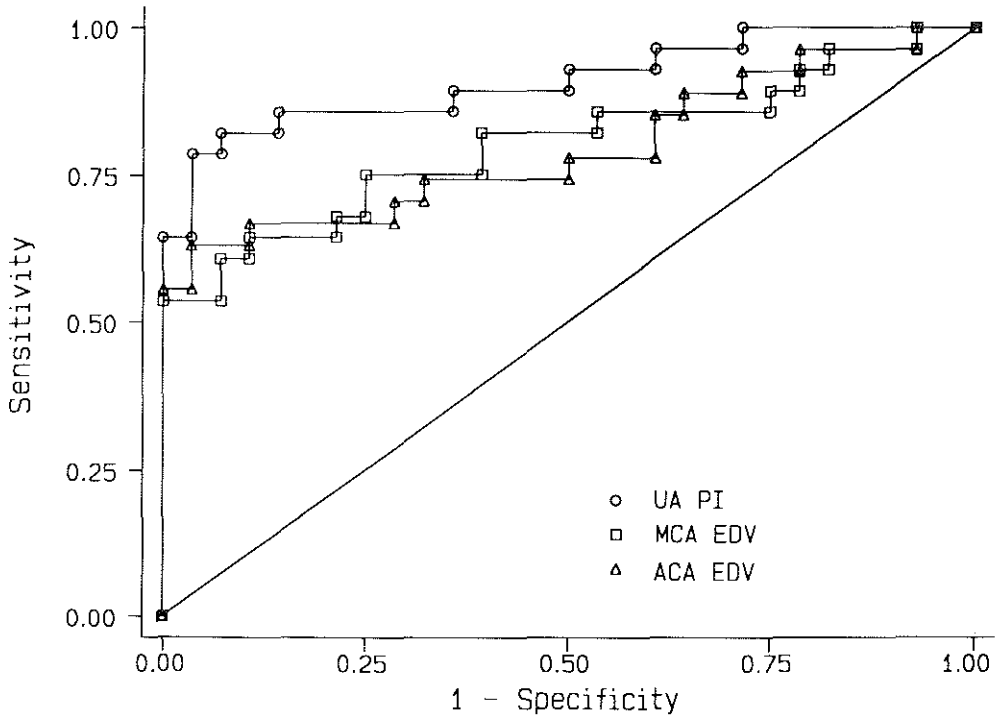

Figure 2: Receiver Operating Characteristics (ROC) curves of the Umbilical Artery Pulsatility Index (UA PI), Middle Cerebral Artery End-diastolic Velocity (MCA EDV) and Anterior Cerebral Artery End-diastolic Velocity (ACA EDV). The diagonal line represents an imaginary test which has no discriminative power.

did not contribute significantly to the discriminative value of UA PI alone. MCA PI and MCA AV were closely correlated in SGA ($r=0.65$; $p<0.01$) and controls ($r=0.37$; $p=0.03$), whereas this was not the case for ACA.

Figure 2 displays ROC-curves for the three most sensitive parameters in this study (UA PI, MCA EDV and ACA EDV). UA PI performs better than both cerebral parameters, whilst there are no large differences between MCA EDV and ACA EDV. UA PI displays a sensitivity and specificity of 82% and 86% at +1 SD score, and of 68% and 96% at +2 SD score. For MCA EDV a sensitivity andspecificity of 64% and 89% is established at +1 SD score, and of 50% and 100% at +2 SD score. Comparable percentages are found for the ACA EDV with a sensitivity and specificity of 67% and 82% at +1 SD score, and of 44% and 100% at +2 SD score.

DISCUSSION

Invasive animal experiments have helped to elucidate fetal cardiovascular adjustments in response to hypoxaemia. Peeters et al (1979) demonstrated that blood flow was increased in inverse relation to arterial oxygen content. This response was found in the heart, brain and adrenal glands.

Vyas et al (1990a) relating umbilical cord blood gases with PI in the middle cerebral artery of human fetuses, established a significant positive relation for PI with PO_2 and pH.

Using conventional real time ultrasound, visualization of blood flow in the internal carotid artery, anterior, middle and posterior cerebral artery was achieved in 89%, 64%, 91% and 58% of normal cases (Van den Wijngaard et al, 1989). Our data show better results using Doppler colour flow imaging with visualization of the posterior cerebral artery as often as 87.5%. Using conventional real-time ultrasound only arterial vessel wall pulsations can be visualised, for small vessels such as the posterior cerebral artery this may be difficult. Doppler colour flow imaging allows proper identification of blood flow direction in a particular vessel. Despite Doppler colour flow imaging, absolute velocity measurements in the umbilical artery remain difficult due to coiling of the arteries.

A recently reported gestational age-related reduction in PI for all intracerebral vessels (Van den Wijngaard et al, 1989) could not be confirmed in the present study. This lack of change in PI may be explained by the fact that most of our data (82%) were collected before 34 weeks of gestation whereas a significant reduction in PI has only been established after that period (Van den Wijngaard et al, 1989). The umbilical artery PI displays a clear reduction with advancing gestational age as has been previously demonstrated (Stewart et al, 1990).

Our study shows that the SGA fetus is associated with a significant increase in end-diastolic velocities and a significant reduction in PI for all four intracerebral vessels, suggesting an overall reduction in cerebral vascular resistance. Raised time-averaged velocities were only observed in the anterior and middle cerebral artery combined with raised peak-systolic velocities in the latter vessel. Vyas (1993) found no correlation between time-averaged velocity and PI in the middle cerebral artery, suggesting that other factors such as cardiac contraction force, vessel compliance and blood viscosity may play a role. Whereas similar findings

were done in the present study for the anterior cerebral artery, a close correlation was established for the middle cerebral artery. These data are, therefore, inconclusive as to the exact mechanism responsible for the observed changes in time-averaged velocity.

The most discriminative intracranial velocity parameter was the end-diastolic velocity in the anterior and middle cerebral artery, suggesting that reduction in down-stream impedance in these two vessels is more pronounced than in the other intracranial arteries. The sensitivity and specificity for the end-diastolic flow velocity is not essentially different between the anterior and middle cerebral artery. Since the fetal head usually faces laterally during the third trimester, the middle cerebral artery seems to be the most accessible as far as conventional Doppler measurements are concerned (Kirkinen et al, 1987). Indeed, this position allows the lowest insonation angle to sample this vessel in the axial plane of scanning.

With the availability of Doppler colour flow imaging and therefore accurate determination of the interrogation angle, measurement of the end-diastolic flow velocity in the middle cerebral artery is to be preferred to calculation of the PI in the detection of reduced cerebral down stream impedance in the SGA fetus. The PI in the umbilical artery exhibits an even more pronounced change in down stream impedance than end-diastolic blood flow velocities in the anterior and middle cerebral artery. A similar observation was done in a previous study comparing the pulsatility index in the umbilical and internal carotid artery (Wladimiroff et al, 1987).

It can be concluded that Doppler colour flow imaging allows easy identification of fetal intracranial arterial vasculature and therefore reliable information on absolute blood flow velocities in these vessels. Whereas for the intracranial vasculature, the end-diastolic blood flow velocities in the anterior and middle cerebral artery are the most sensitive parameters discriminating between SGA and controls, the umbilical artery PI remains the best indicator for SGA.

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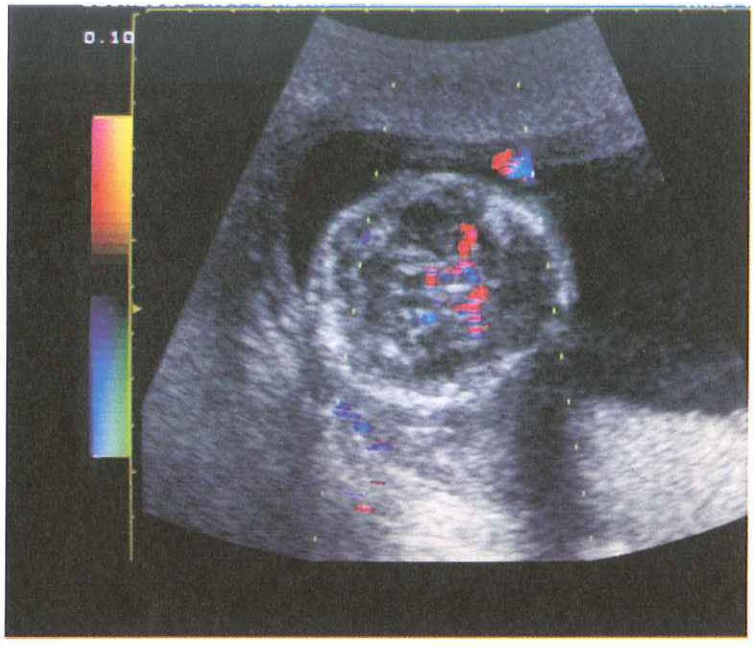

Figure 1 *Circle of Willis in a normal fetus at 20 weeks of gestation with colour Doppler (Toshiba SSA 270 A).*

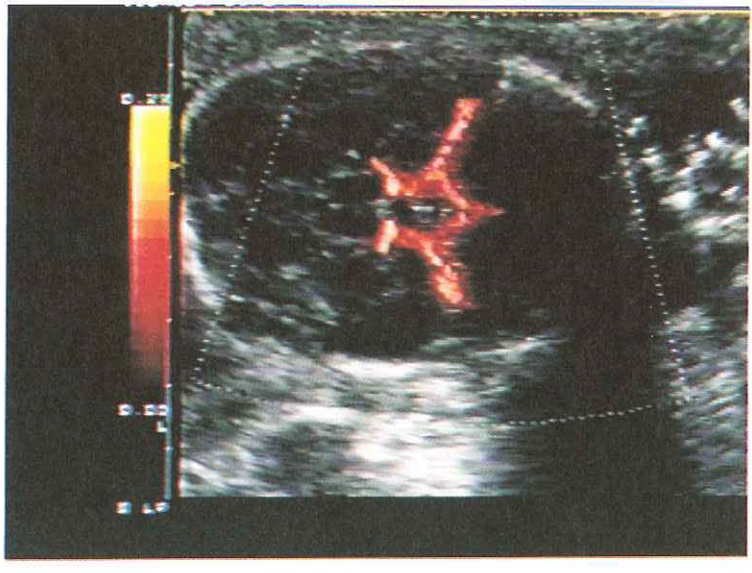

Figure 2 *Circle of Willis in a normal fetus at 32 weeks of gestation with colour angiology (Toshiba SSH 140 A super HG).*

Chapter 5

FETAL BEHAVIOUR

5.1. Literature review

As a result of high quality real-time ultrasound equipment major progress has been made in the study of human fetal behaviour and blood flow.
It became clear that the fetus of 8-10 weeks of gestation moves spontaneously in utero. After 14 weeks bursts of movements are replaced by much larger episodes of fluctuating activities (de Vries et al, 1985;1987). During the second half of pregnancy increasingly rest/activity cycles can be observed (Dawes et al, 1982). Early maturation of fetal cardiac activity is characterized by an initial rise in fetal heart rate from 120-180 bpm between 6 and 10 weeks (Robinson and Shaw-Dunn, 1973), followed by a gradual decrease to about 140 bpm at 19 weeks, and the development of beat to beat variation (Wladimiroff and Seelen, 1973). From the late second trimester onwards fetal heart rate accelerations are clustered within episodes of high heart rate variation. After 34 weeks mean fetal heart rate is higher during periods of general body movements as compared with periods without these movements (Dawes et al, 1981;1982).
Another behaviour variable is fetal eye movements. They can be seen as a sonolucent globe, behind which lies a wedge-shaped echorich area in an oblique cross-section of the fetal face (Bots et al, 1981). Inoue et al (1986) reported that from 30 weeks onwards eye movements were more in long-term clusters.
Prechtl and Beintema (1964) introduced a classification of behavioural states in the full term newborn. In premature infants periods of congruency of state variables may occur; also prenatally the same phenomenon is reported. Nijhuis et al (1982, 1984) introduced a classification from 36-38 weeks of gestation based on the following fetal behaviour states:

State 1F: quiescence, sometimes interrupted by brief gross body movements; no eye movements; stable FHR with isolated accelerations, strictly related to movements.

State 2F: frequent and periodic gross body movements; continually eye movements; FHR variable with frequent accelerations, in association with movements.
State 3F: absence of gross body movements, but eye movements are continually present; FHR regular oscillation frequency, no accelerations.
State 4F: vigorous, continual activity, eye movements present; FHR unstable, with large and long-lasting accelerations.

At 38 weeks the distribution of percentages of stage 1F to 4F is respectively: 32%, 42%, 1% and 7% (Nijhuis et al, 1982).

5.1.1 Fetal behavioural states and cardiovascular dynamics

In studies in fetal sheep it appeared that regional organ blood flow is affected by behavioural state with an increase in blood flow to the brain (Richardson et al, 1985; Jensen et al, 1985; Rankin et al, 1987) and splanchnic viscera (Jensen et al, 1985) during the low-voltage electrocortical state or REM state when compared with the high-voltage electrocortical state or non-REM state. This increase in organ blood flow is largely due to decreases in cerebral and splanchnic vascular resistance as mean arterial blood pressure remains mostly unchanged, and for the brain appears to be coupled with an increase in oxidative metabolism (Richardson et al, 1985).
A marked difference in pulsatility index (PI) between FBS 1F and 2F is demonstrated in the lower thoracic part of the descending aorta in the near term human fetus (van Eyck et al, 1985). As a result of elevated end-diastolic velocities, reflecting a reduced peripheral vascular resistance, the reduced PI during FBS 2F suggests an increased perfusion of the fetal skeletal musculature at trunk and low extremity level. This would be in agreement with a raised energy demand as a result of increased muscular activity in FBS 2F. In the presence of asymmetric growth retardation, flow velocity waveforms in the descending aorta are state independent (van Eyck et al, 1986). This may be explained by the fact that chronic hypoxaemia present in IUGR stimulates the peripheral arterial chemoreceptors (Critchley et al, 1980; Itskovitz et al, 1982) and subsequent release of vasoconstrictive agents, such as vasopressin and catecholamines (Iwamoto and

Rudolph, 1981; Jensen et al, 1982; Mott, 1985; Oosterbaan, 1985). This peripheral vasoconstriction seems to overrule state dependent PI fluctuations.

No behavioural state dependency for renal artery PI could be demonstrated by Oosterhof et al (1993a), while De Koekkoek et al (1994) reported reduced PI values during FBS 2F. If this reduction reflects augmented renal blood flow during FBS 2F, one would expect a higher fetal urinary output. However, this is in contrast with micturition which is almost reduced by half during FBS 2F compared with FBS 1F in the near term fetus (Oosterhof et al, 1993b; de Koekkoek, 1993).

Blood flow velocity waveforms in the umbilical artery show no state dependency (van Eyck et al, 1985; Mulders et al, 1986; Connors et al, 1991), suggesting a fetal origin of state dependent changes in blood flow.

In the human fetal internal carotid artery a reduction in cerebral vascular resistance suggests increased blood flow to the brain during FBS 2F (van Eyck et al, 1987). With maintenance of behavioural state dependency there is a fall in PI in the fetal internal carotid artery during the last four weeks of pregnancy, suggesting a haemodynamic redistribution favouring blood supply to the brain (van den Wijngaard et al, 1988). With the introduction of Doppler colour flow, absolute flow velocity measurements in the cerebral arteries became possible as will be discussed further in chapter 4.2. In IUGR no behavioural state dependency for internal carotid artery PI could be demonstrated. The reduction in PI in IUGR suggest a circulatory redistribution with the aim of favouring cerebral blood flow (brain-sparing effect), sufficient to overrule behavioural state dependency.

At cardiac level mean flow velocities are increased at the foramen ovale (van Eyck et al, 1990) and mitral valve (Rizzo et al, 1990) during FBS 2F, whereas in the ductus arteriosus there is a reduction in mean velocities during this behavioural state. This is suggestive of a redistribution of cardiac output in favour of the left heart during FBS 2F (van Eyck et al, 1990). In late second and early third trimester pregnancy rest-activity state independency has been demonstrated for ductus arteriosus blood flow velocity (Brezinka et al, 1993).

On the venous side, an increase of approximately 30% has been established for both the ductus venosus peak systolic and peak diastolic velocity as well as time-averaged velocity during FBS 2F (Huisman et al, 1994a). The equal rise in peak systolic and peak diastolic flow velocity suggests increased volume flow through the ductus venosus during this behavioural state, considering a redistribution of

volume flow at the level of the umbilical sinus. Flow velocity waveforms in the inferior vena cava are behavioural state independent (Rizzo et al, 1992; Huisman et al, 1994b), suggesting a behavioural state related redistribution may take place at ductus venosus level only.

In the descending aorta, intracerebral arteries and umbilical artery both in FBS 1F and FBS 2F an inverted relationship between PI and fetal heart rate is observed, which can be attributed to the way the PI is calculated (Gosling and King, 1975), i.e. a lower heart rate is associated with a longer end-diastolic period (van Eyck et al, 1985;1987). The same applies for the resistance index and fetal heart rate (Connors et al, 1991). In the middle cerebral artery of fetuses a significant inverse correlation has been found between fetal heart rate and the PI with heart rate decelerations (Mari et al, 1991) and with tachycardia secondary to ritodrine infusion (Rasanen, 1990).

It can be concluded that fetal behavioural states affect regional organ blood flow. Human Doppler studies suggest a redistribution of volume flow at ductus venosus level, with a reduced pulsatility index in the descending aorta and internal carotid artery, and increased flow velocities at left cardiac level. We are interested to know whether behavioural state dependent changes in blood flow velocity occur in all intracerebral arteries, or if there are differences suggesting local cerebral regulating mechanisms (sub-chapter 5.2).

5.2 Doppler colour flow imaging of fetal intracerebral arteries relative to fetal behavioural states in normal pregnancy.

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SUMMARY

In 14 normally developing term fetuses, the relationship between the blood flow velocity waveforms at cerebral arterial level (internal carotid artery, anterior, middle and posterior cerebral artery) and fetal behavioural states was studied using Doppler colour flow imaging. Behavioural state dependent changes in absolute flow velocities occurred in all vessels, except for the middle cerebral artery. These changes suggest preferential blood flow to the left heart resulting in increased flow to the cerebrum during fetal behavioural state 2F (active sleep) when compared with fetal behavioural state 1F (quiet sleep). The middle cerebral artery supplies the neocerebrum. This not yet fully developed part of the cerebrum does not seem to take part in the regulation of fetal behaviour. In the internal carotid artery an inverse relationship between peak systolic velocity and fetal heart rate could be established, which can be explained by a shorter rapid filling phase at raised fetal heart rate according to the Frank-Starling Law.

INTRODUCTION

Combined use of real-time and pulsed Doppler systems has now resulted in a large number of studies on fetal cerebral blood flow (van Eyck et al, 1987; Vyas et al, 1990a; Vyas et al, 1990b; van den Wijngaard et al, 1989; Wladimiroff et al, 1986). Fetal behavioural state dependent changes are demonstrated in the descending aorta (van Eyck et al, 1985), foramen ovale (van Eyck et al, 1990), ductus venosus (Huisman et al, 1993) and internal carotid artery (van Eyck et al,

1987). Doppler colour flow imaging will allow accurate determination of direction of flow movement (Vyas et al, 1990a) and therefore angle dependent measurements of absolute flow velocities.

The objective of the present study was (i) to detect whether behavioural state dependent changes in absolute flow velocities in the intracerebral arteries are present in normal term fetuses, (ii) to establish if these changes are constant in all arteries of the circle of Willis and (iii) to detect a relation between absolute flow velocity and fetal heart rate.

MATERIALS AND METHODS

A total of 14 women with singleton and uncomplicated pregnancies at 38-39 weeks of gestation consented to participate in the study. The gestational age had been calculated from the last menstrual period and confirmed by ultrasonic measurements of fetal crown-rump length or biparietal diameter. All participants were non-smokers and no medication was used. Fetal abdominal circumference was between the 10th and 90th percentile of the reference chart (Campbell and Wilkin, 1975) and birth weight between the 10th and 90th percentile for gestational age according to Kloosterman's tables (1970), corrected for maternal parity and fetal sex. There were no structural anomalies. The protocol of the study had been approved by the Hospital Ethics Committee.

A Toshiba SSA 270 A with a combined curved-linear two-dimensional real-time and pulsed Doppler 3.75 MHz probe was used. The Doppler recordings were performed by one examiner (MJN). In each woman an attempt was made to document Doppler colour flow patterns in the fetal middle cerebral artery (MCA), internal carotid artery (ICA), anterior cerebral artery (ACA) and posterior cerebral artery (PCA). The technique of colour flow imaging to identify the intracranial vasculature has been described previously (Vyas et al, 1990a). A transverse scan through the lower part of the fetal cerebrum shows a heart-shaped cross-section of the brain stem with the anterior lobes representing the pedunculi cerebri (Wladimiroff et al, 1986). Anterior to this heart-shaped structure and on either side of the mid-line the anterior cerebral arteries can be seen. The middle cerebral artery can be required as a major branch of the circle of Willis running antero-laterally towards the lateral edge of the orbit. The internal carotid artery is

visualized at its bifurcation into the middle and anterior branches. The posterior cerebral arteries can be detected laterally of the cerebral peduncles.

Sample volume length ranged between 0.1 and 0.3 cm. The correct position of the pulsed Doppler gate was ensured by two-dimensional ultrasound. Doppler tracings in the intracranial arteries were accepted when the angle between the Doppler cursor and the direction of flow was 10 degrees or less.

All Doppler studies were carried-out two hours following breakfast or lunch, with the woman in a semirecumbent position and during periods of fetal apnoea. Minimal transducer pressure was applied to the maternal abdomen, as fetal head compression is associated with alterations in the fetal intracranial arterial flow velocity waveform (Vyas et al, 1990b).

Maximum flow velocity waveforms were recorded during fetal behavioural states (FBS) 1F and 2F according to the classification of Nijhuis et al (1982). These behavioural states are defined as follows:

State 1F (quiet sleep) - quiescence, which can be regularly interrupted by brief gross body movements, which mostly are startles; absent eye movements and a stable heart rate pattern with a narrow oscillation bandwidth. Isolated accelerations do occur, but these are strictly related to movements.

State 2F (active sleep) - frequent and periodic gross body movements that are mainly stretches and retroflexions and movements of extremities; eye movements almost continually present; a heart rate pattern with a wider oscillation bandwidth than in state 1F and frequent accelerations during movements.

In order to establish fetal behavioural states, the following parameters were simultaneously recorded:

(i) The fetal heart rate (FHR), which was obtained from a Doppler ultrasound cardiotocograph (Hewlett Packard 8040A, carrier frequency 1 MHz);

(ii) Fetal eye movements, which were observed by ultrasonic visualisation of the fetal eye lens in a transverse scanning plane through the orbits using the two-dimensional real-time scanner. Immediately after establishing the presence or absence of eye movements, the transducer was moved in a sagittal scanning plane of the fetal trunk to confirm presence of body movements.

Flow velocity recordings were only performed when a clear fetal behavioural state had been identified and when this state had been present over a period of at least three minutes.

Blood flow velocity waveforms were recorded on videotape, from which hard copies were made. A microcomputer (Olivetti M24), linked to a graphics tablet was used for analysis of the Doppler recordings. Waveform analysis was performed by an independent examiner (FMEH). Peak systolic (PSV, cm/s), end-diastolic (EDV, cm/s), and time-averaged (AV, cm/s) velocities were determined in all four intracerebral vessels. Period time (msec) was established from the time interval between peak systoles from two consecutive cardiac cycles. From this the fetal heart rate (FHR) was calculated. An average of at least three consecutive flow velocity waveforms of optimal quality was used to establish each value.

The relation between the various Doppler parameters on the one hand and FBS (1F and 2F) and fetal heart rate on the other hand were evaluated using repeated measurement analysis of variance (Schluchter, 1990). For each Doppler parameter the mean slope and intercept of individual regression lines for both behavioural states were determined using an iterative search for optimal values (Feldman, 1988). After verifying that the slopes thus derived did not significantly differ between FBS 1F and 2F, the difference in intercepts of the two regression lines which were taken to run parallel, was determined to estimate the FHR-adjusted difference in mean outcome between both behavioural states. This adjustment was necessary because in FBS 2F the fetal heart rate was generally higher as compared to FBS 1F. Statistical significance was tested at the level of 0.01 (two-sided).

RESULTS

A total of 508 technically acceptable blood flow velocity recordings from the intracerebral arteries was analysed. The success rate in obtaining good quality Doppler flow velocity waveforms for both fetal behavioural states was 100% for the MCA, 96.4% for the ICA, 92.8% for the ACA and 82.1% for the PCA. An even distribution of recordings was available for analysis. In the MCA the median number of recordings was 5 (range 4-7) in FBS 1F and 5 (range 4-10) in FBS 2F, in the ICA these numbers were 4 (range 2-7) and 5 (range 0-5), in the ACA 5 (range 0-6) and 5 (range 0-9) and in the PCA 5 (range 0-7) and 5 (range 0-6).

Figure 1 is an example of the applied method of analysis. The measurements of the peak systolic velocity in the ICA obtained in FBS 1F and 2F are given, as well

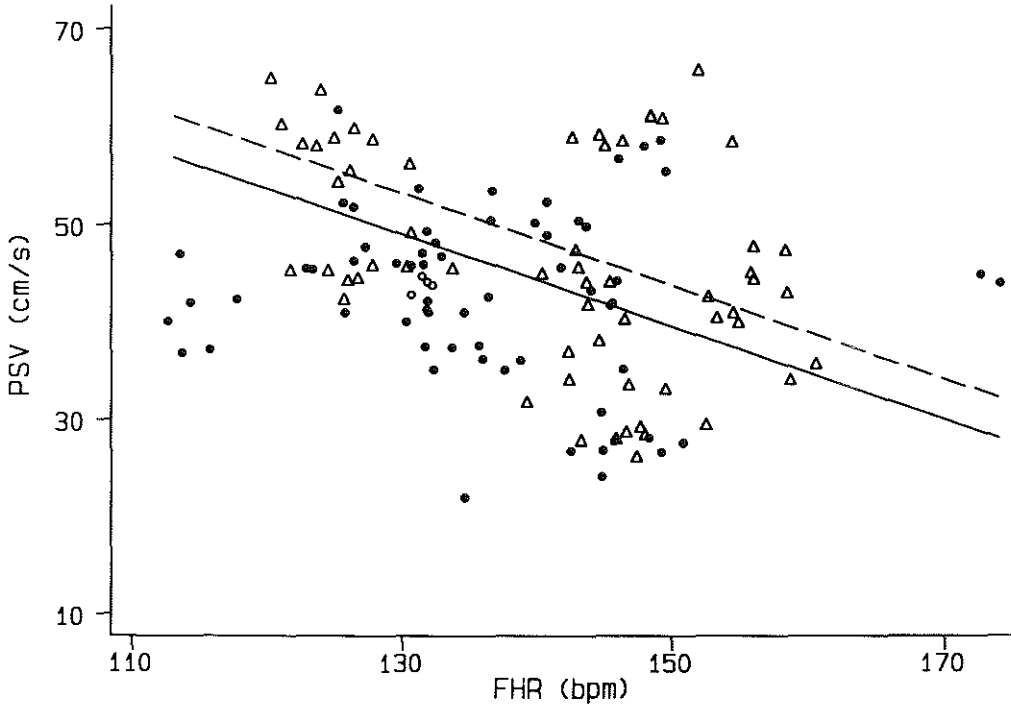

Figure 1: Internal Carotid Artery Peak Systolic Velocity (ICA PSV) measurements obtained in FBS 1F (solid circles) and in FBS 2F (open triangles). Solid and interrupted lines denote regression lines corresponding to the two respective behavioural states.

as the regression lines corresponding to the two fetal behavioural states. As is also demonstrated in Table 1, a statistically significant mean difference in peak systolic velocity existed in the ICA between FBS 1F and 2F ($p<0.01$). ICA PSV demonstrated a statistically significant reduction ($p<0.01$) with increasing fetal heart rate.

Table 1 also presents the mean difference between FBS 2F and 1F for each of the blood flow velocity parameters studied, as well as the slope for the relation between each blood flow velocity parameter and fetal heart rate.

Statistical significance was reached for the mean difference between FBS 2F and 1F for all ICA parameters ($p<0.01$), all ACA parameters ($p<0.01$), PCA PSV ($p<0.001$), and PCA AV ($p=0.001$). No significant difference was found for MCA velocity parameters.

Table 1 *Mean difference between FBS 2F and FBS 1F for all intracerebral arterial flow velocities studied, as well as the slope for the relation between each blood flow velocity parameter and fetal heart rate.*

	Mean difference 2F-1F (cm/s)	Significance of difference (p)	Slope (cm/s/bpm)	Significance of slope (p)
Middle cerebral artery				
PSV	-0.96	0.38	-0.32	0.06
AV	0.76	0.25	-0.22	0.11
EDV	1.20	0.02	-0.13	0.23
Internal carotid artery				
PSV	3.80	<0.01	-0.47	<0.01
AV	2.00	<0.01	-0.16	0.15
EDV	0.98	<0.01	0.01	0.84
Anterior cerebral artery				
PSV	4.48	<0.01	0.21	0.38
AV	3.00	<0.01	0.20	0.15
EDV	1.80	<0.01	0.14	0.04
Posterior cerebral artery				
PSV	4.50	<0.001	0.03	0.72
AV	1.70	0.001	0.06	0.24
EDV	0.29	0.36	0.05	0.11

PSV=peak systolic velocity; AV=time-averaged velocity; EDV=end-diastolic velocity.

DISCUSSION

The entire brain is supplied by two pairs of arterial trunks, the internal carotid arteries and the vertebral arteries. Lateral to the optic chiasm the internal carotid artery divides into a smaller anterior cerebral artery and a larger middle cerebral artery. The middle cerebral artery is regarded as the direct continuation of the internal carotid artery. The vertebral artery arises from the first part of the

subclavian artery and courses along the anterolateral surface of the medulla. Both vertebral arteries unite at the caudal border of the pons to form the basilar artery. The posterior cerebral arteries are formed by the bifurcation of the basilar artery at the rostral border of the pons. The circle of Willis is formed by anastomotic branches of the internal carotid artery and the most rostral branches of the basilar artery (i.e. the posterior cerebral artery).

Recording of blood flow velocity waveforms of different fetal intracerebral arteries has been reported with conventional real time ultrasound and pulsed Doppler (Wijngaard et al, 1989). Using Doppler colour flow imaging however, better visualization of the circle of Willis is achieved (Vyas et al, 1990a). Whilst with conventional real time ultrasound only arterial vessel wall pulsations can be visualized, with Doppler colour flow imaging proper identification of blood flow direction in a particular vessel is obtained, allowing angle dependent measurements of absolute flow velocities.

In the last weeks of pregnancy identifiable fetal behavioural states have become apparent (Nijhuis et al, 1982). Behavioural state has been shown to influence cerebral blood flow in animals (Reivich et al, 1968), human neonates (Mukhtar et al, 1982) and fetuses (van Eyck et al, 1987), i.e. an increase during rapid eye movement sleep (active sleep, FBS 2F) when compared to non-rapid eye movement (quiet sleep, FBS 1F).

The internal carotid artery is one of the most important vessels supplying the fetal brain. All three velocities i.e. the peak systolic, averaged and end-diastolic velocity were significantly increased in FBS 2F compared to FBS 1F. The increased end-diastolic velocity suggests a reduced cerebral vascular resistance during FBS 2F, while the increased peak systolic and averaged velocity could be explained by an increased contraction force of the heart or a redistribution of blood flow during FBS 2F in favour of the left heart. As suggested in earlier reports (Huisman et al, 1994a), a redistribution of volume flow at the level of the umbilical sinus should be considered with increased flow in the ductus venosus during FBS 2F compared to FBS 1F. This is consistent with other studies suggesting a FBS 2F related rise in volume flow at foramen ovale (van Eyck et al, 1990) and mitral valve level (Rizzo et al, 1990). Increased volume flow through the left heart would be necessary to ensure raised cerebral blood flow during FBS 2F which has been demonstrated in animal studies (Jensen et al, 1985; Richardson et al, 1985) and is also suggested

from data on reduced vascular resistence at cerebral level in the human fetus (van Eyck et al, 1987).

In the middle cerebral artery no significant behavioural state related change in flow velocities was found. This could be attributed to the fact that the middle cerebral artery supplies the neocerebrum, i.e. the later developing cerebral hemisphere or midbrain. Although in term fetuses the complex pattern of sulci and gyri is already developed, myelinisation is still incomplete and the number of synapses is still increasing (Pomeroy and Volpe, 1992). It is therefore not surprising that no significant difference between FBS 1F and 2F is demonstrated in this still basic functioning part of the cerebrum. This is in agreement with the conclusion of Chugani et al (1987) which says that according to the PET scan increased glucose metabolic activity in the parietal, temporal and occipital cortices does not occur before the age of three months. Since middle cerebral artery flow velocity waveforms are not subject to fluctuation with fetal behavioural state as are the other intracerebral waveforms, it may be the most useful vessel to study for clinical purposes.

All three parameters i.e. peak systolic, averaged and end-diastolic velocity in the anterior cerebral artery were significantly increased in FBS 2F, which together with the presence of rapid-eye movements suggests raised electro-cortical activity in the frontal lobes.

The posterior cerebral artery is responsible for the oxygen supply to the medulla, pons and part of the cerebellum. The significant increase in peak systolic and averaged velocity in the posterior cerebral artery during FBS 2F could also be explained by the earlier mentioned increased

contraction force of the heart or redistribution in blood flow at cardiac level during FBS 2F. The end-diastolic velocity is not significantly different between FBS 2F and 1F, indicating the peripheral resistance has not changed. These data however, are at variance with the reported role of the pons in the regulation of sleep states in the fetal lamb (Jensen et al, 1985; Richardson et al, 1985).

Van Eyck et al (1985, 1987) established a decrease in PI in the umbilical artery and fetal descending aorta with rising fetal heart rate. This inverse relationship is mainly determined by the definition of Gosling and King (1975) for PI calculations, i.e. at a lower FHR a more gradual end-diastolic slow-down of the blood flow velocity takes place.

The inverse relationship between peak systolic velocity in the internal carotid artery and FHR could be explained by the shorter ventricular filling phase at raised FHR and vice versa as dictated by the Frank-Starling Law. In the other intracerebral arteries this effect could not be established.

It can be concluded that Doppler colour flow imaging allows absolute measurements of fetal cerebral flow velocities. Fetal behavioural state dependent changes occur at cerebral arterial level which are in agreement with changes observed at cardiac and venous inflow level.

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Chapter 6

PHARMACOLOGIC EFFECTS ON THE FETAL CEREBRAL CIRCULATION

6.1 General remarks

Pharmacokinetic differences in metabolism or placental transfer of drugs might have implications with respect to the extent of fetal drug exposure and subsequently possible cerebral blood flow changes. Studies in this area have been carried out in both human fetuses and under animal experimental conditions.

6.1.1 STIMULANTS

It has been demonstrated that maternal cocaine injection causes fetal hypoxemia, hypertension and increased cerebral blood flow. Especially in cerebellum and brain stem, cerebral vascular resistance was decreased in contrast to cerebral hemispheres and caudate. Possible mechanisms for cerebral vasodilatation include hypoxemia, impaired autoregulatory response to increased blood pressure, and/or direct or indirect vascular effects of cocaine or its metabolites (Gleason et al, 1993). Repeated nicotine injections to sheep, however, induce vasoconstriction of the umbilical and fetal cerebral arteries in late gestation and are associated with poor perinatal outcome (Arbeille et al, 1992).

In the human, smoking of one cigarette in an otherwise uneventful pregnancy does not produce an acute haemodynamic effect in the fetus, whereas maternal mean arterial blood pressure and heart rate increased significantly. (Jouppila et al, 1983; Pijpers et al, 1984; Agudelo et al, 1992). The maternal cardiovascular changes described seem to be determined by the deleterious effect of nicotine through the release of catecholamines by the adrenal medulla and chromaffin cells (Quigley et al, 1979; Resnik et al, 1979).

Multiple-dose ethanol infusion to ewes resulted in a fall in fetal cerebral oxidative matabolism, with no dose response or tolerance evident. This appears to be a direct depressant effect that was maximal at rather low fetal ethanol levels which, if prolonged, might well affect cerebral growth and development. Recovery of cerebral metabolic function appeared complete within 24 hours. However, relative

fetal hypoxemia was evident at this time, the mechanism of which remains to be determined (Richardson et al, 1987).

6.1.2 ANAESTHETIC DRUGS

Maternal halothane administration in case of a briefly asfyxiated fetal lamb does not abolish the protective reflexes of increased coronary and cerebral blood flow and decreased cerebral oxidative metabolism (Cheek et al, 1987).

Epidural block using bupivacaine with adrenaline in healthy parturients undergoing elective Caesarean section does not have an adverse effect on vascular resistance in the uteroplacental or fetal circulations (including cerebral) or on fetal myocardial function when bupivacaine-adrenaline is administered fractionally and maternal hypotension is prevented by rapid crystalloid volume loading (Alahuhta et al, 1991).

6.1.3 TOCOLYTIC DRUGS

Terbutaline has been used in obstetrics to treat premature labour. In sheep it does not decrease uterine blood flow or alter fetal pO2 or EEG, but causes transient maternal tachycardia and hypotension. It is further suggested that it reduces maternal and fetal pH due to lactic acidemia. Fetal cerebral blood flow remained unchanged (Ayromlooi et al, 1981).

In human fetuses fenoterol treatment of premature labour resulted in an unchanged pulsatility index of the internal carotid artery. In the umbilical artery, however, a reduced pulsatility index was found, suggesting a decrease in vascular resistance, hence improved utero-placental perfusion (Cheung et al, 1990).

Beta-mimetics like ritodrine, terbutaline and fenoterol are widely used tocolytic drugs, however, their side-effects and lack of proven effect in randomized studies have brought them increasing discredit (King et al, 1988; The Canadian Preterm Labor Investigators Group, 1992).

Indomethacin, a potent inhibitor of prostaglandin synthesis, has been used as a tocolytic agent since the mid-1970s. It crosses the placenta freely (Moise et al, 1990) and can inhibit the synthesis of prostaglandines in fetal tissues. The benefits of preventing premature birth must be weighed against the risks incurred, by constricting the fetal ductus arteriosus and reducing amniotic fluid. Constriction

and subsequent closure of the fetal ductus arteriosus may lead to tricuspid regurgitation, followed by hydrops and ultimately congestive heart failure (Truter et al, 1986). In human fetuses this was studied by Doppler echocardiography (Moise et al, 1988; Mari et al, 1989; Eronen, 1993).

The fetal ductus becomes more reactive to indomethacin with advancing gestational age. Moise observed an increase in fetal ductal constriction when indomethacin was administered after 32 weeks of gestation, similar for singleton and multiple gestations, and advised to restrict indomethacin therapy to gestational ages below 32 weeks (Moise, 1993). In multiple gestations each fetus should be evaluated by echocardiography because the ductal response may vary between individual fetuses. Although indomethacin-induced narrowing of the ductus arteriosus is considered reversible, there is one report documenting how prolonged therapy of more than two weeks' duration led to irreversible ductal constriction (Mohen et al, 1992). Evidence of severe constriction of the ductus arteriosus or tricuspid regurgitation warrants discontinuation of the indomethacin; lesser degrees of ductal constriction can be treated by decreasing the dose of the medication (Moise, 1991). Constriction of the fetal ductus arteriosus is associated with secondary changes, especially in the right ventricle, because of increased afterload. However, no change in peak systolic velocity in the pulmonary trunk has been detected in spite of partial ductal constriction (Rasanen and Jouppila, 1995). Prenatal exposure however, does not decrease the need for patent ductus arteriosus treatment in premature infants (Eronen, 1993).

Also oligohydramnios or reduction in amniotic fluid volume has been reported as a result of maternal indomethacin medication (Hendricks et al, 1990; Nordstroem and Westgren, 1992). In fetal sheep maternal indomethacin administration results in marked changes in fetal blood gas status, renal function and lung liquid production. They do not however explain the reason why clinical use of indomethacin is associated with a reversible oligohydramnios (Stevenson and Lumbers, 1992). Also human fetal renovascular parameters did not change even when the ductus arteriosus is constricted (Mari et al, 1990). During indomethacin tocolysis Kirshon reported a massive decline in hourly fetal urinary output. (Kirshon et al, 1988). During therapy ultrasound assessment of amniotic fluid volume should be done once or twice weekly (Moise, 1991). If oligohydramnios develops, the indomethacin should be discontinued. In cases of severe

polyhydramnios the effect of indomethacin in reducing amniotic fluid may also be used therapeutically.

Nonsteroidal antiinflammatory compounds have been shown to cause severe constriction and, in some cases, closure of the ductus arteriosus, resulting in an increase in pulmonary blood pressure and a significant pressure gradient between the pulmonary artery and the aorta of the fetus. Under conditions of hypoxia these drugs can potentiate vasoconstriction (Heymann and Rudolph, 1976). Although single doses of these drugs do not appear to affect fetal pulmonary vessels, prolonged arterial hypertension resulting from chronic administration may stimulate an increased development of medial smooth muscle in fetal precapillary vessels, resulting in persistent pulmonary hypertension in the newborn (Levin et al, 1978 and 1979; Rudolph, 1981). Inhibitors of prostaglandin synthesis have also been shown to produce a marked increase in fetal respiration, resulting in an increased oxygen requirement (Kitterman et al, 1979). Recently, in a randomized study it appeared that administration of indomethacin to pregnant women threatened with premature labour is associated with an increased risk of bronchopulmonary dysplasia in their infants if delivery occurs early (Eronen et al, 1994).

Effects of indomethacin on cerebral blood flow are different in fetuses from neonates. A study by Van Bel et al in preterm infants showed that indomethacin intravenously for closure of the patent ductus arteriosus induced a drop in cerebral blood flow that lasted for two hours; by three hours, however, the cerebral blood flow was back to normal (Van Bel, 1989). Also in unanesthetized piglets indomethacin administration results in decreased cerebral blood flow and cerebral metabolic rate for oxygen, which return to baseline levels by four hours after treatment, a second dose of indomethacin also results in a decrease in cerebral blood flow similar to that evoked by the first dose (Pourcyrous et al, 1994). In premature human neonates indomethacin has been used in the last decade for the pharmacologic closure of the patent ductus arteriosus and more recently it has been suggested for use in preventing or decreasing the severity of periventricular-intraventricular hemorrhage (Ment et al, 1985; Bada et al, 1989).

Human fetal cerebral blood flow during indomethacin therapy is only changed in the presence of ductal constriction and tricuspid insufficiency. Under these circumstances, the pulsatility index values in the middle cerebral artery were found to be significantly reduced. This suggests hemodynamic changes consistent with

an increase of cerebral blood flow (Mari et al, 1989). This change in flow would be a result of a redistribution of venous return from the right to the left ventricle, as has been demonstrated experimentally in fetal dogs after ligation of the ductus arteriosus (Haller et al, 1967).

A recent retrospective study by Norton et al showed a significantly increased risk of necrotizing enterocolitis, patent ductus arteriosus, intracranial hemorrhage, and renal dysfunction in very small preterm infants born between 24 - 30 weeks of gestation following failed indomethacin tocolysis in comparison with a control group whose mothers had not received indomethacin for the treatment of premature labour (Norton et al, 1993). By Merrill et al (1994) also persistent pulmonary hypertension and aggravation of IRDS by maternal administration of indomethacin had been described.

6.1.4 MISCELLANEOUS

Nifedipine, a dihydropyridine calcium channel-blocking agent, has been used as an antihypertensive and tocolytic agent in obstetrics. Intravenous administration of nifedipine to chronically instrumented pregnant ewes increased (total and regional) fetal cerebral blood flow to brain stem, watershed and subcortical regions without changing fetal oxygenation or cardiac output. Maternal arterial pressure decreased and heart rate increased without variation of arterial blood gases (Harake et al, 1987). In women with pregnancy-induced hypertension the same maternal effects have been demonstrated after oral nifedipine administration. In the fetuses, however, no changes were observed in heart rate pattern or in the umbilical (Moretti et al, 1990) or middle cerebral artery flow velocity waveforms (Pirhonen et al, 1990).

Nimodipine, also a dihydropyridine calcium antagonist, appears to be the most selective cerebral vasodilator (Freedman and Water, 1987), it has a less precipitate antihypertensive effect than the other calcium antagonists. After oral administration of nimodipine a maternal and fetal cerebral vasodilator activity has been observed (Belfort et al, 1994). In vitro the same effect occurred, whereas a more pronounced relaxation was established in the umbilical vein than in the umbilical artery (Belfort et al, 1995).

In the management of pregnancy-induced hypertension magnesium sulfate has been a standard prophylactic anti-seizure agent in various countries for many years. A loading dose of 6 gm of intravenous magnesium sulfate administered to women with pregnancy-induced hypertension, vasodilates the vascular bed distal to the maternal middle cerebral artery, and increases blood velocity in this region. No acute effects were noted in fetal or placental vessels (Belfort et al, 1993). These findings are supported by animal experiments, in which a infusion of magnesium sulfate to ewes led to transient fetal hypotension and tachycardia, but without changes in fetal blood gases, glucose metabolism of brain blood flow (Ayromlooi et al, 1982).

In very low birth weight infants intravenous administration of 0.5 mg/kg diazepam did not change flow velocities in the internal carotid artery and basilar artery, while there was a marked increase of flow velocity in the anterior cerebral artery. Values for carbon dioxide tension, mean arterial blood pressure and heart rate remained stable. Diazepam in this dosage did not cause dangerous haemodynamic changes in the premature brain (Jorch et al, 1990).

CONCLUSION

It can be concluded that various drugs can influence fetal cerebral blood flow. Before these drugs are accepted for wide use in obstetrics, more should be known about the effects on the uteroplacental and fetoplacental circulations and on the influence of neonatal outcome. Since at the time of our own study indomethacin was a widely used and promoted tocolytic agent, we were particularly interested in the effect of a single dose of indomethacin on fetal hemodynamics (see chapter 6.2).

6.2 Fetal Doppler flow after maternal administration of a single dose of indomethacin for premature labour

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INTRODUCTION

Indomethacin has been used in the management of preterm labour. Multiple doses of indomethacin have the ability to cause fetal ductal constriction (Kirshon et al, 1990), tricuspid regurgitation and a significantly lower pulsatility index in the middle cerebral artery (Mari et al, 1989). In our institution a single dose of indomethacin is administered in case premature labour persists, despite fenoterolbromide therapy. Limited information is available on the effect of a single dose of indomethacin on the fetal circulation. Moreover, no data have been reported on maternal indomethacin administration and fetal venous inflow. The purpose of this study was to examine the effect of a single dose of indomethacin on flow velocities at right ventricular outflow, venous inflow and cerebral arterial level.

MATERIALS AND METHODS

The study was performed in the Department of Obstetrics and Gynaecology of the Academic Hospital Rotterdam-Dijkzigt which serves as a tertiary referral centre for pregnancy pathology.

During a period of five months, a total of 18 women with premature labour gave informed consent to participate in the study. The protocol of the study was approved by the Hospital Ethics Committee. Each woman was included in the study only once. Gestational age was calculated from a reliable menstrual history

and confirmed by ultrasonic measurement of the fetal biparietal diameter at 14-20 weeks. Fetal growth was normal as documented by ultrasonic measurements of fetal upper-abdominal circumference (Campbell and Wilkin, 1975). Birth weights were situated between the 10th and 90th percentile, according to Kloosterman's tables corrected for maternal parity and fetal sex (Kloosterman, 1970). There were no structural anomalies.

Only eight patients (44.4%) could be analysed because of delivery during the study or treatment with other drugs i.e. antibiotics because of early signs of intrauterine infection in the other ten patients.

Gestational age varied between 26 and 31 weeks (mean 28.1; SD 1.7). All eight patients were treated with fenoterolbromide (Partusisten^{R}) intravenously with a dose ranging between one and six microgram (mean 3.4; SD 1.8). Premature rupture of membranes occurred in five patients. Betamethason was given intramuscularly (dose 12 mg twice in 48 hrs) two days before the start or after completion of the study. If contractions continued despite fenoterolbromide therapy, a dose of 100 mg indomethacin (suppositary) was administered. Doppler measurements started 60-240 minutes (mean 102.6; SD 21.6) after administration of indomethacin. The Doppler measurements were completed within 75 minutes. The half-life of indomethacin is 1.5-16 hours in vivo; to rule out the effect of indomethacin a second Doppler measurement was carried out 20-48 hours (mean 27.2; SD 9.0) after administration of the drug. Measurement before indomethacin administration was not possible since most patients received the drug shortly after hospital admission.

Flow velocity waveform recording was carried out using a Hitachi EUB 450 combined sector scanner and pulsed wave Doppler system with a 3.5 MHz transabdominal probe. The cut-off level of the high pass filter was set at 100 Hz. The probe operate at a power output of less than 100 mW/cm^2 spatial peak/temporal average in both imaging and Doppler modes by manufacturer's specifications.

In each woman an attempt was made to document Doppler flow patterns in the ductus arteriosus (DA), pulmonary artery (PA), umbilical artery (UA), inferior vena cava (IVC), ductus venosus (DV) and middle cerebral artery (MCA).

Doppler examinations were performed by two examiners (DA, PA and UA by CB, venous flow and MCA by MJN).

Two dimensional imaging was used to ensure the correct position of the Doppler interrogation beam both before and after each Doppler tracing was obtained. Maximum flow velocity waveforms from pulmonary trunk and the ductus arteriosus were recorded from the conventional short axis view (Reed et al, 1988). Pulmonary artery waveforms were obtained immediately distal to the pulmonary valve. Ductal waveforms were collected close to the junction of the ductus arteriosus and descending aorta (Kirshon et al, 1990). Flow velocity waveforms from the inferior vena cava were obtained in a sagittal scanning plane directly under the fetal spine, to the right of and parallel to the descending aorta. The sample volume was placed immediately proximal to the right atrium allowing detailed information on venous return (Huisman et al, 1991). For the ductus venosus the sample volume was near the point of inflow into the venous vestibulum (Huisman et al, 1992). Umbilical artery waveforms were obtained from a free floating loop of the umbilical cord. The middle cerebral artery can be required as a major branch of the circle of Willis running anterolaterally towards the lateral edge of the orbit while making a transverse scan through the lower part of the fetal cerebrum.

Doppler tracings were only accepted if the angle between the Doppler beam and the assumed direction of flow was 30 degrees of less. Sample size was 2-3 mm.

All Doppler studies were performed with the woman in the semirecumbent position and during periods of fetal apnoea while applying minimal transducer pressure on the maternal abdomen in the absence of uterine contractions.

All flow velocity waveforms were recorded on hard copies. A microcomputer (Olivetti M24) linked to a graphics tablet was used for analysis of the Doppler recordings. An average of at least three consecutive flow velocity waveforms of optimal quality was used to establish each value. In the ductus arteriosus and pulmonary artery peak systolic velocity (PSV, cm/s), time-averaged velocity (AV, cm/s), end diastolic velocity (EDV, cm/s) and time velocity integral (TVI) were determined. Peak systolic velocities were measured from the zero line to the highest point of the Doppler velocity tracing. Time-averaged velocity was calculated by dividing the sum of velocities over one period of time by the number of data points. End diastolic velocities were obtained by measuring from the zero line to the highest point at the end of the diastole. Time velocity integral was determined by multiplying time-averaged velocity with period time. For the ductus

Table 1 *Data from Doppler flow velocity recordings in the ductus arteriosus, pulmonary artery, umbilical artery and middle cerebral artery 102.6 (± 21.6) minutes after indomethacin administration (measurement 1) and 27.2 (± 9.0) hours after indomethacin administration (measurement 2); mean values (± SD).*

	Measurement 1	Measurement 2
Ductus arteriosus		
peak systolic velocity (cm/s)	104.1 ± 18.5	97.8 ± 20.5
time-averaged velocity (cm/s)	38.6 ± 9.8	34.3 ± 11.8
end diastolic velocity (cm/s)	11.2 ± 5.0	10.2 ± 6.1
time velocity integral	15.0 ± 3.6	12.7 ± 4.7
Pulmonary artery		
peak systolic velocity (cm/s)	72.8 ± 15.3	66.9 ± 8.5
time-averaged velocity (cm/s)*	23.7 ± 2.9	19.7 ± 2.2
time velocity integral*	9.1 ± 1.2	7.6 ± 0.8
Umbilical artery		
pulsatility index	0.96 ± 0.21	0.96 ± 0.18
Middle cerebral artery		
pulsatility index	1.84 ± 0.27	1.73 ± 0.39

* p=0.02; SD=standard deviation.

venosus and inferior vena cava peak systolic velocity (PSV, cm/s), peak diastolic velocity (PDV, cm/s), and the ratio for peak velocities (peak S/D) were calculated. For the inferior vena cava the percentage reverse flow was calculated from the time velocity integral during the retrograde flow component as percentage of the time velocity integral during the total forward flow component (Reed et al, 1990). In the umbilical artery and middle cerebral artery the pulsatility index (PI) was calculated according to Gosling and King (1975).

Statistical analysis of the data consisted of the paired t-test for the univariate

comparison of the Doppler data from the measurement directly after administration of indomethacin with data from the second measurement.
The level of statistical significance was set at P=0.05 (two-sided).

RESULTS

Delivery took place 2-84 days (mean 31.0; SD 33.4) after the last Doppler measurement. Only one patient delivered by caesarean section because of fetal distress as a result of intrauterine infection.
Perinatal mortality was 12.5%, one neonate of 26 weeks of gestation died 2 days after birth because of respiratory insufficiency.
Table 1 presents the mean (± SD) values for peak systolic velocity (cm/s), time-averaged velocity (cm/s), and time velocity integral in the ductus arteriosus and pulmonary artery. The end diastolic velocity (cm/s) in the ductus arteriosus and the pulsatility index in the umbilical artery and middle cerebral artery are also presented. After maternal administration of one dose of 100 mg
indomethacin a statistically significantly higher time-averaged velocity and time velocity integral (p=0.02) in the pulmonary artery were obtained. No significant differences were observed in the Doppler flow velocity parameters from the ductus arteriosus, umbilical artery or middle cerebral artery after indomethacin administration.
Table 2 displays the results of the Doppler flow velocity measurements from the venous site of the fetal heart, i.e. the inferior vena cava and ductus venosus.
No statistically significant differences in Doppler flow velocity parameters were detected in the ductus venosus or the inferior vena cava following indomethacin administration.

DISCUSSION

Indomethacin may cause constriction of the fetal ductus arteriosus during pregnancy in animals (Levin et al, 1979; Rudolph, 1981) and in human fetuses as shown by Mari et al (1989). In the latter study repeated indomethacin administration (25 mg orally every 6 hours) resulted in ductal constriction within 48

Table 2 *Data from Doppler flow velocity recordings in the ductus venosus and inferior vena cava 102.6 (± 21.6) minutes after indomethacin administration (measurement1) and 27.2 (± 9.0) hours after indomethacin administration (measurement 2); mean values (± SD).*

	Measurement 1	Measurement 2
Ductus venosus		
peak systolic velocity (cm/s)	50.1 ± 15.7	58.1 ± 6.2
time-averaged velocity (cm/s)	35.8 ± 16.0	43.0 ± 5.4
peak diastolic velocity (cm/s)	33.9 ± 20.1	45.6 ± 8.7
S/D ratio	1.38 ± 0.38	1.31 ± 0.19
Inferior vena cava		
peak systolic velocity (cm/s)	38.0 ± 12.3	41.6 ± 20.9
time-averaged velocity (cm/s)	20.5 ± 7.7	23.3 ± 13.4
peak diastolic velocity (cm/s)	21.2 ± 8.7	22.6 ± 12.7
S/D ratio	1.92 ± 0.36	1.94 ± 0.35
reversed flow percentage	11.2 ± 4.5	10.6 ± 4.8

SD=standard deviation; S/D=systolic/diastolic.

hours after the initiation of the treatment. Only part of these fetuses demonstrated tricuspid insufficiency. Also, a decrease of the pulsatility index in the middle cerebral artery was diagnosed when both ductal constriction and tricuspid insufficiency were present.

In our study in which a single dose of indomethacin was administered, there was a trend to higher velocities in the fetal ductus arteriosus, although this increase was not significant.

Prenatal administration of betamethason may enhance the constrictive effect of indomethacin on the fetal ductus arteriosus (Wasserstrum et al, 1989), whereas postnatally it can overcome the vasoconstrictive effects of postnatal administration of indomethacin (van den Anker et al, 1994). However, in the present study betamethason was given at least two days before the start or after completion of the Doppler measurements.

Standardisation of the timing of the Doppler measurements following maternal administration of indomethacin was not possible for clinical management reasons. The majority of measurements took place approximately two hours following indomethacin administration, at which time an effect on the fetal ductus arteriosus still can be expected (Moise et al, 1990b). We have not measured the maternal indomethacin plasma concentration; this would have been of limited value because of variation in absorption, metabolism and reaction to the drug by the individual fetus (Atad et al, 1987; Eronen et al, 1994).

The absence of any significant changes in the pulsatility index from the middle cerebral artery is not surprising in the light of our ductal flow velocity findings and earlier data reported by Mari et al (1989). Also, the pulsatility index in the umbilical artery was not significantly different, which is in agreement with Moise et al (1990a).

Instead of tricuspid valve level, flow velocities were studied at venous inflow of the heart. In the ductus venosus and inferior vena cava no significant changes were detected. This would make tricuspid insufficiency in the present study unlikely. In the pulmonary artery, however, a significant rise in time-averaged velocity and time velocity integral was diagnosed after maternal administration of a single dose of indomethacin. In animals (Rudolph, 1981) prolonged pulmonary arterial hypertension resulting from chronic indomethacin administration may stimulate increased development of medial smooth muscle in fetal precapillary vessels, resulting in persistent pulmonary hypertension in the newborn. In the present study a single dose of indomethacin did affect pulmonary flow velocity, which could be the result of slight ductus arteriosus constriction, according to experiments in the ewe (Levin et al, 1979; Rudolph, 1981). Administration of repeated doses of indomethacin could lead to severe constriction of the ductus arteriosus, fetal pulmonary arterial hypertension, and even right ventricular damage. Amongst the many adverse events described in the literature are besides premature closure of the ductus, persistent pulmonary hypertension, aggravation of IRDS, necrotizing enterocolitis, ileal perforation and renal insufficiency (Norton et al, 1993; Eronen et al, 1994; Merrill et al, 1994). More studies are necessary to establish an effect on human fetal lungs and fetal pulmonary artery blood flow velocities in relation to the ductus arteriosus following indomethacin administration.

If it is possible to obtain reliable blood flow velocity waveforms of the fetal superior

mesenteric artery, there may be the same constrictive effect of indomethacin already demonstrated in preterm infants (van Bel et al, 1990) what may cause the higher incidence of necrotizing enterocolitis after indomethacin.

Indomethacin is a potent tocolytic agent, but because of the possible serious complications in the neonate it is still a controversary drug.

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Chapter 7

GENERAL CONCLUSIONS

In this thesis the human fetal cerebral circulation was studied with combined two-dimensional real-time ultrasound and pulsed or colour Doppler. To interprete data of cerebral Doppler flow velocity waveforms, the influence of changes in peripheral vascular resistance, fetal behaviour states and drugs was examined.

In the fetal lamb a change in placental vascular resistance was studied by embolization of the uteroplacental vascular bed. This resulted in an increase in pulsatility index in the descending aorta of the fetal lamb, suggesting an increased peripheral vascular resistance. Clinically, a chronicly impaired placental perfusion is usually interpreted as uteroplacental insufficiency in case of intrauterine growth retardation.

In animal studies, in the presence of intrauterine growth retardation, compensatory mechanisms in the fetus may result in a redistribution of blood flow favouring brain, heart and adrenal glands. In this thesis, in the small for gestational age human fetus, the pulsatility indices of the internal carotid artery, middle, anterior and posterior cerebral artery were significantly decreased, reflecting a reduced cerebral vascular resistance. With the introduction of colour coded Doppler it became possible to measure absolute cerebral blood flow velocity parameters. In the small for gestational age fetus increased end-diastolic velocities were demonstrated in the internal carotid artery and middle, anterior and posterior cerebral artery. The most discriminative cerebral parameters between small for gestational age and controls were the end-diastolic velocities of the middle and anterior cerebral artery. The pulsatility index of the umbilical artery however, was more discriminating than the cerebral velocities. Fetal outcome in case of intrauterine growth retardation was related to the pulsatility index of the umbilical artery. The pulsatility index of the internal carotid artery alone did not predict fetal compromise.

It is important to take into account the gestational age when measuring fetal cerebral blood flow. Flow velocity waveforms from the internal carotid artery showed a reduced pulsatility index with advancing gestational age, the same

applies for the umbilical artery.

Fetal blood flow velocities at cerebral arterial level (internal carotid artery, anterior and posterior cerebral artery) are dependent of fetal behaviour states, except tor the middle cerebral artery. Studies during the active sleep state suggest that preferential blood flow to the left heart is associated with increased blood flow to the cerebrum. The neocerebrum, supplied by the middle cerebrum artery, does not seem to take part in the regulation of fetal behaviour.

Various drugs influence fetal cerebral blood flow. No difference in blood flow in the middle cerebral artery was demonstrated after maternal administration of a single dose of indomethacin, whereas according to the literature multiple doses may result in a constriction of the fetal ductus arteriosus, tricuspid regurgitation and consequently increased cerebral blood flow. After a single dose no ductal constriction was detected, whereas the averaged velocity of the pulmonary artery was increased. Other studies have demonstrated the negative effects of multiple doses of indomethacin resulting in pulmonary hypertension or bronchopulmonary dysplasia.

Studies of human fetal cerebral blood flow result in more insight in physiological and pathophysiological conditions e.g. redistribution of blood flow in favour of the cerebrum in intrauterine growth retardation with the objective to prevent fetal cerebral hypoxaemia. In predicting fetal compromise the value of cerebral artery Doppler velocimetry alone is limited, ratios with umbilical artery velocimetry have a better predictive value with respect to fetal outcome. In the human fetus, the middle cerebral artery is the most accessible cerebral artery for Doppler flow studies. Its end-diastolic velocity is discriminating between normal and small for gestational age fetus, and this artery is behavioural state independent. The middle cerebral artery is, therefore, the vessel of preference in future cerebral blood flow studies.

Summary

Chapter 1

In this introductory chapter the role of fetal cerebral Doppler examinations in the evaluation of fetal condition and in the prediction of fetal distress and neonatal outcome is pointed out, with emphasis on intrauterine growth retardation, whereby a hemodynamic redistribution occurs with increased blood flow to the fetal brain.
The objectives of the present thesis are focused on (i) Doppler velocimetry in the fetal lamb descending aorta and alterations in arterial down stream impedance at fetoplacental level, (ii) Doppler examinations of the human fetal cerebral circulation in physiological and pathological conditions, and (iii) influences of internal and external variables, like fetal behavioural states and maternal drug administration, on the human fetal cerebral circulation.

Chapter 2

A literature survey is presented on human and animal experimental data concerning changes in peripheral vascular resistance and its impact on the fetal circulation. The placental microvasculature is considered a low resistance pool; alterations in perfusion pressure and resistance influence blood flow to the fetal tissues. In normally developing human fetuses a reduction in fetal, umbilical and placental vascular resistance is suggested with advancing gestational age. In acute animal experiments embolization of the uteroplacental vascular bed results in lower fetal arterial pO_2 and umbilical perfusion, while during superimposed acute hypoxemia a preferential perfusion of vital organs is more pronounced in embolized animals. In sub-chapter 2.2 a animal experiment is presented in which vascular resistance of the peripheral circulation is increased by embolization of the placenta. A rise in peripheral vascular resistance is associated with a reduction in peak and end-diastolic flow velocity and an increase in pulsatility index in the fetal descending aorta. Clinically, these findings are usually interpreted to represent "uteroplacental insufficiency" in case of intrauterine growth retardation.

Chapter 3

To interprete data of pathologic conditions, knowledge of normal fetal cerebral circulation is needed. In this chapter the regulation of cerebral blood flow during fetal life is discussed. Most studies originate from animal experimental work. The fetal lamb is capable of autoregulating its cerebral blood flow. Both hypercapnia and hypoxic hypoxia may interfere with autoregulation. In the human fetus cerebral Doppler flow velocity waveforms can be obtained in the circle of Willis. In sub-chapter 3.2.1 the methodology of intracerebral Doppler studies is discussed.
Most of the studies relate angle-dependent measurements to calculations of the pulsatility index, resistance index or cerebral index. Using new imaging techniques, like colour-coded Doppler, absolute measurements of flow velocities are feasible in cerebral arteries. Initially, fetal cerebral arteries are characterized by absent end-diastolic velocities. With advancing gestational age a reduction in downstream impedance of flow to the brain is suggested; also perinatally changes in resistance indices occur.
Fetal cerebral flow is subject to both internal and external variables like breathing, fetal heart rate and fetal behavioural states. Also, the influence of glucose, contractions, vibro-acoustic stimulation, maternal oxygen administration and fetal head compression have been examined.

Chapter 4

This chapter begins with animal experimental work on chronic fetal hypoxaemia and its influence on the cerebral circulation. In human fetuses hypoxaemia results in a reduction in cerebral pulsatility indices and increase of end-diastolic velocities, suggesting a "brainsparing effect". In case of intrauterine growth retardation antenatally raised ratios between cerebral and umbilical blood flow are associated with poor obstetric outcome. However, in neurological outcome no difference can be established. The brainsparing effect seems to be a mechanism to prevent fetal brain hypoxia rather than a sign of impending brain damage.
In sub-chapter 4.2 the normal distribution of pulsatility indices of the umbilical and internal carotid artery during the third trimester is established. With advancing gestational age the pulsatility index of the umbilical artery shows a linear

reduction, whereas the internal carotid artery pulsatility index appears to be a quadratic reduction.

Fetal outcome in case of intrauterine growth retardation, was significantly related to the pulsatility index of the umbilical artery, but not to the pulsatility index of the internal carotid artery.

In the second paper in sub-chapter 4.3 fetal intracranial arterial flow velocity waveforms have been studied using colour-coded Doppler in small for gestational age fetus and their controls. When comparing these two groups the end-diastolic velocities of the middle and anterior cerebral artery are the most discriminative parameters. The pulsatility index of the umbilical artery however, is the most discriminative factor in case of intrauterine growth retardation.

Chapter 5

In this chapter a literature review of the development of fetal behaviour and its influence on cardiovascular dynamics is presented. In the following sub-chapter the relationship between blood flow velocity waveforms at cerebral arterial level (internal carotid artery, anterior, middle and posterior cerebral artey) and fetal behavioural states was studied in normally developing term fetuses using Doppler colour flow imaging. Behavioural state dependent changes in absolute flow velocities occurred in all vessels, except for the middle cerebral artery. These changes suggest preferential blood flow to the left heart resulting in increased flow to the cerebrum during fetal behavioural state 2F (active sleep) when compared with fetal behavioural state 1F (quiet sleep). The middle cerebral artery supplies the neocerebrum. This not yet fully developed part of the cerebrum does not seem to take part in the regulation of fetal behaviour. In the internal carotid artery an inverse relationship between peak systolic velocity and fetal heart rate could be established, which can be explained by the Frank-Starling Law.

Chapter 6

In this chapter the effects of stimulants and anaesthetic drugs on the fetal circulation are discussed. Widely used tocolytic drugs like fenoterol have no effect on the fetal cerebral circulation. Multiple doses of indomethacin, a potent inhibitor

of prostaglandin synthesis, may result in a constriction of the fetal ductus arteriosus and reduction of amniotic fluid. Severe constriction of the ductus arteriosus may lead to tricuspid regurgitation and ultimately to congestive heart failure, whereas in animal experiments it has been demonstrated that a severe constriction may lead to an increase in pulmonary blood pressure. Administration of indomethacin to pregnant women is associated with an increased risk of bronchopulmonary dysplasia, necrotizing enterocolitis, patent ductus arteriosus, intracranial hemorrhage and renal dysfunction in their infants. In sub-chapter 6.2 a study is presented in which a single dose of indomethacin is administered to patients with premature labour. In the pulmonary artery a significantly higher time-averaged velocity was obtained, while in the ductus arteriosus, middle cerebral artery, and other vessels no significant differences in Doppler flow velocity parameters were detected.

Samenvatting

Hoofdstuk 1

In dit inleidend hoofdstuk wordt de rol beschreven van foetal cerebrale Doppler onderzoeken in de evaluatie van de foetale conditie en in de voorspelling van foetale nood en neonatale uitkomst, met nadruk op intra-uteriene groeivertraging, waarbij een hemodynamische redistributie optreedt met een toename in bloedstroom naar de foetale hersenen.
De doelstellingen van dit proefschrift concentreren zich op (i) Doppler bloedstroomsnelheidsmetingen en veranderingen in arteriele stroomafwaartse impedantie op foeto-placentair niveau, (ii) Doppler onderzoeken van de humane foetale cerebrale circulatie in fysiologische en pathologische omstandigheden, en (iii) invloeden van interne en externe variabelen als foetale gedragstoestanden en toediening van medicatie aan de zwangere op de humane foetale cerebrale circulatie.

Hoofdstuk 2

Hier wordt een literatuuroverzicht gegeven over humaan en dierexperimenteel onderzoek betreffende veranderingen in perifere vaatweerstand in de zwangerschap en de invloed hiervan op de foetale circulatie. De microvasculatuur van de placenta wordt beschouwd als een eenheid met lage weerstand: veranderingen in perfusiedruk en weerstand beinvloeden de bloeddoorstroming van de foetale weefsels. Bij toenemende zwangerschapsduur wordt in de zich normaal ontwikkelende foetus een afname in foetale, umbilicale en placentaire vaatweerstand gesuggereerd. Embolisatie van het uteroplacentaire vaatbed resulteert in acuut dierexperimenteel onderzoek in een lagere foetale arteriele zuurstofdruk en doorbloeding van de navelstreng, terwijl tijdens gesuperponeerde acute hypoxemie bij reeds geemboliseerde dieren juist een voorkeursperfusie van vitale organen meer opvallend is.
In hoofdstuk 2.2 wordt een dierexperiment beschreven waarin de vaatweerstand van de perifere circulatie toegenomen is door embolisatie van de placenta. Een toename van de perifere vaatweerstand blijkt geassocieerd te zijn met een afname

van piek en eind-diastolische bloedstroomsnelheid en een toename in pulsatiliteitsindex in de foetale aorta descendens. In het geval van groeivertraging worden deze bevindingen klinisch gewoonlijk geinterpreteerd als weerspiegeling van "uteroplacentaire insufficientie".

Hoofdstuk 3

Om gegevens van pathologische omstandigheden te kunnen interpreteren is kennis van de normale foetale cerebrale circulatie nodig. In dit hoofdstuk wordt de regulering van cerebrale bloeddoorstroming tijdens het foetale leven besproken. De meeste studies zijn afkomstig uit dierexperimenteel onderzoek. Het foetale lam kan zelf de cerebrale bloeddoorstroming regelen, waarbij zowel hypercapnie als hypoxische hypoxie interfereren met deze zelfregulering. In de humane foetus kunnen in de cirkel van Willis cerebrale Doppler bloedstroomsnelheidsprofielen worden verkregen. In hoofdstuk 3.2.1 wordt de methodologie van intracerebrale Doppler studies besproken.
De meeste studies relateren hoekafhankelijke metingen aan berekeningen van pulsatiliteitsindex, weerstandsindex of cerebrale index. Met nieuwe beeldvormende technieken als bijvoorbeeld kleuren Doppler zijn absolute stroomsnelheidsmetingen in de cerebrale arterien haalbaar. Aanvankelijk zijn er in de zwangerschap afwezige eind-diastolische snelheden in de cerebrale arterien. Bij toenemende zwangerschapsduur wordt er een reductie in stroomafwaartse impedantie voor de bloedstroom naar de hersenen gesuggereerd; ook perinataal treden er veranderingen in weerstandsindices op.
Foetale cerebrale doorstroming is onderhevig aan zowel interne als externe variabelen als ademhaling, foetale hartfrequentie en gedragsstadia. Ook invloeden van glucose, contracties, vibro-acoustische stimulatie, maternale zuurstoftoediening en compressie van foetale caput zijn onderzocht.

Hoofdstuk 4

Dit hoofdstuk begint met dierexperimenteel werk over chronische foetale hypoxaemie en de invloed ervan op de cerebrale circulatie. In de humane foetus

resulteert hypoxaemie in een afname van de cerebrale pulsatiliteitsindices en in een toename van de eind-diastolische snelheden, wijzend op een "hersensparend effect". Bij intrauteriene groeivertragingen zijn antenataal verhoogde ratio's tussen cerebrale en umbilicale bloeddoorstroming geassocieerd met een slechte obstetrische uitkomst. Er kan echter geen verschil worden vastgesteld in neurologische uitkomst. Het hersensparend effect lijkt een mechanisme te zijn om foetale hersenschade te voorkomen in plaats van een teken te zijn van dreigende hersenschade.

In hoofdstuk 4.2 wordt de normale verdeling van pulsatiliteitsindices van de arteria umbilicalis en carotis interna tijdens het derde trimester vastgesteld. Bij toenemende zwangerschapsduur vertoont de pulsatiliteitsindex van de navelstrengarterie een lineaire afname, terwijl die van de arteria carotis interna een kwadratische afname vertoont. In het geval van intrauteriene groeivertraging was de foetale uitkomst, in tegenstelling tot de pulsatiliteits index van de arteria carotis interna, significant gerelateerd aan de pulsatiliteits index van de navelstreng.

In het tweede artikel in hoofdstuk 4.3 zijn de foetale intracraniele arteriele bloedstroomsnelheden in groeivertraagde foetus en hun controles bestudeerd met kleuren Doppler. Tussen deze twee groepen waren de eind-diastolische snelheden van de arteria cerebri media en anterior de meest onderscheidende parameters. De pulsatiliteits index van de navelstreng blijkt echter bij foetale groeivertraging het meest onderscheidend te zijn.

Hoofdstuk 5

In dit hoofdstuk wordt een literatuuroverzicht gegeven over de ontwikkeling van foetaal gedrag en de invloed ervan op de cardiovasculaire dynamica. In het tweede deel wordt de relatie tussen bloedstroomsnelheidscurves op cerebraal arterieel niveau (arteria carotis interna, cerebri anterior, media en posterior) en foetaal gedrag in zich normaal ontwikkelde a terme foetus bestudeerd met behulp van kleuren Doppler. In alle vaten, behalve in de arteria cerebri media, waren er gedragsafhankelijke veranderingen in absolute bloedstroomsnelheden. Deze veranderingen suggereren een voorkeursbloedstroom naar het linkerhart resulterend in een toegenomen bloeddroorstroming van het cerebrum in foetaal

gedragsstadium 2F (actieve slaap) vergeleken met foetaal gedragsstadium 1F (rustige slaap). De arteria cerebri media voorziet het neocerebrum van bloed. Dit nog niet geheel ontwikkelde deel van het cerebrum lijkt niet deel te nemen in de regulering van foetaal gedrag. In de arteria carotis interna wordt een omgekeerde relatie tussen piek systolische snelheid en foetale hartfrequentie aangetoond, welke verklaard kan worden volgens de wet van Frank-Starling.

Hoofdstuk 6

In dit hoofdstuk wordt de invloed van stimulantia en anaesthetica op de foetale circulatie besproken. Vaak gebruikte tocolytica, zoals bijvoorbeeld fenoterol, hebben geen invloed op de foetale cerebrale circulatie. Multipele giften indomethacine, een krachtige prostaglandine synthese remmer, kunnen een constrictie van de foetale ductus arteriosus en afname van vruchtwater veroorzaken. Ernstige vernauwing van de ductus arteriosus kan tot tricuspidalis insufficientie leiden en uiteindelijk tot congestief hartfalen, terwijl in dierexperimenteel onderzoek is beschreven dat een ernstige vernauwing kan leiden tot een stijging van de pulmonale bloeddruk. Toediening van indomethacine aan zwangere vrouwen is geassocieerd met een toegenomen risico op bronchopulmonale dysplasie, necrotiserende enterocolitis, open ductus Botalli, intracraniele bloedingen en renale dysfunctie in hun kinderen.

In hoofdstuk 6.2 wordt een studie beschreven waarin een eenmalige dosis indomethacine wordt toegediend aan patienten met dreigende vroeggeboorte. In de arteria pulmonalis werd een significant hogere gemiddelde snelheid gevonden, terwijl er in de ductus arteriosus, arteria cerebri media, en andere vaten geen significante verschillen in Doppler bloedstroomsnelheidsparameters werden gevonden.

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