DOPPLER STUDIES OF THE FETAL CIRCULATION IN HYPOXAEMIC HYPOXIA AND IN ANAEMIC HYPOXIA

Katia Bilardo

Cover: La Madonna del Parto

Painted probably in 1460 by Piero della Francesca, the Madonna del Parto is one of the masterpieces of the Italian Renassaince. This is undoubtedly the most famous iconography of a pregnant Madonna waiting for the imminent delivery. The construction of the painting, showing a solitary figure flanked with angels and framed by an open and richly embroided curtain (representing heaven) is rather unusual. As unique is the poetry of the dignified expression of the Madonna's face and the gentle gesture of discreetely showing her pregnant abdomen. The Madonna del Parto has also become, throughout the centuries, a subject of cult and pilgrimage for pregnant women, because of its supposed facilitating effect on parturition. The fresco was probably inspired by Piero's mothers' death and painted for the cemeterial chapel of her birthplace, the little village of Monterchi, in Toscany. In a few occasions it was removed from its original place and is at present located in the Pinacoteca of the painters' birthplace, Borgo San Sepolcro, where it has been recently restored in occasion of the fifth centenary of Piero's death. It is still controversial where the restored piece will be permanently put on display: in its original place -the church- or in the municipal Museum. While the ancient controversy between Church and temporal power is being sorted out, it will be put on the front cover of this thesis.

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"Fatti non foste a viver come bruti,
ma per seguire virtute e conoscenza"

Dante Alighieri, La Divina Commedia
Inferno, Canto XXVI, Il viaggio di Ulisse.

A tutti coloro che amo

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Chapter 1

Introduction

1.1 Overview

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 red blood cell isoimmunisation, haemolytic antibodies formed by the mother cross the placenta and cause fetal anaemia. Although placental perfusion and transfer of oxygen to the fetus is normal, since there is impaired oxygen carrying capacity, the fetus is subjected to anaemic hypoxia.

Extensive studies in animals have documented the cardiovascular responses to hypoxaemic and anaemic hypoxia. In the former, there is redistribution of the fetal circulation in favour of the brain, heart and adrenals at the expense of the other organs. In anaemia there is a hyperdynamic circulation with non-specific increase in the perfusion of all organs.

Doppler ultrasonography and ultrasound guided fetal blood sampling (cordocentesis) have now made it possible to investigate haemodynamic alterations in response to varying degrees of hypoxaemic and anaemic hypoxia in the human fetus. Doppler studies of the uterine and umbilical arteries provide information on the perfusion of the utero-placental and feto-placental circulations respectively, while Doppler studies of selected fetal vessels are of importance in detecting the haemodynamic rearrangements that occur in response to fetal hypoxaemia or anaemia.

1.2 Fetal oxygenation

Oxygenation is the process of transporting molecular oxygen from air to the tissues of the body. In the fetus, this involves: (i) oxygen transfer across the placenta, (ii) reversible binding of oxygen to fetal haemoglobin, (iii) oxygen delivery to the tissues by fetal blood flow, and (iv) oxygen consumption for growth and metabolism.

Energy is derived from the combination of oxygen and glucose to form carbon dioxide and water. Removal of carbon dioxide and protection against acidosis is achieved by the reverse of the mechanisms for oxygen delivery and is helped by the rapid diffusion, high solubility and volatility of this gas. In post-natal life, carbon dioxide is excreted in the lungs while bicarbonate and hydrogen ions are removed by the kidney. In the fetus, both these functions are carried out by the placenta. When there is inadequate oxygen supply the Krebs cycle can not operate and pyruvate is converted to lactic acid. This enters the blood leading to systemic acidosis unless it is either metabolized or excreted.

The amount of oxygen bound to haemoglobin is not linearly related to pO_2. Each type of haemoglobin has a characteristic oxygen-dissociation-curve which can be modified by environmental factors, such as pH and the concentration of 2,3-diphosphoglycerate (2,3-DPG). For example, when 2,3-DPG rises, in response to anaemia or hypoxia, it binds to and stabilizes the deoxygenated form of haemoglobin, resulting in a shift of the oxygen dissociation curve to the right and therefore release of oxygen to the tissues. Although, in vitro, both adult and fetal haemoglobin have the same oxygen dissociation curves, human adult blood has a lower affinity for oxygen than fetal blood because of its greater binding of 2,3-DPG. It has been suggested that the higher affinity of fetal blood helps placental transfer of oxygen. Furthermore, since the greatest amount of oxygen is released for a given fall in pO_2 at the steepest part of the oxygen-dissociation-curve, fetal haemoglobin releases more oxygen than adult at low levels of pO_2.

Fetal hypoxia

Fetal hypoxia, oxygen deficiency in the tissues, may result from (i) reduced placental perfusion with maternal blood and consequent decrease in fetal arterial blood oxygen content due to low pO_2 (hypoxaemic hypoxia); (ii) reduced arterial blood oxygen content due to low fetal haemoglobin concentration (anaemic hypoxia); and (iii) reduced blood flow to the fetal tissues (ischaemic hypoxia). Hypoxia of any cause leads to a conversion from aerobic to anaerobic metabolism, which produces less energy and more acid. If the oxygen supply is not restored the fetus eventually dies.

1.3 Doppler Ultrasound

1.3.1 The Doppler principle

When a beam of sound is reflected by a moving object the frequency of the waveform is altered; when the object is moving towards the source the frequency is increased and when it is moving away from the source the frequency is decreased (Doppler 1842, Buys Ballot 1843).

This alteration in frequencies is described by the formula:

$$dF=2F \times V \times (\cos \theta) / C$$

dF is the alteration in the frequency (the Doppler shift),

F is the transmitted frequency,

V is the velocity of the moving object,

θ is the angle between the line of transmission and the line of movement of the object,

C is the velocity of sound in the medium through which it is travelling.

In practice, C= 1540 cm/s (the velocity of ultrasound through tissues) and F is fixed (2-10MHz).

For objects moving perpendicular to the ultrasound beam (cos 90=0), dF will be zero. As the angle becomes smaller, dF increases and a maximum is reached when the angle is zero. In living tissues a variety of Doppler shifts are produced at any given time by the motion of erythrocytes in blood vessels. The frequency and amplitude of all these Doppler shifts are displayed with respect to time to produce a frequency spectrum or flow velocity waveforms (FVW). The intensity of the colour scale indicates the frequency with which a particular Doppler shift occurred at a given time and thus the number of erythrocytes moving with a particular velocity.

The high pass filter

Any source of movement in the path of the ultrasound beam will produce a Doppler shift. Blood vessel walls have a low frequency, high intensity movement (Reneman 1981) and produce a Doppler shift which is superimposed on that produced by the erythrocytes. A filter that removes the first 100-200 Hz is now incorporated into most machines in order to remove this effect.

1.3.2 Equipment

Continuous wave

Continuous wave Doppler ultrasound uses two piezo-electric crystals. One crystal continuously transmits an ultrasound beam and the other acts as a receiver. The frequency of the backscattered signal is compared to that of the transmitted frequency, and the Doppler shift is calculated. The major disadvantage of these systems is that the vessel being insonated is not imaged and it is not possible to

discriminate between signals arising from different moving structures along the beam. Thus, if several blood vessels lie in the path of the beam, the FVW of all the vessels will be superimposed. However, the systems are cheap and require little expertise to operate. They are most useful in examining flow characteristics in vessels that have a unique FVW, such as the umbilical artery where there is pulsatile arterial flow in one direction and venous flow in the other (Fig 1.1)

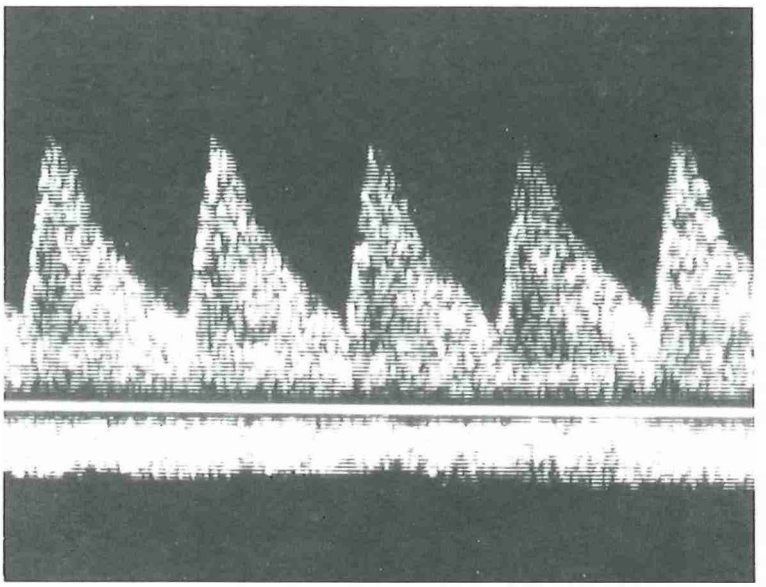

Fig 1.1. Flow velocity waveform from the umbilical cord showing pulsatile arterial flow in one direction and venous flow in the other.

Pulsed wave

A single piezo-electric crystal is used to emit the ultrasound beam in pulses and receive the reflected signal between emissions. By varying the pulse repetition frequency (PRF), the "listening time" can be controlled. Thus, for a high PRF the gaps between pulses are short and only signals reflected by superficial vessels will have returned to the crystal; a low PRF will in addition to the superficial vessels, also

include reflected signals from deeper vessels. The highest Doppler frequencies which can be detected without ambiguity is determined at PRF/2. A time gate allows depth selection by imposing a time delay between the emission of one pulse and the reception of its echo. The duration of the listening time determines the length of the sample volume along the beam axis.

Duplex scanners

Duplex scanners combine conventional B-mode imaging and pulsed Doppler ultrasound. The advantage is that the vessel being insonated can be imaged for selective examination, and the angle of vessel insonation measured (Eik-Nes et al 1980).

1.3.3 Analysis of flow velocity waveforms

The FVW represents the changes in blood velocity with time. Arterial FVW are typically biphasic with a systolic peak and forward diastolic flow, which may continue to the end of the cardiac cycle (Fig 1.2). The time to peak systolic frequency (A) represents cardiac contraction force, the deceleration from peak systole represents a compound function of vessel wall compliance, distance from the aortic valves and the effect of reflected pressure waves from the periphery, and the end diastolic frequencies (B) indicate downstream impedance to flow (Griffin et al 1983).

Doppler indices

Volume flow calculations are fraught with methodological errors and therefore, in Doppler studies, the most commonly used indices are those of mean arterial blood velocity and vascular resistance (flow impedance).

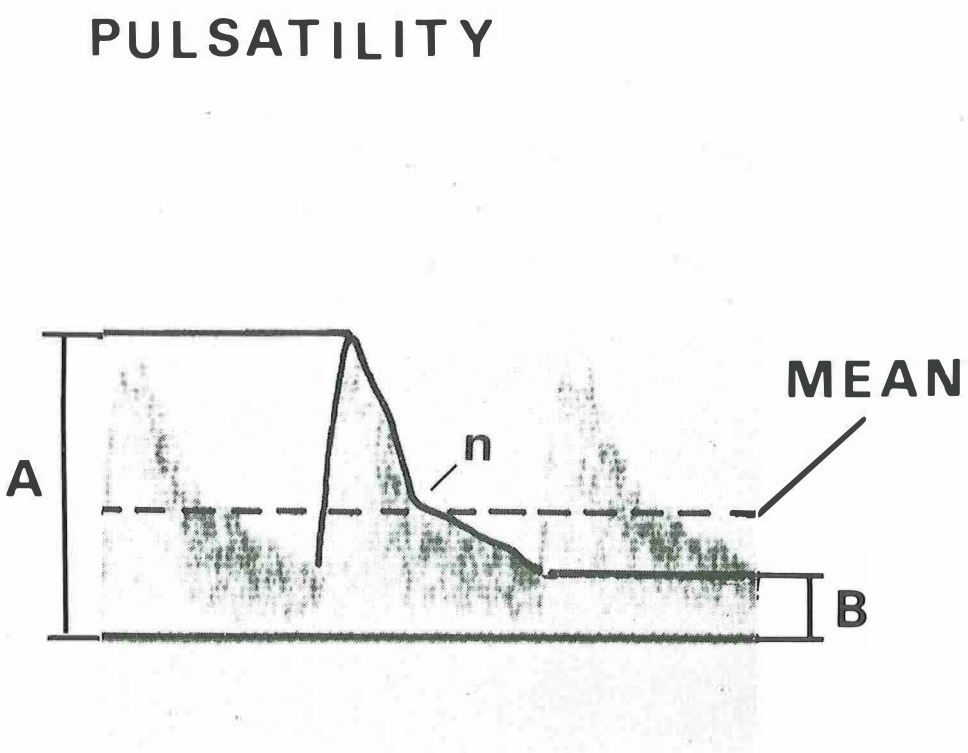

Fig 1.2. Flow velocity waveforms from the fetal descending thoracic aorta. A=Systolic peak, B=End-diastolic frequencies
n=incisural notch. Mean=time averaged mean of the maximum frequency.

Indices of impedance to flow

The three commonly used indices of impedance are: (i) A/B ratio (Stuart et al 1980), (ii) Resistance Index, RI=A-B/A (Pourcelot 1974), (iii) Pulsatility Index, PI=A-B/mean (Gosling & King 1975). For the pulsatility index the denominator (mean) is the mean of the maximum frequency envelope over the complete cardiac cycle. The A/B ratio and RI are related: A/B =1/(1-RI). As the FVW becomes more pulsatile all three

indices increase. However, when end-diastolic frequencies are absent (B=0), resistance index and A/B become unity and infinity respectively and cease to be useful. In contrast, the denominator in the calculation of the pulsatility index will continue to be influenced by the shape of the FVW and is therefore the only index of value in quantifying FVW which have absent end diastolic frequencies.

Mean blood velocity

In duplex pulsed wave systems the Doppler beam is transmitted at a fixed angle to the imaging ultrasound beam. Thus, the angle at which the vessel is insonated by the Doppler ultrasound beam can be determined. By rearranging the Doppler equation and substituting the Doppler shift and the cosine of the angle, the blood velocity (cm/s) can be calculated:

$$V = dF \times C / 2F \times \cos \theta$$

However, since the red blood cells are moving at a variety of velocities, there are a variety of Doppler shifts that are changing during the cardiac cycle. In order to account for these variations, the mean Doppler shift over a cardiac cycle is used. The mean Doppler shift is used and the time-averaged-intensity- weighted mean-blood-velocity (cm/s) can be calculated.

The largest source of error in the calculation of mean-blood- velocity (Vm) is inaccurate measurement of the angle of insonation, and an error of $\pm 5^{\circ}$ is common. The effect of this error on the calculated velocity is directly related to cos θ, and is therefore smaller when the angle of insonation is low (<10% error for angles <50°) and greater at larger angles (>20% error for angles >65°). Therefore, the angle of insonation should be kept to a minimum (<50°) (Griffin et al 1983).

1.3.4 Factors affecting the flow velocity waveform

Fetal heart rate

There is an inverse relation between fetal heart rate and length of cardiac cycle. As the fetal heart rate increases there is a minor decrease in the umbilical artery A/B ratio and RI (Mires et al 1987, Kofinas et al 1989). However, this minor change is of no clinical significance when fetal heart rate is within the physiological range.

Fetal breathing movements and behavioural states

During fetal breathing movements there are variations in the shape of the fetal aortic FVW (Marsal et al 1984). During inspiration there is reduction in frequencies which is more marked in diastole than systole. A reverse pattern is seen during fetal expiration. Therefore, FVW should be recorded only during fetal apnoea.

From 36 weeks' onwards behavioural states exist in the human fetus (Nijhuis et al 1982). As these imply marked changes in fetal heart rate patterns and incidence of fetal body movements, an association with alterations in fetal cardiovascular performance is not unlikely.

Doppler studies in fetuses beyond 36 weeks' should therefore be performed only during quiet sleep, when gross body and breathing movements are absent.

Blood viscosity

Animal studies have demonstrated that increased blood viscosity is associated with reduced cardiac output and increased peripheral resistance and vice versa (Dormandy 1985). However, Giles et al (1986) were unable to demonstrate a significant association between blood viscosity (measured in post-delivery umbilical cord blood) and the A/B ratio of umbilical arterial FVW obtained antenatally. The effect of blood viscosity on FVW remains controversial as also suggested by two recent papers reporting conflicting results (Fairlie et al 1991, Steel et al 1991).

1.3.5 Findings in normal pregnancy

Uterine artery

Impedance to flow in the arcuate, sub-placental and uterine arteries (Campbell et al 1983, Trudinger et al 1985a, Shulman et al 1986) decreases with advancing gestation. This decrease is thought to be the consequence of trophoblastic invasion of the placental bed spiral arteries which strips the musculo-endothelial component of the vessels and converts them into low impedance channels (Brosens et al 1967).

Umbilical artery

Flow velocity waveforms from the umbilical cord have a characteristic saw-tooth appearance of arterial flow in one direction and continuous umbilical venous blood flow in the other. The FVW may be assessed quantitatively, by the determination of various impedance indices, or qualitatively, by noting the absence or presence of end diastolic frequencies. Both methods of analysis represent the interaction between the forward compression wave due to cardiac systole and the reflected waves from the peripheral arteriolar bed. The pulsatility index in the umbilical artery decreases linearly with advancing gestation. This decrease in resistance presumably reflects the progressive maturation of the placenta and increase in the number of tertiary stem villi (Fox 1983).

Fetal descending thoracic aorta

Duplex pulsed Doppler ultrasound has been used to investigate flow characteristics in the fetal descending thoracic aorta. Griffin et al (1984), described alterations in the shape of the FVW with advancing gestation suggestive of decreasing resistance. This is not surprising since 40-60% of blood in the descending aorta supplies the placental circulation where resistance decreases progressively with

advancing gestation. In the third trimester mean velocity measurements and impedance indices do not change with gestation (Griffin 1984, Lingman & Marsal 1986).

Cerebral circulation

In 1986 Wladimiroff et al described the FVW from the internal carotid artery in normal third trimester fetuses. These waveforms are characterized by a continuous forward flow. A progressive fall in impedance indices with advancing gestation has been described for all major intra-cranial arteries (Van den Wijngaard et al 1989; Kirkinen et al 1987).

1.4 Cardiovascular changes in fetal hypoxaemia

1.4.1 Animal studies

Experimentally, fetal oxygen deficiency can be produced by maternal hypoxaemia (Cohn et al 1974), by reducing umbilical blood flow (Iskovitz et al 1987), by restricting uterine blood flow (Wilkening & Meschia 1983), or by removing endometrial caruncles (Robinson et al 1979).

Peeters et al (1979), examined the effect of maternal hypo-oxygenation on the distribution of blood flow in the fetal sheep. Fetal organ perfusion was determined from the amount of radioactivity measured at post-mortem after injection of radioactively labelled microspheres during maternal hypo-oxygenation. Fetal hypoxia was associated with increased blood flow to the heart, brain and adrenal glands; the increase in flow was inversely related to the degree of decrease in arterial oxygen content. In contrast, severe hypoxia was associated with decreased flow to the lungs, digestive tract, pancreas, carcass and kidneys. Placental blood flow was not affected.

The redistribution in the fetal circulation may be at least partly mediated by aortic chemoreceptors, which have been shown, in the mature fetal lamb, to respond to small falls in arterial oxygen tension (pO_2) and to cause release of vasoactive substances such as epinephrine and norepinephrine (Campbell et al 1967, Dawes et al 1968, 1969, Blanco et al 1984, Jensen & Lang 1987). Moreover, hypercapnia appears to increase cerebral flow through a direct local action on cerebral vascular resistance and through a change in hydrogen ion concentration (Kontos et al 1977).

In chronically catheterized sheep fetuses, progressive embolization of the placental arteries and arterioles recreated the waveform changes observed in severely growth retarded human fetuses (Morrow et al 1989). These findings have been recently validated by in vitro studies (Todros et al 1992). The appearance of reverse diastolic flow in the umbilical artery indicates that the lowest vascular resistance in the fetal circulatory network is no longer at placental, but at cerebral level and that pre-placental poorly oxygenated blood is shifted from the descending aorta and pulmonary artery to the fetal brain (Fouron et al 1991).

1.4.2 Doppler findings in human intrauterine growth retardation

Uterine and umbilical arteries

Increased placental resistance may be the result of: (i) reduction in the number of placental terminal capillaries and small muscular arteries in the tertiary stem villi (Giles et al 1985); (ii) increased vasoconstriction at villous level because of local release of vasoactive substances, e.g. thromboxane (Koullapis et al 1982); (iii) arterial wall lesions observed in the placentae of IUGR fetuses (Fok et al 1990). These alterations are triggered by ischaemia of the intervillous space due to reduced utero-placental perfusion.

Cross sectional studies in pregnancies complicated by placental insufficiency and consequent fetal growth retardation, have shown increased impedance to flow in the uterine and umbilical arteries (Griffin et al 1983). These data support the findings from histopathologic studies that in some pregnancies with growth retarded fetuses

there is firstly, failure of the normal development of maternal placental arteries into low resistance vessels (Brosens et al 1972) and therefore reduced oxygen and nutrient supply to the intervillous space, and secondly, reduction in the number of placental terminal capillaries and small muscular arteries in the tertiary stem villi (Giles et al 1985) and therefore impaired maternal-fetal transfer.

Campbell et al (1983), described the FVW obtained from vessels in the left and right lateral uterine walls that they believed to be arcuate arteries. Increased impedance to flow in these vessels was associated with pregnancy and neonatal complications (Campbell et al 1986, 1988). One study included 30 normal pregnancies and 31 pregnancies complicated by maternal hypertension and/or by the delivery of small for gestation infants. In the group with an abnormal utero-placental FVW (lower end-diastolic velocities and the presence of an early diastolic notch, both indicating increased resistance to flow) there was a significantly higher incidence of pre-eclampsia, emergency caesarean delivery, placental abruption, shorter duration of pregnancy, fetal growth retardation and neonatal hypoxaemia than in the group with a normal FVW (Campbell et al 1986).

Similarly, Fleisher et al (1986) reported a significant reduction in birthweight and increased incidence of pre-eclampsia in hypertensive women who had abnormal uterine artery FVW, compared to hypertensive women with normal FVW. Soothill et al (1986b), measured the uterine artery resistance index immediately before cordocentesis for fetal karyotyping in 32 pregnancies with antenatally detected IUGR fetuses. There was a significant association between increased uterine artery resistance index and fetal hypoxaemia, hypercapnia, lactic acidaemia and erythroblastosis.

These studies support the concept that one of the causes of fetal smallness is poor utero-placental perfusion, leading to fetal under-nutrition and hypoxaemia. Abnormal utero-placental FVW are not necessarily accompanied by abnormal umbilical artery FVW, but abnormal fetal flow patterns are the best indicator of fetal compromise and hence of poor perinatal outcome (Hackett et al 1987). Screening studies have reported that if utero-placental FVW are normal after 24 weeks a favourable outcome of the pregnancy can be expected, whereas abnormal FVW in early pregnancy

suggest increased risk of subsequent fetal compromise (Steel et al 1988, Bewley et al 1991). Abnormal fetal FVW alone are suggestive of a pathology confined to the fetus such as viral infections or major fetal anomalies (Campbell & Cohen-Overbeek 1985, Trudinger & Cook 1985, Meizner et al 1987). Trudinger et al (1985a) found more often in IUGR fetuses an association of normal sub-placental FVW and abnormal fetal FVW.

Disparity in results between studies may be due to lack of uniformity in trophoblastic invasion of the spiral arteries. Furthermore, different investigators studied different parts of the utero-placental vascular tree. Recently, the use of colour flow-mapping has clarified that the FVW from the vessels believed to be arcuate arteries are identical to those from the uterine arteries and from their main branches (Campbell et al 1988). By placing the transducer in the lower lateral quadrant of the uterus and angling it medially, it is easy to identify the crossover of the external iliac artery and main uterine artery. It is now generally agreed that the study of both uterine arteries is reproducible and reflects the integrity of the trophoblastic invasion process. Impedance at the placental side is always lower than that at the non placental side.

Clinical studies of umbilical arterial FVW in IUGR reported progressive increase in impedance to flow until absence and, in extreme cases, reversal of end diastolic flow (Shulman et al 1984, Erskine & Ritchie 1985, Trudinger et al 1985b, Rochelson et al 1987). Reuwer et al (1987), used continuous wave Doppler to study umbilical arterial FVW, and reported that they could predict which fetuses developed distress. Nicolaides at al (1988a) measured pO_2 and pH in umbilical cord blood samples obtained by cordocentesis in 39 IUGR fetuses. End diastolic frequencies were absent in 22 cases; 80% of these fetuses were found to be hypoxaemic and 46% also acidaemic. In contrast, only 12% of the fetuses with positive end diastolic frequencies were hypoxaemic and none was acidaemic.

Abnormal umbilical artery FVW are an early sign of fetal impairment. In longitudinal Doppler studies of IUGR fetuses abnormalities in the umbilical artery FVW preceded in 93% of cases the occurrence of cardiotocographic signs of fetal hypoxaemia (Bekedam et al 1990). End diastolic frequencies were absent in 59% of the fetuses; the median time interval between this pathological Doppler finding and the

onset of late decelerations was 12 days (range 0-49 days).

Reversed end diastolic frequencies represent the extreme end of the spectrum and bears a 50% mortality rate. This finding can also be associated with lethal fetal anomalies, 50% of which are chromosomal, mainly trisomy 18 (Brar & Platt 1988).

Fetal descending thoracic aorta

Using duplex pulsed Doppler ultrasound, Griffin et al (1984) obtained FVW from the fetal descending thoracic aorta of 20 IUGR fetuses. End diastolic frequencies were reduced and pulsatility indices increased, suggesting increased downstream impedance to flow; in 45% of cases there was absent end diastolic frequencies. These alterations were ascribed to an abnormal feto-placental circulation and to redistribution of cardiac output away from the abdominal organs.

Similar observations were made by other groups; for the study of aortic FVW in IUGR fetuses, blood velocity measurements appear to be more reliable than pulsatility index measurements (Laurin et al 1987a, Tonge et al 1986). However, the most accurate prediction of growth retardation and operative deliveries for fetal distress is given by a semiquantitative assessment in "blood flow classes" of the FVW (Laurin et al 1987b). Blood flow classes were defined on a combination of pulsatility index and presence or absence of end diastolic frequencies. Although the authors defined four classes, the classes were in reality two, the division being based upon the presence or absence of end diastolic frequencies, thus suggesting that complex measurements of velocity and/or volume flow may not be necessary in clinical practice. Similarly, Hackett et al (1987) studied the outcome of two groups of IUGR fetuses divided according to present or absent end diastolic frequencies in the descending thoracic aorta. Fetuses with absent end diastolic frequencies were more often delivered operatively at an earlier gestational age because of fetal distress; furthermore the degree of smallness and the incidence of neonatal complications such as necrotizing enterocolitis, pulmonary haemorrhage etc., which are probably related to the occurrence of blood flow redistribution, were much higher in this group.

Soothill et al (1986b), found a significant correlation between mean blood velocity in the descending thoracic aorta and fetal blood gases and pH measured in cordocentesis samples from 29 IUGR fetuses. Low velocities were associated with low pO_2 and pH.

Van Eyck et al (1986), studied aortic pulsatility indices in growth retarded fetuses during behavioural states 1F and 2F. During state 2F, growth retarded fetuses were unable, unlike normal fetuses, to increase the peripheral perfusion. A likely explanation may be that the arterial chemoreceptors were already activated by chronic hypoxaemia and no further haemodynamic adjustments could take place.

All these studies suggest that in human fetuses hypoxaemia is associated with centralisation of the fetal circulation and decrease in umbilical flow; this is similar to what was described in animal studies (Clapp et al 1980). Since approximately 50% of the aortic flow supplies the umbilical circulation (Rudolph & Heymann 1967) increased downstream resistance at placental level is reflected in the descending thoracic aorta FVW.

Fetal cerebral circulation

Of the vascular districts "spared " during fetal hypoxaemia, the cerebral circulation is the only one that is currently accessible to Doppler investigation. A 'brain-sparing' effect, in IUGR human fetuses, was first detected by Doppler technique in the common carotid artery (Marsal et al 1984, Arabin et al 1987) and in the internal carotid artery (Wladimiroff et al 1986). Characteristic findings in the cerebral circulation of these fetuses are high diastolic velocities due to reduced downstream resistance; this results in increased blood flow velocities and low pulsatility index values.

Kirkinen et al (1987), described a reduction in the resistance index in 28% of the IUGR fetuses studied. Van den Wijngaard et al (1989), studied all major intra-cranial arteries in IUGR fetuses and reported that the best signals were obtained from

the internal carotid and middle cerebral arteries. The pulsatility index was reduced in all four vessels studied (internal carotid, middle, anterior and posterior cerebral artery), but the reduction was less pronounced in the middle cerebral artery. Similarly, Mari et al (1989), found a higher resistance in this vessel, as compared to other intracranial arteries. The latter authors stress that, in order to compare serial measurements, it is essential to know exactly which cerebral vessel is being investigated. The position of the fetal head in the pelvis, in the second half of pregnancy and the presence of clear anatomical landmarks (great sphenoid wings), make the middle cerebral artery the ideal vessel for Doppler investigations.

Arduini et al (1987), used a ratio of pulsatility indices derived from the umbilical and internal carotid arteries and reported that this ratio could predict IUGR at 26-28 weeks' gestation with a sensitivity of 78% and a specificity of 92%. These findings suggest that haemodynamic readjustments in the fetal circulation may occur at a very early stage in the development of IUGR.

Vyas et al (1990a), found a correlation between reduced middle cerebral artery pulsatility index and the degree of hypoxaemia, measured at cordocentesis. The same authors (Vyas et al 1990b) suggest that while studying FVW from cerebral arteries attention should be paid in avoiding excessive pressure on the maternal abdomen as this may alter the FVW profile. Van Eijk et al (1987), reported that in IUGR fetuses the internal carotid artery pulsatility index remains stable during behavioural state 1F and 2F, suggesting that in IUGR the presence of circulatory readjustments overrules state-dependency.

Fetal heart

In IUGR due to placental insufficiency, selective changes in downstream resistance at placental and cerebral level have a profound influence on cardiac haemodynamics (Peeters et al 1979). Cerebral vasodilatation produces a decrease in left ventricle afterload, whereas increased placental and systemic resistance produce increased right ventricle afterload. Hypoxaemia may also impair cardiac contractility

directly, while changes in blood viscosity due to polycytemia (Soothill et al 1987a) may alter pre-load. Consequently, IUGR fetuses show at the level of the atrio-ventricular valves impaired ventricular filling (lower ratio of early passive to late active ventricular filling phase -E/A ratio-) (Rizzo et al 1988), lower peak velocities in the aorta and pulmonary arteries (Groenenberg 1991), increased aortic and decreased pulmonary time to peak velocity (Rizzo et al 1990a), and a relative increase of left cardiac output associated with decreased right cardiac output (Al Ghazali 1989). These haemodynamic intracardiac changes are compatible with a preferential shift of cardiac output in favour of the left ventricle, leading to improved cerebral perfusion. Thus, in the first stages of the disease, the supply of substrates and oxygen can be maintained (Rizzo & Arduini 1991).

1.5 Cardiovascular changes in fetal anaemia

1.5.1 Animal studies

In adult animals, anaemia is accompanied by increase in tissue perfusion. The primary cardiovascular adjustments to anaemia involve an augmentation in cardiac output and in oxygen extraction that compensate for the decreased oxygen-carrying capacity of the blood (Vatner et al 1972). Additionally, circulatory changes are due to: (i) the ability of tissues to locally regulate perfusion in response to alteration in blood oxygen concentration or oxygen supply resulting from anaemia and (ii) the effects of altered blood viscosity on blood flow. Alterations in blood viscosity affect uniformly all organs and tissues, whereas vasomotor adjustments to changes in oxygen concentration or supply vary considerably among tissues (Fan et al 1980).

The fetal response to anaemic hypoxia has been investigated in chronically catheterised sheep by exchanging fetal blood for plasma. Fumia et al (1984), reported that in isovolemic anaemia blood flow to the heart, brain and adrenal glands (group I organs) was increased, whereas flow to the kidneys, gut, spleen, placenta and

carcass (group II) was maintained. Changes in perfusion in group II organs resulted primarily from altered blood viscosity and were detectable only when haematocrit was either very low or very high. In group I organs, perfusion was also regulated by vasomotor adjustments to reductions in oxygen content.

1.5.2 Doppler findings in red blood cell isoimmunisation

Modified from: Bilardo CM, Nicolaides KH, Campbell S. Doppler studies in red cell isoimmunization. Clinical Obstetrics and Gynecology 1989;32:719-725.

Uterine arteries

In a longitudinal series of 12 fetuses, Copel et al (1988) included the uterine artery pulsatility index, together with the descending thoracic aortic peak velocity, in a multiple regression model to predict whether the fetal haematocrit was below or above 25%. The authors suggested that the significant contribution of uterine artery pulsatility index to the model could be explained by the effect of resolving placental oedema after the correction of fetal anaemia by the second transfusion. However, this is unlikely because there was no difference in uterine pulsatility index or resistance index between hydropic and non-hydropic fetuses.

Umbilical arteries

Rightmire et al (1986), found a significant inverse correlation between umbilical artery resistance index and fetal haematocrit measured at fetoscopy. It was suggested that increased impedance to flow in the feto-placental microcirculation may be due to hypoxia-mediated capillary endothelial cell damage, or clogging of the placental capillaries by the large fetal erythroblasts. In contrast, Warren et al (1987) found that the umbilical arterial systolic to diastolic ratio was not abnormal in pregnancies with

high amniotic fluid bilirubin concentration.

Fetal heart

Meijboom et al (1986), measured maximal and mean temporal velocity and early passive to late active ventricular filling phase (E/A) ratio on the atrio-ventricular orifices in 12 fetuses immediately before fetoscopic blood transfusion. There was a non-significant increase in both maximal and mean temporal velocities. Furthermore, there was a significant reversal in the E/A ratio in the tricuspid valve FVW. In normal fetuses these two peaks present a "M" shape, whereas in anaemic fetuses the E peak is dominant, suggesting that in fetal anaemia there is increased pre-load in the right atrium.

Copel et al (1989), found that anaemic fetuses before any intrauterine transfusion had significantly higher stroke volumes and ventricular outputs than normal controls. The increase was shared proportionally by both ventricles. However, there was no significant relationship between fetal haematocrit and cardiac output. Nevertheless, extremely compromised fetuses demonstrated diminished cardiac function as a terminal finding. In contrast, Barss et al (1987), reported a case of hydrops fetalis where the cardiac output measured before an intravascular transfusion was close to the normal mean for gestation.

Rizzo et al (1990b), measured right and left cardiac output (by multiplying the tricuspid or mitral mean temporal velocities, valvular area and heart rate) in 12 anaemic fetuses before blood transfusion by cordocentesis. Both left and right cardiac outputs were significantly higher for gestation than in 187 normal controls. Furthermore the E/A ratios of both atrio-ventricular valves were higher than normal.

The findings of increased fetal cardiac output in anaemia are in agreement with the results of animal studies and confirm the prediction, from a mathematical model, that in fetal anaemia the cardiac output is increased to maintain an adequate oxygen delivery to the tissues (Fumia et al 1984). Possible mechanisms include: first decreased blood viscosity leading to increased venous return and increased cardiac

preload, and second, peripheral vasodilatation as a result of a fall in blood oxygen content and therefore reduced cardiac afterload. The high E/A ratio is suggestive of increased cardiac preload. Since right to left cardiac output ratio is normal there is no evidence of redistribution in cardiac output similar to that described in hypoxaemic growth retarded fetuses.

Fetal middle cerebral artery

Vyas et al (1990c) measured the pulsatility index in the middle cerebral artery of 24 previously untransfused, non-hydropic fetuses from red cell isoimmunized pregnancies at 18-35 weeks' gestation. Although the mean pulsatility index was significantly lower than the normal mean for gestation there were no significant associations with either the degree of fetal anaemia or the degree of deficit in oxygen content measured in samples obtained by cordocentesis. However, a significant correlation was found between the increase in middle cerebral artery mean velocity and the degree of fetal anaemia measured in samples obtained by cordocentesis.

Fetal descending thoracic aorta

Rightmire et al (1986), from their study of 21 previously untransfused isoimmunized fetuses reported an increase in aortic time-averaged, intensity-weighted mean blood velocity. Furthermore, there was a significant inverse correlation between mean blood velocity and the haematocrit of umbilical cord blood samples obtained by fetoscopy. This association was independent of the significant association between mean blood velocity and gestational age.

Copel et al (1988), measured the peak velocity in 16 fetuses immediately before cordocentesis and derived a series of formulae for the prediction of whether the fetal haematocrit was above or below 25%. The best prediction was achieved for the untransfused fetuses [Haematocrit=7.78-(0.088xVp)+(0.968x weeks gestation)-(10.911

if hydrops is present)]. For subsequent transfusions different formulae had to be used, presumably because of the different rheological properties of adult rather than fetal blood in the fetal circulation.

Fetal venous system

Rightmire et al (1986), measured the fetal inferior vena caval time-averaged mean velocity immediately before the first intravascular fetal blood transfusion in 19 rhesus affected pregnancies at 18-28 weeks'gestation. Although the velocity was higher than in non-anaemic controls there was no significant correlation with fetal haematocrit. In the same study, the intrahepatic umbilical venous velocity was not significantly different from non-anaemic controls.

In contrast, Kirkinen et al (1983) examined 18 rhesus isoimmunized pregnancies within 4 days before delivery and reported that in anaemic fetuses the volume flow in the intrahepatic umbilical vein was significantly increased due to both increased blood velocity and vessel diameter. Similarly, Warren et al (1987) performed serial measurements of fetal blood flow in 51 rhesus isoimmunized pregnancies and reported that increased flow was associated with subsequent development of fetal hydrops or rise in amniotic fluid bilirubin concentration. It was postulated that the increased flow was the result of reduced blood viscosity due to the reduced haematocrit.

1.6 Cordocentesis

Cordocentesis is ultrasound guided fetal blood sampling from an umbilical cord vessel (Daffos et al 1985, Nicolaides et al 1986b).

1.6.1 Technique

At King's College Hospital, London, cordocentesis is performed as an out-patient procedure, without maternal sedation or fetal paralysis (Nicolaides et al 1986). The site and direction of the umbilical cord at its insertion into the placenta are identified by ultrasound scanning with a curvilinear transducer. With the transducer in one hand, held parallel to the intended course of the needle, the chosen site of entry on the maternal abdomen is cleaned with antiseptic solution and local anaesthetic is infiltrated down to the myometrium. When the placenta is anterior or lateral, a 20 gauge needle is introduced trans-placentally into the umbilical cord. When the placenta is posterior, the needle is introduced trans-amniotically and the cord punctured close to its placental insertion. The umbilical cord vessel sampled is identified as artery or vein by the turbulence seen ultrasonically when normal saline solution (400µl) is injected through the sampling needle.

Risks

The risk of fetal death after cordocentesis depends on the indication for sampling and the experience of the operator. Thus, Maxwell et al (1991), after excluding pregnancies that were terminated, noted that the fetal loss rates within two weeks of sampling were 1%, 7%, 14% and 25% in groups of structurally normal, structurally abnormal, growth retarded and hydropic fetuses respectively. In our series of 1169 cases (sampled for prenatal diagnosis of genetic disease, e.g. beta thalassaemia, or for karyotyping in cases of minor fetal malformations, e.g.

hydronephrosis) there were 13 (1%) fetal losses within two weeks of the procedure. In addition there were 17 (1%) perinatal deaths at 4-20 weeks after cordocentesis. Daffos et al (1985), in a series of 562 cases, sampled primarily for diagnosis of toxoplasmosis, reported 7 fetal losses. Weiner et al (1991), reported no losses in 'salvageable' fetuses after cordocentesis in 594 cases, whereas Boulot et al (1990) had 10 fetal losses in 322 cases undergoing cordocentesis for a variety of indications.

1.6.2 Findings in normal pregnancy

Blood gases and pH

In normal fetuses, the blood pO_2 is much lower than in maternal blood (Soothill et al 1986a, Nicolaides et al 1989a) and this may be caused by incomplete venous equilibration of uterine and umbilical circulations or by high placental oxygen consumption. However, the high affinity of fetal haemoglobin for oxygen, together with the high fetal cardiac output in relation to oxygen demand, compensates for the low fetal pO_2 (Battaglia & Meschia 1986).

The umbilical venous and arterial pO_2 and pH decrease with gestational age while pCO_2 increases (Soothill et al 1986a, Nicolaides et al 1989a). Despite the decrease in fetal pO_2, the umbilical venous blood oxygen content does not change because the fetal haemoglobin concentration rises with advancing gestation (Nicolaides et al 1989d, Forestier et al 1991).

Lactate

Blood lactate concentration does not change with gestation (Nicolaides et al 1989a). The umbilical venous blood lactate concentration (mean 0.99, SD 0.32 mmol/l) is higher than the umbilical arterial concentration (mean 0.92, SD 0.21 mmol/l) suggesting that the normoxaemic human fetus is, like the sheep fetus (Burd et al

1975), a net consumer of lactate. Furthermore, the concentration of lactate in umbilical cord blood is higher than in the maternal blood and the two are correlated significantly, suggesting that there is a common source of lactate, which is likely to be the placenta.

Glucose

The mean umbilical venous blood glucose concentration is higher than in the umbilical artery, indicating that there is fetal glucose consumption (Economides & Nicolaides 1989, Nicolini et al 1989). Furthermore, the maternal glucose concentration is higher than the fetal one and the levels in the two compartments are significantly correlated, indicating that the major source of fetal glucose is the mother.

Triglycerides

In normal pregnancies there is no correlation between fetal and maternal triglyceride levels, suggesting that there is no significant transplacental transport of these lipids. Fetal plasma triglyceride concentration decreases exponentially with gestation (Economides et al 1990, Legras et al 1990) and this is likely to be the consequence of the increased utilisation by the fetus for deposition into adipose tissue.

Amino acids

There is a high correlation between fetal and maternal levels for individual amino acids and the concentration in the fetus is higher than in the mother. These findings provide supporting evidence for active transport across the placenta (Economides et al 1989b). The mean feto-maternal amino acid ratio decreases with advancing gestation and this may be due to increased consumption of amino acids by the fetoplacental unit.

Haematological indices

In normal pregnancy the fetal erythroblasts count decreases exponentially with gestation (Nicolaides et al 1989d), while fetal erythrocyte, white blood cell and platelet counts increase (Van den Hof & Nicolaides 1990, Davies et al 1992). These changes presumably reflect the progressive maturation of the haematopoietic system and the declining contribution of extramedullary erythropoiesis with gestation.

1.6.3 Findings in intrauterine growth retardation

Modified from: Bilardo CM, Nicolaides KH. Cordocentesis in the assessment of the small-for-gestational age fetus. Fetal Therapy 1988;3:24-30.

Analysis of blood samples obtained by cordocentesis from severely growth retarded fetuses has provided useful information on the cytogenetic, biochemical and metabolic status of such fetuses. Furthermore, it has provided end points for validation of the various non-invasive tests used in the assessment of fetal wellbeing.

Karyotyping of growth retarded fetuses

Intra-uterine growth retardation is a common feature of many chromosomal abnormalities. In our series of 239 growth retarded fetuses sampled by cordocentesis, the incidence of chromosomal anomalies was 17% (40 cases). The most common chromosomal defect was triploidy (19 cases) which is characterised by severe asymmetrical growth retardation. This is in contrast with the current view that chromosomally abnormal fetuses are symmetrically growth-retarded and that asymmetrical growth-retardation is the result of placental insufficiency.

Blood gases and metabolites in growth retardation

Analysis of blood samples obtained by cordocentesis from IUGR fetuses has shown that some are chronically hypoxaemic and the degree of hypoxaemia correlates well with acidaemia, hypercapnia, hyperlacticaemia and erythroblastosis (Soothill et al 1987a, Nicolaides et al 1989a). These findings demonstrate that asphyxia manifested at birth may not be due to the process of birth itself, but rather it may exist antenatally. The association of fetal hypoxaemia with erythroblastosis suggests that one of the fetal responses to hypoxia is recruitment of extramedullary haematopoiesis in the fetal liver. It is possible that in fetal hypoxaemia due to utero-placental insufficiency there may also be hepatic dysfunction due to infiltration with erythropoietic tissue and this may be, at least partly, responsible for the observed disturbance in carbohydrate, fat and amino acid metabolism.

Hypoxic IUGR fetuses are hypoglycaemic indicating that 'neonatal' hypoglycaemia is not necessarily of neonatal origin. The association could be due to impaired utero-placental perfusion leading to reduced placental transfer of both oxygen and glucose. Alternatively the low glucose concentration could be the result of increased consumption by anaerobic metabolism or reduced glyconeogenesis (Economides at al 1989a).

Some IUGR fetuses are hypertriglyceridaemic and the degree of hypertriglyceridaemia is significantly related to fetal hypoxaemia (Economides et al 1990). Hypertriglyceridaemia may be the result of increased lipolysis of fetal fat stores, impaired oxidation of fatty acids, or decreased utilization of circulating tryglycerides for fat tissue deposition. In IUGR fetuses, as in postnatal protein malnutrition and Kwashiorkor syndrome, there is deficiency in essential amino-acids and increase in non-essential amino-acids (Economides et al 1989b). The decrease in essential amino acids may be due to reduced active transfer across the placenta as a result of hypoxia or, alternatively, due to reduced supply of essential amino acids to the intervillous space, as a consequence of impaired uteroplacental perfusion. The non-essential amino acids are increased presumably because they are utilised for gluconeogenesis, oxidation or protein synthesis.

1.6.4 Findings in red blood cell isoimmunization

Modified from: Bilardo CM, Nicolaides KH, Campbell S. Doppler studies in red cell isoimmunization. Clinical Obstetrics and Gynecology 1989;32:719-725.

Pathophysiology

In red blood cell isoimmunised pregnancies the life span of fetal erythrocytes is reduced because antibody-coated red cells are destroyed in the fetal reticulo-endothelial system. In mild-moderate anaemia there is associated reticulocytosis suggesting a compensatory increase in intramedullary erythropoiesis. With severe anaemia there is recruitment of extramedullary erythropoietic sites resulting in macrocytosis and erythroblastaemia (Nicolaides et al 1988c)

The fetal blood oxygen content decreases in proportion to the degree of anaemia. Fetal blood pO_2, pCO_2 and pH, usually remain within the normal ranges except in extreme anaemia when hypoxia and acidosis occur (Soothill et al 1987b, 1987c, Nicolaides 1989). The fetal 2,3-DPG concentration is increased and the consequent decrease in haemoglobin oxygen affinity presumably improves delivery of oxygen to the tissues (Soothill et al 1988). In moderate anaemia, the umbilical arterial plasma lactate concentration is increased but this is cleared by a single passage through the placenta and normal umbilical venous levels are maintained (Soothill et al 1987b). In severe anaemia, when the oxygen content is less than 2 mmol/l, the placental capacity for lactate clearance is exceeded and the umbilical venous concentration increases exponentially. These data suggest that in the fetus systemic metabolic acidosis can be prevented, unless the oxygen content decreases below the critical level of 2 mmol/l (Soothill et al 1987b).

When the fetal haemoglobin concentration deficit exceeds 7 g/dl hydrops fetalis develops (Nicolaides et al 1988c). This may be the result of extensive infiltration of the liver by erythropoietic tissue leading to portal hypertension, due to parenchymal compression of portal vessels, and hypoproteinaemia, due to impaired protein

synthesis (Nicolaides et al 1985). Furthermore, at this haemoglobin concentration deficit the oxygen content decreases below the critical level of 2 mmol/l.

Diagnosis and treatment of fetal anaemia

The severity of fetal haemolysis can be predicted from (a) the history of previously affected pregnancies, (b) the level of maternal haemolytic antibodies and the amniotic fluid ΔOD 450nm (Nicolaides et al 1986a), (c) the altered morphometry of fetus and placenta (Nicolaides et al 1988b), (d) the presence of pathological fetal heart rate patterns (Nicolaides et al 1989b), and (e) changes in the flow velocity waveforms obtained by Doppler studies of the fetal circulation. However, there is a wide scatter of values around the regression lines describing the associations between the degree of fetal anaemia and the data obtained from these indirect methods of assessment.

The only accurate method for determining the severity of the disease is blood sampling by cordocentesis and measurement of the fetal haemoglobin concentration (Nicolaides et al 1988c). However, the indication for, and the timing of fetal blood sampling in the context of this disease have not yet been defined adequately. Nevertheless, it could be argued that cordocentesis should be performed for all patients with a history of severe disease and those with high haemolytic antibody levels ($\geq$15 IU/ml), pathological fetal heart rate patterns or abnormal flow velocity waveforms (Nicolaides et al 1989b, Rightmire et al 1986).

At cordocentesis a fetal blood sample is first obtained and the haemoglobin concentration is determined (Nicolaides et al 1986c). If this is below the normal range, the tip of the needle is kept in the lumen of the umbilical cord vessel and an appropriate volume (Nicolaides et al 1987) of fresh, packed, rhesus negative blood compatible with that of the mother is infused manually into the fetal circulation through a 10 ml syringe. At the end of the transfusion a further fetal blood sample is aspirated for determination of the final haemoglobin concentration (Nicolaides et al 1986c).

Subsequent transfusions are given at 1-3 weekly intervals until 34-36 weeks

and their timing is based on the findings of non-invasive tests, such as Doppler studies and fetal heart rate monitoring, and the knowledge that following a fetal blood transfusion the mean rate of decrease in fetal haemoglobin is approximately 0.3 g/dl per day (Nicolaides et al 1986c).

1.7 Aim of the Thesis

The aim of this thesis is to investigate changes in fetal blood flow characteristics in the descending thoracic aorta and common carotid artery in two models of fetal hypoxia: first, hypoxaemic hypoxia, as seen in intrauterine growth retardation, and second, anaemic hypoxia, as seen in red blood cell isoimmunisation.

To achieve this aim a series of Doppler studies were undertaken in order to:

1. Establish reference ranges with gestation for mean blood velocity and pulsatility index in the fetal descending thoracic aorta and common carotid artery.

2. Examine in normally grown and growth retarded fetuses the relationship of fetal blood gases with Doppler indices in the uterine and umbilical arteries and in the fetal descending thoracic aorta and common carotid artery. In addition, the effect of maternal hyperoxygenation on fetal blood gases and Doppler indices was investigated.

3. Examine changes in mean blood velocity and pulsatility indices in fetal vessels in relation to fetal anaemia. In addition, the effect of intravascular blood transfusion on Doppler measurements of the fetal circulation, heart rate patterns and fetal movements was investigated.

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Chapter 2

Doppler findings in normal fetuses

Mean blood velocities and flow impedance in the fetal descending thoracic aorta and common carotid artery in normal pregnancy

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Summary

A linear array pulsed Doppler duplex scanner was used to establish reference ranges for mean blood velocities and flow impedance (Pulsatility Index) in the descending thoracic aorta and in the common carotid artery from 70 fetuses in normal pregnancies at 17-42 weeks' gestation. The aortic velocity increased with gestation up to 32 weeks, then remained constant until term, when it decreased. In contrast, the velocity in the common carotid artery increased throughout pregnancy. The pulsatility index in the aorta remained constant throughout pregnancy, while in the common carotid artery it fell steeply after 32 weeks. These results suggest that with advancing gestation there is a redistribution of the fetal circulation with decreased impedance to flow to the fetal brain, presumably to compensate for the progressive decrease in fetal blood pO_2.

Introduction

Combined real-time and pulsed Doppler ultrasound enables non-invasive investigation of the human fetal circulation (Eik-Nes et al 1982, Griffin et al 1983).

Since volume flow measurements have been largely abandoned, due to methodological limitations in measuring the cross-sectional area of small vessels, the fetal circulation has been studied principally by human blood velocity measurements and by flow impedance indices such as the pulsatility index (Eik-Nes et al 1982, Griffin et al 1983, Gosling & King 1975).

The aim of the present study was to establish reference ranges for the aortic and common carotid artery mean velocities and pulsatility indices during the second and third trimester of pregnancy. These two vessels provide information on the distribution of the combined cardiac output to the brain, viscera and placenta. Animal studies have demonstrated that during hypoxia there is a relative redistribution of the fetal circulation with increased blood flow to the fetal brain (Berhman et al 1970, Cohn et al 1974). These reference ranges will allow study of such changes in human pregnancy.

Patients and Methods

The patients comprised an unselected group of 78 healthy women with singleton pregnancy, between 17 and 42 weeks' gestation; they agreed to take part in the study after informed consent. Subsequently, eight cases were excluded from the study because they developed pregnancy complications (pregnancies induced hypertension, one case; antepartum haemorrhage, one case; preterm delivery, two cases; birthweight below the 10th centile, four cases). All the remaining 70 infants were born spontaneously, without fetal distress, between 37 and 42 weeks' gestation and weighed more than the 10th centile for gestational age after correction for maternal parity and infant sex (Thompson et al 1968).

Doppler investigations were performed by a single operator using a linear array pulsed Doppler duplex scanner (Kranzbüehler ADR 5000, F.R.G.) which combines a 3 MHz linear array transducer and a 2 MHz pulsed Doppler probe. The high-pass filter was maintained at 150 Hz. The duration of each examination was between 15 and 30 min. All measurements were taken when no fetal body or breathing movements were present. Doppler signals were processed by the built-in frequency analyzer and

displayed on the monitor. The best flow velocity waveforms (FVW) were recorded on high quality audiotapes. Time averaged intensity weighted mean velocity was calculated automatically by the built-in computer from the Doppler shifted frequencies of two consecutive cycles (Griffin et al 1983). The angle between the Doppler beam and the long axis of the vessel was always kept below 55°.

Immediately following the aortic artery studies, FVW were recorded from the common carotid artery by placing the sample gate on the proximal part of the fetal neck below the level where the vessel splits into the internal and external carotid artery

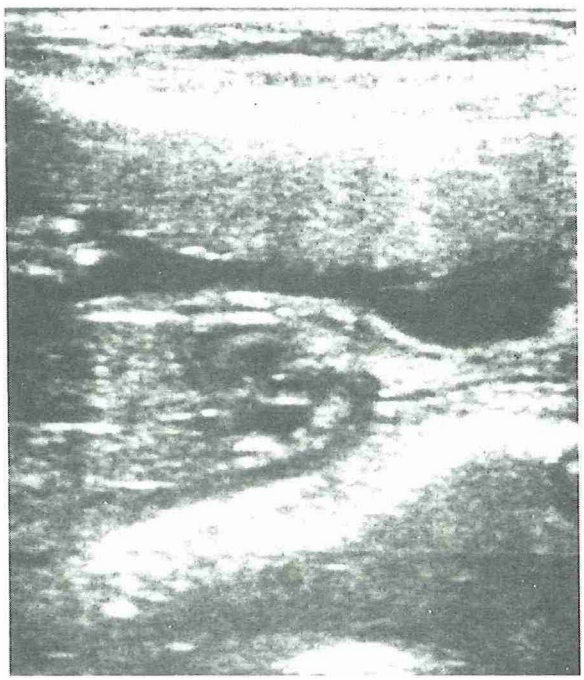
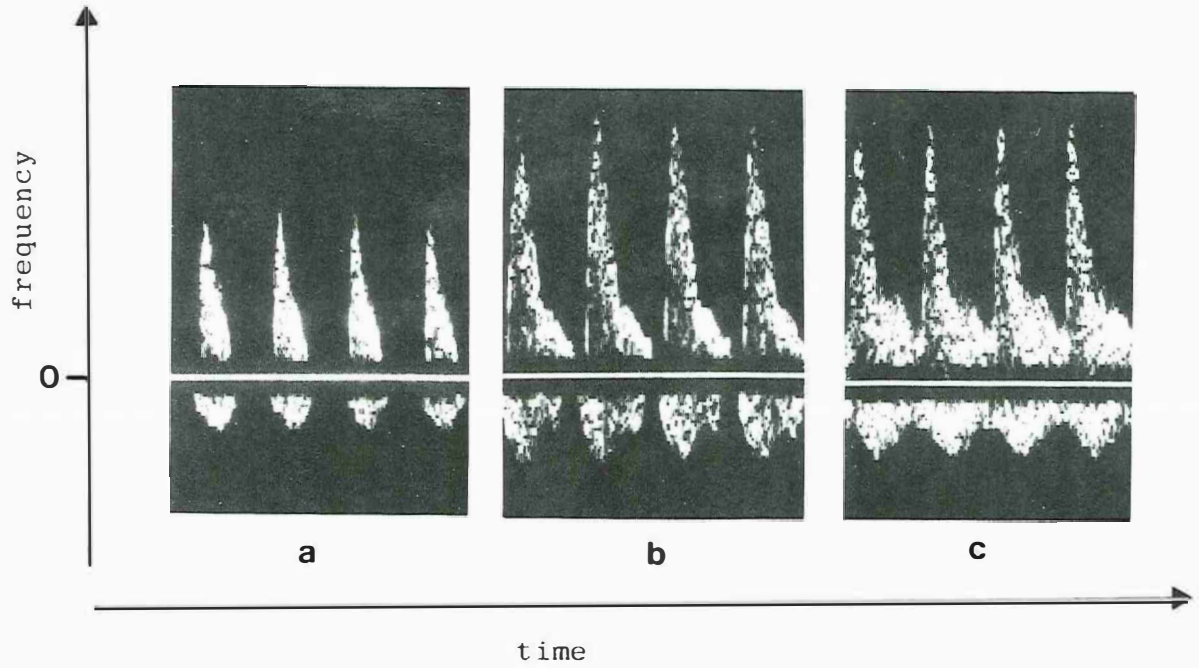


Fig 2.1 Descending thoracic aorta and left common carotid artery in a 25-weeks fetus

To obtain a satisfactory waveform from the common carotid it is necessary to avoid artifacts on the Doppler spectrum caused by the proximity of the fetal spine or other bones encountered by the Doppler beam (ribs, scapula, skull). A satisfactory waveform



Flow velocity waveforms of the common carotid artery (top) and jugular vein (bottom) from fetuses at different gestational ages: 22 weeks (a); 32 weeks (b) and 42 weeks (c).

Fig 2.2 a,b,c

is defined by the clarity of the spectrum and by the presence of the jugular vein waveform in the reverse channel (Figs 2.2 a,b,c). In four cases, because of an unfavourable fetal position, we were unable to obtain satisfactory FVW from this vessel.

Mean blood velocities were measured in the common carotid artery by an identical technique to that described for the aorta. In ten cases the angle between Doppler beam and the vessel was not clearly visualised or was above 55°.

Thus, for the descending thoracic aorta satisfactory FVW and mean velocity measurements were obtained in all cases. For the common carotid artery satisfactory FVW were obtained in 66 cases (95%) and mean velocity measurements in 60 cases (85%).

For pulsatility index measurements, all satisfactory FVW recorded on audiotapes were subsequently analysed with a Doptek spectrum analyser (Doptek Spectrascan Analyser 9000, U.K.). The pulsatility index was calculated automatically by the Doptek computer after the maximum envelope of the Doppler shifted frequencies had been outlined manually with a light pen, as we have found this to be the most reproducible method for measuring this parameter.

A reproducibility study of the measurements of velocities and pulsatility indices in the two vessels was carried out on eight cases by two operators on two different occasions. The difference between operators and occasions were calculated by two-way analysis of variance.

The mean blood velocity and the pulsatility index in the aorta and in the common carotid artery, and the ratios between these two parameters were calculated for each fetus. Ninety per cent reference ranges were calculated by the method of polynomial regression of each variable against the week of gestation. The residuals from the regression analysis were tested for normality using the Anderson-Darling test (Stephen 1974).

Results

The waveform of the fetal descending thoracic aorta in normal and complicated pregnancies has been previously described (Griffin et al 1983). The aortic waveform in early gestation resembles a "ski slope" and, as gestation advances, it becomes more pulsatile and shows an increasingly deep dicrotic notch. The common carotid waveform in the second trimester is characterised by a high systolic peak, and absence of frequencies in the last part of diastole, when the high pass filter is set at 150 Hz (Fig 2.2 a). This suggests the existence of a high resistance to flow to the fetal head. However, with advancing gestation the waveform becomes less pulsatile and end diastolic frequencies, which usually become detectable by 32 weeks, increase progressively (Fig 2.2 b,c).

The reproducibility study of all parameters measured showed no significant inter-observer of intra-observer variation. Therefore variation was ascribed to chance only. The coefficient of variation for aortic mean velocity was 5.9%, for aortic pulsatility index 9.9%, for common carotid mean velocity 12.5% and for common carotid pulsatility index 7.9%.

An adequate fit to the data was provided by either a linear of a quadratic curve; 90% reference ranges for the normal individuals in the sample were derived from the standard deviation (S.D. = 1.65) around the fitted regression line as Y + 1.645 S.D., where Y is the fitted regression line and S.D. is the residual standard deviation (Figs 2. 3-8). All the variables but one, i.e. aortic pulsatility index, showed statistically significant changes with gestational age. The constants which define the regression lines are shown in Table 2.I. None of the variables failed the test of normality of residuals at P = 0.01 level.

The mean blood velocity in the aorta increases with gestation up to 32 weeks, then plateaus in the third trimester and decreases at term (Fig 2.3). The aortic pulsatility index remains constant throughout gestation with a mean of 2.16 (Fig 2.4).

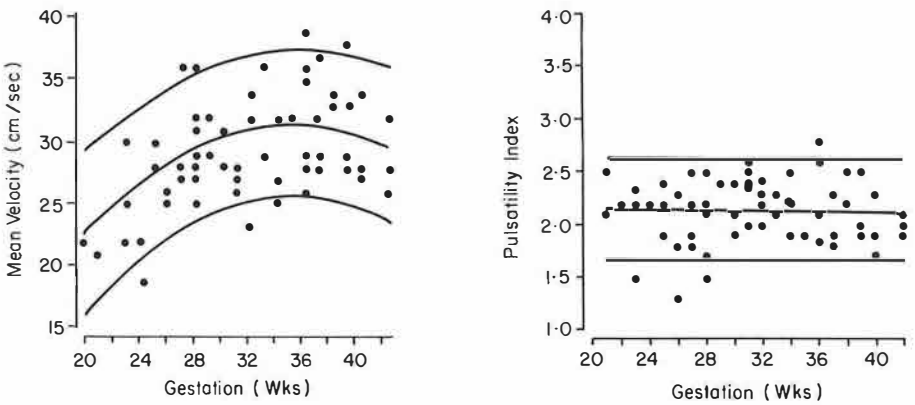


Fig 2.3 Mean intensity-weighted aortic velocity measured in the fetal descending thoracic aorta.

Fig 2.4 Aortic Pulsatility Index (PI).

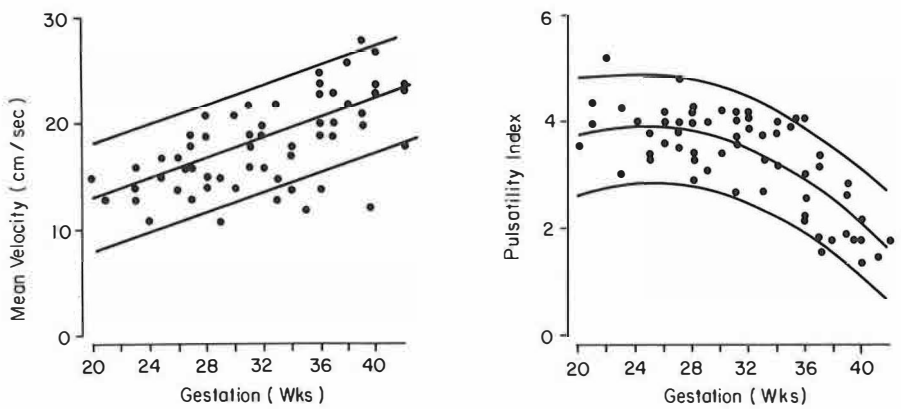


Fig 2.5 Common carotid artery mean intensity-weighted velocity.

Fig 2.6 Common carotid artery Pulsatility Index (PI).

The mean blood velocity in the common carotid artery, which is always lower than that in the aorta, increases throughout pregnancy (Fig 2.5). The common carotid artery pulsatility index is constant until 32 weeks and then falls steeply (Fig 2.6). The mean common carotid artery pulsatility index is higher than the mean aortic pulsatility index until 39 weeks, after which the relationship is reversed. The ratios of common carotid artery and aortic velocities and pulsatility indices are shown in Figs 2.7 and 2.8. Both curves appear to be principally influenced by the large changes with gestational age which characterize the common carotid artery velocity and pulsatility index.

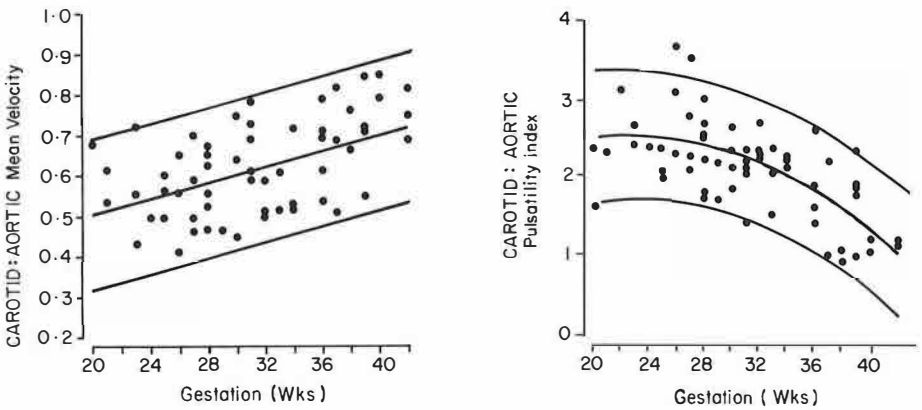


Fig 2.7 Common carotid velocity/aortic velocity ratio.

Fig 2.8 Common carotic PI/aortic PI ratio.

Table 2.I Constants defining the regression lines.

Constants defining the regression lines.

Variable name	Constant term	Linear term	Quadratic term	Residual S.D.	Mean value at 30 weeks	C.V.[a]
Aortic velocity	− 16.3	2.71	− 0.0385	3.58	30.4	12%
Aortic PI	2.143	0	0	0.291	2.143	14%
Common carotid velocity	3.48	0.466	0	2.99	17.5	17%
Common carotid PI	− 0.661	0.370	− 0.00750	0.602	3.69	16%
Common carotid PI/ aortic PI ratio	0.308	0.173	− 0.0035	0.351	2.35	15%
Common carotid velocity/ aortic velocity ratio	0.306	0.00986	0	0.109	0.602	18%

A quadratic term of zero means that a linear fit was sufficient (i.e. little or no curvature was detectable). The quantity Residual Standard Deviation (S.D.) measures the scatter of individual values around the line. The regression lines may be expressed as: $y = Y + e$ = (Constant term) + (Linear term) GA + (quadratic term) $GA^2 + e$; where GA is the gestational age and e is the Residual S.D.

[a]C.V. is the residual S.D. divided by the fitted value from the regression at 30 weeks, multiplied by 100%.

Discussion

In the evaluation of blood velocity and flow impedance to the fetal brain the common carotid artery was chosen, in preference to the internal carotid, because the off-line pulsed Doppler duplex scanner makes the recording of FVW from this vessel relatively easy and reproducible. Furthermore, unlike the internal carotid artery, the common carotid artery is a straight vessel thus allowing accurate measurement of the angle of insonation and consequently of mean velocities. Unlike the internal carotid, the common carotid artery does not reflect exclusively the blood supply to the brain, as it contributes also to the perfusion of the external tissues of the head via the

external carotid artery. However, it seems logical that any modification in blood flow in this vessel will be determined primarily by changes in the circulatory requirements of the fetal brain. The influence of the external carotid on the downstream resistance probably explains why end diastolic velocities in this vessel are detectable at a later stage than in the internal carotid artery (Wladimiroff et al 1986, 1987).

The mean blood velocity results presented show a changing relationship between velocities in the common carotid artery and in the descending thoracic aorta throughout gestation. Thus, the mean velocity in the aorta plateaus at approximately 32 weeks and falls slightly after 40 weeks, unlike the mean velocity in the common carotid artery which increases throughout gestation, suggesting that a progressively increasing fraction of the cardiac output is directed to the fetal brain (De Smedt et al 1987). Studies on baboon fetuses have shown that an increase in the blood supply to the fetal head is accompanied by falling pO_2 levels in the last part of gestation (Paton & Fisher 1984). Our findings suggest that a similar homeostatic readjustment operates in the human fetal circulation which might be related to the changes in blood pO_2 and pCO_2 levels which have been documented with advancing gestation (Soothill et al 1986). The changes of impedance in the common carotid artery also suggest that there is an increased brain perfusion; thus, in the common carotid artery the pulsatility index shows a dramatic fall after 32 weeks, while in the aorta the impedance to flow remains static throughout pregnancy.

Approximately 50% of blood flow in the descending thoracic aorta is distributed to the umbilical artery (Griffin et al 1983). With advancing gestation the pulsatility index in the umbilical artery decreases, due to reduced resistance in the placental compartment (Trudinger et al 1986), whereas in the aorta it remains constant throughout gestation, suggesting that there is a compensatory vasoconstrictive mechanism in the other major branches of aortic flow distribution, namely the mesenteric and renal vascular beds. This would explain the increasingly pulsatile waveform of the descending thoracic aorta in contrast to the umbilical artery waveform, which is characterised by a decreasing pulsatility throughout gestation. Such changes could be the consequence of the redistribution of the fetal circulation in response to falling pO_2 levels. Furthermore, increasing vascular resistance in the

renal compartment might explain the progressive reduction in amniotic fluid volume which occurs towards term.

It is possible that the rise in blood velocity and the parallel steep fall in pulsatility index in the common carotid artery are a response to the changes of blood gases with advancing gestation. When pO_2 falls below and pCO_2 rises above a certain threshold, aortic and carotid chemoreceptors could be "switched on" regulating a vasodilatory response in order to guarantee adequate oxygenation to the fetal brain (Dawes et al 1968). This may be interpreted as a "brain sparing effect" occurring under non-pathological conditions. Studies in pregnancies complicated by fetal hypoxia may reveal an exaggerated flow diversion to the fetal head and reduction in the flow distribution to the viscera in association with low pO_2 levels. The normal reference ranges presented will provide a basis for studying this hypothesis.

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Chapter 3

Doppler findings in growth retarded fetuses

This chapter examines the relationship between fetal blood gases and Doppler indices of the placental and fetal circulations in intrauterine growth retardation. In addition it reports on the effect of maternal hyperoxygenation on the fetal circulation.

3.1 Doppler measurements of fetal and uteroplacental circulation: relationship with umbilical venous blood gases measured at cordocentesis

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Summary

A pulsed Doppler study of the fetal and uteroplacental circulations was performed on 41 pregnant women with small-for-gestational-age and 10 women with appropriate-for-gestational-age fetuses at 19 to 37 weeks' gestation. Blood gases and pH, measured in umbilical venous samples obtained by cordocentesis within 1 hour of the Doppler studies, were correlated individually and as an "asphyxia" index, to the Doppler and ultrasonographic biometric measurements. Although there were significant correlations between the majority of the ultrasonographic biometric and Doppler measurements with the blood gas results, better correlations were found with the ratio of common carotid artery to descending thoracic aorta mean velocity and pulsatility index. The best predictor of asphyxia was an index comprising aortic mean velocity and the common carotid artery pulsatility index. When this index was abnormal, 89% of fetuses had an asphyxia index 1 SD above the mean and 60% 2 SDs above the mean. A normal index was always associated with normal blood gases. The indices

representing the inverse relationship of impedance and velocity in the two major vessels that supply the brain and the abdominal viscera provide the best prediction of the fetal condition because they reflect the haemodynamic response to changes in the partial pressure of respiratory gases.

Introduction

Animal studies have shown that reduced placental perfusion is associated with intrauterine growth retardation (Robinson et al 1983). Furthermore, in fetal hypoxemia there is a redistribution in blood flow with increased blood supply to vital organs, such as the brain, heart, and adrenals, and a simultaneous reduction of perfusion of other organs that include the lungs, gastrointestinal tract, and kidneys (Peeters et al 1979). This redistribution of flow is referred to as the "brain-sparing effect".

Doppler ultrasonography has allowed examination of the human fetus in both physiologic and pathologic conditions (Griffin et al 1983). Reference ranges for intensity-weighted mean blood velocities and impedance indices (pulsatility index and resistance index) with gestation have been established for the fetal descending thoracic aorta, the common carotid artery, the umbilical artery, and the uteroplacental vessels (Bilardo et al 1988, Pearce et al 1988). A series cross-sectional studies in pregnancies complicated by intrauterine growth retardation have demonstrated that increased impedance in the uteroplacental vessels and in the umbilical artery is associated with hypoxemia and poor perinatal outcome (Campbell et al 1986, Soothill et 1986, Nicolaides et al 1988).

Furthermore, in intra uterine growth-retarded (IUGR) fetuses, there is a correlation between reduced aortic intensity-weighted mean velocity and low fetal pO_2 levels.

The absence of end-diastolic frequencies in the aortic flow velocity waveforms is associated with a high incidence of neonatal complications affecting those organs that suffered from the redistribution of flow (i.e. necrotizing enterocolitis, pulmonary haemorrhage, coagulopathy)(Hackett et al 1986). More recently Doppler studies have also demonstrated that in growth-retarded fetuses the cerebral perfusion is increased

(Wladimiroff et al 1987, Arduini et al 1987).

This study examines the relationship between Doppler measurements of velocity and impedance in the common carotid artery and fetal blood gases. A comparison is also made between the various ultrasonographic biometric and Doppler measurements of uteroplacental and fetal circulation in their ability to predict fetal oxygenation.

Patients and methods

Doppler studies of the fetal and uteroplacental circulation were performed 30 to 60 minutes before cordocentesis in 51 patients referred to our centre for fetal assessment at 19 to 37 weeks' gestation. The study was cross-sectional. All fetuses had an ultrasonographic scan and in 41 cases the fetal abdominal circumference was below the 2.5th percentile of our normal range; cordocentesis was performed for fetal karyotyping and determination of acid-base status (Nicolaides et al 1986). In the remaining 10 cases the abdominal circumference was within the normal range for gestation, and the indication for fetal blood sampling was prenatal diagnosis (toxoplasmosis, n = 2; rapid karyotyping for failed amniocentesis or placental biopsy cultures, n = 3; presence of ultrasonographic markers for chromosomal disorders, n = 4; blood grouping, n = 1). All fetuses were subsequently determined to be chromosomally normal and not to be affected by the condition investigated. Gestational age was established by Naegele's rule and from an ultrasonographic measurement of the fetal biparietal diameter at 16 to 18 weeks. The IUGR fetuses were classified on the basis of the head circumference/abdominal circumference ratio into symmetric and asymmetric types if this ratio was below or above the 97,5th percentile, respectively, of our normal range.

A duplexed system consisting of a 2 MHz pulsed Doppler probe attached at a fixed angle of 53° to a 3 MHz linear array transducer (Kranzbühler-ADR 5000, Berlin) was used for the Doppler studies. Flow velocity waveforms were recorded from the major branches of the uteroplacental vessels, umbilical artery, fetal descending

thoracic aorta, and common carotid artery as previously described (Griffin et al 1983, Bilardo et al 1988, Pearce et al 1988). The Doppler sonograms were considered for measurements when there were no fetal gross body or chest movements and the fetal heart rate was between 120 and 140 beats per minute. The high-pass filter was set at 150 Hz. The duration for the Doppler investigation in each patient was approximately 40 minutes (range, 20 to 60 minutes). For velocity determinations a representative pair of cardiac cycles was selected from the flow velocity waveforms of the aorta and of the common carotid artery, and the angle of insonation of the vessel was measured on the frozen image of the linear array display; this angle was always kept below 55°. The mean velocity was calculated automatically by a built-in computer from the intensity-weighted means of the Doppler-shifted frequencies of two consecutive cardiac cycles.

Table 3.I Equations defining the reference ranges for each variable used in the statistical analysis

Variable	*Equation*	*Source*
Po_2	$76.5 - 1.244\ G$	Soothill et al.[14]
Pco_2	$38.29 - \exp(11.873 - 0.5961\ G)$	Soothill et al.[14]
pH	7.38 (constant)	Soothill et al.[14]
UA PI	$\exp(0.585 - 0.2289\ G)$	Pearce et al.[5]
UP RI	$\log_e - 0.454 - 0.015$	Pearce et al.[5]
Ao Vm	$-16.27 + 2.706\ G - 0.03845\ G^2$	Bilardo et al.[4]
Ao PI	$0.4294 + 0.1118\ G - 0.00175\ G^2$	Bilardo et al.[4]
CC Vm	$3.482 + 0.4655\ G$	Bilardo et al.[4]
CC PI	$-0.6613 + 0.3701\ G - 0.0075\ G^2$	Bilardo et al.[4]
CA PI (ratio)	$0.4046 + 0.1316\ G - 0.0029\ G^2$	Bilardo et al.[4]
CA Vm (ratio)	$0.3059 + 0.00986\ G$	Bilardo et al.[4]

G, Gestational age; *UA PI*, umbilical artery pulsatility index; *UP RI*, uteroplacental resistance index; *Ao Vm*, aortic mean velocity; *Ao PI*, aortic pulsatility index; *CC Vm*, common carotid artery mean velocity; *CC PI*, common carotid artery pulsatility index; *CA PI*, carotid-aortic pulsatility index; *CA Vm*, carotid-aortic mean velocity.

Velocity measurements were repeated twice and the mean of the two measurements was considered. The coefficient of variation for mean velocity measurements in the

aorta and in the common carotid artery were 6% and 12%, respectively (Bilardo et al 1988). The pulsatility index, as defined by Gosling, was measured in all fetal flow velocity waveforms as previously described. The coefficient of variation for this measurement is 10% for the aorta, 8% for the common carotid artery, and 7% for the umbilical artery (Bilardo et al 1988, Pearce et al 1988). In flow velocity waveforms from the uteroplacental vessels, the resistance index, as defined by Pourcelot, was calculated on three consecutive cardiac cycles.

The umbilical venous pO_2 (n = 51), pCO_2 (n = 51), and pH (n = 50) were measured by a blood gas analyzer (Radiometer ABL 330, Copenhagen, Denmark) immediately after cordocentesis in samples collected in heparinized syringes, and the values were compared to those of our reference ranges (Soothill et al 1986). Identification of the umbilical cord vessel sampled was made at the time of cordocentesis by the intravascular injection of 0.4 ml of normal saline solution (Nicolaides et al 1986). Because of the larger size of the umbilical vein this vessel is more often sampled, and in this study we have considered the data obtained from umbilical venous samples only.

Statistical analysis

In normal pregnancy measurements of fetal size, blood gases, and Doppler parameters change with gestational age (Bilardo et al 1988, Pearce et al 1988, Soothill et al 1986). To allow for this effect, each measurement in this study was subtracted from the normal mean for gestational age and expressed as difference (Δ). Table 3.I shows the equations to define the reference ranges for each Doppler and blood gas variable considered in the study. For the ultrasonographic biometric measurements, the normal means were derived from the normal ranges used in our ultrasonography unit.

Principal component analysis was used to create from the data an "asphyxia" index that would gather as much information as possible on fetal well-being as

expressed by individual measurements of pO_2, pCO_2 and pH (Chatfield & Collins 1980). This index is defined by the following equation: Asphyxia = $-\Delta pO_2 + 1.43 (\Delta pCO_2) - 180.2 (\Delta pH)$. The index encompassed 77% of the combined variance of blood gases and pH. Similarly, by means of principal component analysis a Doppler "aortic-carotid" index, combining the two most reproducible measurements of the central fetal circulation, i.e. aortic mean velocity (AoVm) and common carotid artery pulsatility index (CCPI), was defined by the equation: Aortic-carotid index = ΔAoVM + 4.2 (ΔCCPI). The combined variance of the two Doppler measurements encompassed by the index was 82%.

Multiple regression analysis (computer program BMDP9R, P. Royston, London) was used to determine the ability of each Doppler and ultrasonographic parameter, both singly and in all possible combinations, to predict fetal pO_2, pCO_2, and pH individually, and then combined in the asphyxia index. Combined Doppler measurements included the ratios between common carotid and aortic velocities and pulsatility indexes and the aortic-carotid index.

Results

The correlation coefficients and the residuals SD of the fetal blood gases, pH, and asphyxia index, regressed on each Doppler and ultrasonographic measurement, are shown in Table 3.II

The mean values for these parameters, expressed as Δ values, are listed in Tabel 3.III. Among the individual Doppler measurements, considered in a rank order, the predictors that showed the highest correlations with the asphyxia index were the Δ aortic mean velocity, Δ aortic pulsatility index, and Δ common carotid artery pulsatility index.

Table 3.II Correlation of ultrasonographic biometric and Doppler measurements with fetal blood gases, pH and asphyxia index.

	Po_2		Pco_2		*pH*		*Asphyxia*	
Measurement	*r*	*RSD*	*r*	*RSD*	*r*	*RSD*	*r*	*RSD*
ΔAC	0.28	8.9	−0.48	6.0	0.49	0.050	−0.48	22.1
ΔHC	0.32	8.9	−0.44	6.2	0.37	0.049	−0.44	22.8
ΔHC/AC	−0.30	9.0	0.37	6.4	−0.44	0.047	0.42	23.0
ΔUP RI	−0.58	7.7	0.35	6.5	−0.33	0.049	0.48	22.4
ΔUA PI	0.52	8.0	−0.40	6.4	0.49	0.043	−0.54	21.1
ΔAo Vm	0.51	8.0	−0.59	5.6	0.54	0.044	−0.62	19.7
ΔAo PI	−0.47	8.3	0.57	5.7	−0.57	0.043	0.61	20.0
ΔCC Vm	−0.28	9.0	0.41*	6.4	0.38*	0.040	−0.43	23.0
ΔCC PI	0.63	7.3	−0.43	6.2	0.51	0.045	−0.60	20.2
$\Delta CC/Ao_{Vm}$	0.63*	7.4	0.62*	5.4	0.57*	0.043	−0.68	19.0
$\Delta CC/Ao_{PI}$	0.66	7.1	−0.54	5.8	0.55	0.043	−0.66	19.3
Ao-CC index	0.62	7.4	−0.58	5.6	0.58	0.043	−0.67	18.7

Δ, Difference between obtained measurement and normal mean value for gestational age; *r*, correlation coefficient; *RSD*, residuals S-D; *AC*, abdominal circumference; *HC*, head circumference; *HC/AC*, head to abdominal circumference ratio; *UP RI*, uteroplacental resistance index; *UA PI*, umbilical artery pulsatility index; *Ao Vm*, aortic intensity-weighted mean velocity; *CC*, common carotid artery; *CC/Ao Vm*, ratio of *CC* and *Ao Vm; CC/Ao PI*, ratio of *CC* and *Ao PI; Ao-CC* index, aortic-carotid score created by principal component analysis.

*Required quadratic term in the regression: r is the square root of the index of determination r^2. $r = 0.28$, significant at $p = 0.05$. $r = 0.36$, significant at $p = 0.01$. $r = 0.45$, significant at $p = 0.001$.

The predictive ability of the individual Doppler measurements was greater if the ratios of common carotid to aortic velocity and pulsatility index were considered.

Table 3.III Means and SDs for each variable considered in the study, corrected for gestational age

Variable	*N*	*Mean*	*SD*	*SE*	*Minimum*	*Maximum*
Po_2	51	−15.46	9.24	1.29	−35.01	5.23
Pco_2	51	3.74	6.82	0.96	−9.34	25.21
pH	50	−0.03	0.05	0.01	−0.14	0.06
Asphyxia index	50	26.30	25.00	3.50	−29.40	84.30
AC	51	−5.31	3.41	0.48	−11.40	5.40
HC	50	−2.92	2.26	0.32	−7.20	1.50
HC/AC	50	0.15	0.12	0.02	−0.25	0.39
UP RI	50	0.71	0.18	0.02	0.35	0.96
UA PI	51	−1.27	1.37	0.19	−7.51	0.88
Ao Vm	51	−6.51	4.82	0.67	−16.00	4.71
Ao PI	51	0.39	0.56	0.08	−0.78	1.86
CC Vm	51	2.70	4.75	0.66	−7.13	14.40
CC PI	51	−1.33	0.87	0.12	−2.89	0.50
CC/Ao Vm	49	0.32	0.32	0.04	−0.26	1.01
CC/Ao PI	49	−0.66	0.63	0.09	−1.51	1.00
Ao-CC index	51	−12.10	7.70	1.10	−25.90	5.57

See Tables I and II for abbreviations.

The best combined predictor of asphyxia (i.e., that with the lowest residuals SD and the highest coefficient correlation value) was the aortic-carotid index (Fig 3.1).

Table 3.IV shows the prediction of percentiles of asphyxia index obtained from the aortic mean velocity and common carotid artery pulsatility index measurements adjusted for gestational age.

Table 3.IV Percentiles of asphyxia index for given values of aortic mean velocity and common carotid Pulsatility Index (PI) adjusted for gestational age and expressed as Δ values

	Ao Vm (Δ)								
CC PI (Δ)	*−15.0*	*−12.5*	*−10.0*	*−7.5*	*−5.0*	*−2.5*	*0.0*	*2.5*	*5.0*
−3.00	100.0	100.0	99.9	99.7	99.1	97.8	95.3	90.7	83.5
−2.75	100.0	99.9	99.8	99.5	98.7	97.0	93.7	88.0	79.6
−2.50	100.0	99.9	99.7	99.2	98.1	95.8	91.6	84.9	75.2
−2.25	100.0	99.9	99.6	98.9	97.3	94.3	89.1	81.2	70.4
−2.00	99.9	99.8	99.3	98.4	96.3	92.4	86.1	77.0	65.1
−1.75	99.9	99.6	99.0	97.7	94.9	90.1	82.6	72.3	59.5
−1.50	99.8	99.4	98.6	96.7	93.2	87.3	78.6	67.1	53.8
−1.25	99.7	99.2	97.9	95.5	91.1	84.0	74.1	61.7	47.9
−1.00	99.5	98.8	97.1	93.9	88.5	80.2	69.1	56.0	42.1
−0.75	99.3	98.2	96.0	91.9	85.3	75.9	63.8	50.2	36.5
−0.50	98.9	97.5	94.6	89.5	81.7	71.1	58.2	44.3	31.1
−0.25	98.4	96.5	92.7	86.6	77.6	65.9	52.4	38.6	26.2
0.00	97.8	95.1	90.5	83.2	73.0	60.3	46.5	33.1	21.6
0.25	96.9	93.5	87.8	79.2	67.9	54.6	40.8	28.0	17.6
0.50	95.7	91.4	84.5	74.8	62.5	48.8	35.2	23.3	14.0

See Tables I and II for abbreviations. Underlined values are beyond the 95th percentile for normal fetuses.

Δ Ao Vm and Δ CC PI are calculated by subtracting the normal expected mean for gestation from the measured Doppler value. The normal expected values for *Ao Vm* and *CC PI* from 20 to 42 weeks' gestation are listed below. For example, a fetus at 20 weeks' gestation with an *Ao Vm* of 17.5 cm/sec ($\Delta Ao\ Vm = -5$) and a *CC PI* of 0.99 ($\Delta CC\ PI = -2.75$) has a 98.7% chance of having an asphyxia index above the 95th percentile of its normal range.

Gestational age (wk)	*Aortic mean velocity (cm/sec)*	*Common carotid PI (units)*
20	22.5	3.74
21	23.6	3.80
22	24.7	3.85
23	25.6	3.88
24	26.5	3.90
25	27.4	3.91
26	28.1	3.89
27	28.8	3.87
28	29.4	3.82
29	29.9	3.77
30	30.3	3.69
31	30.7	3.61
32	31.0	3.50
33	31.2	3.39
34	31.3	3.26
35	31.4	3.11
36	31.3	2.95
37	31.2	2.77
38	31.1	2.58
39	30.8	2.37
40	30.5	2.15
41	30.1	1.91
42	29.6	1.66

The 50 individual values and the 95% intervals for the variation among individuals around the regression line of the asphyxia index on the aortic-carotid index are shown in Fig.3.1. In 38 fetuses the aortic-carotid index was at least 2 SDs below the normal mean; in all these cases the fetal asphyxia index was above the normal mean. In 34 cases (89% of the cases with abnormal aortic-carotid index) it was 1 SD above and in 23 (60%) it was 2 SDs above the normal mean. All fetuses with a normal aortic-carotid index (n = 12) had normal blood gas results (no false negatives). Multiple regression analysis did not improve the prediction of blood gases, pH, or asphyxia index above that of the best single predictor in each case; therefore linear regressions only are presented.

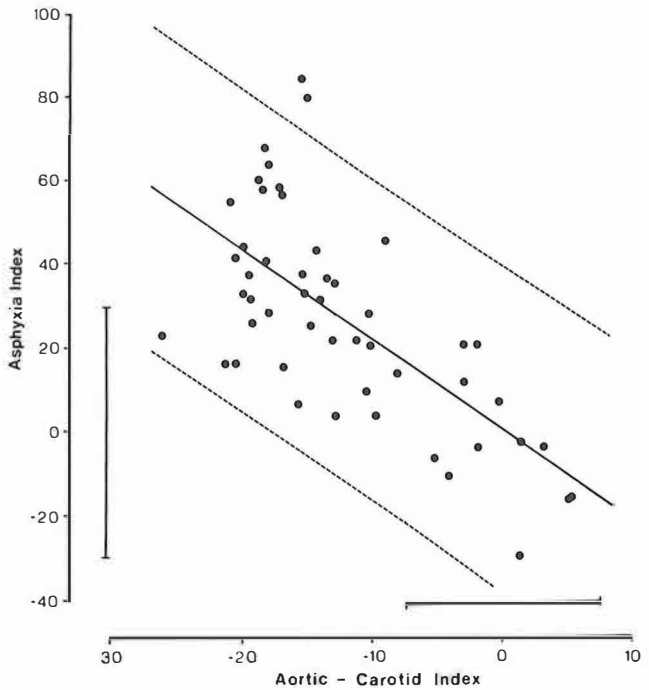

Fig 3.1 Individual values (n=50) and 95% intervals for the regression line of fetal asphyxia [$-\Delta pO_2 + 1.43\ (\Delta pCO_2 - 180.2\ (\Delta pH)]$ versus Doppler aortic-carotid index [Δaortic mean velocity + 4.2 (Δ common carotid artery pulsatility index)]. The two vertical and horizontal lines represent the normal range (mean ± SD) for the asphyxia index and the aortic-carotid index, respectively. A normal Doppler index was always associated with normal fetal blood gases (n= 12). When this index was abnormal 89% of the fetuses had an asphyxia index 1 SD above the normal range and 60% 2SD above the mean.

Discussion

Doppler ultrasonographic investigation facilitates the recognition of circulatory changes that occur in the human fetus under physiologic and pathologic conditions. This study examines the relationship between Doppler findings and the state of fetal oxygenation.

Impaired uteroplacental perfusion, as demonstrated by the increased impedance to flow in the uteroplacental circulation, is significantly correlated with fetal hypoxemia. This supports the findings from histopathologic studies that in some pregnancies with IUGR fetuses there is a failure of the normal development of maternal placental bed arteries into low resistance vessels, and the concept that one of the causes of fetal growth retardation is poor maternal blood supply leading to fetal malnutrition (Brosens et al 1977). Therefore reduced oxygen supply to the intervillous space results in fetal hypoxemia. Increased uteroplacental resistance index correlates significantly with fetal hypoxemia, but not necessarily with hypercapnia and acidosis because these are more closely related to the metabolic response to hypoxia and to damage to the vasculosyncytial membrane.

Whereas study of uteroplacental flow velocity waveforms provides information about the maternal side of the intervillous space, studies of flow velocity waveforms from the umbilical artery represent the fetal side of the exchange mechanism. Increased placental resistance may result from reduction in the number of placental terminal capillaries and small muscular arteries in the tertiary villi (Giles et al 1985), or from vasoconstriction mediated by the hypoxia-induced release of vasoactive substances. Thus the increase in pulsatility index correlates with the degree of fetal asphyxia and explains why increased resistance in the umbilical artery is associated with poor perinatal outcome. However, umbilical artery pulsatility index shows a weaker correlation with fetal asphyxia than the Doppler measurements of central fetal circulation, which are more directly related to fetal oxygenation.

Aortic mean velocity and common carotid artery pulsatility index are among the best individual predictors of fetal asphyxia. These are also the most reproducible Doppler measurements of the fetal circulation. The finding that common carotid arterial

mean velocity is a weaker predictor than common carotid pulsatility index may be caused by inaccuracies in the measurement of the angle of insonation to the vessel.

However, the altered fetal blood pO_2-pCO_2 homeostasis is better represented by the inverse relationship of resistance and velocities in the descending thoracic aorta and common carotid artery rather than by the measurement of only one of them. This suggests that the human fetus responds to hypoxia in a similar fashion to that described in animals. Thus in hypoxia there is an increase in the blood supply to the brain and reduction in the perfusion of the gastrointestinal tract, kidneys, and lower extremities (Peeters et al 1979). Although knowledge of the factors governing circulatory readjustments and their mechanism of action is incomplete, it appears that partial pressures of oxygen and carbon dioxide play a role, presumably through their action on chemoreceptors. Previous studies have attempted to make use of knowledge obtained from animal studies of hypoxia-induced centralization of flow by examining the ratio of the umbilical artery to the internal carotid artery pulsatility index in relation to growth retardation (Wladimiroff et al 1987, Arduini et al 1987). However, unlike the situation of the descending thoracic aorta, the umbilical arterial flow velocity waveforms are primarily influenced by the state of resistance in the placental microcirculation and not by the fetal chemoreceptor activity.

The ultrasonographic biometric measurements are weaker predictors of the fetal condition than Doppler measurements and, surprisingly, the symmetry or asymmetry of the growth pattern does not improve the correlation. These findings are compatible with the concept that growth retardation is only one of the causes of fetal "smallness", and the degree of smallness depends on the severity of the growth-retarding insult and on the original growth potential of the individual fetus. Therefore it is not surprising that Doppler ultrasonography constitutes a more accurate method of diagnosing fetal asphyxia than the widely used biometric methods.

The correlations between Doppler measurements and fetal condition imply that the degree of abnormality of the Doppler findings parallels the severity of fetal compromise. Nonetheless, there is still a substantial amount of random variation, which can be seen as "scatter" around the regression line in Fig. 3.1. This could be partly a result of technical inaccuracies in the Doppler measurements or the biologic

variation in the responsiveness of the individual fetus to the same stimulus.

When the aortic-carotid index was abnormal, 60% of fetuses were severely asphyxiated, whereas a normal ratio was always associated with good fetal oxygenation. Furthermore, the simple combination of common carotid artery pulsatility index and aortic mean velocity measurements can be used to establish the probability of a given fetus being hypoxemic and acidemic.

We thank Patrick Royston for the statistical assistance.

3.2 Doppler study of the fetal circulation during long-term maternal hyperoxygenation for severe early onset intrauterine growth retardation

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Abstract

In 21 severely growth-retarded, hypoxemic fetuses at 22-30 weeks' gestation, the effect of long-term maternal hyperoxygenation on serial Doppler measurements of the fetal descending thoracic aorta mean velocity (Vm), common carotid artery pulsatility index (PI) and umbilical artery PI was investigated. The treatment was continued on average for 4 weeks and delivery, at 26-34 weeks, was decided for fetal or maternal indications. In the subgroup of 12 fetuses that survived, the mean aortic Vm increased within 72 h of maternal hyperoxygenation. This increase continued for 1-8 weeks, after which there was a decrease to pretreatment values. In the subgroup of neonatal deaths (n = 5), there was a non-significant increase in mean aortic Vm. In the subgroup of intrauterine deaths (n = 4), there was a non significant trend for continuing deterioration in mean aortic Vm throughout the period of maternal hyperoxygenation. The mean carotid PI did not change significantly in any of the subgroups during maternal hyperoxygenation. However, in the subgroup that survived there was a tendency for improvement and in the subgroup of intrauterine deaths a tendency for deterioration. The mean umbilical artery PI did not change significantly in any of the groups or subgroups during maternal hyperoxygenation. Therefore, measurement of aortic Vm is a useful indicator of fetal response to maternal hyperoxygenation and its increase constitutes a favourable prognostic factor.

Introduction

Intrauterine growth retardation in the presence of impaired uteroplacental or fetoplacental circulations is associated with fetal hypoxemia and acidemia (Nicolaides et al 1989, Bilardo et al 1990). Furthermore, there is an associated redistribution in fetal blood flow in favour of the brain and at the expense of the viscera and musculoskeletal system (Cohn et al 1974, Peeters et al 1979). These hemodynamic adjustments can be detected by Doppler studies of the fetal circulation (Bilardo et al 1990, Bilardo et al 1988). The best indices reflecting this redistribution in fetal hypoxemia are a decreased blood velocity in the fetal descending thoracic aorta and a decreased impedance to flow in the fetal common carotid artery (Bilardo et al 1988).

In some hypoxemic growth-retarded fetuses, maternal hyperoxygenation is associated with return of fetal blood oxygen pressure (pO_2) to within the normal range and with increased blood velocity in the fetal aorta (Nicolaides et al 1987). This study examines the role of Doppler studies in monitoring the fetal hemodynamic response to prolonged maternal hyperoxygenation and the relationship between this response and fetal outcome.

Patients and methods

During a 5-year period (September 1985-December 1990), 407 patients with severely small-for-gestational-age fetuses were referred to our unit at 17-39 weeks' gestation for cordocentesis to determine fetal karyotype and blood gases (Nicolaides et al 1986).

The fetal karyotype was abnormal in 73 (18%) and normal in 334 of the cases. In the chromosomally normal group, the umbilical venous or umbilical arterial blood pO_2 was within the 90% confidence intervals of the appropriate reference range for gestation in 90 fetuses and below the 5th percentile in 244 cases. The parents of the chromosomally normal but hypoxemic fetuses were counselled extensively as to the available options depending on gestational age, estimated fetal size and degree of fetal hypoxemia, and the following decisions were made:

(1) Delivery within 24-48 h of cordocentesis (n = 91);

(2) Elective abortion (n = 15);

(3) Expectant management (n = 103);

(4) Maternal hyperoxygenation (n = 35).

In 21 of the group of 35 fetuses managed by maternal hyperoxygenation, serial measurements of the time-averaged, intensity-weighted mean blood velocity (Vm) in the fetal descending thoracic aorta were performed by Doppler ultrasound; additionally, in 18 of the cases, the pulsatility index (PI) in the fetal common carotid artery was measured. The mothers were hospitalized, rested in bed and given humidified oxygen to breath via an MC face mask at the rate of 8 l/min (delivering about 55% of oxygen) continuously, a part from the daily needs of hygiene and alimentation. The Doppler studies were performed twice a week without discontinuing the oxygen administration to the mother. In two of the 35 patients undergoing hyperoxygenation, but none of the 21 who had Doppler studies, therapy was interrupted for 2 days because of maternal hyperemesis. There were no other maternal complications.

The first Doppler measurements were performed immediately before cordocentesis. With the patients in a semi-recumbent position, flow velocity waveforms were recorded by a pulsed Doppler duplex scanner (Kranzbühler 8130, Berlin, West Germany) from the maternal uterine arteries, from the umbilical artery and from the fetal descending thoracic aorta and common carotid artery, as previously described (Bilardo et al 1988, Bilardo et al 1990). The high-pass filter was set at 150 Hz. All recordings were taken in the absence of fetal body or chest movements. For the uterine arteries, the resistance index (RI) was measured and the presence of a diastolic notch was noted. For the umbilical artery the pulsatility index (PI) was measured and the presence of end-diastolic frequencies noted. The fetal aortic Vm and common carotid artery PI were calculated (Bilardo et al 1988).

The results were not disclosed to the clinicians managing the patients and delivery was undertaken for maternal of fetal indications.

Statistical analysis

In each case fetal biometry, blood gases and Doppler results were expressed as the number of standard deviations (SDs) by which the measured values differed from the appropriate normal mean for gestation (Δ value)(Nicolaides et al 1989, Bilardo et al 1990, Yudkin et al 1987). Friedman's analysis of variance and Page's trend test were used to compare four series of Doppler measurements: (A) the measurement taken immediately before cordocentesis; (B) at 24-72 h after the onset of maternal hyperoxygenation; (C) representing the mean value of all measurements obtained during the period of maternal hyperoxygenation (excluding measurements B and D); and (D) taken within 3 days before delivery. The Wilcoxon rank sum test was then used to compare these four groups of measurements for different pregnancy outcome groups.

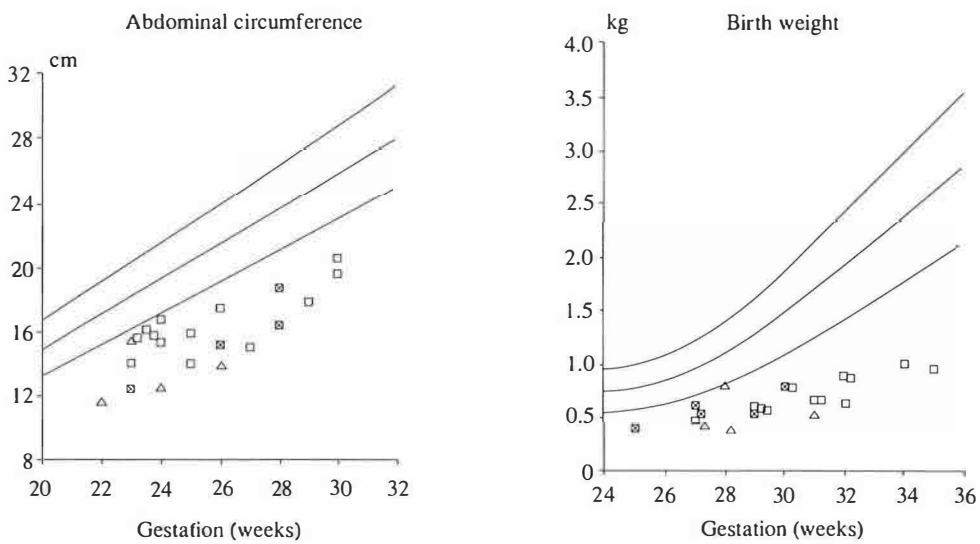

Fig 3.2 Fetal abdominal circumference at presentation and birth weight in 21 severely growth-retarded fetuses treated with maternal hyperoxygenation, plotted on the reference ranges (mean, 95th and 5th percentiles) for gestation. There were four intrauterine (▵) deaths and five neonatal (⊠) deaths; 12 babies survived (□).

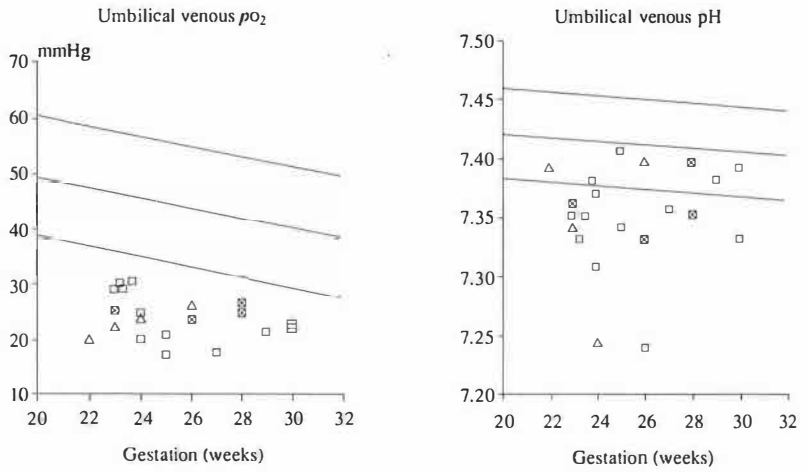

Fig 3.3 Umbilical venous blood pO_2 and pH in 21 severely growth-retarded fetuses treated with maternal hyperoxygenation, plotted on the reference ranges (mean, 95th and 5th percentile) for gestation. Subsequently, there were four intrauterine (△) deaths and five neonatal (⊠) deaths; 12 babies survived (□).

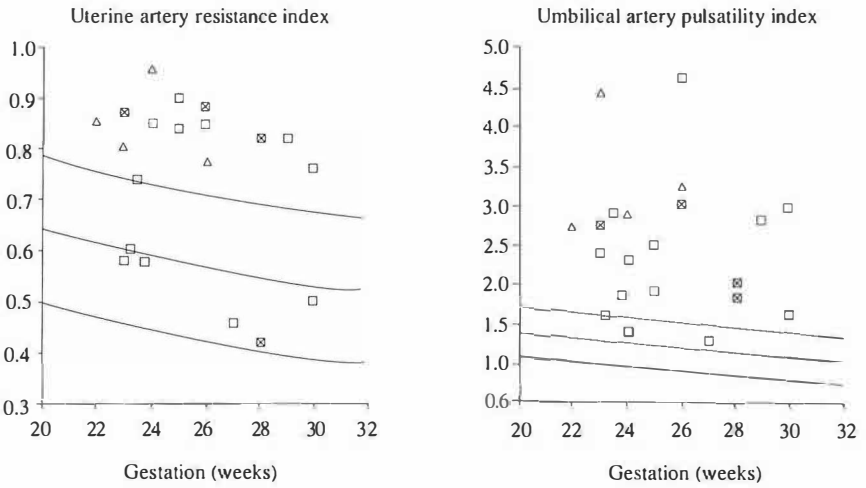

Fig 3.4 The highest uterine artery resistance index (RI;left) and umbilical artery pulsatility index (PI;right) in 21 severely growth-retarded fetuses treated with maternal hyperoxygenation, plotted on the reference ranges (mean, 95th and 5th percentile) for gestation. Subsequently, there were four intrauterine (△) deaths and five neonatal (⊠) deaths; 12 babies survived (□).

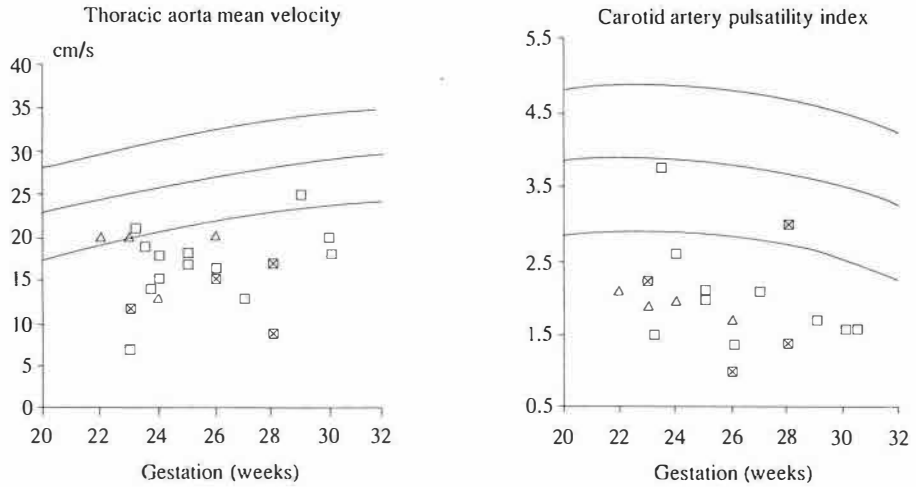

Fig 3.5 Fetal aorta time-averaged, intensity weighted mean blood velocity (Vm;left) and carotid artery pulsatility index (PI;right) in 21 severely growth-retarded fetuses treated with maternal hyperoxygenation, plotted on the reference ranges (mean, 95th and 5th percentile) for gestation. Subsequently, there were four intrauterine (△) deaths and five neonatal (⊠) deaths; 12 babies survived (□).

Table 3.V Standard deviation scores (Δ) for abdominal circumference, umbilical venous pO_2, pH, umbilical artery pulsatility index (PI), aortic mean velocity (Vm) and common carotid PI in the group of fetuses that survived and those that either died in utero or in the neonatal period.

	Survivors			*Neonatal death*			*Intrauterine death*		
	Median	*Range*		*Median*	*Range*		*Median*	*Range*	
Gestation (weeks)	24 ± 3	23	30	25 ± 6	23	28	23 ± 4	22	26
Δ abdominal circumference	−4.8	−8.0	−1.9	−5.5	−7.7	−4.1	−6.6	−8.1	−2.1
Δ pO_2	−2.5	−3.7	−2.0	−2.4	−2.7	−1.7	−2.7	−4.3	−2.0
Δ pH	−2.5	−4.7	−0.3	−2.5	−6.6	−0.7	−2.1	−6.6	−0.8
Δ umbilical PI	4.5	0.5	10.0	7.8	3.5	18.6	8.2	5.0	10.9
Δ aortic V_m	−2.9	−5.2	−1.3	−3.3	−5.8	−3.3	−1.9	−3.8	−1.3
Δ carotid PI	−3.5	−4.0	−0.1	−4.0	−4.8	−1.3	−3.3	−3.6	−2.9

Table 3.VI Standard deviation scores (Δ) for umbilical artery pulsatility index (PI), aortic mean velocity (Vm) and common carotid PI at different stages of maternal hyperoxygenation (A= before; B= within 72 hours; C= mean over the total period with exclusion of measurements A,B and D; D= within 3 days of delivery) in the total group of fetuses and in the subgroups of different outcomes.

	Mean standard deviation score			
	Total (n = 21)	*Survivors* (n = 12)	*Neonatal death* (n = 5)	*Intrauterine death* (n = 4)
Δ *Umbilical artery PI*				
A	6.8	4.5	7.8	9.7
B	6.5	5.0	6.7	9.5
C	5.4	4.4	6.5	6.7
D	6.8	6.4	10.3	8.8
Δ *Aortic* V_m				
A	−3.2	−2.9	−3.5	−1.9
B	−2.6	−2.0	−3.7	−2.6
C	−2.1	−1.1*	−2.8	−2.8
D	−2.9	−2.1*	−3.1	−3.4
Δ *Common carotid PI*				
A	−3.3	−3.2	−4.0	−3.3
B	−3.2	−3.2	−3.1	−3.3
C	−2.8	−2.5	−3.2	−3.2
D	−3.2	−2.8	−3.2	−3.9*

*significant change; $p < 0.05$

Results

In the 21 cases treated with maternal hyperoxygenation, the mean gestational age at cordocentesis was 25 weeks (range 22-30 weeks). In all cases the fetal abdominal circumference was below the 5th percentile of our reference range for gestation (Fig. 3.2). The umbilical venous blood pO_2 was below the 5th percentile in all cases, and 14 of the fetuses were acidemic (Fig. 3.3).

In 16 of the 21 cases, the highest uterine artery RI was above the 95th percentile (Fig. 3.4), and in 18 of the cases there was an early diastolic notch in the waveform from this vessel.

The umbilical artery PI was above the 95th percentile in 19 cases; in 16 of the cases there was absence of frequencies at the end of diastole in the waveform from this vessel, and in an additional two cases there was reversed flow (Fig. 3.4). The fetal aortic Vm was below the 5th percentile in 17 cases (Fig. 3.5), and the fetal carotid PI

was below the 5th percentile in 15 of the 18 cases in which it was measured (Fig. 3.5).

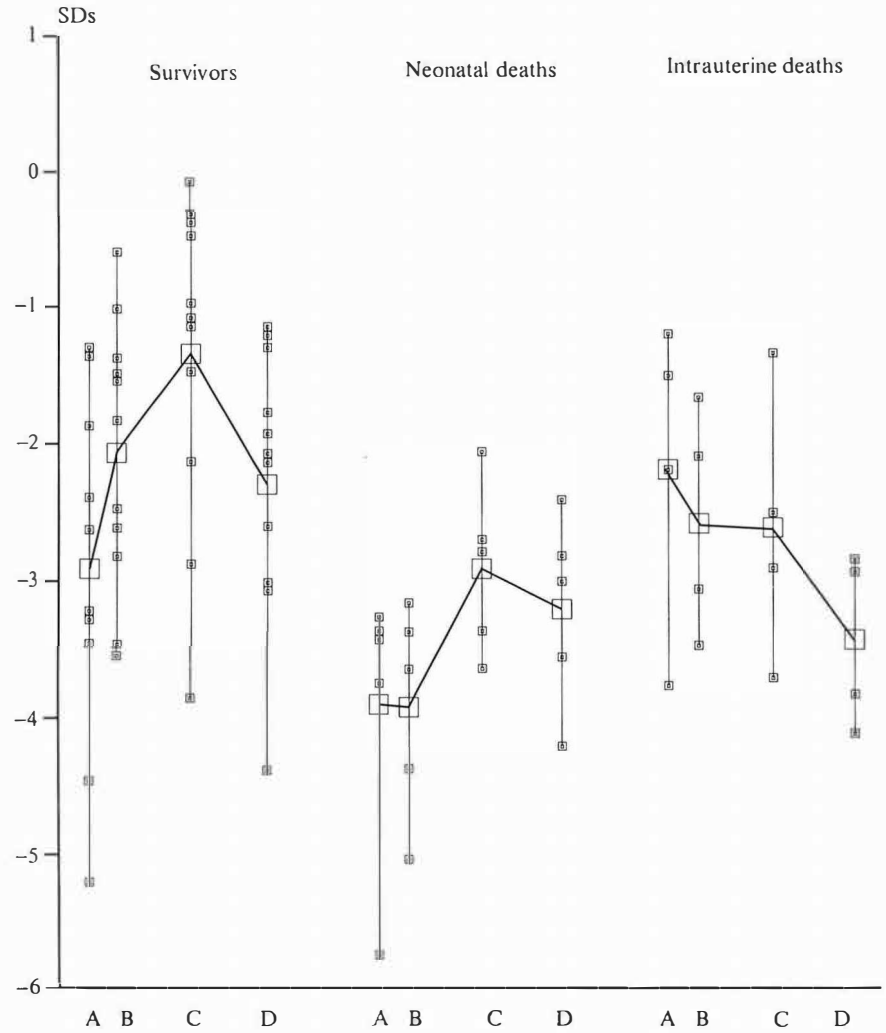

Fig 3.6 Changes in fetal aortic mean velocity (Vm) during maternal hyperoxygenation in the three outcome groups. In the subgroup of 12 fetuses that survived, the aortc Vm increased significantly within 72 hours of maternal hyperoxygenation and this increase was maintained for 1-8 weeks before decreasing to pretreatment values. In the subgroup of neonatal deaths there was a non-significant increase in mean aortic Vm. In the subgroup of intrauterine deaths there was a non-significant trend for continuing deterioration.

There were four intrauterine deaths after 3-5 (mean 4) weeks of maternal hyperoxygenation (gestation at death 27-31 weeks); although there was cardiotocographic evidence of fetal distress, delivery was not undertaken because the degree of growth retardation was considered to be too severe for postnatal survival. In the remaining 17 cases, delivery by Cesarean section was performed at 26-35 (mean 30) weeks' gestation and after 1-9 (mean 4) weeks of maternal hyperoxygenation.

The indications for delivery were antepartum hemorrhage (n=3), severe proteinuric pregnancy-induced hypertension (n=4), and decelerative fetal heart rate pattern (n=10).

Five infants died in the neonatal period and twelve are alive and now, at 1 - 4 years old, they are developing normally. The gestation at delivery and birth weight are shown in Fig. 3.2.

At the time of cordocentesis, there were no significant differences in gestational age, Δ abdominal circumference, ΔpO_2, ΔpH, Δ aortic Vm or Δ umbilical artery and Δ common carotid PI between the group of fetuses that survived and those that either died *in utero* or in the neonatal period (Table 3.V).

In the subgroup of 12 fetuses that survived, the mean aortic Vm increased significantly for 1-8 weeks, after which there was a decrease to pretreatment values ($Z = 3.09$, $p < 0.01$ and $Z = -2.13$, $p < 0.05$ respectively). In the subgroup of neonatal deaths (n = 5), there was a non-significant increase in mean aortic Vm and in the subgroup of intrauterine deaths (n = 4), there was a non-significant trend for continuing deterioration in mean aortic Vm throughout the period of maternal hyperoxygenation (Fig. 3.6, Table 3.VI; $Z = 1.78$, $p < 0.08$ and $Z = -174$, $p = 0.08$, respectively). The mean carotid PI and the umbilical artery PI did not change significantly in any of the subgroups (Fig. 3.7 and 3.8, Table 3.VI). However, in the subgroup that survived there was a tendency for improvement of common carotid PI and in the subgroup of intrauterine deaths a tendency for deterioration ($Z = 1.63$, $p = 0.10$ and $Z = -1.91$, $p = 0.06$, respectively).

After 24-72 h of maternal hyperoxygenation, the aortic Vm increased in 13 cases (Fig. 3.9). In this group of responders there were ten survivors and three deaths

(one intrauterine and two neonatal). No change or decreased aortic Vm was observed in eight cases. In this group there were two survivors and six deaths (three intrauterine and three neonatal). An increase in carotid PI was observed in only five of the 18 cases in which it was measured; two infants survived and three died in the neonatal period.

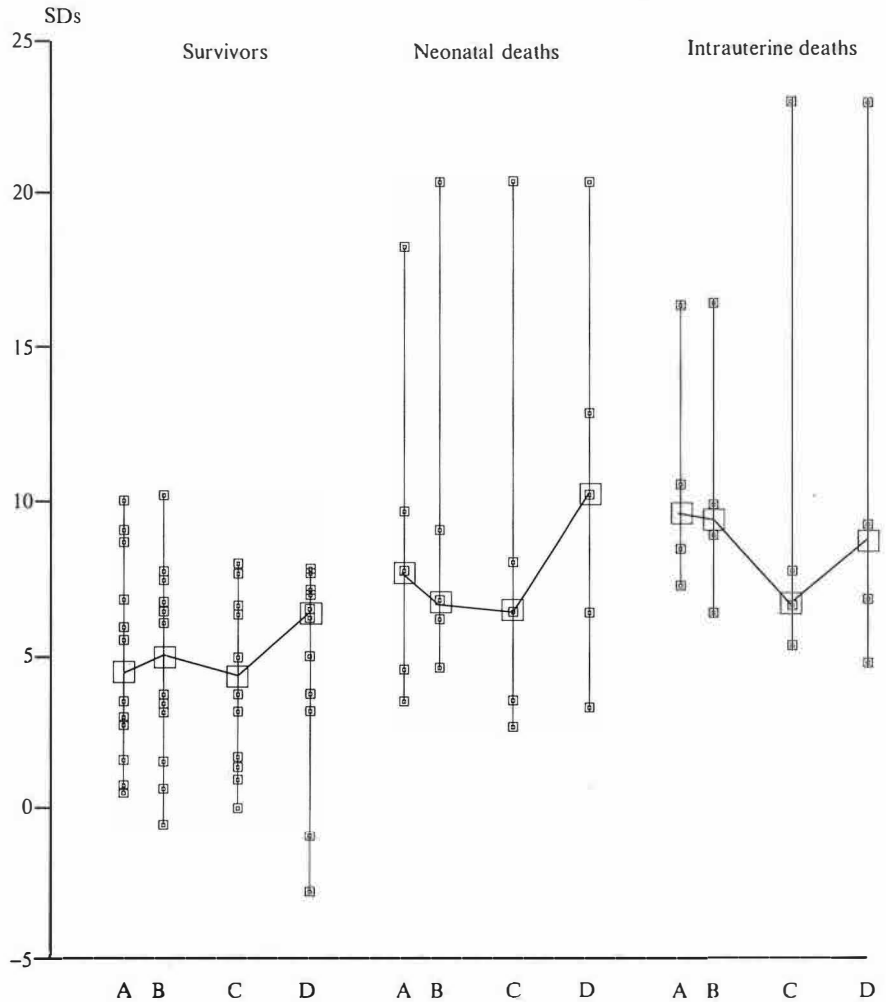

Fig 3.7 Changes in umbilical artery pulsatility index (PI) during maternal hyperoxygenation in the three outcome groups. The mean umbilical artery PI did not change significantly in any of the three groups. In the two fetuses with highest umbilical artery PI, there was persistent reversed flow at the end of diastole.

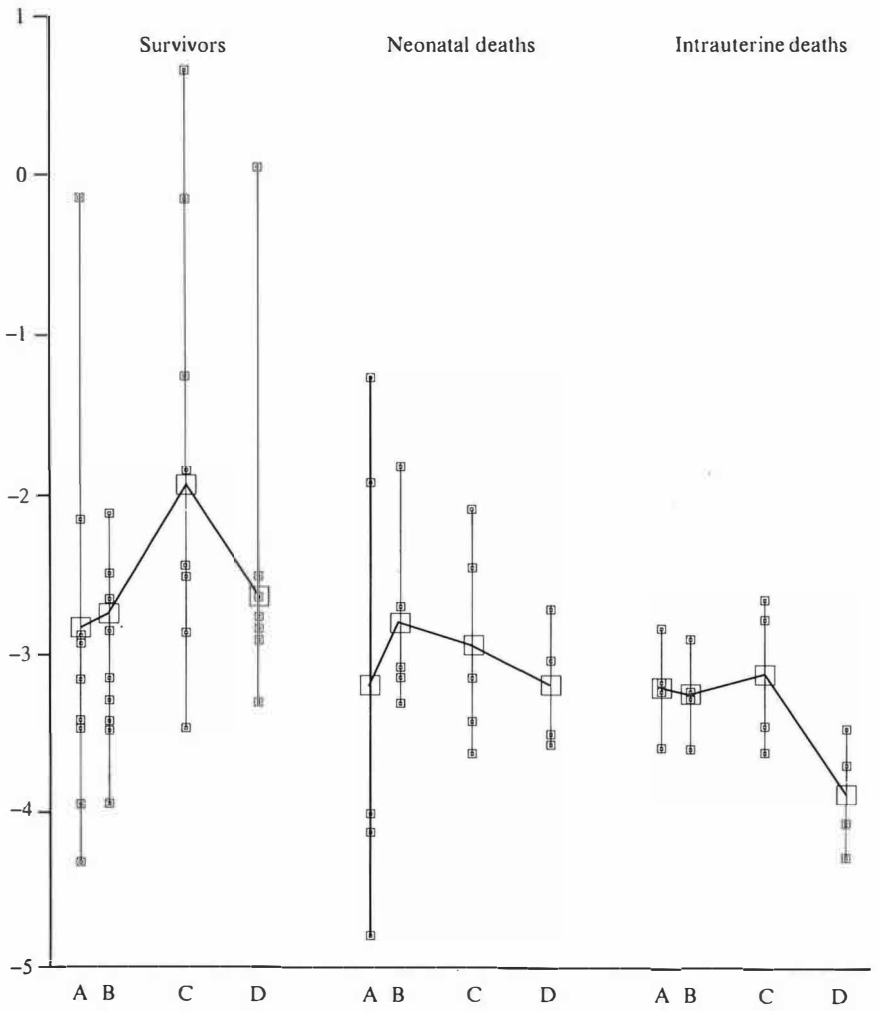

Fig 3.8 Changes in fetal common carotid artery pulsatility index (PI) during maternal hyperoxygenation in the three outcome groups. The mean common carotid PI did not change significantly in any of the three subgroups. However, in the fetuses that survived, there was a tendency for improvement and in the subgroups of neonatal and intrauterine deaths there was a non-significant trend for continuing deterioration.

Discussion

In the group of hypoxemic, chromosomally normal, severely growth-retarded fetuses, the most likely cause of growth retardation was impaired uteroplacental and/or

fetoplacental perfusion, as indicated by the increased impedance to flow in the uterine artery and umbilical artery. It was, therefore, reasonable to assume that, since the most likely cause of fetal hypoxemia was reduced materno-fetal exchange, maternal hyperoxygenation would improve fetal oxygenation. Direct evidence for improved fetal blood gases was provided by cordocentesis (Nicolaides et al 1987).

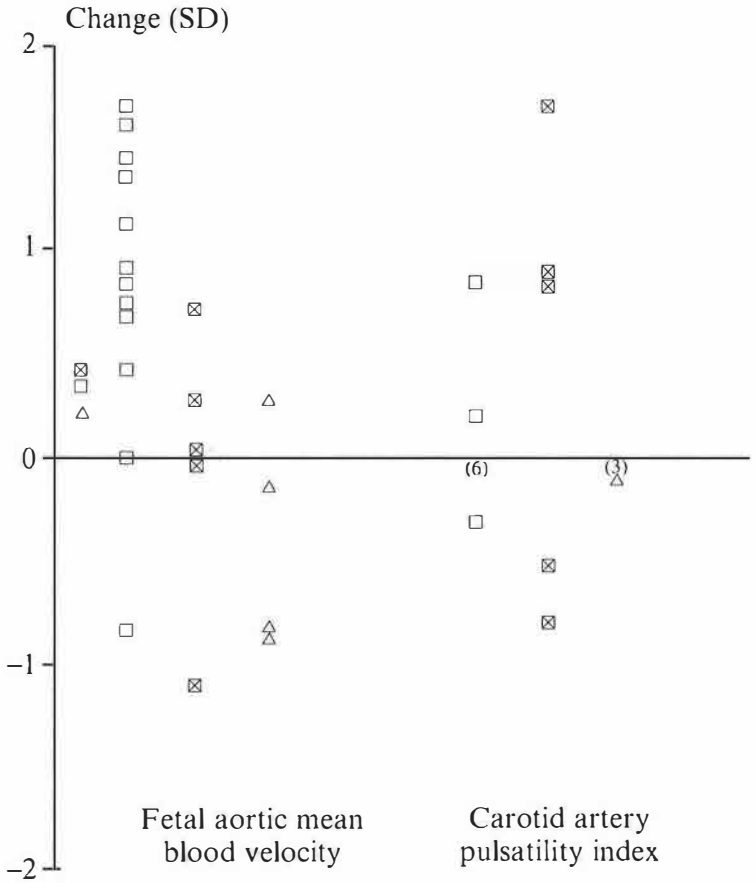

Fig 3.9 Changes in fetal aortic mean velocity (Vm) and common carotid artery pulsatility index (PI) after 24-72 hours of maternal hyperoxygenation. The distance of each symbol from the zero line represents the degree of change from pre-treatment measurements in SDs. In the group where the aortic Vm increased there were ten survivors (□), two neonatal deaths (⊠) and one intrauterine death (△). In contrast, in the group with no change or decrease in fetal aortic mean blood velocity there were six deaths and only two survivors. Increase in carotid artery PI was observed in only five of the 18 cases in which it was measured: two infants survived and two died in the neonatal period.

Furthermore, several studies in intrauterine growth retardation have variably demonstrated that short-term maternal hyperoxygenation is associated with increased incidence especially of fetal breathing movements and increased fetal heart rate variation (Gagnon et al 1990, Bekedam et al 1991).

In fetal hypoxemia there is an associated decrease in aortic Vm and carotid PI. These findings have been attributed to chemoreceptor-mediated redistribution in blood flow in favour of the brain and at the expense of the viscera and musculoskeletal system (Bilardo et al 1990, Peeters et al 1979). The observed increase in fetal aortic Vm in response to maternal hyperoxygenation can be the consequence of improved fetal oxygenation and reversal of the chemoreceptor-mediated redistribution in fetal circulation. However, the increase in aortic Vm was not accompanied by increased carotid PI. Therefore, an alternative explanation for the observed Doppler changes is improved cardiac oxygenation leading to increased cardiac output and blood velocity in the descending thoracic aorta, without alteration in impedance to flow in the brain. Rizzo et al (1990). have demonstrated that during hyperoxygenation there is a change in the distribution of cardiac output in favour of the right side and therefore in aortic Vm.

These findings are in contrast to those of Arduini et al. who examined 22 third-trimester small-for-gestational-age fetuses (mean gestation 32 weeks) with abnormal fetal velocity waveforms in the aorta and internal carotid artery (Arduini et al 1989). During 20 min of maternal hyperoxygenation, impedance to flow in the aorta decreased and in the internal carotid increased to normal in 12 of the fetuses; in ten cases there was no hemodynamic response.
Subsequently, the non-responders developed acute fetal distress (abnormal fetal heart rate patterns) and were delivered within 3-9 days of the test. In contrast, the responders were delivered 7-28 days (median 18 days) after the test. All infants survived.

In the study of Arduini et al (1989), since the reversal of redistribution was immediate, this is likely to be the consequence of a chemoreceptor-mediated effect. Our fetuses were much younger and more severely growth-retarded and, although their carotid PI was well below the normal range, it did not change significantly in

response to maternal hyperoxygenation. These findings suggest that chemoreceptor control of the cardio-vascular system either occurs after 30 weeks' gestation or, if it occurs earlier in normal pregnancy, it is delayed in severe growth retardation. The low carotid PI both before and during maternal hyperoxygenation could be a consequence of local metabolite-mediated cerebral vasodilation.

Irrespective of the underlying mechanism, the lack of significant effect of maternal hyperoxygenation on fetal carotid PI could be beneficial for the fetus. Hypoxemic growth-retarded fetuses are also hypoglycemic (Economides & Nicolaides 1989). If the increased cerebral perfusion of hypoxemic fetuses was suppressed during maternal hyperoxygenation, the result would be a decreased supply of glucose and other essential nutrients to the brain.

Long-term maternal hyperoxygenation was associated with three patterns of change in fetal aortic Vm and this was related to outcome. In the group of fetuses that died *in utero*, the aortic Vm continued to decrease despite maternal hyperoxygenation, presumably because the extreme impairment of placental perfusion did not allow an increased diffusion of oxygen into the fetal circulation or, alternatively, the fetus was already so irreversibly compromised that no response to the increased pO_2 could take place.

Similarly in those babies that died in the neonatal period, maternal hyperoxygenation did not improve fetal oxygenation and there was no significant change in aortic Vm during therapy. Alternatively, in these fetuses a tendency for improved oxygenation was counterbalanced by a trend of worsening placental function; the fetal pO_2 was maintained and the aortic Vm did nor change. In the group of fetuses that survived, there was a significant increase in aortic Vm and in some cases improvement was such that delivery could be postponed for several weeks. Indeed, in seven of these cases delivery was undertaken for maternal complications, such as antepartum hemorrhage or worsening hypertension, rather than abnormal fetal heart rate patterns. In the latter group, after an initial temporary increase in aortic Vm, the velocity decreased to pretreatment levels and this was followed by the development of abnormal fetal heart rate patterns which prompted an emergency delivery.

The value of maternal hyperoxygenation for the treatment of severe, early onset, hypoxemic growth retardation remains to be established. Nevertheless, the findings of the present study suggest that lack of improvement in aortic blood velocity within 72 h of maternal hyperoxygenation is associated with a very poor prognosis. In those fetuses that do respond, serial Doppler measurements may be useful in timing delivery.

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Chapter 4

Doppler findings in anaemic fetuses

This chapter examines the relationship between fetal haemoglobin concentration and Doppler indices of the placental and fetal circulation in red blood cell isoimmunisation. In addition it reports on the effects of intrauterine blood transfusion on the fetal circulation and on other parameters indicative of the fetal condition.

Modified from:

CM Bilardo, KH Nicolaides, S Campbell. Doppler studies in red cell isoimmunization. Clinical Obstetrics and Gynecology 1989;32:719-725.

KH Nicolaides, CM Bilardo, S Campbell. Prediction of fetal anaemia by measurement of mean blood velocity in the fetal aorta. American Journal of Obstetrics and Gynecology 1990;162:209-212

4.1 Doppler findings before fetal blood transfusion

Summary

This study examines the relationship between the degree of fetal anaemia in red blood cell isoimmunised pregnancies and Doppler indices of the placental and fetal circulation. Doppler studies were performed immediately before cordocentesis for measurement of haemoglobin concentration. There were significant correlations between the degree of fetal anaemia and increased velocity in the fetal descending thoracic aorta and common carotid artery. The highest correlations were found in previously untransfused fetuses. These findings suggest that Doppler assessment of the fetal circulation may be useful in identifying the anaemic fetus and therefore in timing cordocentesis. Furthermore, Doppler studies have improved our understanding of fetal cardiovascular responses to anaemic hypoxia.

Introduction

The underlying pathophysiology of red blood cell isoimmunisation is fetal haemolysis and consequent anaemia (Nicolaides et al 1988b, Nicolaides 1989). The fetus presumably compensates for moderate degrees of anaemia by haemodynamic adaptations. With severe anaemia, tissue hypoxia occurs, as shown by the rise in fetal lactate levels (Soothill et al 1987a). When the haemoglobin deficit exceeds 7 g/dl the functional reserve of the cardiovascular system is exhausted and hydrops fetalis develops (Nicolaides et al 1985, 1988b).

Prediction of the severity of the disease has depended traditionally on the history of previous affected pregnancies, the type and level of haemolytic antibody in the maternal circulation, the amniotic fluid ΔOD 450nm, and more recently on monitoring of the fetal heart rate pattern (Visser et al 1982, Nicolaides et al 1989), and on ultrasonographic measurements of the fetus, the umbilical vein and placenta (Nicolaides et al 1988a). However, ultrasonographic measurements and fetal heart rate monitoring are of limited use because of the high false-negative rate and Liley charts are unreliable before 26 weeks (Nicolaides et al 1986b). The only accurate method for assessment of the severity of the disease is blood sampling by cordocentesis and measurement of the fetal haemoglobin concentration (Nicolaides et al 1988b). However, even in experienced hands, cordocentesis carries a risk of miscarriage and of fetomaternal haemorrhage which would worsen the severity of the disease. Thus, the indication for, and the timing of fetal blood sampling in the context of this disease need to be defined adequately.

Doppler studies have been regarded as a possible non-invasive tool for the identification of fetuses in need of a transfusion (Kirkinen & Jouppila 1983, Gill et al 1984, Griffin et al 1983, Rightmire et al 1986).

The aim of this study was to gain a better understanding of the haemodynamic responses to anaemia in human fetuses and to evaluate the role of Doppler in the prediction of the severity of fetal haemolysis.

Patients and methods

This was a study of red blood cell isoimmunised pregnancies that were referred to our centre for assessment and treatment by fetal intra-vascular transfusion. Doppler studies of the uterine artery (n=78), umbilical artery (n=125), fetal descending thoracic aorta (n=150) and common carotid artery (n=57) were performed within 2 hours before fetal blood sampling. Gestational age ranged between 17 and 38 (mean 25) weeks. In 78 cases Doppler measurements were performed before the first fetal transfusion.

For the uterine and umbilical arteries continuous wave Doppler was used and the resistance index and pulsatility index respectively were measured. For the fetal descending thoracic aorta and common carotid artery mean blood velocity was measured using duplex-pulsed wave Doppler. The equipment and techniques are as described in Chapters 1 and 2.

In all cases a detailed ultrasound examination was performed for fetal biometry and documentation of fetal skin oedema and collection of extravascular fluid in the serous cavities (hydrops fetalis). Hydrops was detected in 17 fetuses. At cordocentesis, fetal blood was obtained for measurement of haemoglobin concentration. When the fetuses were anaemic an intravascular blood transfusion was given as previously described and at the end of the transfusion the haemoglobin concentration was measured (Nicolaides et al 1986a).

Since in normal pregnancy both fetal haemoglobin concentration and the various Doppler indices change with gestation, the individual values from the red blood cell isoimmunised pregnancies were expressed as deviation in SD's from the appropriate normal mean for gestation (Royston 1991). Subsequently, regression analysis was used to determine the significance of any associations between the degree of fetal anaemia and deviations in Doppler indices.

Results

Fetal heart rate was not significantly higher in anaemic fetuses as compared to normal fetuses. The flow velocity waveforms (FVW) from the descending thoracic aorta of severely anaemic fetuses demonstrated characteristic changes from normal (Fig. 4.1). There was narrowing of the spectrum with a translucent window under the systolic curve, a late systolic hump and increase in diastolic frequencies, presumably due to reduced peripheral resistance. The latter was even more pronounced in the abdominal aortic FVW. Because of the high aortic velocity the phenomenon of aliasing was commonly encountered, requiring the use of a higher pulsed repetition frequency.

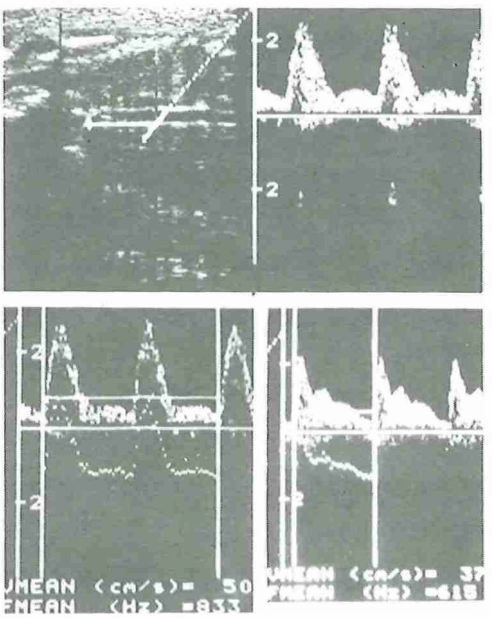

Fig 4.1 Characteristic appearance of flow velocity waveforms from the fetal descending thoracic aorta in severe fetal anaemia. **(Top left)** Longitudinal section of the fetal chest. The sample gate is placed on the vessel and the interrogation angle is demonstrated. **(Top right)**: Aortic Flow Velocity Waveforms (FVW) with aliasing phenomenon(the peaks of the waveforms are cut off and appear in the bottom channel). **(Bottom left)** Narrowing of the spectrum and translucent window under the systolic curve in the aortic FVW. **(Bottom right)** Late systolic hump in the abdominal aortic FVW of a hydropic fetus. The measured velocities are 2SD above the normal mean for gestation.

The relationship between the degree of fetal anaemia and deviations in the various Doppler measurements are shown in Table 4.I. There were no significant correlations between fetal anaemia and either uterine artery resistance index or umbilical artery pulsatility index. There was an overall significant correlation of aortic mean velocity with the degree of anaemia; this was even stronger in untransfused fetuses (n=78). For the common carotid mean velocity a significant correlation was found in untransfused fetuses only (n=12).

Table 4.I Relationship between fetal haemoglobin concentration and placental or fetal Doppler parameters expressed as deviations (in SDs) from the appropriate normal mean for gestation. PI=pulsatility index, RI=resistance index, Vm=mean velocity.

	All Data		Before First Transfusion	
DOPPLER PARAMETER	n	r	n	r
Uterine RI	78	0.151	24	0.087
Umbilical Artery PI	125	-0.004	35	-0.184
Aortic Vm	150	-0.297**	78	-0.511***
Common Carotid Vm	57	-0.121	12	-0.640*
Carotid / Aortic Vm	55	-0.063	12	0.121

* $p<0.05$; constant=-0.495, slope=-0.125, residual SD=0.606
** $p<0.001$; constant=-0.366, slope=-0.197, residual SD=1.766
*** $p<0.0001$;constant=-0.410, slope=-0.268, residual SD=1.606

For the non-hydropic fetuses, there was a significant positive correlation between the deviation in aortic mean velocity and the deviation in haemoglobin concentration (Fig 4.3; n=39, r=0.75, $p<0.0001$, constant=-0.25, slope=1.25, SD=2.9). For the hydropic fetuses, there was a significant negative correlation between these two parameters (Fig 4.3; n=15, r=0.67, $p<0.05$, constant=300, linear constant=-66, quadratic constant=3.7, SD=7.7).

For the non hydropic fetuses the accuracy of predicting the haemoglobin concentration deficit by measurements of the aortic mean velocity is shown in Table 4.II If the cut-off level for the aortic mean velocity is set at 2 SD's above the normal mean for gestation, more than 77% of the severely anaemic fetuses (haemoglobin deficit $\geq$7 g/dl) will be detected with a false-negative rate (haemoglobin deficit $\leq$2 g/dl) of <11%

Table 4.II Accuracy of Aortic mean velocity measurements in predicting the fetal haemoglobin deficit

Cutoff value of Deviation in Aortic Mean Velocity	Fetal Haemoglobin Deficit (g/dl)									
	0 %	1 %	2 %	3 %	4 %	5 %	6 %	7 %	8 %	9 %
+2SD	0	5	11	19	33	50	64	77	88	94
+1SD	15	25	40	55	71	82	91	96	100	100
0	48	62	77	87	94	97	100	100	100	100
-1SD	82	90	96	100	100	100	100	100	100	100
-2SD	97	100	100	100	100	100	100	100	100	100

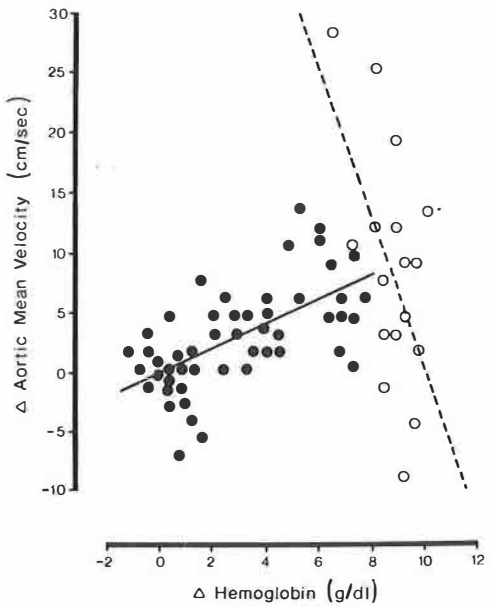

Fig 4.2 Relation between deviation (Δ) in aortic mean velocity (Δ = observed aortic mean velocity minus normal mean for gestation) and haemoglobin deficit (Δ =normal mean haemoglobin concentration for gestational age minus observed value) in 51 nonhydropic (●) and 17 hydropic (O) fetuses from red blood cell isoimmunised pregnancies.

Discussion

The adult compensates for anaemia by increasing cardiac output and blood flow to the tissues (Duke & Ablemann 1969). The finding of our study that in red blood cell isoimmunised pregnancies the mean blood velocity in the fetal aorta and common carotid artery are increased suggests that the same haemodynamic adjustments may operate in the human fetus. These results are at variance with the findings of Fumia et al (1984) that in fetal lambs there was no increase in cardiac output at low haematocrits. However, our results are compatible with data from fetal cardiac Doppler studies indicating that cardiac output in anaemic human fetuses is increased (Visser et al 1988, Copel et al 1989; Rizzo et al 1990).

The increase in velocity is likely to reflect an increase in cardiac stroke volume leading to an increase in both peripheral and central blood flow. This is based on the observation that heart rate is not affected by anaemia and the assumption that the cross sectional area of the aorta and common carotid artery are not altered. This may confirm the prediction, from a mathematical model, that in fetal anaemia cardiac output is increased to maintain an adequate oxygen delivery to the tissues (Huikeshoven et al 1985).

As in post-natal life, the correlation between anaemia and cardiac output may be mediated by an increase in stroke volume due to: first, decreased viscosity leading to increased venous return (pre-load); second, hypoxic peripheral vasodilation and therefore decreased peripheral resistance (after-load); and third, hypoxic stimulation of chemoreceptors leading to improved myocardial contractility (Guyton et al 1958, Daniel et al 1986).

As a result of these mechanisms, increased peak velocity in the ductus venosus of anaemic fetuses may be a compensatory mechanism to maintain adequate myocardial and cerebral oxygen supply (Oepkes et al 1993).

The increase in common carotid artery mean velocity presumably reflects the anaemia associated increase in cardiac output rather than a chemoreceptor-mediated redistribution in blood flow as seen in hypoxaemic growth retarded fetuses (Chapter 2). A similar increase in cerebral blood flow in anaemic fetuses was reported by Vyas

et al (1990), who examined the middle cerebral artery.

Although in severe anaemia the fetus is subjected to varying degrees of hypoxia (low oxygen content), blood pO_2, pCO_2 and pH generally remain within the normal ranges for gestation (Soothill et al 1987b, Nicolini et al 1988, Westgren et al 1989). This suggests that changes in tension of respiratory gases, rather than in oxygen content, may regulate chemoreceptor activity.

Copel et al (1988), measured peak velocity in the descending thoracic aorta immediately before cordocentesis and derived a series of formulae for the prediction of fetal haematocrit (above or below 25%). Similarly to our findings the best prediction was achieved for previously untransfused fetuses. Prediction of anaemia by Doppler velocity measurements becomes less accurate at subsequent transfusions, presumably because of the different properties of adult rather than fetal blood in the fetal circulation.

In hydropic fetuses, the haemoglobin concentration deficit was $\geq$7 g/dl and in these cases the aortic mean velocity decreased with worsening anaemia. These findings suggest that in severe anaemia hypoxia and lactic acidosis may decrease cardiac contractility (Soothill et al 1987a, 1987b). Moreover, impaired venous return due to liver infiltration with haemopoietic tissue may contribute to cardiac decompensation (Nicolaides et al 1985, Nicolaides 1989). Furthermore, increased downstream resistance could be due to clogging of placental capillaries with large immature red blood cells because in severe anaemia there is recruitment of extramedullary erythropoiesis and an increase in circulating erythroblasts (Nicolaides et al 1988c). Hypoxic myocardial dysfunction may also be responsible for the increased umbilical venous pressure found in hydropic fetuses (Weiner et al 1989a).

Rightmire et al (1986), found a significant inverse correlation between umbilical arterial resistance index and fetal haematocrit and suggested that increased impedance in the placental microcirculation may be due to clogging of the placental capillaries by the large fetal erythroblasts. However, in our study of a much larger number of cases there was no change in impedance to flow either in the umbilical or the uterine arteries. Therefore, it is unlikely that fetal anaemia alters the utero-placental or feto-placental circulation.

In conclusion, Doppler studies have improved our understanding of fetal cardiovascular responses to anaemic hypoxia. In the prediction of fetal anaemia the diagnosis of hydrops fetalis by real-time ultrasonography identifies a group of fetuses with a haemoglobin deficit of 7 g/dl or more. In the absence of hydrops, the finding of an aortic mean velocity above the normal range suggests that the fetus is probably anaemic, whereas if the aortic mean velocity is at or below the normal mean for gestation the fetus is unlikely to be anaemic. However, because of the large overlap in values, as shown in Fig.4.2, in the clinical management of red blood cell isoimmunized pregnancies the finding of an aortic mean velocity within normal range for gestation cannot reassure that the fetus is not anaemic.

Increased aortic mean velocity measurements may be useful in identifying the anaemic fetus and therefore in timing the first cordocentesis. Furthermore, serial weekly Doppler studies may help identifying the transfused fetus that is developing unexpectedly rapid anaemia.

4.2 Doppler findings following blood transfusion

Summary

Doppler studies of the placental and fetal circulation were performed before and after intravascular fetal blood transfusion. Transfusion was not associated with changes in the utero-placental and umbilical circulation. In the fetal circulation there was a decrease in mean blood velocity in both the descending thoracic aorta and the common carotid artery. These findings suggest that transfusion is associated with acute cardiovascular overload and that the fetus responds by reducing its cardiac output.

Introduction

Doppler studies in fetuses with immune hydrops undergoing intraperitoneal blood transfusion have demonstrated an immediate but temporary increase in umbilical venous blood flow followed by a gradual decrease to values within the normal range (Kirkinen et al 1983, Warren et al 1987). It was suggested that the gradual decrease in flow, coinciding with resolution of the fetal ascites, was the result of absorption of the transfused blood and correction of the fetal anaemia. Copel et al (1988), measured impedance to flow in the uterine and umbilical arteries and peak velocity in the descending thoracic aorta immediately before and 12 hours after fetal exchange transfusion by cordocentesis and found no significant differences.

The aim of this study was to investigate with Doppler technique the haemodynamic changes in the utero-placental and fetal circulation before and immediately after intravascular top-up transfusion for the correction of fetal anaemia.

Patients and methods

In red blood cell isoimmunised pregnancies undergoing fetal blood transfusions by cordocentesis (n=43), Doppler studies of the umbilical artery and fetal circulation were performed (as described in Chapters 1 and 2) immediately before and within 30 minutes after the transfusion. The mean gestation at cordocentesis was 28 weeks (range 18-36 weeks).

Cordocentesis was performed without maternal sedation or fetal paralysis. A fetal blood sample was first obtained for measurement of the haemoglobin concentration. The tip of the needle was kept in the lumen of the umbilical cord vessel and an appropriate volume of fresh, packed, rhesus negative blood compatible with that of the mother was infused manually into the fetal circulation through a 10 ml syringe (Nicolaides et al 1986a, 1987). The rate of transfusion was 5-15 ml/min, which represents on average an increase in the fetoplacental blood volume of 10%/min (Nicolaides et al 1987). The fetal heart rate and the flow of the infused blood were monitored continuously throughout the procedure by ultrasonography. At the end of the transfusion a further fetal blood sample was aspirated for determination of the final haemoglobin concentration.

Results

After transfusion there was a significant decrease in mean velocity in both the descending thoracic aorta ($t=-8.68$; $p<0.05$ Fig 4.3) and common carotid artery ($t=-2.37$, $p<0.05$). This decrease was more marked in the aorta as demonstrated by the increase in the mean carotid to aortic velocity ratio from 0.385 to 1.191.

There was a significant correlation between the differences in aortic and common carotid mean velocities measured before and after transfusion ($n=28$, $r=-0.4$, $p<0.05$). No significant correlation was found between the change in the Doppler parameters and either the volume of blood transfused and the feto-placental plasma volume expansion or the rate of expansion.

The umbilical arterial pulsatility index was not affected significantly by the transfusion. There was a non-significant decrease in fetal heart rate.

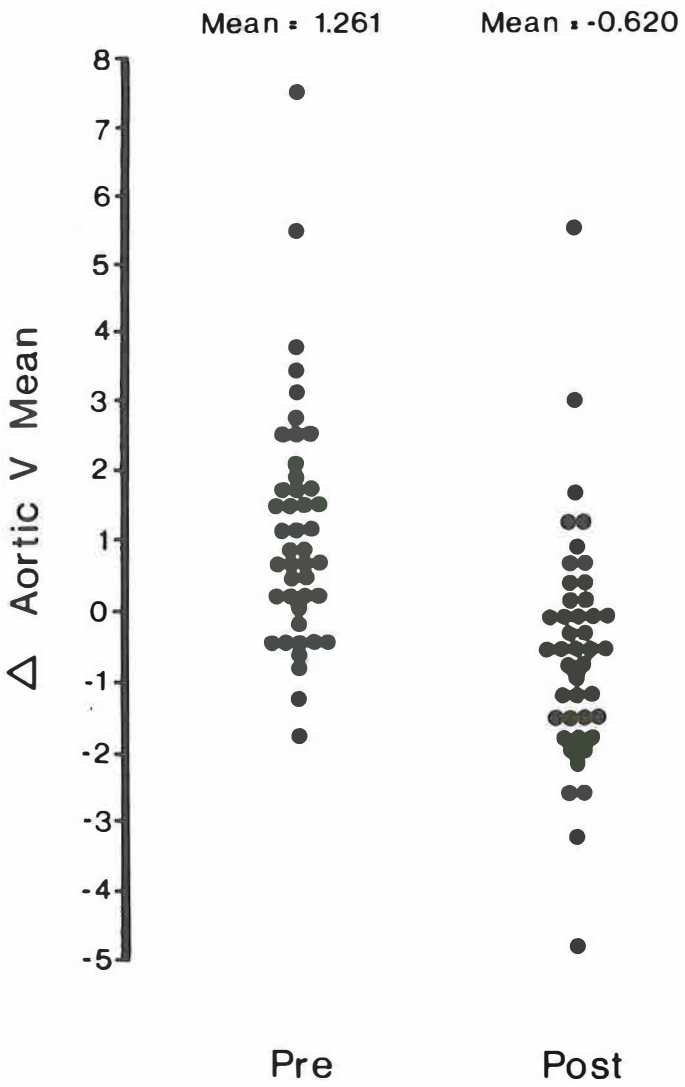

Fig 4.3 Pre-transfusion and post-transfusion Δ aortic mean velocities (SD's from normal mean for gestation).

Discussion

The data of this study demonstrate that intrauterine transfusion is associated with a decrease in aortic and common carotid artery mean velocities. These findings may be the consequence of decrease in cardiac output following the transfusion.

The fall in velocity was more marked in the aorta, but a significant correlation was found between the differences in aortic and common carotid velocities measured before and after transfusion, suggesting that the most likely explanation for these changes is a symmetrical reduction of right and left cardiac output. This was primarily the result of a decrease in stroke volume rather than in heart rate.

Confirmatory evidence of a decline in cardiac output following transfusion was provided by Moise et al (1990) and Rizzo et al (1990). Moise et al (1990), found that within 2 hours of a combined intra-vascular and intra-peritoneal transfusion there was an increase in venous pressure and a decrease of left and right ventricular output by 19% and 22% respectively. Rizzo et al (1990), measured left and right cardiac output at the atrio-ventricular valves before and at 15 minute intervals for two hours after intravascular transfusion. They reported a significant temporary fall in both right and left cardiac output. Furthermore, the ratios of early passive to late active ventricular fillings (E/A ratios) in both the tricuspid and mitral valves were increased, suggesting that cardiac pre-load was also increased. Within two hours of the transfusion both parameters had returned towards the normal range. The fall in cardiac output was significantly related to the amount of expansion of the feto-placental volume due to the transfusion.

The underlying mechanisms for the suggested decrease in cardiac output following blood transfusion include: (i) increased blood haemoglobin concentration and consequently increased viscosity that may result in decreased venous return (decreased pre-load) and (ii) correction of low blood oxygen content may abolish the hypoxia-induced peripheral vasodilatation (increased after-load). Increased mean arterial pressure and systemic vascular resistance, as observed in transfused animals (Brace 1989, Chestnut et al 1989, Fan et al 1980), may account for increased after-load. Alternatively, the reduced cardiac output may be the consequence of temporary congestive heart failure due to overloading of the fetal circulation, or cardioinhibition

due to increased baroreceptor activity. The latter is unlikely because transfusion is not associated with an increase but rather a decrease in fetal heart rate.

Animal studies have shown that the fetal heart has very limited reserve capacity to increase its output in response to acute overload (Gilbert 1980) and that an acute increase in fetal blood volume is associated with a decrease in cardiac output (Weiner et al 1989a). However, cardiovascular overload is rapidly normalized. After transfusion there is rapid loss of fluid (Brace 1989) and rapid recovery in E/A ratios and cardiac output (Rizzo et al 1990). Supportive evidence is provided by the finding that renal artery pulsatility index is reduced, presumably indicating elimination of excessive fluid (Mari et al 1991).

The short lived nature of the haemodynamic effects of blood transfusion can also explain the findings of Mari et al (1990a, 1990b) who reported that the pulsatility index in intra-cranial arteries, aorta, renal artery and umbilical artery before and the day after fetal transfusion were not significantly different. Similarly, Copel et al in a study of aortic velocity (1988) and cardiac output (1989) at 12 hours after intravascular blood transfusion found no significant differences from pre-transfusion values.

Immediately after transfusion we could not document any significant change in umbilical artery pulsatility index. This is in disagreement with the findings of Weiner & Anderson (1989) and Hanretty et al (1989) who reported a significant decrease in impedance immediately after fetal blood transfusion. It was postulated that simple needling of fetal vessels stimulated a humoral vasodilator mechanism. Supportive evidence was provided by the finding that vasoactive substances with vasodilatory effects, like prostaglandins and atrial natriuretic peptide, are increased in the fetal blood stream after intravascular transfusion (Robillard & Wiener 1988, Weiner & Anderson 1989, Panos et al 1989). However, the possible changes in indices of impedance after an intrauterine transfusion may not be simply due to vasodilatation (Kingdon et al 1991), but to the complex influence of improved fetal oxygenation, altered whole blood viscosity, increased number of scattering particles (red cells). In particular, as suggested by sheep experiments, central cardiovascular changes may overshadow the effect of vasodilator peptides on the fetal circulation (Brace et al 1989).

4.3 Fetal cardiovascular and behavioral responses to blood transfusion

Summary

This study investigates fetal cardiovascular and behavioural responses to a sudden feto-placental volume expansion. In red blood cell isoimmunised pregnancies fetal heart rate and its variation, generalised body movements and Doppler aortic blood flow velocities were recorded before and for one hour immediately after fetal blood transfusion by cordocentesis. After transfusion, in some fetus baseline heart rate decreased but variation increased and in others there was tachycardia with decrease in variation. Generalised body movements and aortic blood flow velocities decreased by 75% and 35% respectively, with the most striking reduction occurring in the tachycardic sub-group. These findings suggest that fetal blood transfusion entails considerable cardiovascular and behavioural changes. Tachycardia and the associated fetal responses may be due to increased fetal vulnerability to circulatory overload.

Introduction

In the management of red blood cell isoimmunisation, fetal anaemia is corrected by the infusion of donor blood into the fetal circulation (Nicolaides et al 1986a). In order to restrict the number of procedures and their duration, an amount of donor blood exceeding what is necessary to normalize a low fetal haemoglobin is transfused rapidly into the fetal circulation. This results in an abrupt expansion of the feto-placental blood volume.

Previous studies reported that fetal blood transfusion is associated with a temporary decrease in fetal intra-cardiac and aortic blood flow velocities (Copel et al 1989, Rizzo et al 1990, Warren et al 1987). The aim of this study was to investigate the effect of transfusion on other parameters indicative of the fetal condition, such as fetal heart rate pattern and fetal movements.

Patients and methods

The study population consisted of 10 red blood cell isoimmunised women who required repeated fetal blood transfusions for the correction of fetal anaemia. In eight cases two consecutive transfusions, at approximately three weeks interval, were monitored. In two cases the study was performed only once. The studies took place between 2.30 and 7.30 p.m. and all women had their last meal around noon.

The design of the study is illustrated in Fig 4.4. Fetal heart rate was recorded for one hour before and directly after transfusion with the woman in a semi-recumbent position (Hewlett Packard 8041A cardiotocograph, Boblingen, Germany). Heart rate and its variation were quantified using numerical analysis as previously described (Dawes et al 1985). Simultaneously, gross fetal body movements were observed by real-time ultrasound (Doptek 1000 duplex scanner, Chichester, England) and quantified using a hand-held push button. This information was fed into the same mini-computer as used for fetal heart rate analysis. With this system only one movement was accepted every 3.75 seconds (Dawes et al 1985). Mean blood flow velocity in the fetal descending thoracic aorta was measured (as described in Chapters 1 and 2) immediately before and after transfusion and at 30 and 60 minutes after transfusion. Complete and accurate measurements of aortic velocities both before and after transfusion were obtained in 11 of the 18 cases.

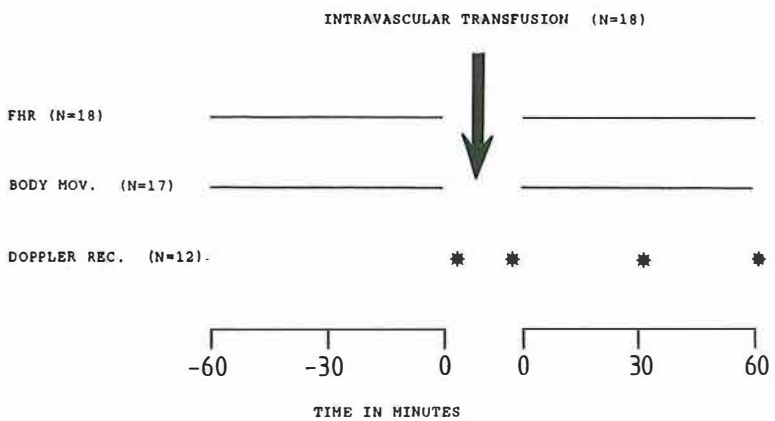

Fig 4.4 Study design: FHR = Fetal heart rate, **Body mov.**= Fetal body movements, **Doppler rec.**= Intensity weighted mean aortic velocity.

Results

Table 4.III provides data on the fetal blood transfusions. All fetuses survived.

Table 4.III Mean (SD) of gestation at transfusion, pre and post transfusion haemoglobin concentration blood oxygen tension and pH, and fetoplacental blood volume expansion during transfusion

Gestational age (wks)	28.9 ± 4.3
Pre-transfusion haemoglobin (g / dl)	8.7 ± 3.1
Post-transfusion haemoglobin (g / dl)	15.4 ± 2.0
Pre-transfusion blood oxygen tension	35.1 ± 8.3
Post-transfusion blood oxygen tension	33.3 ± 6.3
Pre-transfusion blood pH	7.37 ± 0.03
Post-transfusion blood pH	7.31 ± 0.05
Fetoplacental blood volume (ml)	105 ± 56
Fetoplacental blood volume expansion (%)	80 ± 31
Blood volume expansion rate (% / min)	11.6 ± 5.8

The median fetal heart rate was 140 bpm before transfusion and this fell to 127 bpm directly afterwards; this fall was accompanied by a widening of the interquartile range (Fig 4.5). Analysis of the data showed that the wider interquartile range was due to the presence of two sub-groups of fetuses (Fig 4.6). Six fetuses became tachycardic after transfusion and in 12 there was a decrease in fetal heart rate. In the tachycardic sub-group the median fetal heart rate before transfusion was already slightly higher than in the other sub-group. Approximately 15 minutes after transfusion fetal heart rate in both groups tended to return towards pre-transfusion values.

The median fetal heart rate variation did not change significantly after transfusion but the interquartile range became wider (Fig 4.7). Separate analysis of the two sub-groups showed that in the fetuses that subsequently became tachycardic fetal heart rate variation before transfusion was lower and after transfusion it decreased further (Fig 4.8).

Generalised body movements fell after transfusion by approximately 75% (Fig 4.9). In the fetuses that became tachycardic movements were absent for an average of 50 minutes after transfusion.

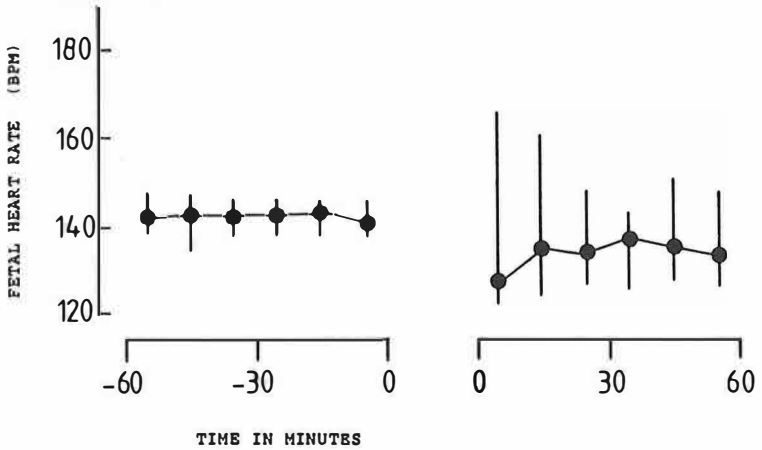

Fig 4.5 Median and interquartile range of fetal heart rate (beats per minute) recorded for one hour before and one hour after transfusion. (n= 18 occasions).

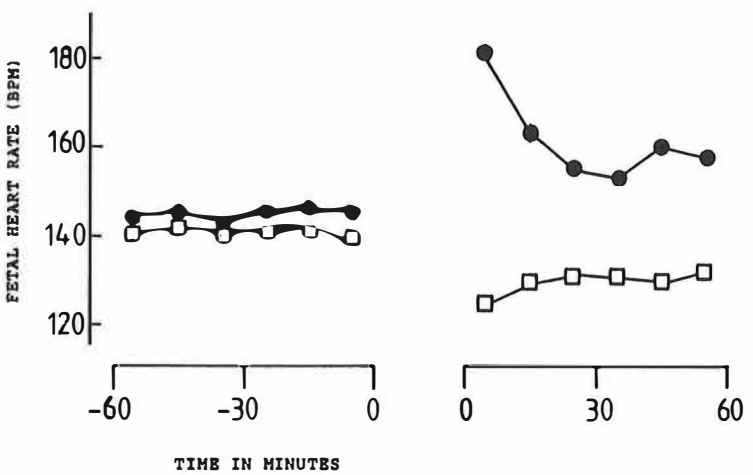

Fig 4.6 Median fetal heart rate (beats per minute) recorded for one hour before and one hour after transfusion. Separate analysis according to post-transfusion reaction: (●) =Tachycardic group (n=6), (□)= Normocardic group (n=12).

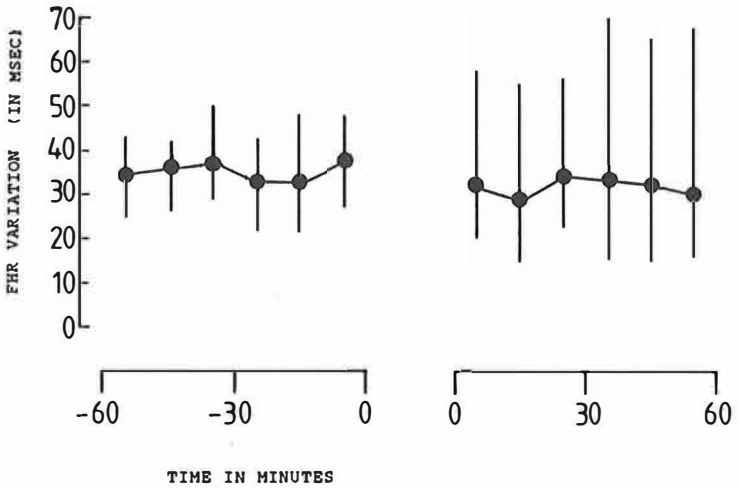

Fig 4.7 Median and interquartile range for fetal heart rate (FHR) variation (milliseconds) recorded for one hour before and one hour after transfusion (n=18).

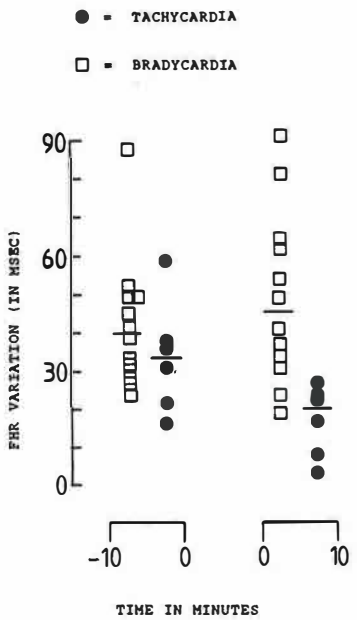

Fig 4.8 Median of fetal heart rate (FHR) variation (milliseconds) in the ten minutes before and ten minutes after transfusion. Separate analysis for the tachycardic group (n=6) and the normocardic group (n= 12).

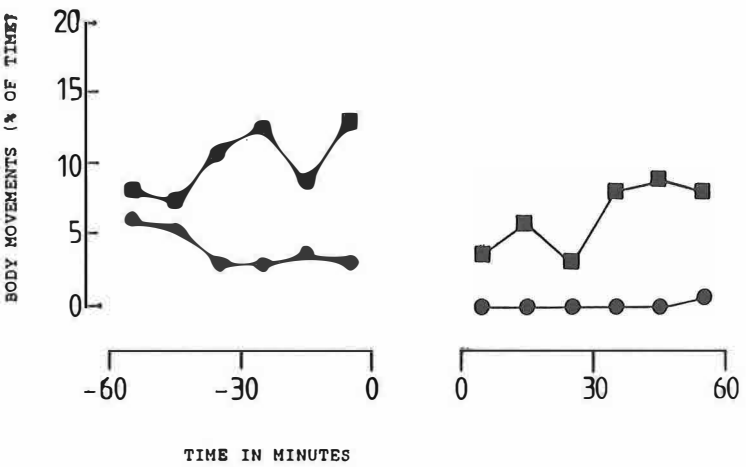

Fig 4.9 Median percentage (%) of the time spent by the fetus moving during ultrasound recording of fetal motor activity (one hour before and one hour after transfusion). (●)= Tachycardic group. (■)= Normocardic group.

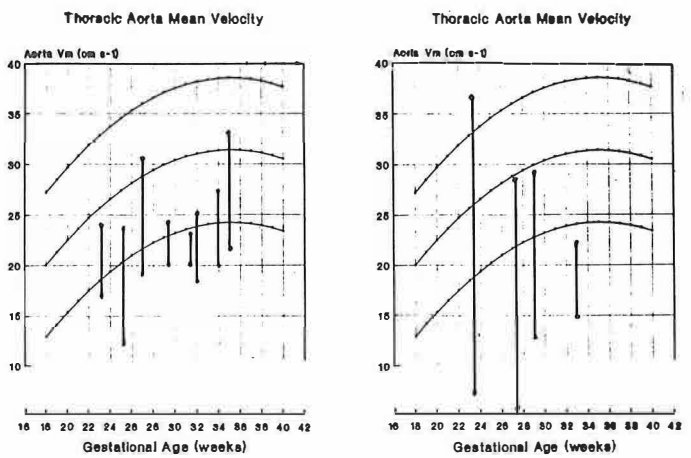

Fig 4.10 Normal range for gestation (16-42 weeks) for thoracic aorta mean velocity measurements. The ends of the vertical bars represent the readings immediately before and immediately after transfusion. Left= normocardic group (n=8). Right= tachycardic group (n=4).

Aortic blood velocity fell after transfusion by an average of 35%. All post-transfusion values were below the normal range for gestation (Fig 4.10).

The fall was more pronounced in the tachycardic sub-group and in most cases there was no return to pretransfusion values during the one hour observation period (Fig 4.11). Absence of end-diastolic frequencies was observed in two cases; in one only at the time of the first post-transfusion measurement and in the other for the whole one hour observation period. In the latter case we were unable to measure aortic velocity for up to one hour after transfusion because the velocity was below the threshold of detection of our equipment.

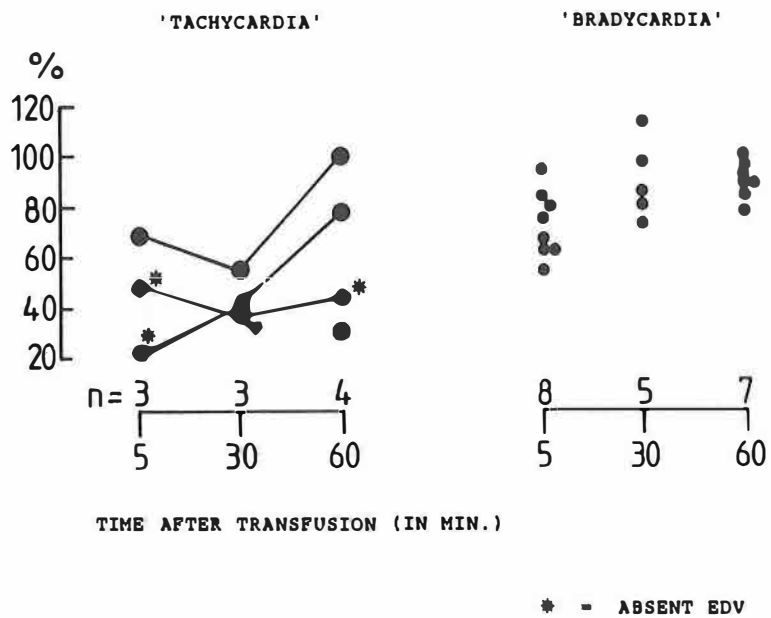

Fig 4.11 Percentual reduction of post transfusion mean aortic velocity measured at 5, 30 and 60 minutes of the transfusion (expressed as % of the pre-transfusion measurement).
Left= Tachycardic group (n=4). Right= Normocardic group (n=8).

Of the parameters measured before and after transfusion statistically significant differences between the two sub-groups of fetuses were observed only for pre-transfusion pH which was lower in the tachycardic sub-group (Table 4.IV).

Table 4.IV Differences between the two sub-groups

	Tachycardic	Non-tachycardic
Gestational age (wks)	26.17± 4.87	30.6 ± 3.03
Δ pre-transfusion haemoglobin	-5.8 ± 3.3	-3.9 ± 2.4
Δ post-transfusion haemoglobin	1.8 ± 1.7	1.9 ± 2.0
Δ pre-transfusion oxygen tension	-1.06± 1.22	0.05 ± 1.14
Δ post-transfusion oxygen tension	-1.31± 1.15	-0.17 ± 1.09
Δ pre-transfusion blood pH	-1.29± 0.97*	-0.21 ± 0.51
Δ post-transfusion blood pH	-3.29± 0.49	-2.45 ± 1.38
Fetoplacental blood volume (ml)	80 ± 52	121 ± 54
Blood volume expansion (%)	76 ± 24	83 ± 41
Volume expansion rate (% / min)	10.8 ± 6.5	13.1 ± 6.5

* $p<0.005$ (Mann-Whitney U test)

Discussion

The findings of this study demonstrate that large and rapid expansion of the feto-placental blood volume involves major cardio-vascular readjustments as documented by changes in fetal heart rate pattern and aortic blood velocity.

The inverse relationship between haematocrit and cardiac output has been previously described in animal studies (Fan et al 1980). In anaemic human fetuses right and left cardiac output is increased (Rizzo et al 1990, Moise et al 1990). After fetal blood transfusion there is a temporary fall in right and left cardiac output. Haemodynamic changes may affect both pre-load and after-load and variably contribute to the decline in cardiac output. This may be the result of vascular overload, as demonstrated by its direct relationship with fetoplacental volume expansion (Rizzo et al 1990) and/or of decreased pre-load due to increased viscosity and to massive

venodilatation due to prostaglandins and atrial natriuretic factor release in response to transfusion (Weiner & Robillard 1989, Robillard & Weiner 1988, Panos et al 1989).

Alternatively, the decrease in cardiac output may be the consequence of increased after-load due to increased viscosity. Additionally, there may be an increase in mean arterial pressure due to catecholamine-mediated generalized vasoconstriction induced by baroreceptor stimulation (Nicolini et al 1989). Confirmatory evidence of increased mean arterial pressure and systemic vascular resistance was observed in transfused fetal lambs (Brace 1989, Chestnut et al 1989) and in adult dogs (Fan et al 1980).

Reduced aortic mean velocity, after transfusion, may be the result of both reduced cardiac output and of increased down stream-resistance. Supportive evidence for the latter is provided by the fact that absence of end diastolic frequencies in aortic FVWs was observed in some cases after transfusion. Indeed in one case the reduction in velocity was so marked that the back- scattered frequencies were below the threshold of detection of our equipment and no signal could be recorded for up to one hour after transfusion.

The short-lived nature of the post-transfusional circulatory changes is supported by the overall normalization, within one hour, of Doppler measurements. Twelve hours after transfusions no difference in Doppler measurements are detectable (Copel et al 1988, Mari et al 1990a).

Blood transfusion was associated with a major reduction in generalized body movements. Similar observations were reported by Spencer et al (1992), suggesting that the transfused fetus avoids supplementary oxygen demand.

Post-transfusion pH is lower than the pre-transfusion value. This is explained by the relative "acidity" of the donor blood. (Soothill et al 1987, 1988, Westgren et al 1989, Nicolini et al 1988). This temporary acidaemia may directly affect heart contractility and cause the temporary reduction in fetal motor activity

Fetal heart rate was non-significantly lower after transfusion. This is in agreement with the findings of previous studies both in human fetuses (Pielet et al 1988) and in fetal lambs (Brace 1989). However, six fetuses responded differently to the procedure and became tachycardic. The post-transfusion effects were more

dramatic in this group (steep fall in aortic velocities and total suppression of body movements) and it took much longer for normalization of all parameters compared to the non-tachycardic group. In the comparison between variables in the two groups of reactions a lower pre-transfusion pH was the only parameter which reached statistical significance. However, in the tachycardic group there was a non-significant trend for a younger gestational age, a lower pre-transfusion haemoglobin concentration and a higher degree of blood volume expansion. Nicolini et al (1989) found in an acidotic fetus a higher pre-transfusion umbilical venous pressure. This is compatible with pathological conditions like hypoxic cardiac inhibition. Moreover, temporary hypoxia may have caused a catecholamine-mediated generalized vasoconstriction.

In hydropic fetuses the relative increase in fetal haematocrit resulting from an intra-vascular transfusion was strongly predictive of intra-uterine death (Radunovic et al 1992). It is possible that these fetuses, because of acidemia and of an early gestational age were more vulnerable to overloading of the fetal circulation and therefore had increased risk of congestive heart failure. Alternatively, because of acidemia these fetuses may be more vulnerable to a small procedure-related complication (vasospasm, cord tamponade or haemorrhage). As we did not measure venous pressures or catecholamines levels before and after transfusion, elucidation of the underlying mechanisms remains unclear.

Whether the development of tachycardia is a frankly pathological consequence or it represents one of a spectrum of physiological responses to intra-vascular transfusion remains to be determined. In the meantime, it is best if in this group of fetuses circulatory over-load is avoided.

In conclusion, despite the remarkable capability of the human fetus to tolerate rapid and large expansions of its circulating blood volume, a massive intra-vascular transfusion may represent a stressful event for the fetus. These data may prove useful in choosing alternative treatment modalities (exchange transfusions or combined intravascular-intraperitoneal transfusion) based on gestational age, severity of anaemia and pre-transfusion fetal condition.

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Chapter 5

Discussion

Doppler ultrasound has enabled non-invasive studies of the fetal circulation under physiologic and pathologic conditions.

5.1 Findings in normal fetuses

In Chapter 2 the physiologic changes in velocity and impedance in the descending thoracic aorta and common carotid artery are described. In these two vessels, changes in impedance and velocity with advancing gestation suggest that circulatory adjustments take place to meet increased oxygen demand of the growing and developing fetal brain.

In the fetus, arterial oxygen tension is 25-33% of that in the adult and there is a progressive fall in oxygen tension and increase in pCO_2 with advancing gestation (Soothill et al 1986). This "physiologic fetal hypoxia" (Meschia et al 1989), may stimulate arterial chemoreceptors and trigger preferential cerebral perfusion or "physiologic brain sparing effect".

In the study of brain perfusion we have chosen to examine the common carotid artery. From Doppler studies of intra-cranial arteries it appears that impedance is not uniform in all cerebral vessels, but preferential perfusion of certain cerebral districts may occur (van den Wijngaard et al 1989, Mari et al 1989, Hata et al 1991). Moreover, absolute certainty about which vessel is being sampled can be obtained by colour-flow mapping only (Locci et al 1992). The advantage of studying the common carotid artery is that the flow velocity waveforms (FVW) from this vessel may be more representative of overall brain perfusion. Furthermore, even in the pre-colour flow mapping era, it was relatively easy to visualize and consequently sample this vessel. The equipment used for our studies (off-line duplex Doppler) is ideal for the Doppler studies at optimal angles of vessels running parallel to the long fetal axis. Moreover, the insonation angle can be measured and mean blood velocity calculated. Velocity measurements are

more stable and reproducible than pulsatility index calculations, which can be affected by changes in cardiac contractility without changes occurring in downstream resistance (Gosling et al 1991). While waiting for technical improvements that will enable accurate actual flow measurements, mean velocity measurements remain the closest we can come to actual flow estimate.

5.2 Findings in intrauterine growth retarded fetuses (IUGR)

In Chapter 3 Doppler measurements of the utero-placental and fetal circulation were correlated with blood gases and pH in umbilical venous blood obtained at cordocentesis. This study provided evidence that the human fetus reacts to hypoxaemia in a similar fashion to what has been described for the fetal lamb (Cohn et al 1974, Peeters et al 1979) by centralizing its circulation and increasing cerebral perfusion (the "brain sparing effect"). Inevitably the best predictors of fetal oxygenation were combinations of the Doppler measurements of both the descending thoracic aorta and the common carotid artery. Changes in velocities and impedance measured in these two vessels represent the haemodynamic adaptation to changes in fetal blood gases and pH (increased cerebral perfusion at the expense of kidneys, gut and musculoskeletal systems).

Supportive evidence for the concept that Doppler measurements of the fetal and placental circulation presumably reflect the haemodynamic adaptation to changes in respiratory gases rather than oxygen content was also provided by Ferrazzi et al (1988); they found significant correlations between umbilical artery pulsatility index and fetal blood gases, pH and lactate but not oxygen content.

Since our studies were cross-sectional it was not possible to make predictions on the evolution of cerebral vascular dilatation in IUGR. Arduini et al (1992) examined IUGR fetuses longitudinally and described a curvilinear relationship between impedance in cerebral vessels and the state of fetal oxygenation; the progressive fall in impedance reached a nadir two weeks before the onset of late fetal heart rate decelerations. This suggests that the maximum degree of vascular adaptation to

hypoxaemia precedes the critical degree of impairment of fetal oxygenation. Similarly, Potts et al (1992) described a curvilinear relationship between cerebral vascular response and hypercapnia. Vyas et al (1990), reported that concomitant to severe oxygen deficit, there was a sudden rise in middle cerebral artery pulsatility index; they suggested that vascular dilatation may be blunted by the development of cerebral oedema. An alternative explanation may be that in severe hypoxaemia an increase in pulsatility index may be the consequence of alterations in flow due to reduced cardiac contractility and to a fall in absolute cardiac output (De Vore 1988, Rizzo et al 1991). Moreover, in fetal sheep, chronic hypoxaemia was found to alter cerebral vascular contractility through changes in vascular smooth muscle and endothelial cells, with the net result of a relative decrease in cerebral blood flow (Longo & Pearce 1991).

The finding of abnormal Doppler results can be associated to a spectrum of degrees of oxygen deficit, whereas the presence of normal Doppler results is associated with normal fetal oxygenation. This is in line with the results of other studies that have confirmed the value of Doppler ultrasound in discriminating between fetal "smallness" and "growth retardation", the former being a substantially "benign" condition (Burke et al 1990, Rognerud et al 1991; Pardi et al 1993, Soothill et al 1993).

5.2.1 Role of Doppler in clinical management of IUGR

The role of Doppler ultrasound in current clinical practice remains controversial. Initial expectations that Doppler would become "the" test of antenatal surveillance have not been substantiated by subsequent research. However, Doppler is finding its place as another useful test in the assessment of the at-risk fetus.

Prediction of IUGR

Several studies have demonstrated that examination of umbilical artery FVW on a single or on more occasions during the second half of gestation has no potential value in screening for IUGR and unfavourable outcome of low-risk populations (Beattie

et al 1989, Hanretty et al 1989, Sijmons et al 1989, Newman et al 1990, Davies et al 1992, Newnham et al 1993). In contrast, encouraging results were reported when Doppler studies are applied to a high-risk population (Tyrrel et al 1990, Omtzigt 1990, Pattison et al 1991, Trudinger et al 1991, Gudmundsson & Marsal 1991, Marsal 1991, Rognerud et al 1991, Almström et al 1992, Chandran et al 1993, Soothill et al 1993, Groenenberg et al 1993).
In a high-risk population Doppler ultrasound can identify at an early stage which fetuses are "sick small" or "normal small".

Sequence of Doppler changes to development of abnormal heart rate patterns

In the sequence of deterioration of the condition of the IUGR fetus the first pathological finding is abnormal umbilical artery FVW. This is followed by abnormalities in fetal behavioural states organisation, by a reduction in amniotic fluid volume and by the occurrence of antenatal late fetal heart decelerations (Ribbert 1993, Visser et al 1991). The time interval between first abnormal Doppler results and the onset of late fetal heart rate decelerations differs considerably among fetuses and is shorter in late than early pregnancy and in the presence of hypertensive disease (Reuwer et al 1987, Arabin et al 1988, Divon et al 1989, Bekedam et al 1990, Arduini et al 1993).

Late fetal heart rate decelerations are preceded by approximately two weeks with Doppler evidence of a nadir in the "brain sparing effect" and by a few days in an abrupt increase in resistance in the umbilical arteries (Arduini et al 1992). These findings are compatible with those of animal studies that have demonstrated differences in vascular sensitivity to hypoxaemia of cerebral and peripheral vessels (Richardson et al 1989).

Longitudinal cardiac Doppler studies in IUGR have shown that compensatory haemodynamic mechanisms can be sustained until the onset of progressive deterioration in cardiac function, as suggested by declining time peak velocities and cardiac output (Rizzo et al 1991).

Recent Doppler studies in IUGR fetuses suggest that impending cardiac decompensation may also be identified by studying the fetal venous compartment. The supply of oxygen and nutrients to the fetus depends on flow returning from the placenta to the heart via the umbilical vein, ductus venosus and inferior vena cava. In animal models it has been shown that a progressive increase in placental resistance creates an altered haemodynamic state. The brain becomes the circulatory district with the lowest vascular resistance in the fetal circulatory network and consequentely, during diastole, there is a shift of poorly oxygenated pre-placental blood from the aortic arch to the brain (Fouron et al 1991). The same author (Fouron et al 1993), postulated that increased cerebral perfusion in IUGR also implies increased venous return from the brain to the right atrium. This would result in abnormal diastolic atrial filling with blood being shifted from the superior to the inferior vena cava. This retrograde venous flow may cause changes in the FVW of the inferior vena cava, ductus venosus, intra-hepatic and umbilical veins respectively (Indik et al 1991, Reed et al 1992, Rizzo et al 1992, Kiserud et al 1991, 1992, Huisman et al 1992, Hecher et al 1993). In the FVW of the umbilical vein these changes are detectable as "pulsations". These are reported to be a late event in the process of fetal deterioration (Arduini & Rizzo 1993) and may well be associated with the so called "terminal" fetal heart rate pattern in which (shallow) late decelerations are supposed to be induced by myocardial ischaemia rather than by chemoreceptor activation.

Timing of delivery

Which criterion should be adopted as to when to deliver the IUGR fetus? IUGR fetuses delivered when severe waveform abnormalities of fetal vessels or umbilical artery are present have a greater morbidity and mortality than those with end-diastolic frequencies still present (Bekedam et al 1990, Hackett et al 1987). IUGR fetuses with antepartum decelerations are more likely to develop a severe degree of intraventricular haemorrhage or show abnormal neurological signs during the newborn period than those without decelerations (Westgren et al 1986, Visser 1988).

Fetuses delivered before 34 weeks of gestation have a poorer cognitive development at the age of two years when antenatal fetal heart rate abnormalities had been present, than when only abnormal Doppler result had been obtained (Todd et al 1992). Moreover, IUGR fetuses who were found acidaemic at cordocentesis (Soothill et al 1992) or at elective caesarean section (Visser 1988) have a poorer neonatal and subsequent neurodevelopment than non-acidaemic fetuses.

These data may lead to the conclusion that IUGR fetuses should be delivered before severely abnormal antenatal tests are present (Hackett et al 1987). However, in none of these studies were patients randomized. Moreover, gestational age and birthweight were lower in the population with a poorer outcome.

In another study, when IUGR fetuses with and without end-diastolic velocities in the umbilical artery were matched for weight and gestational age at delivery, no difference in outcome were found (Bekedam et al 1990). The authors suggest that absence of end-diastolic velocities may be more a marker of early and severe IUGR - which by itself has an effect on outcome - than a marker purely related to outcome.

In conclusion, when should the IUGR fetus be delivered? early, i.e. before signs of severe hypoxaemia occur, with a consequent risk of prematurity-related neonatal complications or at a later gestational age, but after a longer exposure to chronic malnutrition and hypoxaemia?

This dilemma mainly plays a role at early gestation and only controlled trials in which early delivery is compared to an expectant management can solve this question.

At a later gestational age (from 34 weeks onwards) the risks of prematurity are less and termination of the pregnancy before signs of severe hypoxaemia and/or acidaemia occur may be beneficial.

5.2.2 Role of cordocentesis in the management of IUGR

Cordocentesis has played a vital role in the assessment of IUGR. It has provided data on the association between IUGR and chromosomal anomalies. Additionally, cordocentesis has provided end-points, such as antenatal blood gases, for better understanding of fetal physiology and assessment of the efficacy of non-invasive methods for the prediction of fetal hypoxaemia and acidaemia.

In the clinical assessment of IUGR, we now have a better understanding of what to look for by ultrasound and what are the relationships between fetal blood gases and fetal biophysical profile, fetal heart rate patterns and flow velocity patterns in the placental and fetal circulation.

It is now possible to be relatively confident that a small fetus with no ultrasonographic markers of chromosomal abnormalities, a normal biophysical profile and normal Doppler findings in the placental and fetal circulation is likely to be normal and well oxygenated. Cordocentesis with its associated risk of mortality (at least 1% in experienced hands) under these circumstances may be unjustified. Similarly, cordocentesis may be unnecessary in the assessment of an anatomically normal fetus in the presence of Doppler evidence of impaired placental perfusion and redistribution in the fetal circulation, reduced movements and pathological fetal heart rate patterns; if such fetus is viable it is best if delivery is undertaken as soon as possible.

It could be argued that small fetuses that may benefit from fetal blood sampling are (i) those with early onset severe asymmetrical IUGR (they may have triploidy), (ii) those with even minor defects, such as choroid plexus cysts or 'clenched fists' (may be chromosomally abnormal), and (iii) those with inconsistent results from non-invasive assessment of fetal oxygenation, such as pathological fetal heart rate patterns with perfectly normal Doppler findings and vice versa (Snijders 1993). Cordocentesis for measurement of blood gases may also be useful in previable fetuses with highly pathological Doppler and fetal heart rate findings; in these cases confirmation of severe acidosis may help in counselling parents as to the likely poor prognosis and they may choose for abstention from any form of active management.

5.2.3 Role of maternal hyperoxygenation in severe IUGR

Chapter 3 describes the circulatory changes occurring in severe early IUGR after long-term maternal hyperoxygenation. An improvement in aortic blood velocity, within 72 hours of the onset of maternal hyperoxygenation, was associated with a more favourable fetal outcome than when no improvement occurred. The lack of significant reversal of "brain sparing effect" in this study may indicate immaturity or delayed chemoreceptor activity. In the fetal lamb aortic chemoreceptors are inactive prior to 90 days' gestation and mature progressively during later fetal life (Dawes et al 1968, 1969, Iwamoto et al 1989). Consequentely, in very young fetuses, cerebral blood flow and vascular tone may be regulated locally by a number of other vaso-active compounds (Longo & Pearce 1991). Alternatively, the effect of improved oxygen tension might be counterbalanced by the effect of persisting fetal hypercapnia. This is reported to decrease selectively cerebral resistance (Potts et al 1992, Veille & Penry 1992).

It has been argued that maternal oxygen administration will have no major effect on fetal oxygenation because maternal arterial blood is almost completely saturated with oxygen; therefore, increasing the maternal arterial pO_2 will only increase the amount of oxygen physically dissolved, which is relatively little compared to the oxygen bound to haemoglobin. It has long been shown that in hypoxaemic fetuses maternal oxygen breathing produces a rise in fetal pO_2 (Nicolaides et al 1987). Moreover, animal experiments have shown that maternal oxygen administration has a general positive effect on fetal oxygenation: in sheep fetuses where umbilical venous oxygen saturation had been lowered by reductions in uterine blood flow, maternal oxygen administration significantly increased oxygen saturation and oxygen content (Paulick et al 1992). In spontaneous hypoxaemic ovine fetuses, maternal oxygen breathing also increased oxygen consumption (Goetzman et al 1984). Umbilical blood flow is not affected by reductions in uterine blood flow (Wilkening et al 1983, Skillman et al 1985); consequently, maternal oxygen administration will also produce an increase in fetal oxygen delivery.

Oxygen content measurements were not performed in our series. However, during maternal hyperoxygenation an increase in fetal oxygen saturation has been reported by Battaglia et al (1992).

The lack of reversal of the brain sparing effect could have been beneficial for these fetuses. Besides being hypoxaemic these fetuses were deficient in essential nutrients. If maternal hyperoxygenation would have resulted in reduced brain perfusion without correction of fetal malnutrition, the result would have been a further decrease in the supply to the brain of glucose and other essential nutrients.

In line with our data, Ribbert et al (1991) found no change in the internal carotid artery pulsatility index during maternal oxygen breathing at 27-28 weeks' gestation. Neonatal mortality in their study (50%) was similar to that of a control group; the neonates had better blood gases at birth, but neonatal complications such as hypoglycaemia, thrombocytopenia and disseminated intravascular coagulation were more frequent. Battaglia et al (1992) reported that the perinatal mortality of an oxygen treated group was 29 % (mean birthweight 1070 gm and mean gestation at delivery 31.7 weeks). In our study of second-trimester severe IUGR (mean birthweight 605 gm; mean gestational age at delivery 29.3 weeks) perinatal mortality was 43%, and the neonatal survival rate was 70%. These results are more favourable than those reported in the literature for premature growth retarded infants of similar weights and gestational age (Amon et al 1987). Moreover, in our group an increased incidence of neonatal complications was not observed. However, not only survival but long-term outcome (mental development and neuromotor function at school age) should be carefully evaluated before any conclusion on the value of such a therapy can be drawn (van Veen et al 1991, Soothill et al 1992).

The value of maternal hyperoxygenation for the treatment of severe IUGR remains to be established. However, the demonstration of improvement of aortic velocities within 72 hours of maternal oxygen breathing may be a useful prognostic test giving an insight into the degree of compromise of fetal vascular reactivity and placental transfer.

5.3 Findings in anaemic fetuses

In 1985 it was first suggested that fetal anaemia should be detectable by ultrasound measurements of increased cardiac output and/or umbilical blood flow (Huikeshoven et al 1985).

Animal studies have established that during fetal anaemia cardiac output is increased (Fan et al 1980, Fumia et al 1984). Doppler ultrasound has confirmed that similar cardiovascular adjustments operate in the anaemic human fetus (Visser et al 1988, Copel et al 1989, Moise et al 1990, Rizzo et al 1990). Increased cardiac output and reduced peripheral resistance produce a hyperdynamic circulation with increased perfusion to all vascular beds in order to increase oxygen delivery to the tissues (Huikeshoven et al 1985). Thus, increased peak velocity in the ductus venosus of anaemic fetuses may be a compensatory mechanism to maintain an adequate myocardial and cerebral oxygen supply (Oepkes et al 1993b).

Red cell isoimmunisation provides a model of fetal hypoxaemia (low oxygen content) in the presence of normal tension of respiratory gases. In contrast, the low oxygen content of IUGR is due to a low pO_2. In fetal anaemia increased cerebral flow (Chapter 4, Vyas et al 1990) is a feature of the generalised increase in tissue perfusion, unlike the hypoxaemic IUGR where there is redistribution of flow.

Prediction of the degree of anaemia

Ultrasonographic demonstration of fetal ascites identifies a group of severely anaemic fetuses in urgent need for blood transfusion. In the absence of hydrops, ultrasonographic measurements of the fetus, umbilical vein and placenta (Witter & Graham 1983; Nicolaides et al 1988; Chitkara et al 1988) can not provide accurate prediction of the severity of fetal anaemia.

The findings of our studies (Chapter 4.1) suggest that Doppler has a useful role in the management of this condition. In particular, in previously untransfused, non-

hydropic fetuses, the finding of an aortic mean velocity above the normal range suggests that the fetus is likely to be anaemic, whereas if the aortic mean velocity is at or below the normal mean for gestation the fetus is unlikely to be anaemic.

Although a low haemoglobin concentration may be associated with increased aortic mean velocities there is a wide scatter of results in the relation between fetal haemoglobin concentration and velocity measurements. It is possible that the combined use of cardiac Doppler studies and velocity measurements from several vessels may increase the sensitivity of Doppler measurements in identifying anaemic fetuses.

Following the first transfusion aortic mean velocity measurements lose part of their predictive power. However, knowledge of daily haemoglobin decline (approximately 0.3 g/dl), maternal surveillance of fetal motor activity and antenatal fetal heart rate monitoring are useful in timing the need for a subsequent transfusion (usually 2-3 weeks interval). Oepkes et al (1993a) have recently shown that serial fetal spleen perimeter measurements may also be useful; correction of fetal anaemia is associated with spleen shrinkage, while severe haemolysis is associated with spleen enlargement.

Responses to blood transfusion

After intravascular fetal blood transfusion there is correction of the hyperdynamic circulation, as suggested by reductions in mean blood velocity measured in the aorta and in the common carotid artery (Chapter 4.2). An explanation for this fall could be a symmetrical decrease in left and right cardiac output (Moise et al 1990), presumably as result of reduced stroke volume.

Several mechanisms have been proposed to explain this decrease. Firstly, reduced venous return (reduced pre-load), secondary to increased blood viscosity or cordocentesis-induced release of venodilator (Weiner et al 1989). However, the increase in fetoplacental volume, in umbilical venous pressure (Moise 1990) and in the ratio between early (passive) and active ventricular filling (E/A ratio) (Rizzo et al 1990) are indicative of increased, rather than of decreased pre-load. Secondly, increased

blood viscosity, increased systemic vascular resistance (Nicolini et al 1989), and reversal of the hypoxia-induced vasodilatation may increase after-load and determine a decline in cardiac output (Moise et al 1990).

In our study of post-transfusion reactions (Chapter 4.3), absence of end diastolic flow in aortic FVW was occasionally detected after intra-vascular transfusion. This is known to reflect increased downstream resistance and would support the second proposed mechanism of decreased cardiac output.

Despite the capability of the human fetus to tolerate sudden expansion of the circulating volume, the transfusion represents a remarkable challenge, as demonstrated by the temporary changes in fetal heart rate, its variation and fetal body movements (Chapter 4.3). It is possible that a combined intravascular-intraperitoneal or an exchange transfusion would better suit young fetuses or fetuses which are found to be mildly acidotic at cordocentesis. However this hypothesis requires further investigations.

5.4 Summarising conclusions

Doppler investigations of the fetal and placental circulation have contributed to the understanding of pathophysiologic haemodynamic adaptations during fetal life.

In normal fetuses the Doppler findings are compatible with preferential flow to the brain with advancing gestation.

In IUGR due to impaired placental perfusion there is redistribution in the fetal circulation with preferential flow to the brain at the expense of other organs. Doppler examination of the fetal circulation can predict the degree of fetal hypoxaemia, hypercapnia and acidaemia. In severe, early onset IUGR, serial Doppler studies allow the detection of fetal circulatory changes secondary to maternal hyperoxygenation; lack of haemodynamic response constitutes a unfavourable prognostic factor.

In red blood cell isoimmunisation, there is evidence of a hyperdynamic fetal circulation the degree of which is proportional to the severity of fetal anaemia. Following blood transfusion and massive expansion of the fetoplacental blood volume there are temporary alterations in cardiovascular and behavioural functions.

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Samenvatting

Met behulp van Doppler ultrageluid kan bij de menselijke foetus informatie verkregen worden omtrent bloedstroom en bloedstroomsnelheden in de verschillende bloedvaten. Tevens kan het bloedstroomprofiel worden bestudeerd ("Pulsatility Index": V max - V min/V mean); deze index wordt beinvloed door een aantal variabelen, maar is primair een maat voor de perifere weerstand.

In dit proefschrift wordt Doppler onderzoek beschreven bij twee ziektebeelden waarbij sprake is van een verstoring van het zuurstoftransport. Bij foetale groeivertraging op basis van placentaire insufficientie berust deze verstoring op onvoldoende transport van zuurstof over de placenta. Het foetale bloed heeft hierdoor een te lage zuurstofspanning (pO_2). Bij het Rhesus-antagonisme functioneert de placenta naar behoren, doch neemt de transportcapaciteit van het bloed voor zuurstof af door een progressieve foetale anaemie; de pO_2 is normaal maar het zuurstofgehalte is verlaagd. De betekenis van Dopplermetingen van de foetale circulatie voor het inschatten van de ernst van deze ziektebeelden wordt in dit proefschrift bestudeerd door deze metingen te relateren aan foetale bloedgaswaarden en aan de hemoglobineconcentratie. Deze "gouden standaarden" werden verkregen door het antepartum uitvoeren van navelstrengpuncties. Onderzoek naar bloedstroom en bloedstroomprofielen in het verloop van de ongestoorde zwangerschap ging vooraf aan het bestuderen van de veranderingen die optreden onder patho-fysiologische omstandigheden.

In hoofdstuk 1 worden de basisprincipes van de Doppler-ultrageluidstechniek besproken, alsmede literatuurgegevens omtrent bevindingen bij normale en gecompliceerde zwangerschappen. De cardiovasculaire veranderingen die optreden bij foetale groeivertraging en anaemie worden toegelicht aan de hand van dierexperimenten. Tot slot worden de techniek van en de bevindingen bij navelstrengpuncties besproken.

Hoofdstuk 2 omvat een cross-sectioneel onderzoek bij 70 ongecompliceerde zwangerschappen. Gemiddelde bloedstroomsnelheden en pulsatility index werden bepaald in de foetale aorta thoracalis en in de arteria carotis communis tussen 17 en 42 weken zwangerschapsduur.
De bloedstroomsnelheid in de foetale aorta nam toe tot 32 weken, bleef daarna constant en daalde licht rond de à terme datum. De pulsatility index bleef de gehele periode constant. De gemiddelde bloedstroomsnelheid in de a. carotis nam lineair toe tot aan het einde van de graviditeit en de pulsatility index nam na 32 weken progressief af. Deze gegevens suggereren dat met het toenemen van de duur van de zwangerschap een herverdeling optreedt van bloed naar het hoofd, met afname van de weerstand in de cerebrale vaten. Deze "fysiologische redistributie" zou heel wel kunnen samenhangen met de daling in pO_2 die plaatsvindt aan het einde van de zwangerschap.

Bij 41 foetussen die te klein waren voor de duur van de zwangerschap en bij 10 normaal ontwikkelde foetussen, werd de relatie bestudeerd tussen Dopplerbloedstroomsnelheden en - profielen en foetale bloedgaswaarden en pH (Hoofdstuk 3.1). Al de individuele Doppler variabelen toonden een statistisch significante relatie tot bloedgassen en pH; de hoogste correlatiecoëfficienten werden echter verkregen door combinatie van Dopplergegevens van aorta en arteria carotis communis (respectievelijk gemiddelde bloedstroomsnelheid en pulsatility index; r = 0.57 - 0.68). In geval van een normale ratio waren bloedgassen en pH steeds normaal; bij een afwijkende ratio was 60% van de foetussen asfyctisch. Deze gegevens wijzen op een redistributie van bloed ten gunste van het hoofd en ten koste van het lichaam onder hypoxaemische omstandigheden. Het is aannemelijk dat deze redistributie veroorzaakt wordt door stimulatie van de chemoreceptoren in de aorta.

Bij 21 ernstig in groei vertraagde en hypoxaemische foetussen werd het effect bestudeerd van continue toediening van extra zuurstof aan de moeder op de foetale circulatie (Hoofdstuk 3.2). De zwangerschapsduur bij het begin van de behandeling bedroeg 21 tot 30 weken en bij de geboorte 26 tot 34 weken. Vier foetussen overleden

in utero en bij alle vier nam de bloedstroomsnelheid in de aorta progressief af en daalde de pulsatility index in de a. carotis communis verder. De 12 kinderen die de perinatale periode overleefden toonden als reactie op de hyperoxygenatie een toename van de bloedstroomsnelheid in de aorta en een (niet significante) stijging van de pulsatility index in de carotis; met andere woorden een tendens tot normalisatie van de circulatie. De overige vijf kinderen overleden neonataal; de veranderingen in circulatie tijdens hyperoxygenatie hielden het midden tussen die van de eerder beschreven subgroepen. Deze gegevens tonen dat een tendens tot normalisatie van bloedstroom- en bloedstroomverdeling tijdens maternale hyperoxygenatie prognostisch een gunstig teken is. Het is echter nog omstreden of maternale hyperoxygenatie een rol heeft bij het "behandelen" van in groeivertraagde foetussen.

Foetale anaemie ten gevolge van het Rhesus-antagonisme blijkt een andere aanpassing van de foetale circulatie te geven (Hoofdstuk 4.1). Zowel de gemiddelde bloedstroomsnelheid in de aorta als die in de arteria carotis communis blijkt gecorreleerd aan de mate van anaemie. Met andere woorden, foetale anaemie veroorzaakt een gegeneraliseerde hyperdynamische circulatie met daarbij waarschijnlijk een toename van het hartminuutvolume. De correlatie tussen bloedstroomsnelheden en mate van anaemie was aanmerkelijk beter voorafgaande aan de eerste bloedstransfusie (n=78), dan na de eerste of volgende transfusies (n=72). Bij foetussen bij wie nog geen transfusie heeft plaats gevonden, wijst een bloedstroomsnelheid in de aorta boven de 90e percentiel sterk in de richting van foetale anaemie, terwijl snelheden onder de 50e percentiel anaemie uiterst onwaarschijnlijk maken (correlatiecoëfficient -0.51).

Bij 43 zwangeren werd het effect van intravasculaire transfusies op de bloedstroomsnelheden in de foetale circulatie bestudeerd (Hoofdstuk 4.2). Transfusie blijkt te leiden tot een direkte afname van bloedstroomsnelheden in de aorta en in de arteria carotis communis, wat wijst op afname van de cardiac output van linker en rechter ventrikel. Deze afname wordt mogelijk veroorzaakt door acute overbelasting van de circulatie, maar correctie van de anaemie speelt waarschijnlijk eveneens een

rol.

Hartactie (variabiliteit) en foetale lichaamsbewegingen werden bestudeerd bij 18 zwangeren, direkt vóor en na intravasculaire transfusie (Hoofdstuk 4.3). Na transfusie daalde de (mediane) foetale hartfrequentie gering en bleef de (mediane) hartactievariabiliteit gelijk. Foetale bewegingen namen aanzienlijk af. Bij nadere analyse bleek er een subgroep te bestaan (n=6), waarin de foetale hartfrequentie na transfusie sterk toenam en foetale bewegingen het gehele uur na transfusie nagenoeg afwezig waren. De gemiddelde bloedstroomsnelheid in de aorta (gemeten bij 4 van deze foetussen) was tijdens deze periode dramatisch gedaald. Intravasculaire transfusies blijken bij deze subgroep van -jongere en relatief acidaemische foetussen- dus aanleiding te geven tot een tijdelijke maar aanzienlijke verslechtering van de foetale conditie. Waarschijnlijk wordt dit veroorzaakt door overbelasting van de foetale circulatie en een andere behandeling (zoals wisseltransfusies) verdient in zulke gevallen mogelijk voorkeur.

Samenvattend kan gesteld worden dat Doppler onderzoek van de foetale circulatie het inzicht in fysiologische veranderingen die optreden in het verloop van de ongestoorde zwangerschap en in veranderingen optredend onder patho-fysiologische omstandigheden, aanzienlijk heeft doen toenemen. In het verloop van het derde trimester van de normale zwangerschap vindt een herverdeling van de bloedstroom plaats ten gunste van het hoofd. Bij foetale groeivertraging is deze redistributie meer uitgesproken en gaat zij samen met een afname van de circulatie in de aorta. Bij foetale anaemie is de circulatie hyperdynamisch met toename van bloedstroom(snelheden) in aorta en arteria carotis communis. Doppleronderzoek kan gebruikt worden voor het bepalen van de ernst van foetale asyfxie of van de mate van foetale anaemie. De voorspellende waarde is echter beperkt, gegeven het feit dat correlatiecoëfficienten in het algemeen niet hoger zijn dan 0.60.

Sommario della Tesi

Capitolo I: Introduzione e scopo della tesi

Grazie alla velocimetria Doppler è possibile studiare la velocità di flusso in vari vasi fetali. Inoltre, con l'applicazione di indici di valutatione qualitativa del profilo flussimetrico -tra cui l'indice di pulsatilità- è possibile valutare l'entità delle resistenze periferiche.

In questa tesi queste valutazioni flussimetriche vengono applicate a due condizioni di patologia fetale caratterizzate da carente ossigenazione fetale: il ritardo di accrescimento fetale e l'isoimmunizzazione Rh. Nel primo caso l'ipossiemia fetale è da ascriversi a un difetto della diffusione trans-placentare del gas dovuta ad un difetto di adattamento dell'albero vascolare uterino alle esigenze di perfusione dell'unità feto-placentare (inefficiente modificazione, da parte del trofoblasto, della parete vascolare delle arterie spirali). In questa condizione la tensione di ossigeno (pO_2) nel sangue fetale è ridotta e si parla di ipossia ipossemica.
Nell'altra condizione -l'isoimmunizzazione Rh o eritroblastosi fetale- la carenza di ossigeno è legata all'anemia fetale, al ridotto tasso di emoglobina e quindi alla ridotta capacità di trasporto di ossigeno del sangue fetale. La tensione di ossigeno è in questo caso normale, mentre il contenuto totale di ossigeno [O_2] è ridotto. In questo caso si parla di ipossia anemica.
In ambedue le condizioni studi in animali hanno documentato alterazioni circolatorie caratteristiche: nel primo caso ridistribuzione del flusso a favore degli organi privilegiati (cervello, cuore e surrenali) e nel secondo un carattere iperdinamico della circolazione per compensare al basso contenuto di ossigeno. Grazie alla flussimetria Doppler tali alterazioni del flusso sono state rilevate anche nel feto umano.

L'introduzione della funicolocentesi nella diagnostica e nella terapia di queste due condizioni, ha fornito la possibilità di correlare le misurazioni velocimetriche a parametri finora inaccessibili -quali i gas, il ph e il tasso di emoglobina- misurati direttamente nel sangue fetale.

Obiettivo della tesi è stato quello di stabilire range di normalità in gravidanze fisiologiche (70 gravidanze comprese tra 17 e 42 settimane) per la velocità e la resistenza al flusso nell'aorta toracica discendente e nell'arteria carotide comune. Questi due vasi rappresentano rispettivamente la perfusione cerebrale e la perfusione placentare e viscerale fetale.
In un secondo studio, misurazioni flussimetriche in questi due vasi sono state correlate con le tensioni di ossigeno, di anidride carbonica e con il ph misurati al momento della funicolocentesi in 41 feti con ritardo di accrescimento e in 10 feti appropriati per l'età gestazionale. L'obbiettivo era quello di stabilire il grado di accuratezza con cui misurazioni flussimetriche possono predire la condizione fetale.
Analogamente, nel caso dell'isoimmunizzazione Rh le misurazioni velocimetriche sono state correlate alle misurazioni dirette del tasso di emoglobima fetale onde valutare il valore predittivo della flussimetria riguardo alla severità dell'anemia fetale.
Inoltre sono stati effettuati studi volti a valutare le modificazioni flussimetriche determinate da tentativi terapeutici nelle due condizioni: l'iperossigenazione materna, nel caso del ritardo di accrescimento fetale e la trasfusione fetale intravascolare diretta, nel caso dell'anemia fetale.

Capitolo II: Velocità media e resistenza al flusso nella aorta toracica discendente e nell'arteria carotide comune nella gravidanza fisiologica

Nella gravidanza fisiologica la velocità del sangue nell'aorta aumenta progressivamente nel corso del secondo trimestre e si stabilizza dopo le 32 settimane. Nell'arteria carotide comune la velocità del sangue è inferiore a quella misurata nell'aorta, ma, a differenza di questa, continua a crescere progressivamente fino al termine della gravidanza. L'indice di pulsatilità nell'aorta non varia considerevolmente nel corso della gravidanza, mentre nella carotide comune si registra, dopo le 32 settimane, un calo progressivo della resistenza al flusso. Questi risultati suggeriscono che una proporzione crescente della portata cardiaca fetale viene diretta, nell'ultima parte della gravidanza, verso l'estremo cefalico. Se questo dato viene correlato al calo

progressivo, in gravidanza, della tensione di ossigeno nel sangue fetale, si potrebbe ipotizzare che anche in condizioni fisiologiche vi sia una perfusione cerebrale preferenziale.

Capitolo III: I) Correlazione tra gas e ph fetali misurati alla funicolocentesi e misurazioni Doppler. II) Studio delle modificazioni velocimetriche della circolazione fetale in corso di iperossigenazione materna in caso di precoce e severo ritardo di accresimento fetale.

I) Nella correlazione tra misurazioni flussimetriche e tensione dei gas respiratori e ph, il valore predittivo più elevato della condizione fetale è stato raggiunto dalla velocità misurata nell'aorta e dall'indice di pulsatilità misurato nell'arteria carotide comune e da combinazioni di queste due misurazioni. In particolare un indice matematico comprendente i gas respiratori e il ph fetale, chiamato "Indice di asfissia", è stato predetto con maggiore accuratezza da un indice matematico comprendente le due suddette misurazioni Doppler e chiamato "indice aorta-carotide" (coefficiente di correlazione= 0.67 deviazione standard dei residui 18.7). Questi risultati non sono sorprendenti in quanto confermano dati già noti da esperimenti in feti di animali resi ipossiemici e in cui c'era evidenza di una risposta compensatoria all'ipossiemia consistente in una ridistribuzione di flusso a favore del cervello, del cuore e delle surrenali e a spese di altri organi meno vitali (polmoni, intestino, reni, apparato muscolo-scheletrico), la cui perfusione diminuisce. Sembra logico che le misurazioni Doppler nei vasi interessati da tale redistribuzione possano meglio predire ciò che regola l'entità di tale redistribuzione, cioè le variazioni nei gas respiratori fetali.
In presenza di misurazioni Doppler comprese nei range di normalità i valori di ossigenazione fetale sono risultati anche nella norma, mentre misurazioni Doppler alterate si sono accompagnate a vari gradi di anomalia dell'ossigenazione fetale, suggerendo che alterazioni di flusso precedono l'ipossiemia fetale grave.

Iperossigenazione materna -attraverso una maschera facciale- è stata adottata in 21 casi di severo e precoce ritardo di accrescimento intra-uterino (all'inizio della terapia:

21-30 settimane -media 25-; al termine: 26-35 settimane -media 30-; durata: 1-9 settimane -media 4-). Misurazioni Doppler della circolazione fetale sono state ripetute serialmente. Si sono potuti registrare differenti pattern di reattività circolatoria fetale: in particolare un aumento della velocità nell'aorta e un aumento (non significativo) dell'indice di pulsatilità nella carotide comune entro 72 ore dall'inizio della terapia, si sono accompagnati ad un esito favorevole della gravidanza (12 casi), mentre nei casi ad esito sfavorevole (4 morti intrauterine e 5 morti perinatali) si è registrata una reazione scarsa o assente della circolazione fetale all'inalazione materna di ossigeno. Poichè in questo studio -a differenza di un nostro studio precedente- la determinazione della pO_2 fetale dopo l'inizio della terapia materna non è stata ripetuta, è impossibile pronunciarsi sull'effetivo miglioramento -in quali casi e per quanto tempo- dell'ossigenazione fetale. Permangono molti dubbi sul reale beneficio di una tale stressante terapia, ma in casi di severo e precoce ritardo di accrescimento una reazione, entro 72 ore dall'inizio della terapia, della circolazione fetale, sembra avere un valore prognostico favorevole ed indicare che il meccanismo di diffusione trans-placentare dell'ossigeno è intatto.

Capitolo IV: Misurazioni flussimetriche nell'anemia fetale:I) prima della trasfusione intravascolare fetale; II) Reazioni circolatorie alla trasfusione ; III) Reazioni circolatorie, cardiotocografiche e del comportamento fetale alla transusione intravascolare.

I) In caso di eritroblastosi fetale, la circolazione risulta iperdinamica, con un aumento della velocità di flusso nell'aorta e nella carotide comune. Questa circolazione iperdinamica è dovuta all'aumento della portata cardiaca, alla ridotta viscosità del sangue e alla vasodilatazione periferica. Si tratta di meccanismi compensatori alla ridotta capacità di trasporto del sangue fetale. In 78 feti mai transfusi in precedenza, l'aumento della velocità di flusso nell'aorta fetale è correlata positivamente ($r=0.51$; $p<0.001$) al grado di anemia fetale. Nei feti idropici, per via dello scompenso cardiaco progressivo, tale correlazione diventa negativa ($r=-0.547$; $p<0.05$). Dopo la prima trasfusione le correlazioni tra emoglobina fetale e misurazioni Doppler perdono parte

del loro valore, probabilmente per le proprietà differenti del sangue trasfuso. In conclusione, per la valutazione indiretta della severità dell'anemia fetale, se un feto è idropico, il deficit di emoglobina è sicuramente maggiore di 7 gr/dl, mentre in assenza di idrope un'aumento della velocità aortica superiore a 2 deviazioni standard depone fortemente per anemia fetale e per la necessità immediata di una trasfusione. Se invece la velocità non è aumentata, è probabile che il feto non sia anemico.

II) In 43 occasioni l'effetto della trasfusione intravascolare fetale diretta sulla circolazione fetale è stata valutata con studi flussimetrici. Immediatamente dopo la trasfusione c'è un calo sensibile della velocità misurata nella carotide comune e soprattutto nell'aorta. Tale calo è dovuto alla riduzione della portata cardiaca, all'aumento della viscosità e alla correzione della vasodilatazione periferica.

III) In 18 occasioni una registrazione cardiotocografica e la registrazione dei movimenti fetali sono state effettuate per un'ora prima e un'ora immediatamente dopo la trasfusione fetale. Misurazioni velocimetriche dell'aorta fetale sono state effettuate immediatamente prima e rispettivamente 5, 30 e 60 minuti dopo la trasfusione intravascolare diretta fetale. Dopo la trasfusione la frequenza cardiaca fetale è risultata non significativamente ridotta e la variabilità pressochè invariata. L'attività motoria fetale è apparsa, al contrario, fortemente ridotta. Un'analisi ulteriore ha rivelato che dei 18 casi studiati, sei feti sono diventati, dopo la trasfusione, fortemente tachicardici. In questo gruppo si sono registrate le variazioni più spiccate nei vari parametri studiati. In particolare, l'abolizione totale di movimenti per l'intera ora di osservazione dopo la trasfusione e un calo marcato della velocità aortica. In due casi si è anche notata assenza di flusso di fine diastole. Tutti i parametri hanno mostrato una tendenza alla normalizzazione durante il periodo di osservazione dopo la trasfusione, rivelando la loro temporaneità. Nell'analisi delle differenze tra i due gruppi di reazione fetale (tachicardia e normocardia) l'unica differenza statisticamente significativa è stata un ph più basso nel gruppo tachicardico e una tendenza non significativa ad un'età gestazionale più precoce e ad un maggiore sovraccarico circolatorio. Questo studio suggerisce che, nonostante la notevole capacità del feto di tollerare un incremento

consistente ed improvviso del volume circolatorio, la trasfusione costituisce uno stress non indifferente. Il sovraccarico circolatorio va probabilmemte evitato in feti giovani e già lievemente acidotici prima della trasfusione. In alternativa un' altra modalità di trasfusione (es. trasfusione-scambio) potrebbe essere più indicata in questi casi.

Capitolo V : conclusioni

La flussimetria Doppler ha fornito la possibilità di studiare in modo non invasivo la circolazione fetale in condizioni fisiologiche e patologiche. Osservazioni già note da esperimenti acuti in animali sono state estese anche al feto umano studiato nel suo ambiente indisturbato. Nel corso del terzo trimestre di gravidanza si verifica una ridistribuzione fisiologica del flusso a favore del cervello fetale. In caso di ritardo di accrescimento fetale dovuto ad insufficienza placentare, lo studio flussimetrico fetale rivela indirettamente lo stato dell'ossigenazione fetale. Tuttavia le correlazioni tra misurazioni Doppler e gas fetali hanno un valore limitato (0.67 le più elevate). Lo studio con tecnica Doppler della circolazione fetale è insostituibile nel chiarire la natura (benigna-idiopatica o patologica-da insufficienza placentare) del ritardo di accrescimento intra-uterino. Informazioni più attendibili sullo stato dell'ossigenazione fetale vengono fornite da studi longitudinali volti a cogliere trend di peggioramento della condizione fetale e dall'integrazione con altre tecniche di monitoraggio.

In caso di anemia fetale dovuta ad eritroblastosi fetale lo studio della circolazione fetale prima e dopo la trasfusione fetale ha arricchito le nostre conoscenze circa la fisiopatologia di questa condizione. Se lo studio flussimetrico non si è rivelato in grado di sostituirsi alla determinazione diretta -tramite funicolocentesi- del grado di anemia fetale, può fornire comunque informazioni orientative sulla necessità di effettuare la prima trasfusione. Nell'intervallo tra una trasfusione e la seguente misurazioni flussimetriche possono servire da monitoraggio per individuare una precoce ed in-aspettata recrudescenza dell'emolisi fetale. Inoltre, lo studio delle reazioni circolatorie, neuro-vegetative e del comportamento fetale possono costituire un'indicazione all'uso di techiche alternative di trasfusione.

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Curriculum vitae

Caterina Maddalena Bilardo (from very early on called Katia), was born at home, at 32 weeks' gestation, in the ancient piedmontese town of Savigliano (CN), in Italy. It happened on the 7th of January 1954, after one of the heaviest snow falls of the century. Despite the stormy beginning (1750 grams and no neonatal care whatsoever) she managed, in 1973, to get the Diploma of "Maturità Classica" in the Classic Lyceum "G. Arimondi" in Savigliano. Six years later, in 1979, she completed cum laude her medical studies at Torino's University and shortly thereafter got a place in the Specialization School in Obstetrics & Gynaecology of the same University, under the supervision of Prof. L. Gagliardi. She qualified as medical specialist in 1983. In 1980-1981, with a grant of the Italian National Research Board (C.N.R.) she spent the first year at King's College Hospital, in London. There, under the supervision of Prof. S. Campbell and together with David Griffin the first fetal Doppler studies were pioneered. In 1984-1985 she worked as a gynaecologist in the Department of Obstetrics & Gynaecology of the "Santissima Annunziata" hospital in Savigliano. Thereafter she joined the research team of the Department of Obstetrics and Harris Birthright Centre at King's College Hospital for the second time (Heads: Prof S Campbell and Prof K Nicolaides). There she worked as a research fellow-honorary registrar from October 1985 until March 1989 . From May 1989 she worked for a short period of time as a registrar in the Department of Obstetrics & Gynaecology of the Academisch Ziekenhuis Groningen. Before applying for registration in the Dutch Specialist's register she worked for one and a half year as registrar in the Department of Obstetrics & Gynaecology of the R K Ziekenhuis in Groningen (Opleidings cluster Groningen). In June 1991 she was registered in the Dutch Specialist's Register. Since October 1992 she works, with a 60% appointment, as a specialist in the department of Obstetrics of the University of Amsterdam in the A M C.

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