Doppler studies in fetal hypoxemic hypoxia

Based on Doppler in Obstetrics: by K Nicolaides, G Rizzo, K Hecher

FETAL OXYGENATION

Oxygenation is the process of transporting molecular oxygen from air to the tissues of the body. In the fetus, this involves, first, oxygen transfer across the placenta, second, reversible binding of oxygen to fetal hemoglobin and fetal blood flow, and, third, 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 by the reverse of the mechanisms for oxygen delivery and is helped by the rapid diffusion, high solubility and volatility of this gas. In the adult, 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 cannot 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 hemoglobin is not linearly related to oxygen tension (pO2). Each type of hemoglobin 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 anemia or hypoxia, it binds to and stabilizes the deoxygenated form of hemoglobin, resulting in a shift of the oxygen dissociation curve to the right and therefore release ofoxygen to the tissues. Although, in vitro , both adult (HbA) and fetal (HbF) hemoglobins have the same oxygen dissociation curves, human adult blood has a lower affinity for oxygen than fetal because of its greater binding of 2,3-DPG. The higher affinity of fetal blood helps placental transfer of oxygen. Furthermore, since the P50 of fetal blood is similar to the umbilical arterial pO2, the fetus operates over the steepest part of the hemoglobin oxygen dissociation curve and, therefore, a relatively large amount of oxygen is released from the hemoglobin for a given drop in pO2.

Normal fetal oxygenation

In normal fetuses, the blood oxygen tension is much lower than the maternal, and it has been suggested that this is due either to incomplete venous equilibration of uterine and umbilical circulations and/or to high placental oxygen consumption.[1,2] Studies in a variety of animals have also demonstrated that the umbilical venous blood pO2 is less than half the maternal arterial pO2 and this observation led to the concept of `Mount Everest in utero'. However, the high affinity of fetal hemoglobin for oxygen, together with the high fetal cardiac output in relation to oxygen demand, compensates for the low fetal pO2.[3] The umbilical venous and arterial pO2 and pH decrease, while pCO2 increases, with gestation.[1,2] The blood oxygen content increases with gestational age because of the rise in fetal hemoglobin concentration.[2] Fetal blood lactate concentration does not change with gestation and the values are similar to those in samples obtained at elective Cesarean section at term.[2] The umbilical venous concentration is higher than the umbilical arterial, suggesting that the normoxemic human fetus is, like the sheep fetus, a net consumer of lactate.[4] Furthermore, the concentration of lactate in umbilical cord blood is higher than in the maternal blood and the two

are correlated significantly. This suggests a common source of lactate, which is likely to be the placenta.

Fetal hypoxia

Fetal hypoxia, oxygen deficiency in the tissues, 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 dies. Hypoxia may result from:

- Reduced placental perfusion with maternal blood and consequent decrease in fetal arterial blood oxygen content due to low pO2 (hypoxemic hypoxia);

- Reduced arterial blood oxygen content due to low fetal hemoglobin concentration (anemic hypoxia);

- Reduced blood flow to the fetal tissues (ischemic hypoxia).

Hypoxemic hypoxia (uteroplacental insufficiency)

Small-for-gestational age fetuses may be constitutionally small, with no increased perinatal death or morbidity, or they may be growth-restricted due to either low growth potential, the result of genetic disease or environmental damage, or due to reduced placental perfusion and `uteroplacental insufficiency'.

Analysis of samples obtained by cordocentesis has demonstrated that some small-for-gestation fetuses are hypoxemic (Figure 1), hypercapnic, hyperlacticemic and academic.[2,5]
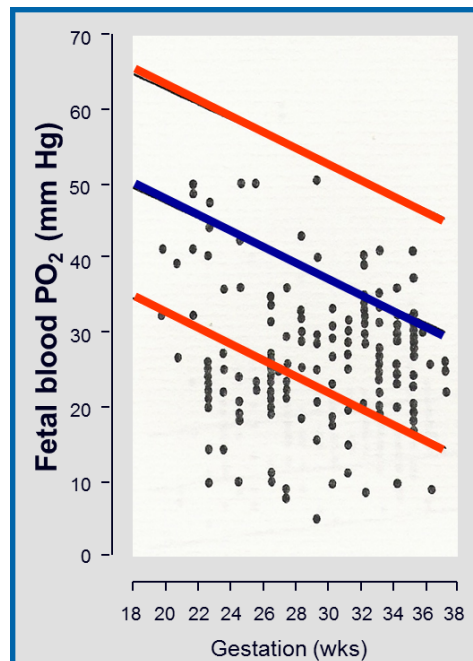

Figure 1: Analysis of samples obtained by cordocentesis has demonstrated that some small-for-gestation fetuses are hypoxemic.

Both respiratory and metabolic acidemia increase with hypoxemia. In umbilical venous blood, mild hypoxemia may be present in the absence of hypercapnia or acidemia. In severe uteroplacental insufficiency, the fetus cannot compensate hemodynamically and hypercapnia and acidemia increase exponentially.[2] The carbon dioxide accumulation is presumably the result of reduced exchange between the uteroplacental and fetal circulations due to reduced blood flow. The association between hypoxemia and hyperlacticemia supports the concept of reduced oxidative metabolism of lactate being the cause of hyperlacticemia, and, under these circumstances, the fetus appears to be a net producer of lactate. Hypoxemic growth-restricted fetuses also demonstrate a whole range of hematological and metabolic abnormalities, including erythroblastemia, thrombocytopenia, hypoglycemia, deficiency in essential amino acids, hypertriglyceridemia, hypoinsulinemia and hypothyroidism.[5-10]

Cross-sectional studies in pregnancies with growth-restricted fetuses have shown that increased impedance to flow in the uterine and umbilical arteries is associated with fetal hypoxemia and academia.[11,12] These data support the findings from histopathological studies that, in some pregnancies with small-for-gestation fetuses, there are:

- Failure of the normal development of maternal placental arteries into low-resistance vessels and therefore reduced oxygen and nutrient supply to the intervillous space;[13]

- Reduction in the number of placental terminal capillaries and small muscular arteries in the tertiary stem villi and therefore impaired maternal-fetal transfer.[14]

Animal studies have demonstrated that, in fetal hypoxemia, there is a redistribution in blood flow, with increased blood supply to the brain, heart and adrenals and a simultaneous reduction in the perfusion of the carcase, gut and kidneys.[15] Doppler ultrasound has enabled the non-invasive confirmation of the so-called `brain-sparing' effect in human fetuses.

PATHOLOGICAL FINDINGS IN PREECLAMPSIA AND FETAL GROWTH RESTRICTION

Preeclampsia (PE) and fetal growth restriction (FGR) are associated with an inadequate quality and quantity of the maternal vascular response to placentation. In both conditions, there are characteristic pathological findings in the placental bed. Brosens et al. examined placental bed biopsies from pregnancies complicated by PE and reported absence of physiological changes in the spiral arteries beyond the decidual-myometrial junction in >80% of the cases.[13] Robertson et al. examined placental bed biopsies from hypertensive women and found a difference between the lesions seen in women with PE and those with essential hypertension.[16] In PE there was a necrotizing lesion with foam cells in the wall of the basal and spiral arteries, which was referred to as `acute atherosis'. In essential hypertension, there were hyperplastic lesions in the basal and spiral arteries.

Sheppard and Bonnar reported that, in pregnancies with FGR (irrespective of whether there is coexistent PE or not), there are atheromatous-like lesions that completely or partially occlude the spiral arteries; these changes are not present in pregnancies with PE in the absence of FGR.[17] In contrast, Brosens et a. reported lack of physiological changes in all cases of PE, irrespective of the birth weight, and in most cases of FGR; however, acute atherosis was found only in PE.[18] Khong et

al. reviewed some of the archived biopsies of Brosens et al.[18,19] They assessed the proportion of spiral arteries converted to uteroplacental arteries. In all cases of PE and in two-thirds of those with FGR (defined as birth weight <10th centile), there was no evidence of physiological change in the myometrial segments. Furthermore, complete absence of physiological change throughout the entire length of some spiral arteries was seen in approximately half the cases of PE and FGR.

DOPPLER STUDIES

Uterine arteries

In pregnancies complicated by PE and/or FGR, impedance to flow in the uterine arteries is increased (Figure 2). Studies in women with hypertensive disease of pregnancy have reported that, in those with increased impedance, compared to hypertensive women with normal flow velocity waveforms, there is a higher incidence of PE, FGR, emergency Cesarean delivery, placental abruption, shorter duration of pregnancy and poorer neonatal outcome.[20-23]
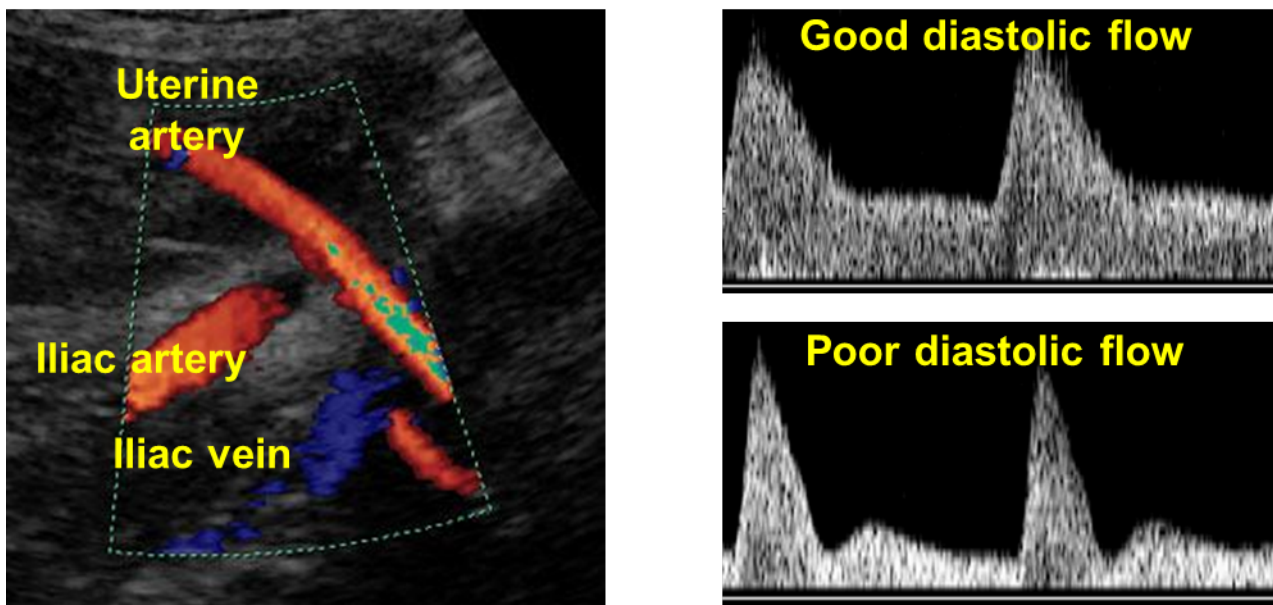

Figure 2: Visualisation of the uterine artery by transabdominal ultrasound with normal (top right) and abnormal (bottom right) flow velocity waveforms at 20 weeks' gestation.

Umbilical arteries

Pathological studies have demonstrated that increased impedance in the umbilical arteries becomes evident only when at least 60% of the placental vascular bed is obliterated.[14] In pregnancies with reversed or absent end-diastolic frequencies (EDF) in the umbilical artery, compared to those with normal flow, mean placental weight is reduced and the cross-sectional diameter of terminal villi is shorter.[24]

In pregnancies with FGR, those with absent EDF, compared to those with normal Doppler, have

more fetal stem vessels with medial hyperplasia and luminal obliteration, and those with reversed end-diastolic flow have more poorly vascularized terminal villi, villous stromal hemorrhage, `hemorrhagic endovasculitis' and abnormally thin-walled fetal stem vessels.[25] In pregnancies with absent EDF in the Doppler waveform from the umbilical arteries, the capillary loops in placental terminal villi are decreased in number, they are longer and they have fewer branches than in normal pregnancies.[26] The reduced number and maldevelopment of peripheral villi result in a marked impairment of oxygen extraction from the intervillous space. In contrast, placentas from pregnancies with FGR and positive EDF have a normal pattern of stem artery development, increased capillary angiogenesis and development of terminal villi, as signs of an adaptative mechanism.[27]

Clinical studies of umbilical arterial flow velocity waveforms in FGR have reported progressive increase in impedance to flow until absence and, in extreme cases, reversal of EDF (Figure 3).[28-32] The latter represents the extreme end of the spectrum and this finding is associated with a high perinatal mortality, as well as an increased incidence of lethal fetal structural and chromosomal defects.[33,34]

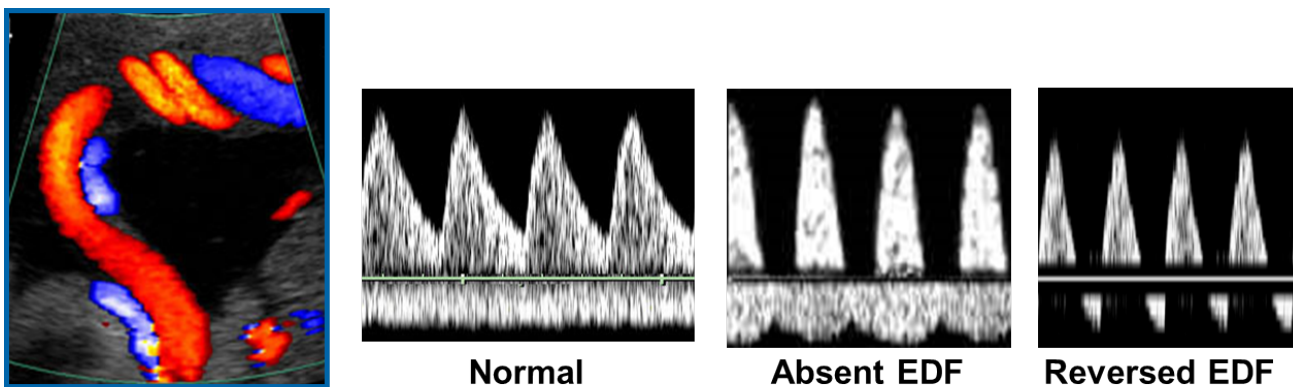**Normal**   **Absent EDF**   **Reversed EDF**

Figure 3: Umbilical artery Doppler. Flow velocity waveforms with normal, absent and reversed end diastolic frequencies.

Nicolaides et al. measured blood gases in umbilical cord blood samples obtained by cordocentesis in 39 cases of FGR.[12] End-diastolic frequencies were absent in 22 cases; 80% of these fetuses were found to be hypoxemic and 46% also acidemic. In contrast, only 12% of the fetuses with positive EDF were hypoxemic and none was acidemic.

In a multicenter study involving high-risk pregnancies, the patients were subdivided into three groups depending on the flow velocity waveforms in the umbilical artery (positive EDF, n = 214; absent EDF, n = 178; and reversed EDF, n = 67).[35] The overall perinatal mortality rate was 28% and the relative risk was 1.0 for patients with present frequencies, 4.0 for those with absent frequencies and 10.6 for those with reversed frequencies. Significantly more neonates in the groups with absent or reversed frequencies needed admittance to the neonatal intensive care unit and they had a higher risk of cerebral hemorrhage, anemia or hypoglycemia.[35] In addition to increased fetal and neonatal mortality, FGR with absent or reversed EDF in the umbilical artery is associated with increased incidence of long-term permanent neurological damage.[36]

A Cochrane review of 18 studies in high-risk pregnancies that compared the use of Doppler ultrasound of the umbilical artery with no Doppler or with cardiotocography (CTG) concluded that use of Doppler ultrasound reduces the risk of perinatal deaths and may result in fewer obstetric interventions.[37] Use of Doppler was associated with fewer perinatal deaths (risk ratio 0.71, 95% confidence interval 0.52 to 0.98), fewer inductions of labour (risk ratio 0.89, 95% confidence interval 0.80 to 0.99), and fewer caesarean sections (risk ratio 0.90, 95% confidence interval 0.84 to 0.97).

In terms of monitoring FGR pregnancies, abnormal waveforms in the umbilical artery are an early sign of fetal impairment. For example, Bekedam et al. followed up growth-restricted fetuses longitudinally and reported that abnormalities in the umbilical artery preceded the occurrence of cardiotocographic signs of fetal hypoxemia in more than 90% of cases.[38] The median time interval between absence of EDF and the onset of late decelerations was 12 days (range 0-49 days).

Fetal arterial blood flow redistribution

In fetal hypoxemia, there is an increase in the blood supply to the brain, myocardium, adrenal glands and spleen (decreased PI in cerebral, coronary, splenic and adrenal arteries) and reduction in the perfusion of the kidneys, gastrointestinal tract and the lower extremities (increased PI in descending aorta, renal and femoral artery) (Figures 4 and 5).[39-66]

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. This mechanism allows preferential delivery of nutrients and oxygen to vital organs, thereby compensating for diminished placental resources. However, compensation through cerebral vasodilatation is limited and a plateau corresponding to a nadir of pulsatility index (PI) in cerebral vessels is reached at least 2 weeks before the development of the fetus is jeopardized. Consequently, arterial vessels are unsuitable for longitudinal monitoring of growth-restricted fetuses. Cardiac and venous velocity waveforms give more information regarding fetal well-being or compromise.
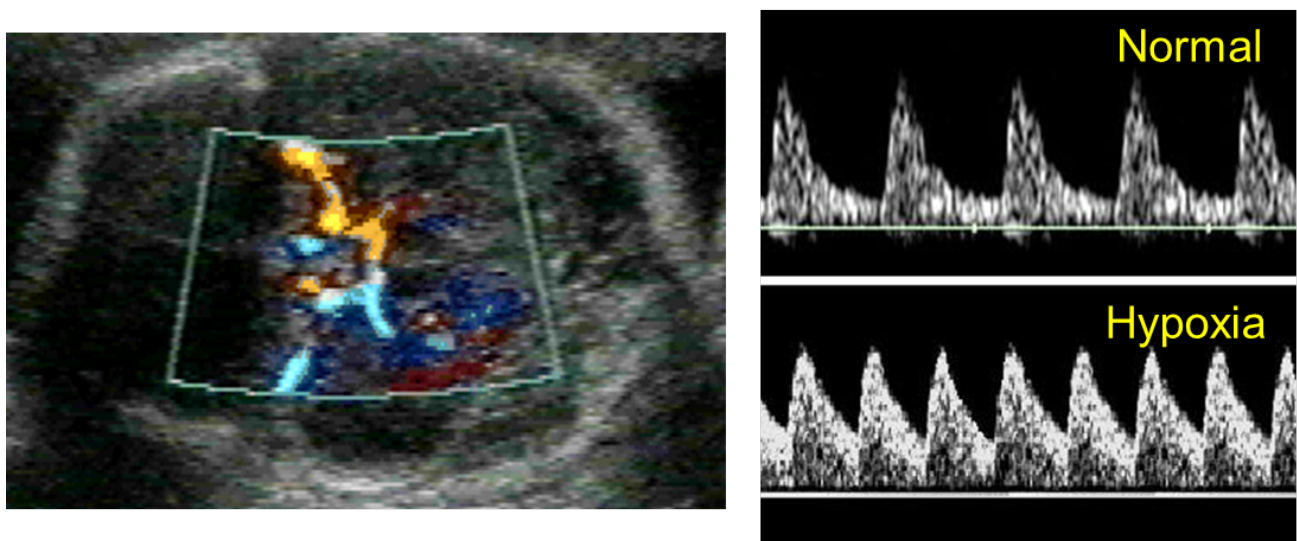

Figure 4: Color Doppler examination of the circle of Willis). Flow velocity waveforms from the middle cerebral artery in a normal fetus with low diastolic velocities (right, top) and in a growth-restricted fetus with high diastolic velocities (right, bottom).
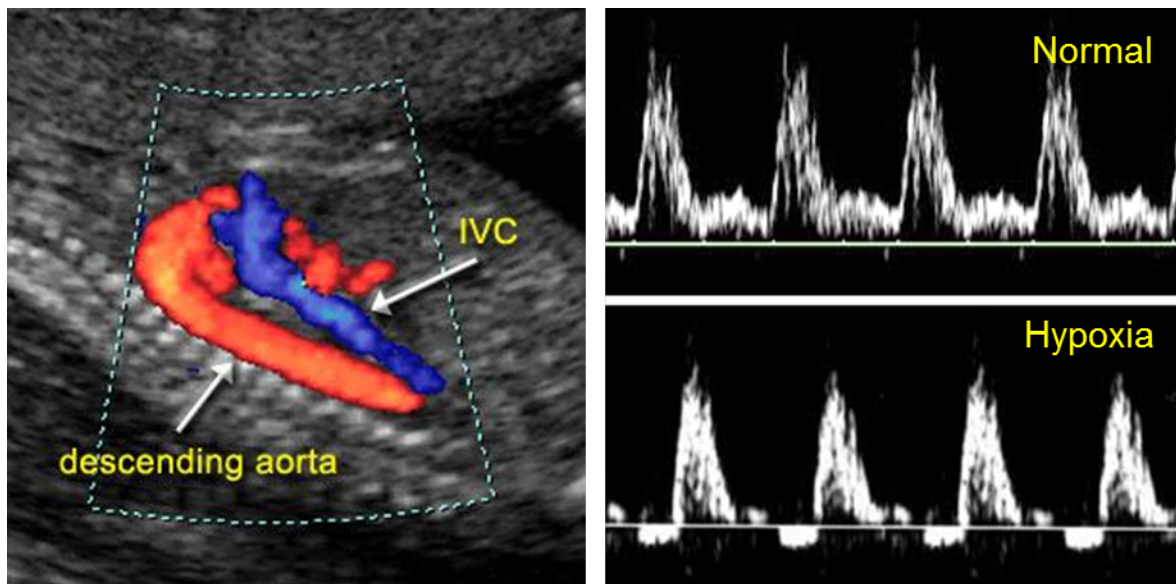
Figure 5: Color Doppler examination of the descending thoracic aorta with normal flow velocity waveforms showing positive flow velocities during diastole (right, top) and in a growth-restricted fetus with reversed end-diastolic velocities (right, bottom).

Fetal arterial Doppler studies are useful in the differential diagnosis of small-for gestation fetuses. In the hypoxemic group, due to impaired placental perfusion, the PI in the umbilical artery is increased and, in the fetal middle cerebral artery, the PI is decreased; consequently, the ratio in PI between the umbilical artery and middle cerebral artery (UA/MCA) is increased.[58-61] Bahado-Singh et al. reported that an abnormally low cerebroplacental ratio is associated with increased perinatal morbidity and mortality and that the ratio improves the prediction of perinatal outcome compared with umbilical artery PI alone.[65] There is no evidence that the use of other peripheral arterial fetal vessels, such as renal artery, splenic artery or peripheral pulmonary arteries provides any advantage in the identification of intrauterine growth-restricted fetuses.

Fetal cardiac Doppler

Cardiac flow is greatly influenced by the modifications of arterial impedance to flow. Cerebral vasodilatation produces a decrease in left ventricle afterload, whereas increased placental and systemic resistance produce increased right ventricle afterload. Hypoxemia may also impair cardiac contractility directly, while changes in blood viscosity due to polycythemia may alter preload. Consequently, growth-restricted fetuses show, at the level of the atrioventricular valves, impaired ventricular filling (lower ratio of early passive to late active ventricular filling phase - E/A ratio),[67] lower peak velocities in the aorta and pulmonary arteries.[68-70] These hemodynamic intracardiac changes are compatible with a preferential shift of cardiac output in favor 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 at near normal levels despite any absolute reduction of placental transfer.

Longitudinal studies of deteriorating growth-restricted fetuses have shown that peak velocity and cardiac output gradually decline, suggesting a progressive worsening in cardiac function.[71] Similarly, there is a symmetrical decrease in ventricular ejection force at the level of both ventricles, despite

the dramatically different hemodynamic conditions present in the vascular district of ejection of the two ventricles (i.e. reduced cerebral resistance for the left ventricle and increased splachnic and placental resistance for the right ventricle).[72] This supports a pivotal role of the intrinsic myocardial function in the compensatory mechanism of the growth-restricted fetus following the establishment of the brain-sparing effect. Ventricular ejection force dramatically decreases in a short time interval (about 1 week), showing an impairment of ventricular force close to fetal distress. As a consequence, cardiac filling is also impaired.

Fetal venous Doppler

Animal studies have shown that, in severe hypoxemia, there is redistribution in the umbilical venous blood towards the ductus venosus at the expense of hepatic blood flow. Consequently, the proportion of umbilical venous blood contributing to the fetal cardiac output is increased. There is a doubling of umbilical venous-derived oxygen delivery to the myocardium and an increase in oxygen delivery to the fetal brain.[73,74] In vitro perfusion studies have shown that, at reduced umbilical venous pressures, a proportionally greater fraction of umbilical venous flow is directed through the ductus venosus in comparison to blood flow through the liver.[75]

The same is true during perfusion with blood of high hematocrit. Mechanical forces seem to play a key role in the regulation of umbilical venous flow distribution between the liver and the ductus venosus. Under unfavorable conditions, the ductus venosus seems to ensure blood flow directly to the fetal heart and, in extreme conditions, umbilical blood may pass exclusively through the ductus venosus. This may lead to an impaired perfusion of the liver with potential impact on its metabolic properties. Blood flow measurements with chronically implanted electromagnetic flow transducers in fetal sheep have shown an increase of the amplitude of vena caval pulsations during hypoxemia and increased afterload.[76]Flow waveforms show an increase in peak systolic forward flow, and during atrial contraction retrograde flow occurs. In contrast, reductions in afterload are associated with an increase in peak diastolic forward flow, indicating that fetal systemic vascular resistance has a major influence on venous return and filling patterns of the right heart. Increased placental resistance and peripheral vasoconstriction, as seen in fetal arterial redistribution, cause an increase in right ventricular afterload, and thus ventricular end-diastolic pressure increases. This may result in highly pulsatile venous blood flow waveforms and umbilical venous pulsations due to transmission of atrial pressure waves through the ductus venosus.[77]

Studies in growth-restricted human fetuses have demonstrated that, in the inferior vena cava, an increase of reverse flow during atrial contraction occurs with progressive fetal deterioration, suggesting a higher pressure gradient in the right atrium (Figure 6).[78,79] The next step of the disease is the extension of the abnormal reversal of blood velocities in the inferior vena cava to reversed a-wave in the ductus venosus (Figure 7). Finally, the high venous pressure induces a reduction of velocity at end-diastole in the umbilical vein, causing typical end-diastolic pulsations.[80] The development of these pulsations is close to the onset of abnormal fetal heart rate patterns and is frequently associated with fetal academia.[81,82] At this stage, coronary blood flow may be visualized with higher velocity than in normally grown third-trimester fetuses and, if fetuses are not delivered, intrauterine death may occur within a few days.[83] In a study of 37 fetuses with absent EDF in the umbilical artery, the main factors determining the length of the interval between the first occurrence of absent EDF were gestational age (the lower the gestation, the longer was the interval), PE (shorter interval) and the presence of pulsations in the umbilical vein; the neonatal mortality in this group with pulsatile venous flow was 63%, compared to 19% in fetuses without pulsations.[84]
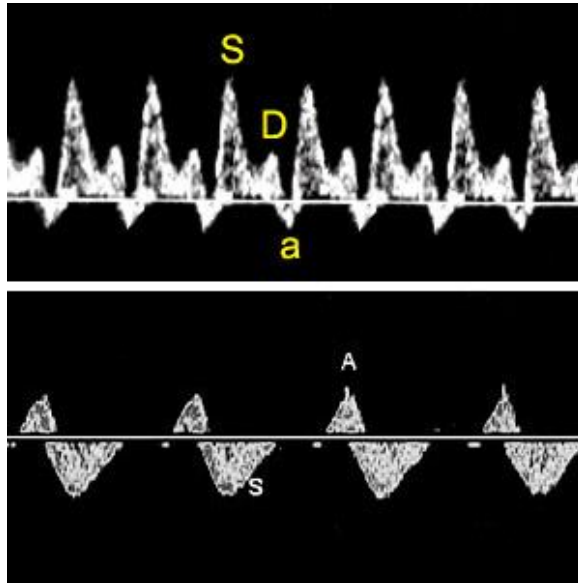
Figure 6: Color Doppler examination of the inferior vena cava with normal flow velocity waveforms (top). Abnormal waveform with increase in reversed flow during atrial contraction in a growth-restricted fetus (bottom).
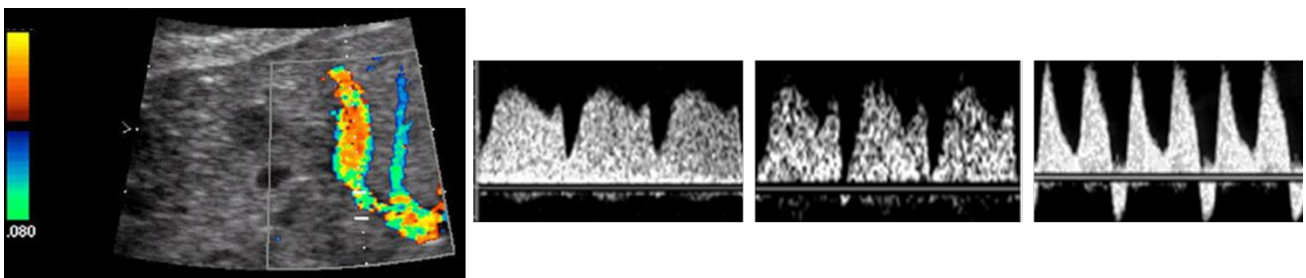

Figure 7: Color Doppler examination of the ductus venosus with normal flow velocity waveforms (left), absent a-wave (middle) in fetal hypoxemia and reversed a-wave (right) in fetal acidemia.

Fetal venous Doppler studies are useful in monitoring the growth-restricted redistributing fetus. Normal venous flow suggests continuing fetal compensation, whereas abnormal flow indicates the breakdown of hemodynamic compensatory mechanisms.[79] Hecher et al. compared fetal venous and arterial blood flow with biophysical assessment in 108 high-risk pregnancies after 23 weeks of gestation.[85] The results of this study suggest that venous Doppler findings in the late third-trimester fetus may not be as reliable as during the late second and early third trimesters. However, the most interesting results were found in a group of 41 fetuses displaying arterial blood flow redistribution. There were no significant differences in arterial PI values between fetuses with normal and abnormal biophysical assessment parameters (except for the aorta and abnormal fetal heart rate trace), whereas venous pulsatility was significantly increased in compromised fetuses compared to the non-compromised group.

Fetal hypoxemia is associated with a reduction in umbilical venous blood flow, but, despite this decrease, a normal peak velocity in the ductus venosus is maintained.[86] In the growth-restricted fetus, the percentage of umbilical venous blood passing through the ductus venosus is increased

from about 40% (in normal fetuses) to about 60%.[87] Therefore, there is a redistribution in venous blood flow in favor of the ductus venosus at the expense of hepatic blood flow. Unlike peak velocity during ventricular systole, there were reduced or even reversed flow velocities during atrial contraction. One may speculate that increased end-diastolic right ventricular pressure would not influence ductus venosus blood flow velocities during atrial contraction, as flow is preferentially directed through the foramen ovale to the left atrium. However, the foramen ovale is closed during atrial contraction and blood flow velocity through the foramen ovale decreases to zero.

Alterations of venous flow velocity waveforms are in a closer temporal relationship to intrauterine fetal jeopardy, compared to changes in arterial flow, which may occur quite early during the course of impaired placental function. The degree of fetal acidemia can be estimated from Doppler measurements of pulsatility in both the arterial system and the ductus venosus. This was shown in a cross-sectional study of 23 severely growth-retstricted fetuses, examining the relationship between Doppler measurements and umbilical venous blood gases obtained at cordocentesis.[88] With moderate acidemia (pH between -2 and -4 standard deviations from the normal mean for gestational age), almost all fetuses had a middle cerebral artery PI below two standard deviations, whereas there was a wide scatter of individual results for the ductus venosus, with the majority of measurements being still within the reference ranges. With increasing severity of hypoxemia and acidemia, ductus venosus PIs increased and, in the most severe cases, velocities with atrial contraction were reduced to zero or even became negative. In a study investigating the association of arterial and venous Doppler findings with adverse perinatal outcome in severe fetal growth restriction, abnormal Doppler velocimetry of the ductus venosus was the only significant parameter associated with perinatal death and low 5-min Apgar scores.[89]

There are two possible mechanisms for abnormal venous blood flow waveforms: increasing right ventricular afterload and myocardial failure. As long as the fetus is able to compensate for a reduced placental supply by arterial redistribution, there is preferential myocardial oxygenation, which delays development of right heart failure, despite an increasing afterload. Therefore, fetal Doppler measurements show high placental resistance and arterial redistribution in the presence of normal venous waveforms. At this stage, the majority of fetuses have normal, reactive heart rate traces and biophysical profiles. Progressive changes in the venous circulation may indicate failure of the compensatory mechanism and herald the development of right heart failure due to myocardial hypoxia. Another interesting aspect has been raised by a study examining fetal central venous pressure. The pressure waveform from the inferior vena cava was recorded by following the movement of the vessel wall and thereby recording changes in the vessel lumen diameter.[90] There were two groups of abnormal waveforms: one with a high pulsatile pattern and the other with a shallow and low pulsatile pattern. Both groups had significantly worse clinical outcomes compared to the normal waveform group. However, fetuses in the low pulsatile group were the most severely compromised, all of them showing an abnormal heart rate pattern. It was postulated that impaired contractility and reduced ventricular output, with a concomitantly reduced ventricular filling, were responsible for this waveform pattern.

Timing of delivery

In the management of the very preterm (<33 weeks' gestation) growth-restricted fetus, there is uncertainty as to whether iatrogenic delivery should be undertaken before the development of signs of severe hypoxemia, with a consequent risk of prematurity-related neonatal complications, or whether delivery should be delayed, but with the risks of prolonged exposure to hypoxia and

malnutrition imposed by a hostile intrauterine environment. A growth-restricted fetus leading an ascetic existence from chronic starvation during the late second or early third trimester is capable of tolerating chronic hypoxemia without damage for much longer than a well-nourished late third-trimester fetus with a high energy consumption.

Postnatal follow-up studies, at the age of 7 years, have reported that growth-restricted fetuses with abnormal aortic velocity waveforms had minor neurological dysfunction and impaired intellectual outcome.[91,92] If these findings are confirmed in prospective studies with adequate controls for confounding variables, such as degrees of prematurity, smallness, and management, it may be advisable to deliver growth-restricted fetuses before these blood flow alterations occur. On the other hand, fetuses showing the brain-sparing effect did not have an increased risk for moderate or severe neurological handicap at the age of 2 years.[93] It will always be a challenge to weigh the risks and benefits of early interventions against each other and it is a dynamic process, in which advancements in both fetal and neonatal medicine are of crucial importance for the counselling of parents and the management of these pregnancies.

In the growth-restricted hypoxemic fetus, redistribution of well-oxygenated blood to vital organs, such as the brain, heart and adrenals, represents a compensatory mechanism to prevent fetal damage. When the reserve capacities of the circulatory redistribution reach their limits, fetal deterioration may occur rapidly. In clinical practice, it is necessary to carry out serial Doppler investigations to estimate the duration of fetal blood flow redistribution. The onset of abnormal venous Doppler results indicates deterioration in the fetal condition and iatrogenic delivery should be considered.

In the sequence of deterioration of the condition of the growth-restricted fetus, the first pathological finding is increased impedance to flow in the umbilical artery. This is followed by evidence of arterial redistribution in the fetal circulation and, subsequently, the development of pathological fetal heart rate patterns. On average, the time interval between the onset of abnormal umbilical arterial Doppler results and the onset of late fetal heart rate decelerations is about 2 weeks, but this interval differs considerably among fetuses and is shorter in late than early pregnancy and in the presence of hypertensive disease.[31,38,84,94,95] Increased impedance to flow in the umbilical artery is usually associated with evidence of arterial redistribution in the fetal circulation; this is best monitored by examining the PI in the middle cerebral artery, which is decreased.

Late fetal heart rate decelerations are preceded by approximately 2 weeks with Doppler evidence of a nadir in the brain-sparing effect and by a few days with an abrupt increase in impedance in the umbilical arteries.[55] In the first stages of the disease, there is a preferential shift of cardiac output in favor of the left ventricle, leading to improved cerebral perfusion, but with deterioration in the fetal condition, there are a decline in cardiac output and progressive worsening in cardiac function.[71] Normal venous flow suggests continuing fetal compensation, whereas abnormal flow indicates the breakdown of hemodynamic compensatory mechanisms.[79]

An abrupt increase in pulsatility of ductus venosus waveforms with loss of a-wave precede the onset of pathological fetal heart rate patterns and decreased short-term variation (STV). A multicentre, randomised study (TRUFFLE trial) examined whether in pregnancies with FGR at 26-32 weeks' gestation and umbilical artery PI >95th percentile, compared changes in ductus venosus flow and cardiotocographic decreased fetal heart rate short-term variation (STV) as indications for delivery.[96] The primary outcome was survival without cerebral palsy or neurosensory impairment, or

a Bayley III developmental score <85, at 2 years of age.

The patients were randomly allocated to three timing of delivery plans:
- Reduced cardiotocograph fetal heart rate STV
- DV PI >95th percentile
- DV absent or reversed a-wave

The study found that there was no significant difference between the three groups in the proportion of infants surviving without neurological impairment. However, in the babies that survived more infants more infants were free of neurological impairment in the group where delivery was based on DV absent or reversed a-wave. It was concluded that timing of delivery based on late changes in the DV waveform might produce an improvement in developmental outcomes at 2 years of age.

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