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REVIEW ARTICLE

Doppler Sonography in Obstetrics

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ABSTRACT

Doppler sonographic applications in pregnancy are the widely accepted functional methods of evaluating fetal wellbeing. Flow velocity waveforms provide important information from the early stages of pregnancy to term. Doppler ultrasound is a noninvasive technique whereby the movement of blood is studied by detecting the change in frequency of reflected sound.

This method became an important tool for qualifying pregnancies in risk. Information obtained with Doppler sonography helps obstetricians managing patients in situations like pregnancies complicated by intrauterine growth restriction (IUGR), rhesus alloimmunization, multiple pregnancies and anamnestic risk factors. Examination of the uteroplacental and fetomaternal circulation by Doppler sonography in the early second trimester helps predicting pregnancy complications like preeclampsia, IUGR and perinatal death.

This chapter aims to discuss Doppler sonographic examinations in modern obstetrics. To date, randomized controlled trials were able to establish important clinical value of Doppler velocimetry in obstetrics to improve perinatal outcome in high-risk situations.

Keywords: Doppler sonography, Flow velocity waveforms, Intrauterine growth restriction, Perinatal outcome, High-risk pregnancy.

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INTRODUCTION

Doppler sonographic applications in pregnancy are the widely accepted functional methods of evaluating fetal wellbeing. Flow velocity waveforms provide important information from the early stages of pregnancy to term. As applications proliferate, awareness of the complexity of fetal and placental circulations, in normal pregnancy and in sequential responses to compromise, has also grown.[1] One of the main aims of routine antenatal care is to identify the 'at risk' fetus in order to apply clinical interventions which could result in reduced perinatal morbidity and mortality.

Doppler ultrasound is a noninvasive technique whereby the movement of blood is studied by detecting the change in frequency of reflected sound. Doppler ultrasound has been used in obstetrics since 1977 to study the fetoplacental (umbilical) circulation,[2] and since the 1980s to study the uteroplacental (uterine) circulation[3] and fetal circulation.[4] Recently, this method became an important tool for qualifying pregnancies in risk.

Information obtained with Doppler sonography helps obstetricians managing patients in situations like pregnancies complicated by intrauterine growth restriction (IUGR), Rhesus alloimmunization, multiple pregnancies and anamnestic risk factors. Examination of the uteroplacental and fetomaternal circulation by Doppler sonography in the early second trimester helps predicting pregnancy complications like pre-eclampsia, IUGR and perinatal death.[5-13]

This chapter aims to introduce Doppler sonographic examinations in modern obstetrics. Doppler blood flow velocity waveforms (FVWs) of the fetal arterial side (umbilical arteries, descending aorta and middle cerebral arteries) and maternal side (uterine arteries) are discussed and nomograms for routine obstetric practice are presented.

THE SAFETY OF DOPPLER ULTRASOUND IN OBSTETRICS

The data available suggests that diagnostic ultrasound has no adverse effects on embryogenesis or fetal growth. In addition, ultrasonographic scanning has no long-term effects on cognitive function or change visual or hearing functions. According to the available clinical trials, there is a weak association between exposure to ultrasonography and non-right handedness in boys (odds ratio 1.26; 95% CI, 1.03-1.54).[14] However, although B and M mode scans are safe during pregnancy, color, power and pulsed Doppler procedures should be performed with caution, especially in the early stages of pregnancy, due to possible thermal effects. Studies concerned with the safety of ultrasound included mostly exposures before 1995, when the acoustic potency of the equipment used was lower than in modern machines. Over the years, there has been a continuous trend of increasing acoustic output, and the findings of the previous studies necessarily apply to currently used equipment. Because of weak regulation of ultrasound equipment output, fetal exposure using current equipment can be almost eight times greater than that used previously, regardless of whether gray-scale imaging, the three-dimensional technique, color Doppler or duplex Doppler is employed. A short acquisition time of any kind of diagnostic ultrasonic wave may decrease exposure and thus unknown effects on fetal development.[15]

In particular, the use of pulsed Doppler involves the use of higher intensities compared to diagnostic ultrasound, and

hence may cause significant tissue heating and thermal effects. However, these thermal effects depend on the presence of a tissue/air interface and may therefore not be clinically significant in obstetric ultrasound examinations.[16] The principle known as ALARA (as low as reasonably achievable) is generally supported and encourages the balance between the necessary medical information, minimal settings and exam time.[17]

In a randomized controlled prospective study, considering the long-term effect of ultrasound examinations on childhood outcome up to 8 years of age, it was shown that exposure to multiple prenatal ultrasound examinations from 18 weeks' gestation onward might be associated with a small effect on fetal growth, but is followed in childhood by growth and measures of developmental outcome similar to those in children who had received a single prenatal scan.[18]

DEPENDENCY OF DOPPLER FLOW VELOCITY WAVEFORMS ON GESTATIONAL AGE

The amount of perfusion in trophoblastic tissue is related to gestational age. For this reason, in interpreting the Doppler sonographic findings, gestational age must be taken into account. That is, nomograms for Doppler sonographic measurements should be standardized according to gestational age. In the routine use of ultrasound in practice, the accepted time for starting Doppler sonographic examinations is the beginning of the second trimester. This is the right time that allows modifications in antenatal care in a high-risk pregnancy. For specific conditions, earlier timing of measurements may be considered.[19]

The main objective in constituting fetomaternal Doppler sonographic nomograms is to improve perinatal outcome in high risk pregnancies. Curves presented below depict normal fetal and maternal Doppler sonographic values, and can be used in routine practice.

Indices

Blood flow velocity in the fetal circulating system depends on the type of vessel: the arteries always have a pulsatile pattern, whereas veins have either a pulsatile or continuous pattern.

Analysis of Doppler sonographic FVWs quantitatively, is more difficult than analyzing qualitatively. Qualitative analysis also overcomes erroneous measurements in small vessels. There are plenty of indices for qualitative analysis.

Following are the most frequently used indices:

- Systolic/Diastolic ratio (S/D ratio, Stuart 1980)
- Resistance index (RI, Pourcelot 1974)
- Pulsatility index (PI, Gosling and King 1977).

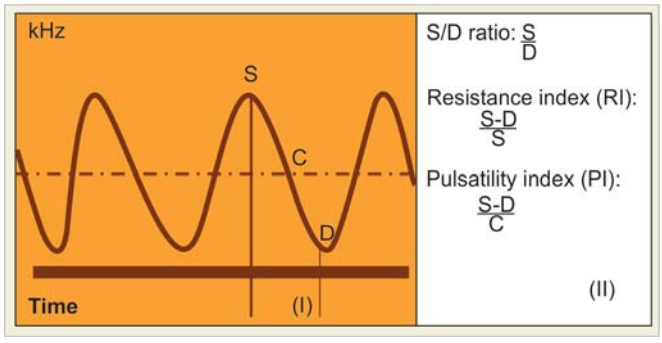

Fig. 1: Scheme of the Doppler curve (I). S: systolic; D: diastolic; C: temporal average of maximum frequency. Calculation formulas of the main Doppler sonographic indices (II)

In analyzing sonographic results and calculating indices, following characters are used:

S = Temporal peak of maximum frequency
D = End-diastolic maximum frequency
C = Temporal average of maximum frequency, F_{mean}
I = Instantaneous spatial average frequency
E = Temporal average of spatial average frequency

Calculations of formulas are as follows (Fig. 1):

S/D ratio = S/D
RI = (S-D)/S
PI = (S-D)/C

While calculating PI values, in some sonographic devices, E values are used instead of C values. As a result PI values increase slightly.

The above presented indices overcome also a very serious problem involved with the angle between the ultrasound beam and the direction of blood flow (insonation angle). These indices are relatively angle independent and are therefore easily applied in clinical practice.

In practice, none of the indices is superior to the other[20-22] and any index may be used. Although the S/D ratio is easily calculated, RI is the easiest to interpret. Resistance index values approach to zero if the resistance decreases and approach to one if resistance increases. If end-diastolic flow is absent, PI is the only index making evaluation of blood flow possible, because in this situation S/D will equal to infinite and RI to one. The PI is more complex because it requires the calculation of the mean velocity, but modern Doppler sonographic devices provide those values in real time.

Doppler sonographic nomograms are used for the differentiation of normal and abnormal blood FVWs, which helps to determine pregnancies at risk. By taking threshold values of pathologic pregnancies into consideration, nomograms are capable to differentiate between normal and abnormal. The nomograms are presented for meeting this target.[23] While confronting with these nomograms, it must always kept in mind that the values on these nomograms should not be taken as mathematical equations, and that limitations of sensitivity and specificity exist.

Using Nomograms in Practice

Just like the defense mechanism of peripheral vasoconstriction in an adult in the face of hemorrhagic shock, the 'brain sparing' mechanism (brain-sparing effect) becomes active in a fetus with hypoxia or chronic placental insufficiency. As a result of the brain sparing effect, resistance either in the umbilical artery (UA) and fetal descending aorta (FDA) increases. As a consequence Doppler indices related to these vessels increase. The end-diastolic blood flow increases in middle cerebral arteries (MCA) by the same effect. Doppler indices for this vessel decreases consequently.

Some points should be considered while using Doppler sonographic nomograms:

- Among the measurements performed on the UA and FDA, values between 90 and 95th percentiles should be considered as borderline and repeat follow-ups should be planned. Values exceeding the 95th percentile are considered abnormal.
- Doppler values between 5 and 10th percentiles in MCA should be considered as borderline and repeat follow-ups should be planned. Values below the 5th percentile are considered abnormal.
- Measurements taken after 24 weeks' gestation from uterine arteries are more valuable. The early diastolic notching, and values exceeding the 95th percentile are considered as abnormal. One point to remember is that notching predicts an increased risk of pre-eclampsia.

CHANGES IN DOPPLER SONOGRAPHIC RESULTS DURING THE COURSE OF PREGNANCY AND COMPLICATED PREGNANCIES

During the course of pregnancy and in some specific pregnancy complications, Doppler sonographic results of fetomaternal vessels display changing values.

UMBILICAL ARTERY (UA)

It has been shown in a longitudinal observational study that Doppler ultrasound of the UA is more helpful than other tests of fetal wellbeing (e.g. heart rate variability and biophysical profile score) in distinguishing between the normal small fetus and the 'sick' small fetus.[24] However, its exact role in optimizing management, particularly timing of delivery, remains unclear, and is currently being investigated by many study groups. The optimal timing of delivery in pregnancies complicated by highly pathological Doppler flow findings is still an issue to be resolved. To resolve this question and to improve the perinatal morbidity and mortality some multicenter clinical trials[25] have been

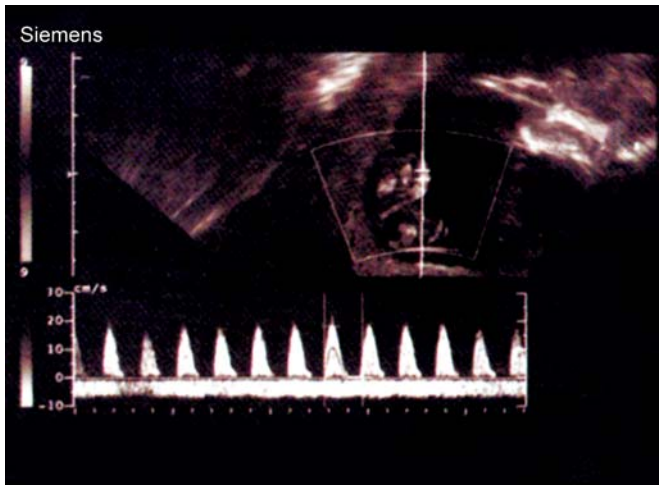

Fig. 2: Absent end-diastolic flow of the umbilical artery in the first trimester (physiologic) with pulsations of the umbilical vein (physiologic)

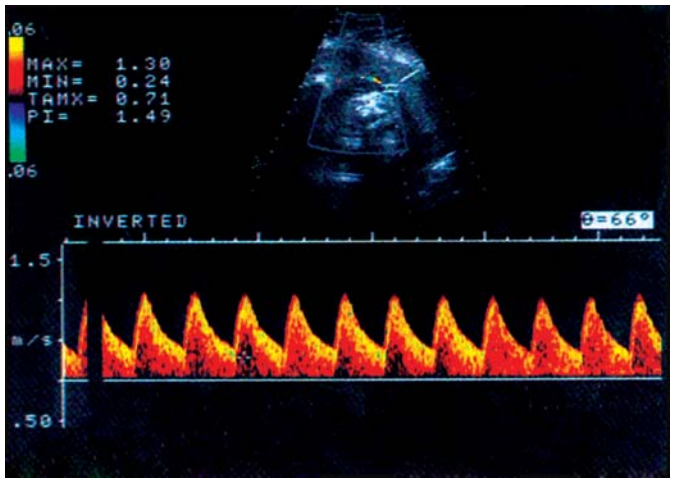

Fig. 3: Normal flow velocity waveforms of the umbilical artery in the third trimester

undertaken. Gestational age, Doppler waveforms, antenatal testing, and maternal status should all be taken into consideration to guide optimal timing of delivery to minimize extreme prematurity, but also to prevent intrauterine injury, in the case of the compromised fetus.

Blood flow velocity in the UA increases with the advancing gestation. As a result impedance to blood flow continuously decreases due to increasing arterial blood flow in the systole and diastole. End-diastolic velocity is often absent in the first trimester[2,26] and the diastolic component increases with advancing gestation[27] (Fig. 2). With advancing gestational age, end-diastolic flow becomes evident during the whole heart cycle (Fig. 3), proven with previous longitudinal studies of Fogarty et al[22] and Hünecke et al,[28] as with many cross-sectional studies.[27,29]

Trudinger et al[30] explained this phenomenon with the following mechanisms:

- Continuous maturation in placental villi
- Continuous widening of placental vessels cause a continuous decrease in vascular resistance

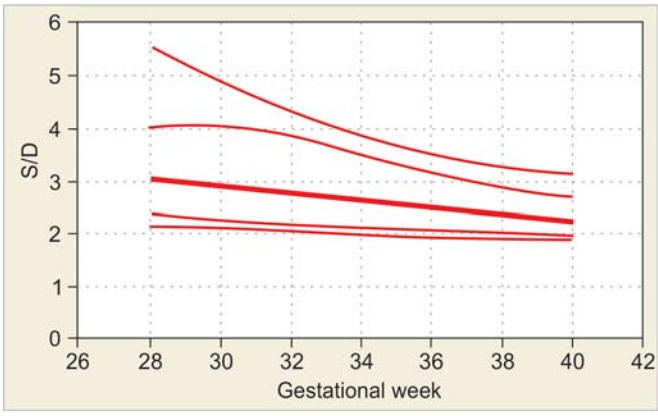

Fig. 4: Umbilical artery systolic/diastolic (S/D) ratio nomogram

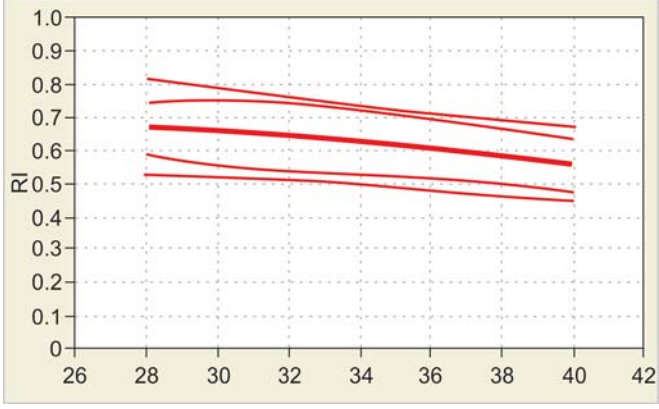

Fig. 5: Umbilical artery resistance index (RI) nomogram

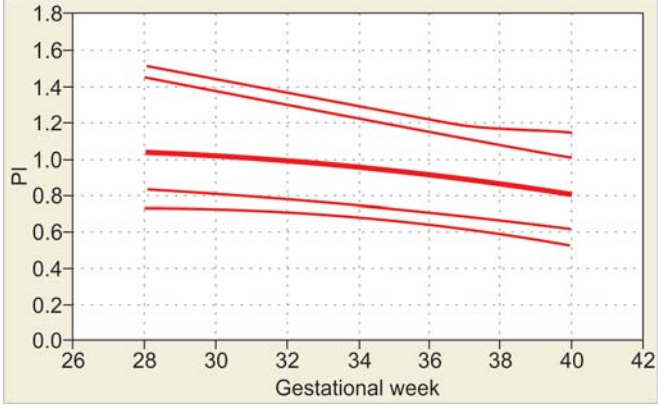

Fig. 6: Umbilical artery pulsatility index (PI) nomogram

- Continuous increase in fetal cardiac output
- Continuous changes in the vessel compliance
- Continuous increase in fetal blood pressure.

Especially in the third trimester of pregnancy, depending on the above factors normal values become scattered on nomograms (Fig. 4). This scattering is more prominent in the S/D ratio than the PI. Resistance index is not affected by above factors after 28 weeks' gestation (Figs 4 to 6).

Flow velocity waveforms of the UA are slightly different at the abdominal wall and the placental site, with indices higher at the fetal abdominal wall than the placental insertion.[31] The difference, however, is minimal, and therefore in clinical practice it is not important to obtain the FVWs always at the same level. Flow velocity waveforms must always be obtained during fetal apnea periods because fetal breathing affects the waveforms.

In case of an abnormal test, clinical experience and randomized controlled trials showed significant association with an adverse perinatal outcome.

Intrauterine Growth Restriction

The IUGR fetus is a fetus that does not reach its potential growth. Environmental factors responsible for IUGR may be due to maternal, uteroplacental and fetal factors (Table 1). Many authors have reported on the association between an abnormal UA Doppler FVW and IUGR.

Differentiating the fetus with pathologic growth restriction that is at risk for perinatal complications from the constitutionally small but healthy fetus has been an ongoing challenge in obstetrics. Not all infants whose birth weight is below the 10th percentile have been exposed to a pathologic process *in utero*; in fact, most small newborns are constitutionally small and healthy. Doppler sonography has become the most important investigation method to differentiate between these fetuses.

Pathophysiology of abnormal FVWs in placental insufficiency:[32] In the presence of placental insufficiency, there is greater placental resistance, which is reflected in a decreased end-diastolic component of the UA FVWs.[33-37] An abnormal UA FVW has a S/D ratio above the normal range. As the

Table 1: Factors responsible for intrauterine growth restriction

Maternal factors
• Cardiorespiratory diseases
• Renal disease
• Anemia
• Drugs (antineoplastic agents, narcotics)
• Smoking
• Alcohol abuse
Uteroplacental factors
• Impaired uteroplacental blood flow
• Chronic hypertension
• Pre-eclampsia
• Gestational diabetes
• Collagen vascular disease
• Uterine anomalies
• Leiomyomatosis
Placental factors
• Abruptio placentae
• Placenta previa
• Placental infarction
• Placentitis, vasculitis
• Placental cysts, tumors (chorioangioma)
Fetal factors
• Infections
• Cardiac disease
• Anomalies
Chromosomal anomalies

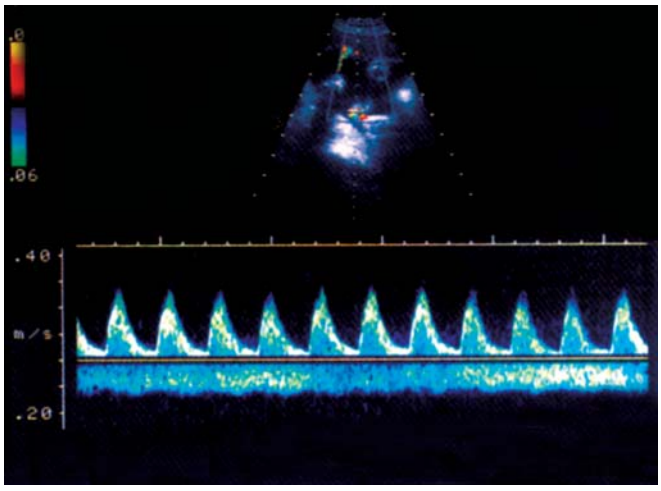

Fig. 7: Abnormal flow velocity waveforms of the umbilical artery in the third trimester (high resistance index)

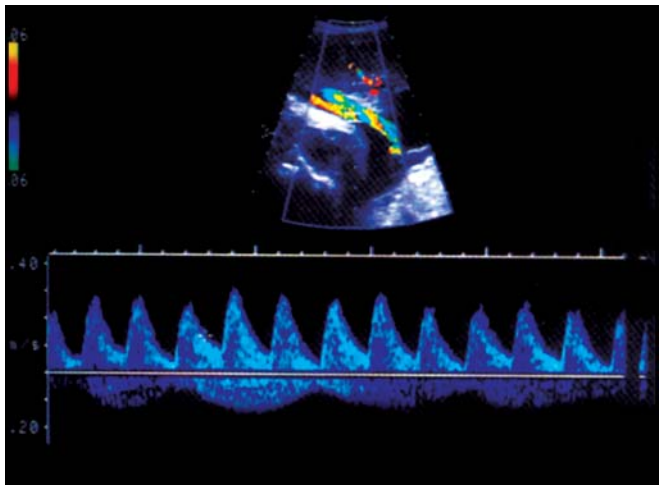

Fig. 10: Pitfalls in umbilical artery Doppler velocimetry (fetal breathing)

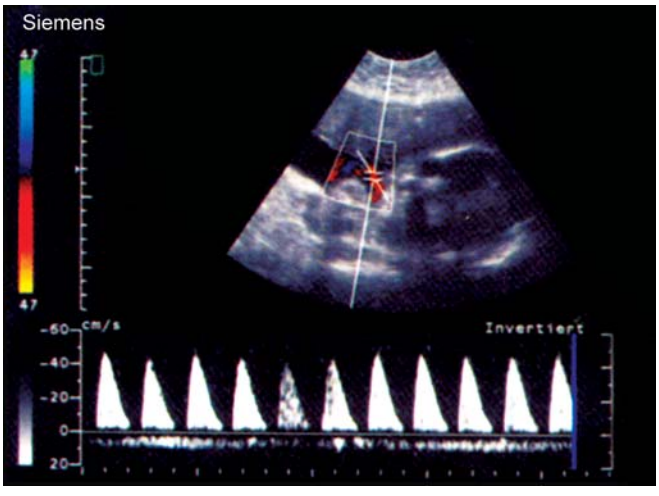

Fig. 8: Absent end-diastolic flow (AEDF) of the umbilical artery in the third trimester

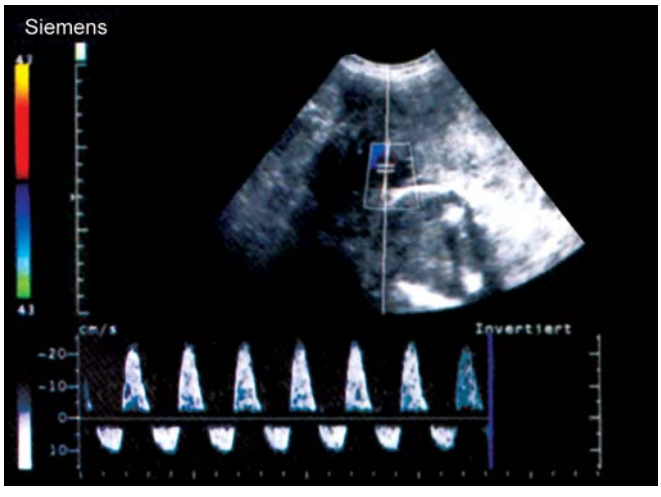

Fig. 9: Reverse flow (RF) of the umbilical artery

placental insufficiency worsens, the end-diastolic velocity decreases (Fig. 7), then become absent (Fig. 8) and finally it is reversed (Fig. 9). Some fetuses have decreased end-diastolic velocity that remains constant with advancing gestation and never become absent or reversed, which may be due to a milder form of placental insufficiency. Pitfalls can be caused due to a high selected wall filter or fetal breathing (Fig. 10).

Abnormal UA Doppler studies, but not normal results were found to be associated with lower arterial and venous pH values, an increased likelihood of intrapartum fetal distress, more admissions to the neonatal intensive care unit (NICU), and a higher incidence of respiratory distress in IUGR fetuses.[38] Therefore, intensive antenatal surveillance in fetuses with suspected IUGR with a normal UA Doppler FVW was not recommended by the authors. Conflicting data were presented by McCowan et al;[39] they confirmed that abnormal UA Doppler studies are associated with a poor perinatal outcome in IUGR fetuses but also concluded that the perinatal outcome in small for gestational age fetuses with normal UA Doppler studies is not always benign (i.e. low ponderal index, postnatal hypoglycemia, admission to the NICU). Recently, our study group[40] suggested that reversed flow should be seen as a particular clinical entity with the higher incidences of severe IUGR, perinatal and overall mortality compared to absent end diastolic flow (Figs 8 and 9).

In our clinical experience, when an IUGR fetus is suspected, the UA, FDA and MCA are the first fetal vessels to be assessed. The ductus venosus (DV), umbilical vein, inferior vena cava Doppler examinations are secondary vessels to be examined, only when an abnormal FVW is detected on the arterial vessels. Adding serial Doppler evaluation of the UA, MCA and DV to IUGR surveillance will enhance the performance of the biophysical score in the detection of fetal compromise and therefore optimizing the timing of intervention.[41]

Chromosomal Abnormalities

It was shown that absent end-diastolic flow in the UA is associated with chromosomal abnormalities like trisomies, triploidies or chromosomal deletions.[42] Setting out from the point that structural anomalies are more frequent in fetuses with chromosomal aberrations, a rapid acquisition of a karyotype in fetuses with congenital anomalies and an absent end-diastolic flow in the UA is recommended.[43]

Impact on Perinatal Consequences

Abnormal UA FVWs are associated in IUGR fetuses with one of the following outcomes: early delivery, reduced birth weight, oligohydramnios, NICU admission and prolonged hospital stay.[32,44] In a meta-analysis, it was shown that the use of UA Doppler sonography in pregnancies complicated by IUGR reduces perinatal mortality up to 38% and improves perinatal outcome.[45] A review consisting of 7,000 high-risk pregnancies[46] found that Doppler ultrasound was associated with a trend toward reduction in perinatal death especially in pregnancies complicated with pre-eclampsia or IUGR. The Doppler ultrasound use was also associated with fewer inductions of labor and fewer hospital admissions, without reports of adverse perinatal effects. The reviewers concluded that the use of Doppler ultrasound in high-risk pregnancies is likely to reduce perinatal mortality.

Neonatal Intraventricular Hemorrhage

Fetal status as well as neonatal complications of prematurity in IUGR both contribute to adverse perinatal outcome and increase the risk for the development of intraventricular hemorrhage (IVH). Data suggest that absent and reversed end-diastolic flow in the UA early in gestation carries a high-risk of subsequent neonatal IVH.[47] However, this observation is not independent of other perinatal variables: prematurity and difficult births remain the most important determinants of this complication.

Neuromotoric Outcome

Valcomonico et al[44] evaluated the association of UA Doppler velocimetry with long-term neuromotoric outcome in IUGR fetuses with normal (n = 17), reduced (n = 23) and absent or reversed (n = 31) UA end-diastolic flow. The infants who survived the neonatal period were observed for a mean of 18 months. Their postural, sensorial and cognitive functions were evaluated at 3, 6, 9, 12 and 18 months of age. Although, due to small number of cases, the results did not reach statistical significance, the incidence of permanent neurological sequelae increased as the UA end-diastolic flow decreased (35% with absent or reversed flow, 12% with reduced flow, and 0% with normal flow). Recently, in another study[48] 23 IUGR fetuses with absent or reversed UA end-diastolic flow were matched with fetuses with appropriate growth. All children were followed for 6 years and intellectual and neuromotor development was significantly diminished in fetuses with abnormal FVWs. Only social development was not impaired in fetuses with abnormal UA FVWs. Similar results were previously published by our working group, too.[49,50]

Intrapartum Studies

A review of intrapartum UA Doppler velocimetry for adverse perinatal outcome gave disappointing results.[51] Out of 2,700 pregnancies, which were evaluated for the intrapartum use of Doppler velocimetry showed that it is a poor predictor for measures like low Apgar scores, intrapartum fetal heart rate abnormalities, umbilical arterial acidosis and cesarean section for fetal distress.

Umbilical Artery Doppler Ultrasound in Unselected Patients

Theoretically, the use of routine UA Doppler ultrasound in unselected or low-risk pregnancies would be to detect those pregnancies in which there has been failure to establish or maintain the normal low-resistance umbilical and uterine circulations (a pathological process leading to placental dysfunction and associated with intrauterine growth retardation and pre-eclampsia), before there is clinical evidence of fetal compromise. In practice, observational and longitudinal studies of Doppler ultrasound in unselected or low-risk pregnancies have raised doubts about its application as a routine screening test, and authors have cautioned against its introduction into obstetric practice without supportive evidence from randomized trials.[52-54] The relatively low incidence of significant, poor perinatal outcomes in low risk and unselected populations presents a challenge in evaluating the clinical effectiveness of routine UA Doppler ultrasound, as large numbers are required to test the hypothesis.

Multiple Gestation

The S/D ratio of twins at the UA are in agreement with singleton pregnancies in the third trimester.[55] Twins with an abnormal UA FVW tend to be born earlier, have a higher perinatal mortality and morbidity, and have more frequent structural anomalies than fetuses without abnormal Doppler results.[56]

Discordant growth between the twins may occur in the cases of twin-twin transfusion syndrome, a poor placental

implantation site or chromosomal anomalies. Discordant growth is a very high-risk situation, with a high perinatal mortality and morbidity. The diagnosis is made mainly by ultrasound biometry. The best predictor for the diagnosis of discordant twins appears to be the presence either a difference in the UA S/D ratio greater than 15% or a different estimated fetal weight greater than 15%.[57] Recently it has been reported that abnormal UA FVW can be observed in small twins more often in monochorionic than dichorionic twins.[58] Doppler ultrasound abnormalities of the UA in either twin are associated with poor perinatal outcome in twin-twin transfusion syndrome.

The Biophysical Profile and Multivessel Doppler Ultrasound in IUGR

Biophysical profile scoring (BPS) and Doppler surveillance are the primary methods for fetal assessment in IUGR. As placental insufficiency worsens, the fetus adapts by progressive compensation. Previously, it has been suggested that the sequential changes in arterial and venous flow occur before some biophysical parameters (fetal tonus, movement, breathing, amniotic fluid volume and nonstress test)) decline.[59,60] Baschat et al[41] evaluated whether multivessel Doppler parameters (UA, UV, MCA, DV and inferior vena cava) precede biophysical fetal parameters in fetuses with severe IUGR. They found that combining multivessel Doppler and composite BPS will provide significant early warning and a definitive indication for action in the management of severe IUGR, and suggested that delivery timing may be based on this new standard. In the preterm growth-restricted fetus, timing of delivery should be critically determined by the balance of fetal versus neonatal risks.[61]

Fetal Descending Aorta (FDA)

Beside the UA, routine Doppler sonographic examination at the descending fetal aorta is possible. Flow velocity waveforms of the FDA are usually recorded at the level of the diaphragm. Infact, FVWs at the level of the diaphragm and distally to the origin of the renal arteries are different.[62] Normal blood FVWs in the FDA is highly pulsatile, with a minimal diastolic component (Fig. 11). The descending part of the aorta provides perfusion to the fetal abdominal organs, umbilical-placental circulation and lower extremities. The FVW of the FDA shows a continuous forward stream during the whole heart cycle, but when compared to the FVW of the UA, the end-diastolic flow is less than the systolic component. Due to this reason the S/D ratio in the fetal aorta goes far than the S/D ratio in the UA. As pregnancy advances, the fetal aortic diameter gets wider, which decreases peripheral resistance and increases diastolic flow component. Nevertheless, this does not cause a significant S/D ratio decrease in the FDA.[63] Resistance and pulsatility indices in the last trimester are also not affected significantly, and show a similar course as in the UA.

Increased placental impedance combined with redistribution of blood flow from nonvital to vital organs may result in changes in the aortic FVWs. An elevated S/D ratio, RI and PI (Figs 12 to 15) is associated with both IUGR and adverse perinatal outcomes, such as severe growth restriction, necrotizing enterocolitis, fetal distress and perinatal mortality.[64-71] Absent end-diastolic flow at the FDA is also a predictor of fetal heart rate abnormalities (Fig. 16). It was shown that absent flow in the FDA were detected 8 days prior to the onset of decelerations at fetal heart rate monitoring.[68] The sensitivity and specificity of absent end-diastolic flow in the FDA for prediction of IUGR with fetal heart rate abnormalities are 85 and 80%, respectively.[70,71]

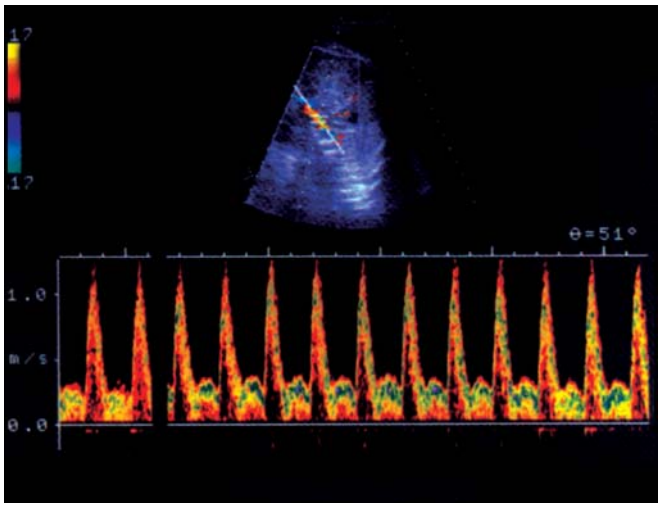

Fig. 11: Normal flow velocity waveforms of the fetal descending aorta in the third trimester

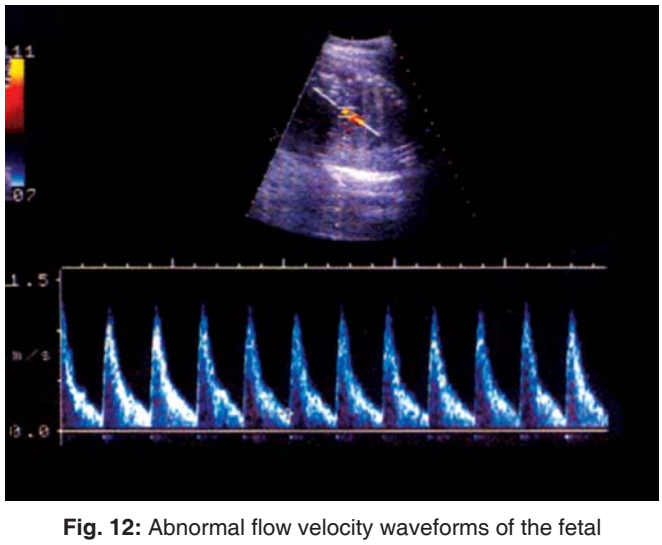

Fig. 12: Abnormal flow velocity waveforms of the fetal descending aorta in the third trimester (high resistance index)

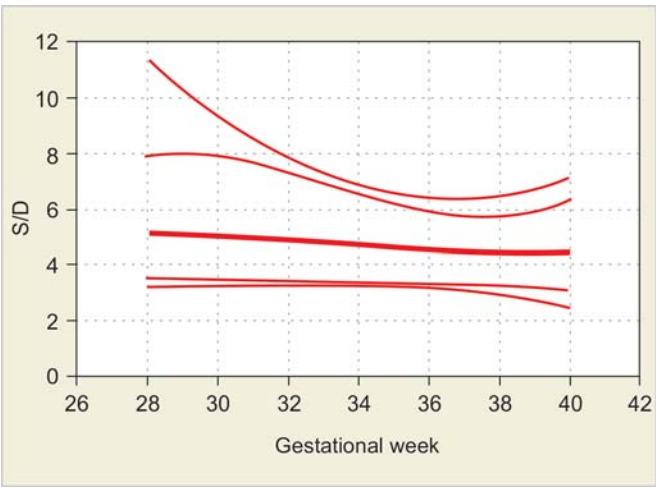

Fig. 13: Descending fetal aorta S/D ratio nomogram

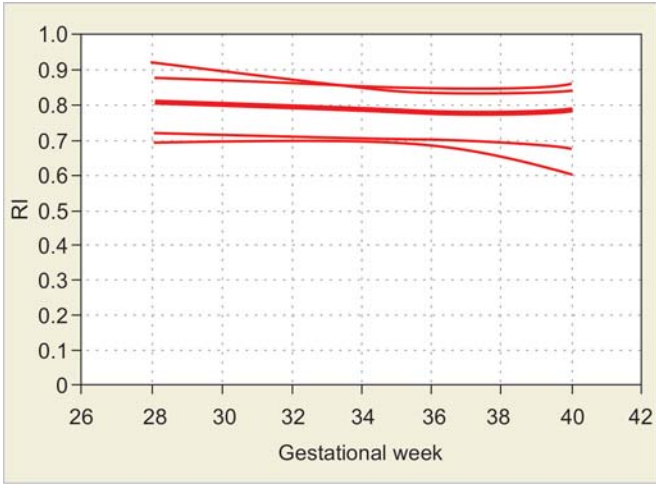

Fig. 14: Descending fetal aorta RI nomogram

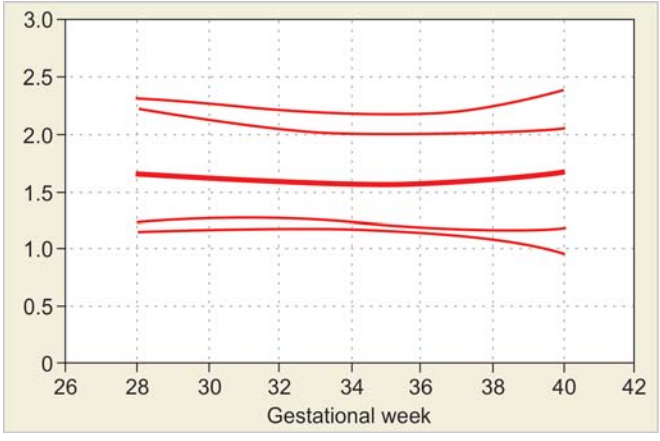

Fig. 15: Descending fetal aorta PI nomogram

Abnormal FVWs of the FDA were also evaluated for intellectual function, and minor neurological dysfunction.[49,50,72,73] At 7 years of age, verbal and global performances as well as neurological examination were significantly better in the fetuses with normal aortic FVWs. The association found between abnormal fetal aortic

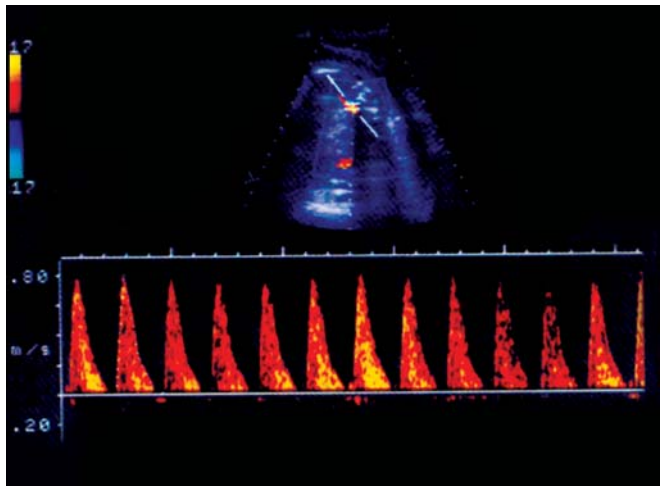

Fig. 16: Absent end-diastolic flow (AEDF) of the fetal descending aorta (FDA) in the third trimester

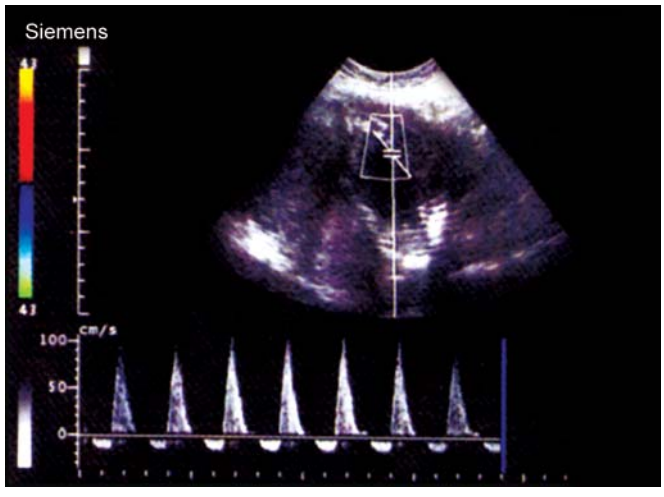

Fig. 17: Reverse flow (RF) in the fetal descending aorta

velocity waveforms and adverse outcome in terms of minor neurological dysfunction suggests that hemodynamic evaluation of the fetus has a predictive value regarding postnatal neurological development.[72]

Albeit, most of the studies showed Doppler velocimetry abnormalities of the FDA is a predictive test for the onset of decomposition due to placental insufficiency in the IUGR fetuses (Figs 16 and 17), it cannot be recommended as a screening or diagnostic test for IUGR in an unselected obstetric population.[74]

Middle Cerebral Artery (MCA)

The circle of Willis is composed anteriorly of the anterior cerebral arteries (branches of the internal carotid artery that are interconnected by the anterior communicating artery) and posteriorly of the two posterior cerebral arteries (Branches of the basilar artery that are interconnected on either side with internal carotid artery by the posterior communicating artery).[75] These two trunks and the MCA, another branch of the internal carotid artery, supply the hemispheres on each side (Fig. 18). All of the defined

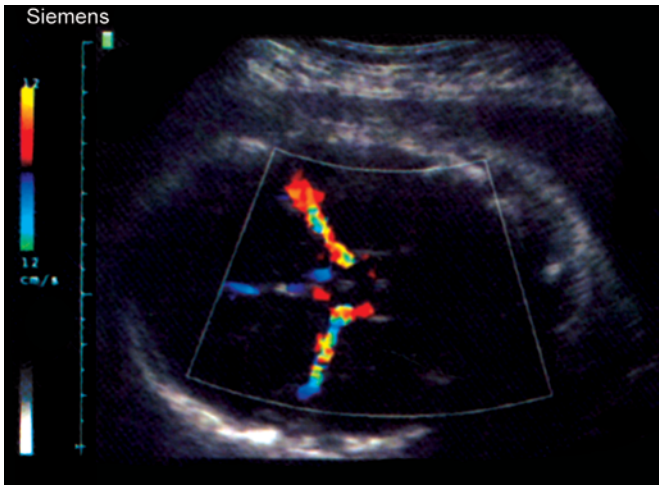

Fig. 18: Circle of Willis and middle cerebral artery visualized with color Doppler

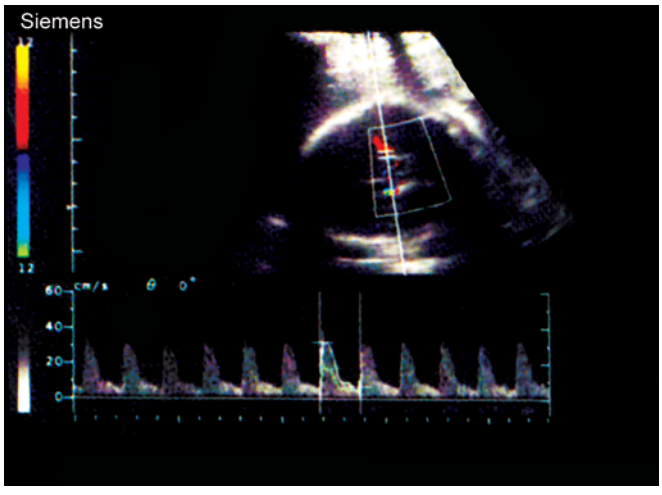

Fig. 19: Normal flow velocity waveforms of the middle cerebral artery in the third trimester

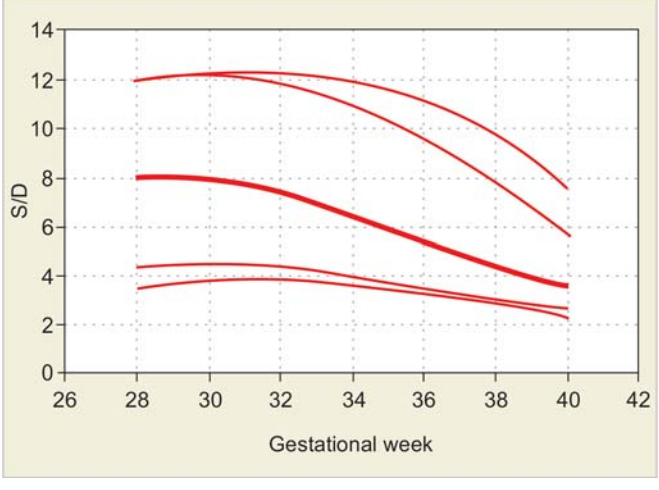

Fig. 20: Middle cerebral artery S/D ratio nomogram

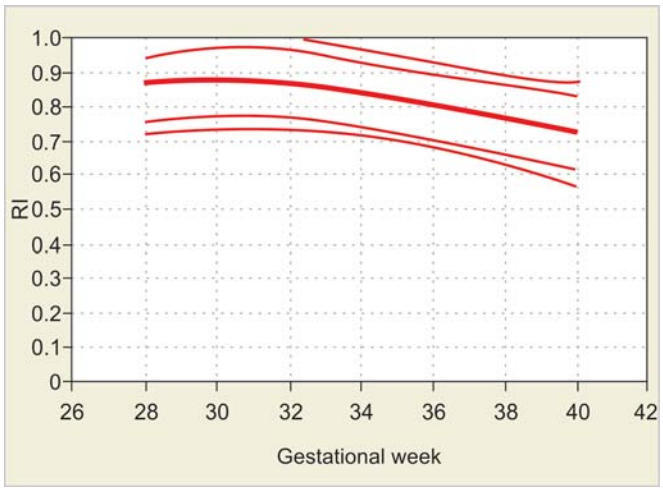

Fig. 21: Middle cerebral artery RI nomogram

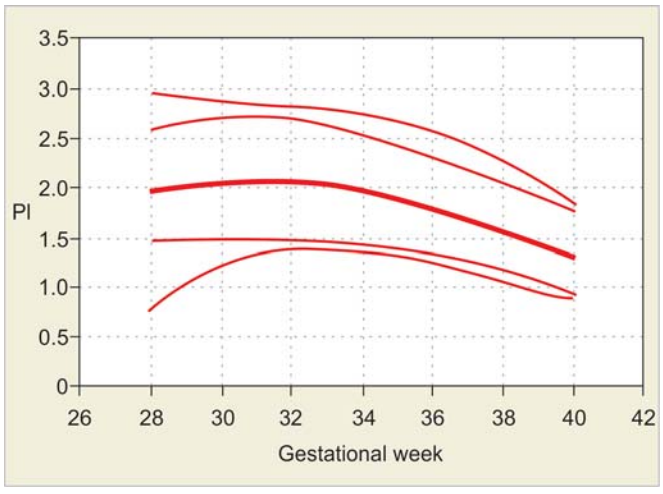

Fig. 22: Middle cerebral artery PI nomogram

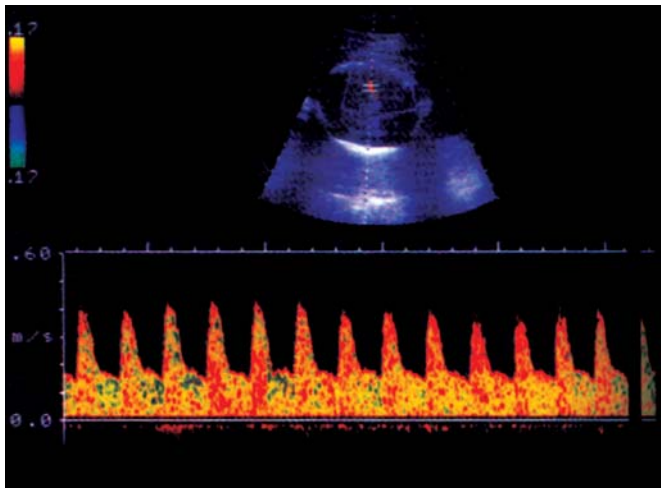

Fig. 23: Abnormal flow velocity waveforms of the middle cerebral artery in the third trimester (brain sparing effect)

arteries have different FVWs, therefore, it is important to know which artery is being examined during clinical practice.[76]

The most favorably positioned vessel for Doppler sonographic examination of fetal brain perfusion is the MCA. As the pregnancy advances, the vascular resistance in the MCA decreases (Fig. 19) and the Doppler indices change (Figs 20 to 22).[77] During the early stages of pregnancy, end-diastolic flow velocities in cerebral vessels are small or absent, but velocities increase toward the end

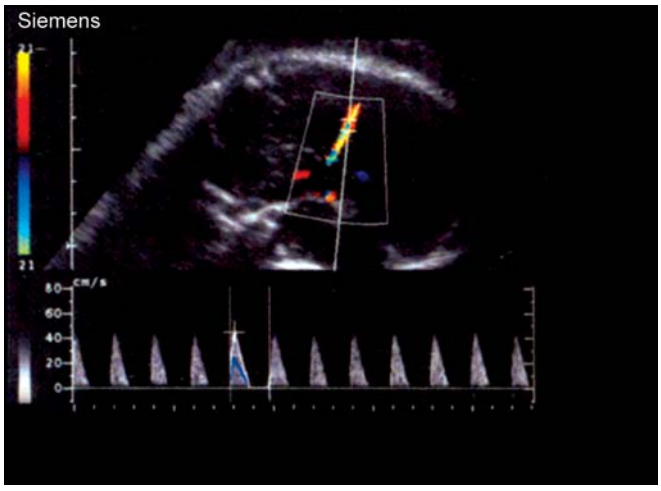

Fig. 24: Absent end-diastolic flow after the brain sparing effect (de-centralization) this presumably reflects the prefinal stage due to development of brain edema

of gestation. In the normal developing fetus, the brain is an area of low vascular impedance and receives continuous forward flow throughout the cardiac cycle. Intrauterine growth restriction due to placental insufficiency is likely to be caused by redistribution of fetal blood flow in favor of the fetal brain and 'stress organs', at the expense of less essential organs such as subcutaneous tissue, kidneys and liver. Finally, the already low resistance to blood flow in the brain drops further to enhance brain circulation (Fig. 23). This results with increased end-diastolic velocities, and a decrease in the S/D ratio of the MCA (Brain sparing effect).[78]

Abnormalities of the UA flow correlated with fetal compromise better than intracerebral artery blood flow impairment. This suggests that high placental impedance precedes the onset of the 'brain sparing effect'. In a study, in which 576 high risk pregnancies were evaluated for the UA and MCA velocimetry, neither test was able to predict adverse perinatal outcome in the normal growing fetus.[79] Results showed that simultaneous assessment of UA and MCA velocimetry in IUGR fetuses did not improve the perinatal outcome. When the UA velocimetry was normal, the MCA velocimetry did not improve the prediction of IUGR or adverse perinatal outcome. However, when both arteries velocimetric values were abnormal, the risk of being growth restricted and having an adverse perinatal outcome was doubled.

It has been reported that the MCA PI is below the normal range when pO_2 is reduced.[80] Maximum reduction in PI is reached when the fetal pO_2 is 2 to 4 standard deviations below normal for gestation. When the oxygen deficit becomes greater, there is a tendency for the MCA PI to rise; this presumably reflects the prefinal stage due to development of brain edema (Fig. 24).

Hyperactivity of fetus, increase of intrauterine pressure (e.g. polyhydramnios), and external pressure to the fetal head (e.g. by the probe) might erroneously increase end-diastolic flow velocities in the MCA.[81] Different investigators have undertaken studies —utilizing data obtained from the UA and MC—to develop indices for evaluation of intrauterine risk.[75]

Prediction of Fetal Hemoglobin in Red Cell Alloimmunization

Fetal anemia caused by red cell alloimmunization can be detected noninvasively by Doppler ultrasound on the basis of an increase in the peak systolic velocity in the MCA.[82,83] Although there is not a strong correlation between these two parameters when the fetus is nonanemic, the correlation becomes stronger as the hemoglobin levels decrease.[83] Prospective evaluation of the MCA peak systolic velocity to detect fetuses at risk for anemia in red cell alloimmunization showed that 90 of the 125 anticipated invasive procedures could be avoided.[84]

In anemic fetuses, changes in hematocrit lead to a corresponding alteration in blood viscosity and to an impaired release of oxygen to the tissues. Increased cardiac output and vasodilatation are the main mechanisms by which the fetus attempts to maintain the oxygen and metabolic equilibrium in various organs. It is likely that when the fetus is nonanemic or mildly anemic, there are only minor or insignificant hemodynamic changes. Therefore, the blood velocity does not change. When the fetus becomes more anemic, various mechanisms compensate to maintain the oxygen and metabolic equilibrium in the various organs. The MCA peak systolic velocity changes proportionally to the hemoglobin deficiency.

Doppler measurements appear to be valuable for estimating hemoglobin concentration in fetuses at risk for anemia. Doppler sonography of the MCA has the potential to decrease the need for invasive testing (amniocentesis, cordocentesis) and its potential risks.[85,86]

FETAL VENOUS CIRCULATION

In recent years research on the fetomaternal circulation has focused more on the venous side of the fetal circulation. Physiologically, blood flow velocities in the umbilical vein (UV) and the portal circulation are steady and nonpulsatile. However, it has been shown that both fetal body and breathing movements can interrupt these venous FVWs. In a recent review, it was concluded that several pathologic conditions such as nonimmune hydrops, severe IUGR, and cardiac arrhythmias also result in an abnormal, pulsatile venous blood flow.[87] However, the relationship between

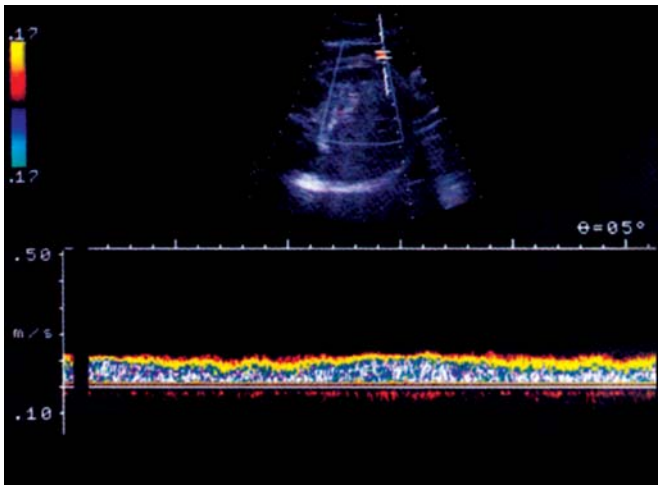

Fig. 25: Normal flow in the umbilical vein in the third trimester (without pulsations)

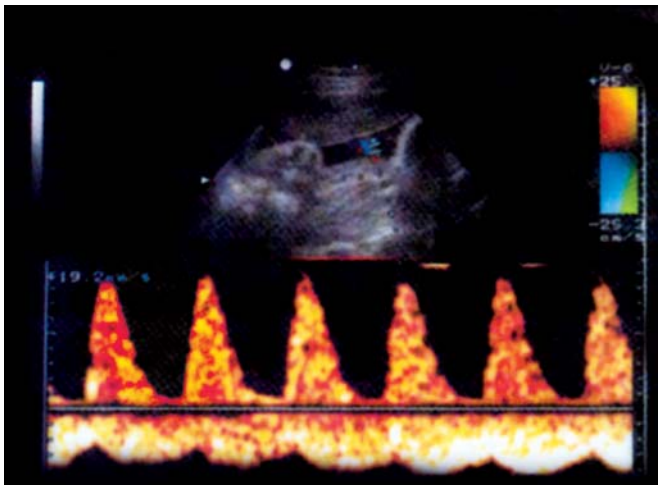

Fig. 26: Abnormal flow in the umbilical vein (single pulsating pattern during the heart cycle)

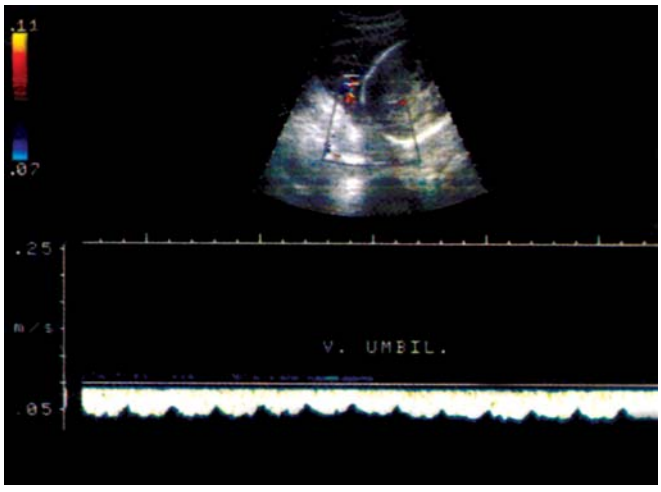

Fig. 27: Highly pathological flow velocity waveforms of the umbilical vein (double pulsating pattern during the heart cycle)

fetal venous blood flow patterns and imminent fetal asphyxia or fetal death is still unknown. Many studies on venous circulation in the fetal brain[88] and pulmonary venous circulation in the diagnosis of pulmonary hypoplasia were performed.[89] Recent findings promote the use of venous Doppler to aid in timing delivery of severely growth-restricted fetuses. Whereas initially it appeared that abnormalities in ductus venosus waveform were the endpoint for pregnancies afflicted with intrauterine growth restriction, newer data suggest that these abnormalities may plateau prior to further fetal deterioration as witnessed by changes in the biophysical profile.[90]

Umbilical Vein (UV)

Oxygenated blood returning from the placenta runs from the UV through DV and inferior vena cava. Approximately 20 to 30% of the blood in the UV goes through the DV and the remaining well oxygenated blood perfused the left lobe of the liver[91] (Figs 25 to 27). Normally after 15 weeks' gestation the umbilical vein has continuous forward blood flow.[90] The presence of UV FVW pulsatility has been associated with increased perinatal morbidity and mortality.[92,93] In an animal model, Reed et al evaluated the UV Doppler flow patterns and concluded that pulsations of the UV velocity reflect atrial pressure changes that are transmitted in a retrograde fashion.[94] In some studies, it was also observed that UV pulsations are detected in fetuses with abnormal UA FVWs and/or fetal heart rate abnormalities.[93] More recently, Ferrazzi et al[95] showed that UV blood flow is reduced in IUGR fetuses and suggested that long-term studies be performed to evaluate the clinical implications of their finding. Umbilical vein pulsations were also reported in pregnancies with nonimmune hydrops fetalis.[96] In this study, all the fetuses without venous pulsations survived, but only 4 of the 14 fetuses with pulsations survived. Fetuses with pulsation in the UV in late gestation have a higher morbidity and mortality, even in the setting of normal UA blood flow.[97] When UV pulsations are found in an IUGR fetus, it is often accompanied by reversal of the umbilical artery end-diastolic flow and reversal of the atrial 'kick' on ductus venosus waveform, which is an ominous sign.[90]

Inferior Vena Cava

The flow profile within this vessel is complex: it consists of two phases of forward flow (Systolic and early diastolic), followed by a component of reversed flow in late diastole[87] (Figs 28 and 29). Like other venous flow patterns, the FVWs are affected by fetal body and breathing movements. The FVW can be used for diagnosis of fetal arrhythmias, by comparing it with the FVW of the fetal aorta due to its proximity.[98] In IUGR fetuses, the FVW is characterized by an increased reversed flow during atrial contraction.[99] The mechanism of this increase is attributed to abnormal ventri-

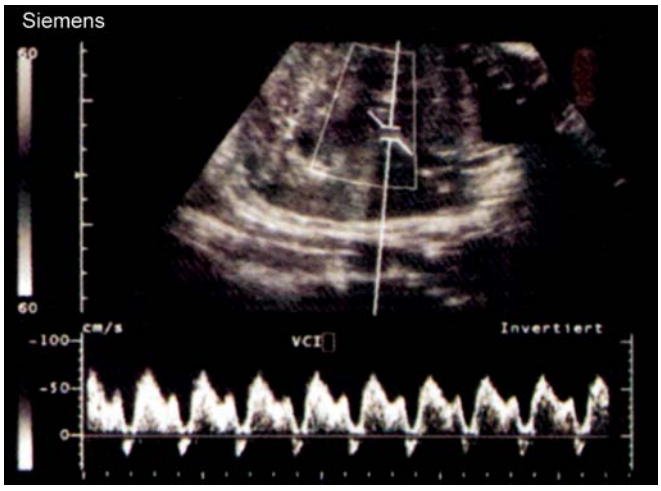

Fig. 28: Normal flow velocity waveforms of the inferior vena cava (with reverse flow during the end-diastole)

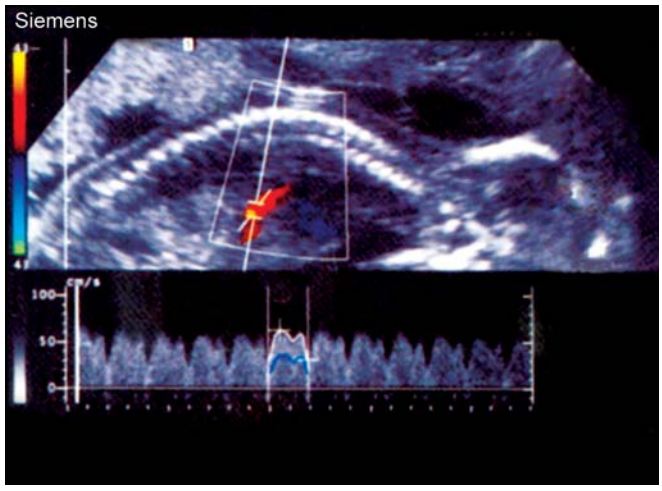

Fig. 30: Visualization of the ductus venosus with color Doppler and normal flow velocity waveforms (with forward flow during diastole and A-wave: corresponding to atrial contraction during the late diastole)

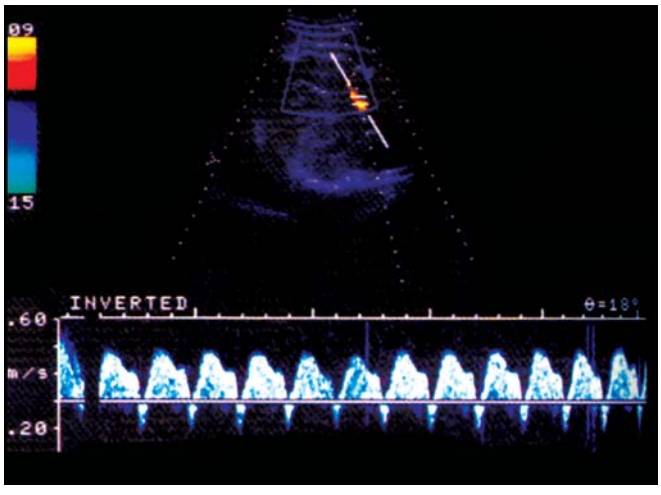

Fig. 29: Abnormal flow velocity waveforms of the inferior vena cava (with increasing reversed flow during end-diastole)

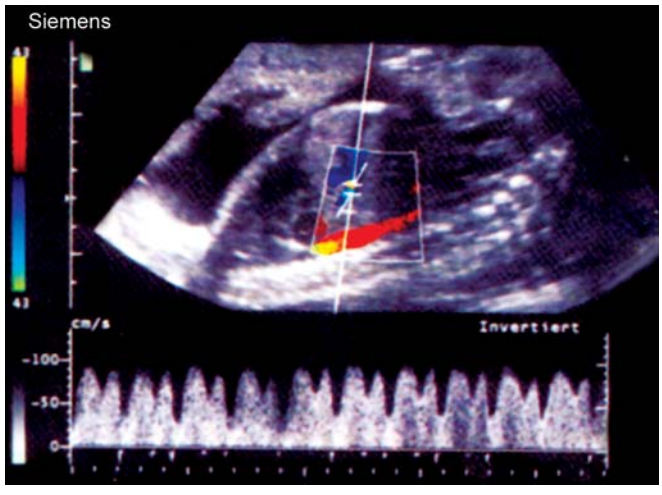

Fig. 31: Normal flow velocity waveforms in the ductus venosus (with forward flow during diastole and A-wave)

cular filling characteristics, an abnormal ventricular wall compliance, or abnormal end-diastolic pressure.

Ductus Venosus (DV)

The DV transports oxygenated blood from the UV directly through right atrium and foramen ovale to the left atrium and ventricle, and then to the myocardium and brain.[100-106] The ductus venosus carries the most rapidly moving blood in the venous system, and thus is easily identifiable by the aliasing seen on Doppler ultrasound. The DV originates from the portal sinus. Thus, the frequently expressed concept that the DV originates from the left portal vein or UV is anatomically inaccurate.[107] No anatomical continuity between the UV and DV exists, as incorrectly described, in recent Doppler ultrasound studies.[108] It is well accepted that the DV plays a major role in the regulation of fetal circulation by modifying the volume of its flow depending on the pressure gradient between the UV and the heart.[91]

In normal fetuses, color Doppler demonstrates the DV as a vessel bridging the left portal vein and the inferior vena cava with an obvious gradient in velocity compared with the left portal vein.[91] A common error is the sampling of the left hepatic vein rather than the DV.[75] Physiologically, this FVW shows continuous forward flow during the heart cycle, mimicking the pattern of the inferior vena cava (Figs 30 and 31). The high pressure gradient between the UV and the DV results in high blood flow velocities within this vessel. In contrast to other venous FVWs, reversed flow in the DV is an abnormal finding, except for the first trimester due to the immaturity of the sphincter of ductus venosus. However, abnormal FVWs of the DV between 11 and 14 weeks' gestation was suggested to be a screening test of fetal chromosomal abnormalities and/or cardiac defects.[109] Abnormal ductus venosus FVW (retrograde atrial-wave) is a strong predictor of fetal cardiac abnormality, may enhance the detection of Down syndrome, is a good predictor of diverse causes of fetal hydrops and may be a distant precursor of severe placenta-based IUGR.[1]

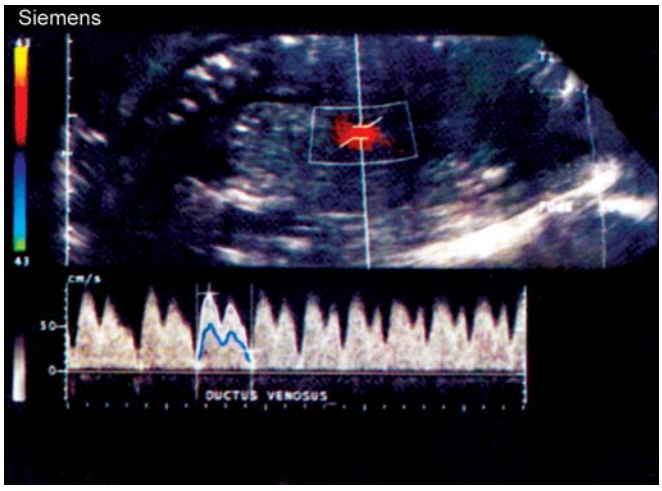

Fig. 32: Initial pathological flow velocity waveforms of the ductus venosus (with forward flow and decreasing A-wave)

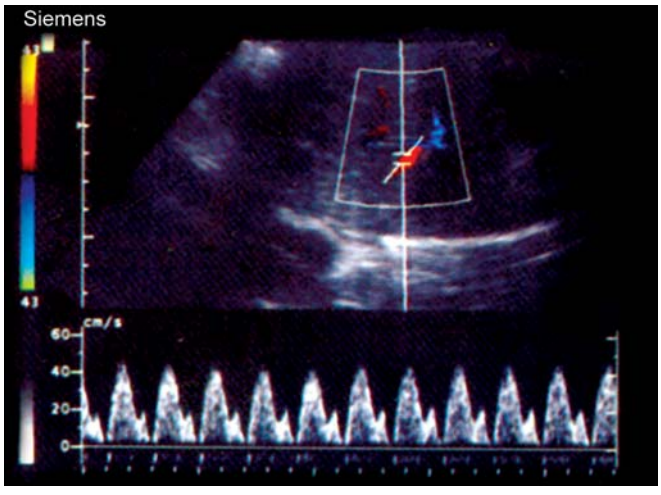

Fig. 33: Abnormal flow velocity waveforms of the ductus venosus (absent A-wave)

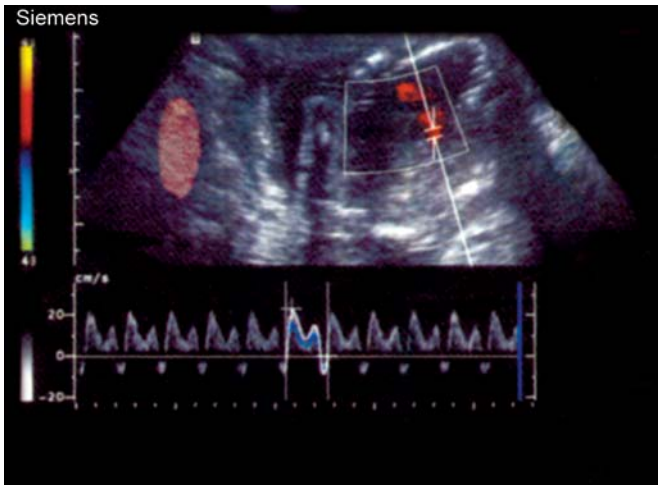

Fig. 34: Highly pathological flow velocity waveforms of the ductus venosus (reversed A-wave)

In IUGR fetuses, reversed flow in the DV is an ominous sign (Figs 32 to 35). Reversed flow in the ductus venosus results from a decline and subsequent reversal in forward blood flow velocity during atrial systole. The abnormality

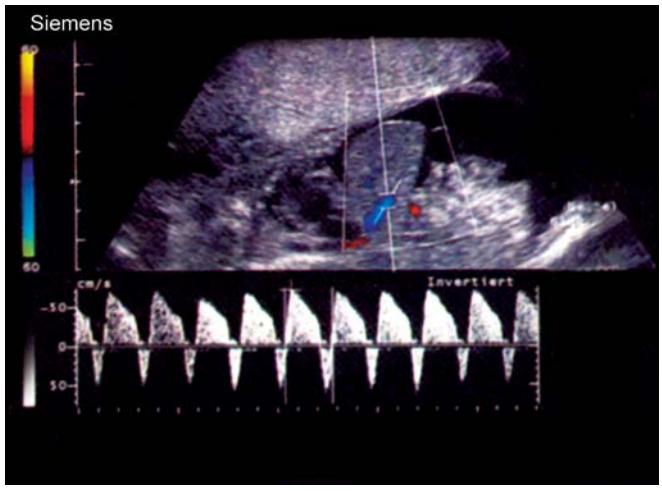

Fig. 35: Highly pathological flow velocity waveforms of the ductus venosus (prefinal situation)

in forward cardiac function may be related to worsening placental disease, impaired cardiac function due to metabolic compromise, redistribution of hepatoportal blood flow through the liver or a combination of these. It was reported that reverse flow patterns of the DV in IUGR fetuses is the only significant parameter associated with perinatal death.[110]

It has been suggested that changes in DV blood flow pattern precede the appearance of abnormal fetal heart rate patterns in pregnancies complicated with placental insufficiency.[59,111] One should bear in mind, however, that these studies are technically difficult and that blood flow patterns within the DV are also modulated by fetal behavioral states, breathing movements and cardiac anomalies/arrhythmias.[74,112,113]

Timing of Delivery in Pregnancies Complicated with IUGR

The optimal timing of delivery in pregnancies complicated by IUGR is still an issue to be resolved. Clinicians have to balance the risks of prematurity against the risks of prolonged fetal exposure to hypoxemia and acidemia, possibly resulting in fetal damage or death. In a cross-sectional Doppler study of the fetal circulation, the appearance of significant changes in venous Doppler FVWs from the DV, inferior vena cava and hepatic veins was observed after fetal arterial blood flow redistribution from the FDA to the MCA was established.[59] Furthermore, the changes in the venous circulation seemed to be closely related to the onset of abnormal fetal heart rate patterns. Reduced fetal heart rate variation and occurrence of fetal heart rate decelerations have been associated with fetal hypoxemia,[114] whereas extremely low values of short-term variation were found to be a reliable predictor of metabolic acidemia at delivery or fetal death.[115] In a longitudinal study,[116] the DV pulsatility index and short-term variation of fetal- heart rate were found to be important indicators

for the optimal timing of delivery before 32 weeks' gestation, and delivery was advised if one of these parameters becomes persistently abnormal.

In another study[117] to determine time for delivery, the changes in the hepatic vein, DV and UV were investigated. Results of this study suggested that adding venous Doppler ultrasound to the arsenal of fetal surveillance in IUGR fetuses might assist in timing of delivery with less morbidity and mortality. The venous indices of the right hepatic vein and the DV, and double UV pulsations were found to be the most useful tools for this condition. Finally it was stated that venous Doppler evaluation could give valuable clinical information for surveillance in high-risk pregnancies.

In the recently published Growth Restriction Intervention Trial study (GRIT: multicentered randomized controlled trial) it was evaluated and compared if the expectant management of the IUGR cases was superior to the early delivery method.[118] The main outcome was death or disability at or beyond 2 years of age. Overall rate of death or severe disability at 2 years was 55 (19%) of 290 immediate births and 44 (16%) of 283 delayed births. With adjustment for gestational age and umbilical-artery Doppler category, the odds ratio (95% CI) was 1.1 (0.7-1.8). Also the results of this study guided clinicians minimally in constructing guidelines for timing delivery in IUGR cases.

UTEROPLACENTAL PERFUSION

In order to evaluate uteroplacental perfusion, examinations performed at uterine arteries (UtA) give more accurate information than the arcuate arteries.[22] Velocities obtained from UtA are higher than from arcuate arteries (Fig. 36). This is important in interpreting Doppler study results, and it should always be paid attention on which vessel examinations were performed.

In the nonpregnant uterus, the UtA FVWs are characterized by high impedance blood flow, and almost always early diastolic notches. Kurjak et al reported the average UtA RI at the proliferative phase to be 0.88 ± 0.04 (2SD).[119] A high resistance to flow during the midluteal phase of the cycle (day 21) has been associated with infertility.[120] In women undergoing *in vitro* fertilization, those with a higher PI on the day of follicular aspiration have a lower probability of successful pregnancy.[121] Such findings suggest a potential value for UtA Doppler velocimetry in identifying endometrial receptivity in infertile patients.

In the first trimester, the intervillous maternal circulation is established at 7 to 8 weeks.[122] The impedance to blood flow within the intervillous space significantly decreases toward the midpregnancy and then remains stable. Blood flow velocities are reaching a plateau between 16 and 22 weeks of gestation, then after these parameters remain almost constant until the 36th gestational week.

From 6 to 12 weeks, FVWs obtained from the UtA are characterized by a high systolic and low diastolic component (elevated S/D ratio), and the presence of a notch in the early diastolic period (Fig. 37). Flow velocity waveforms of the arcuate arteries also show notching, but with a higher diastolic component.[123] In the second and third trimester of pregnancy, the UtA diameter enlarge,[124] the systolic peak velocity and volume flow rates increase,[125,126] and a progressive fall in impedance to blood flow can be detected.[127] The early diastolic notch and the difference between S/D ratios of the placental *vs* nonplacental sites should disappear after 24 to 26 weeks' gestation.[125,128] Absence of this transition from high to low impedance, and of similar bilateral FVWs is associated with a higher incidence of hypertensive disease, abruption, intrauterine fetal demise, preterm birth and IUGR.

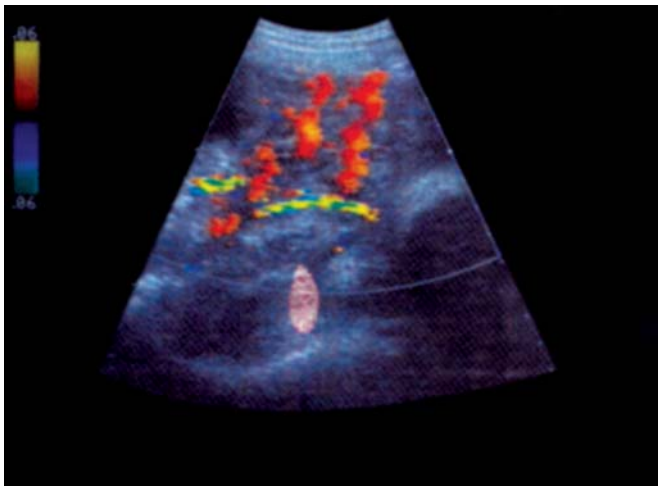

Fig. 36: Uterine and arcuate arteries visualized with color Doppler

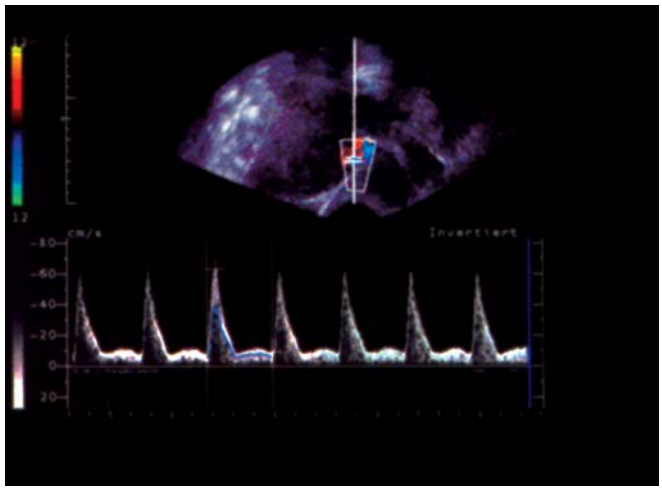

Fig. 37: Normal flow velocity waveform of the uterine artery in the first trimester (high resistance with an early diastolic notch)

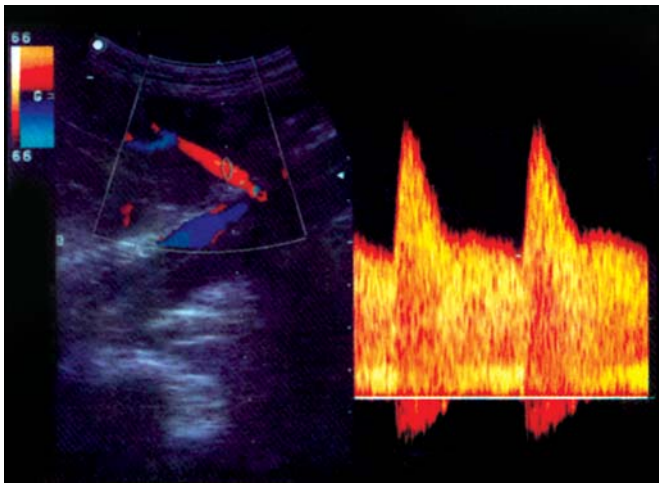

Fig. 38: Normal flow velocity waveform in the uterine artery in the third trimester (high end-diastolic flow without notching)

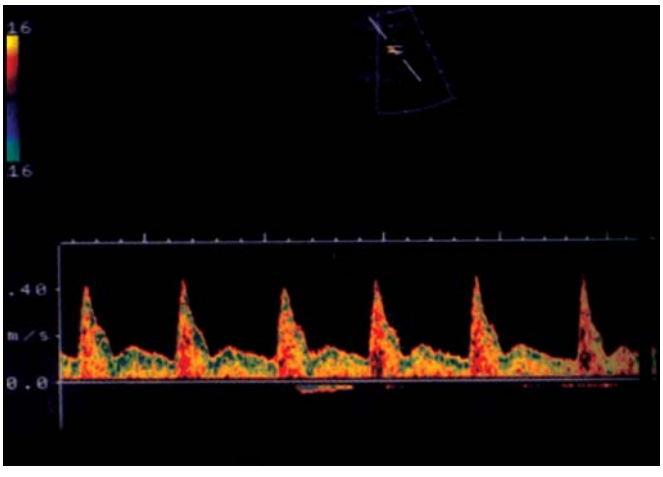

Fig. 39: Abnormal flow velocity waveform in the uterine artery in the third trimester (low end-diastolic flow with an early diastolic notch)

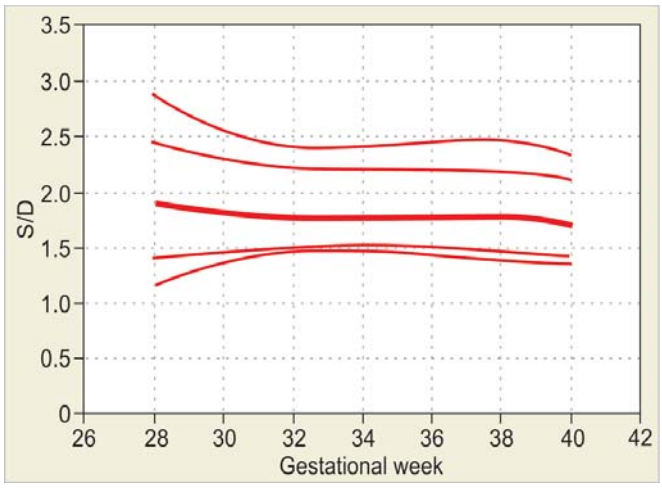

Fig. 40: Uterine arteries S/D ratio nomogram

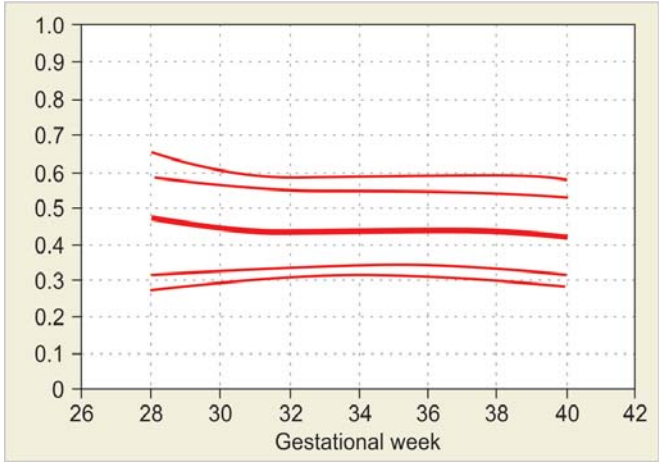

Fig. 41: Uterine arteries RI nomogram

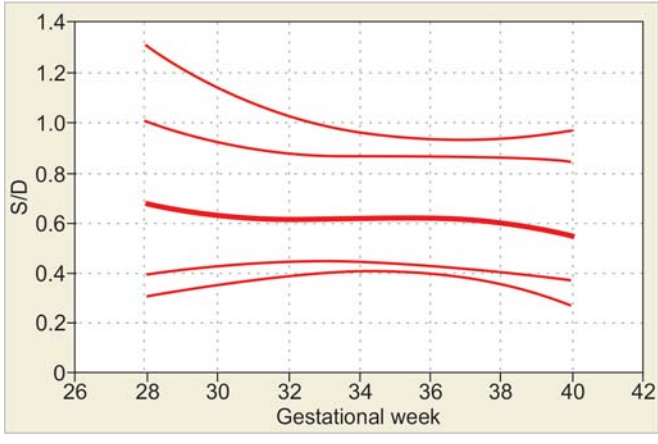

Fig. 42: Uterine arteries PI nomogram

Blood flow velocities in uterine arteries depend on the localization of placenta and gestational age.[129] If the placenta is laterally located, blood flow velocities in the ipsilateral uterine artery are more important than the flow velocities of the contralateral vessel. Differences between flow velocities of the right and left uterine artery are evident at the early stages of pregnancy. But in the third trimester, the difference between the S/D ratio of the vessels decrease to a minimum[22] (Fig. 38). If an abnormal flow pattern is observed in the uterine arteries, this most probably indicates the defective perfusion of fetoplacental unit, which predicts a high probability for developing pre-eclampsia, resulting with intrauterine growth retardation[5] (Fig. 39).

At the early stages of pregnancy, end-diastolic flow velocities in placental arteries are low, but systolic flow is evident.[22] With trophoblastic invasion and maturation of the uteroplacental vessels, beyond the second trimester the high pressure system is converted to a low pressure system, and vascular resistance declines.[130] The biologic variability after 20 to 24 weeks' gestation becomes almost stable (Figs 40 to 42).

Before 24 weeks' gestation, early diastolic notching due to the immature uteroplacental vascular system is normally observed. Beyond this gestational age, persistent early diastolic notching is associated with pre-eclampsia.[7,10,12] Elevated RI, PI or S/D ratios and the presence of a diastolic notch are considered as abnormal UtA FVWs.

Prediction of Complicated Pregnancies with Uteroplacental Doppler Velocimetry

Pregnancies complicated with pre-eclampsia and IUGR show evidence of impaired trophoblastic invasion and maturation.[131] A scoring system was proposed to predict the chance of adverse outcomes (pre-eclampsia, IUGR, preterm delivery, or fetal demise) using UtA Doppler. This score awarded 1 point for a notch and 1 point for a low end-diastolic flow in each waveform, bilaterally. In example, a score of 4 would indicate bilaterally high S/D ratios with bilateral notches. Those with a score of 4 had an 83% rate of adverse perinatal outcomes, 48% with a score of 3, 31% for a score of 2, and little increased risk for a score of less than 2.[132] Another group proposed a two stage screening protocol for pre-eclampsia with UtA Doppler at 18 to 22 weeks and when abnormal re-evaluation at 24 weeks.[5] In that study, 59% of the re-examined patients showed normal UtA Doppler FVWs.[133] Persistence of an abnormal FVW increased the relative risk for developing pre-eclampsia by 24-fold. Persistent notch in the early diastolic component of the FVW increased the predictive value (from 4.3% to 28%) and was associated with a 68-fold risk for developing pre-eclampsia.

There were also some studies suggesting Doppler assessment of the UtA can be carried out at 11 to 14 weeks' gestation and that screening at this early gestation can also identify pregnancies at the risk of developing complications associated with impaired placentation.[134] Chromosomal defects are associated with IUGR,[135] and in the case of trisomy 18 and 13, but not in trisomy 21, the IUGR is evident from the first trimester of pregnancy.[136,137] In a study, in which UtA Doppler between 11 and 14 weeks of gestation was performed to examine whether the high lethality and IUGR is associated with chromosomal abnormalities, the authors showed that UtA impedance is not associated with chromosomal anomalies,[138] and suggested that the placental histological changes may be responsible for increased impedance in the UA, but not in the UtA.

The relationship between abnormal uterine artery Doppler velocimetry and pre-eclampsia, IUGR and adverse perinatal outcomes are well established. Some paradoxical findings are attributed to differences in patient selection, gestational ages for screening, type of equipment, multiple definitions of FVWs, different vessels examined and heterogeneous outcome criteria.[139] The sensitivity of the UtA examination improves as the gestational age approaches to 26 weeks and when persistent diastolic notch is one of the criteria for analysis.[140] However, whether its use as a routine screening test ultimately results in a decrease in maternal and perinatal morbidity and mortality remains questionable. Current data do not support the use of Doppler ultrasonography for routine screening of patients for pre-eclampsia. However, several studies show that the combination of the measurement of uterine perfusion in the second trimester and analysis of angiogenic markers have a high detection rate, especially for early onset pre-eclampsia.[141] Among high-risk patients with a previous pre-eclampsia, UtA Doppler has an excellent negative predictive value, thus it is an important tool in patient management and care which is of paramount benefit for patients with pre-eclampsia in a previous pregnancy. A recently published systematic review[142] assessed the use of Doppler ultrasonography in case of pre-eclampsia. A total of 74 studies (69 cohort studies, 3 randomized controlled trials and 2 case-control studies) with a total number of 79,547 patients, of whom 2,498 developed pre-eclampsia, were included. The authors showed that UtA Doppler was less accurate in the first trimester, than in the second trimester. The combined data showed that the pulsatility index, alone or in combination with a persistent notching after 24 weeks of gestation is the most predictive parameter of Doppler ultrasonography to predict pre-eclampsia.

Although, considering the use of antiplatelet agent prophylaxis during pregnancy, the results of some multicenter randomized trials (Collaborative Low-Dose Aspirin Study-CLASP[143] and ECPPA)[144] were not encouraging, a moderate but consistent reduction in the relative risk of pre-eclampsia, of birth before 34 weeks' gestation, and of having a pregnancy with a serious adverse outcome.[145] There is good evidence that anti-platelet agents (principally low dose aspirin) prevent pre-eclampsia. A Cochrane Review[146] identified moderate, but clinically important, reductions in the relative risks of pre-eclampsia (19%), preterm birth (7%) and perinatal mortality (16%) in women receiving antiplatelet agents. These effects are much smaller than had initially been hoped for but, nevertheless, potentially they have considerable public health importance.

SUMMARY

Doppler ultrasound is a noninvasive technique that is commonly used to evaluate maternal and fetal hemodynamics. Examination of fetomaternal vessels using Doppler sonography has been subject of intensive investigation in recent years. To date, randomized controlled trials were able to establish important clinical value of Doppler velocimetry in obstetrics to improve perinatal outcome in high-risk situations. Umbilical artery, fetal descending aorta and middle cerebral artery Doppler velocimetric studies are acceptable tools in the diagnosis and management of

intrauterine growth restricted fetuses, and in the reduction of perinatal mortality in high-risk pregnancies. But there is no evidence that routine umbilical Doppler in a general or low-risk population leads to any improvement in the health of women or their infants. Although other trials are needed before asserting a definite lack of benefit, umbilical Doppler examinations cannot be recommended as a routine test in low-risk pregnancies.

The majority of severely compromised fetuses also show pathological venous velocimetry, which might give valuable clinical information for surveillance in high-risk pregnancies and their optimal perinatal management. In addition, Doppler sonography might have a role in predicting long-term neuromotoric outcome. Large scale randomized controlled trials are needed to establish the clinical utility of Doppler ultrasound in obstetrics.

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