Chapter 18

Doppler Ultrasound in the Diagnosis and Management of Intrauterine Growth Restriction

William J. Ott

Introduction

The antenatal recognition of fetal intrauterine growth restriction (IUGR) is an important goal for every obstetrician, since significant neonatal complications may be associated with altered fetal growth. Numerous studies have reported a 5%–27% incidence of congenital abnormalities associated with IUGR, as compared with a 0.1%–4% anomaly rate in control groups of normally grown neonates [1, 2]. The incidence of chromosomal abnormalities in IUGR infants is four to five times that of average-for-gestational-age (AGA) infants (2% vs 0.4%), and intrauterine infection, especially cytomegalovirus, has been reported in 0.3%–3.5% of IUGR infants [1, 2]. In addition, growth-restricted infants have up to an eight- to ten-fold increase in stillbirth and neonatal mortality [3–8]. Other developmental problems, such as necrotizing enterocolitis or intraventricular hemorrhage, also can be related to IUGR. Those infants that survive the immediate perinatal period are still at risk for neonatal hypothermia, hypoglycemia, polycythemia, or other complications, and have increased risk for long-term neurological or developmental complications [1, 4, 9–11].

Although there is no uniform agreement as to an exact definition of IUGR, it is usually equated with the small-for-gestational-age (SGA) infant, and this is not necessarily the best definition to use. In addition, there is no agreement as to which weight cut-off point (i.e., the 10th, 5th, or 3rd percentile, or two or more standard deviations from the mean) should be used to define it [12–14]. Controversy also exists as to which growth curve should be used. Numerous birth weight curves exist, and there is no universally accepted national standard. It is also controversial as to whether birth-weight-for-gestational-age curves or fetal weight-for-gestational-age curves should be used. Work at our own institution and at other centers has shown that IUGR infants are over-represented in premature deliveries, and therefore the use of birth-weight curves will significantly under-estimate the incidence of IUGR in the premature infant [15–21]. Using fetal weight curves would seem to be more appropriate. Table 18.1 shows the combined fetal weight for gestational age curve that is used in the author's institution [20], whereas Fig. 18.1 shows a comparison of the 10th percentile birth-weight curve of Alexander et al. [22] to the 10th percentile fetal weight curve, illustrating the potential under-estimation of IUGR in premature infants (20–33 weeks' gestation) if the neonatal weight curve is used.

Fig. 18.1. Comparison of the 10th percentile curves of the birth weight (*open symbols*) to the fetal weight (*closed symbols*) for gestational age. Between 20 and 33 weeks' gestation the birth weight curve underestimated the incidence of intrauterine growth restriction (IUGR)

Table 18.1. Fetal weight for gestational age (weight in grams)

Age (weeks)	5th	10th	50th	90th	95th
15	115	119	139	158	162
16	127	131	152	174	178
17	150	155	180	205	210
18	184	190	221	251	257
19	229	237	274	312	319
20	285	294	340	386	395
21	350	362	418	474	486
22	426	439	508	576	589
23	510	526	608	690	706
24	603	622	720	817	837
25	704	727	842	957	979
26	813	840	974	1108	1131
27	930	960	1115	1270	1301
28	1053	1088	1266	1444	1479
29	1183	1223	1426	1628	1668
30	1318	1364	1594	1823	1869
31	1460	1511	1770	2028	2079
32	1606	1663	1953	2243	2300
33	1757	1821	2144	2467	2531
34	1912	1983	2342	2700	2771
35	2071	2149	2546	2942	3020
36	2233	2320	2756	3192	3278
37	2399	2493	2971	3449	3544
38	2566	2669	3192	3715	3818
39	2736	2848	3418	3987	4099
40	2907	3029	3648	4266	4388
41	3079	3211	3882	4552	4684
42	3252	3395	4119	4844	4987

Decreased size at birth may be caused by a variety of processes [23–31]. Maternal demographic and anthropometric factors, socioeconomic conditions, and environmental factors all play a role in determining neonatal size at birth [23–29]. Most importantly, the intrinsic growth potential of each fetus may result in an infant that is smaller than standard cut-off value but is otherwise totally normal [30, 31]; therefore, a better definition of IUGR would be: an infant that fails to obtain its inherent growth potential. Although methods to determine what an infant's inherent growth potential may be do exist, they are controversial and frequently inaccurate. Currently (though not the ideal), the definition of IUGR that is most commonly used is to equate it with the SGA infant.

The Antenatal Diagnosis of IUGR

The diagnosis of IUGR begins with the identification of those patients significantly at risk for delivering a growth-restricted infant. Many socioeconomic and medical complications can lead to IUGR [25, 32–35]. The two most significant historical factors related to IUGR are maternal smoking and a history of a previously growth-restricted infant. The most common maternal medical complication associated with IUGR is hypertensive disease, and a study by Duverot et al. suggests a possible mechanism: early defective volume adaption to pregnancy [36]. Mounting evidence also indicates that both premature labor and IUGR are also related to chronic placental inflammation [37].

Table 18.2. Ultrasound parameters and the diagnosis of intrauterine growth restriction. *AC* abdominal circumference, *HC/AC* head circumference/abdominal circumference ratio, *AC/FL* abdominal circumference/femur length ratio, *PPV* positive predictive value, *NPV* negative predictive value

	Fetal weight	AC	HC/AC	AC/FL	Doppler
Sensitivity (%)	65.8	62.2	49.1	28.9	66.7
Specificity (%)	88.9	90.7	83.7	47.8	68.5
PPV (%)	63.6	67.3	47.1	47.8	38.4
NPV (%)	89.8	89.8	84.8	81.3	87.5
False positive (%)	8.6	7.2	12.6	7.2	24.4
False negative (%)	7.8	8.0	11.6	16.2	7.8

One of the most common methods of screening for and identification of the SGA and suspected IUGR infant is the measurement of various fetal parameters by real-time ultrasound [38–45]. A number of ultrasound parameters have been proposed for the antenatal diagnosis of IUGR [46]. In 1986 Benson et al. analyzed a number of these parameters and reported that estimated fetal weight was the most sensitive criterion for the diagnosis of IUGR, while an elevated head circumference/abdominal circumference ratio (HC/AC) was the most specific criterion and had the best positive predictive value [47]. Although other ultrasound parameters or the use of 3D ultrasound have been used to diagnose IUGR, calculation of estimated fetal weight by the standard 2D method is the method most commonly used [48–50].

Ott evaluated a number of ultrasonic parameters for the diagnosis of IUGR in 501 patients at increased risk for IUGR [51]. One hundred fourteen neonates were classified as IUGR (22.8%). Table 18.2 shows the sensitivity, specificity, positive and negative predictive values, and false-positive and false-negative results for the ultrasound parameters used to identify IUGR. Doppler evaluation of the umbilical artery showed the best sensitivity, although this was not a statistically significant improvement. Both abdominal circumference alone and estimated fetal weight showed similar specificity, positive and negative predictive value, and lowest false-positive and false-negative results. Logistic regression analysis confirmed the univariant results. When used in combination, both abdominal circumference and Doppler, or estimated fetal weight

and Doppler, showed almost identical improvements in all of the predictive values. Combining either abdominal circumference (alone) or fetal weight estimation with Doppler studies of the umbilical artery improves the accuracy in diagnosing IUGR. These findings are consistent with previous studies at our own institution and reports from other investigators [52–54].

Doppler Ultrasound

True intrauterine growth restriction caused by abnormalities in uteroplacental perfusion is characterized by selective changes in peripheral vascular resistance that can be evaluated using any of the angle-independent indices of Doppler velocity flow studies in the fetal peripheral vessels [55–65]. Comparison studies of systolic/diastolic ratios (S/D) between normal controls and IUGR infants by Trudinger et al. [63], and of multiple ratios between normal controls and IUGR infants by Erskine et al. [64] showed significantly increased ratios in IUGR infants, indicating marked increased uteroplacental resistance with IUGR. Giles et al. [65] compared the placentas of patients with normal S/D ratios with a group of patients with elevated S/D ratios and found a significant decrease in modal small arterial vessel count in the placentas of patients with elevated S/D ratios, giving pathological correlation supporting increased uteroplacental resistance in patients with increased S/D ratios. Hitschold et al. studied the placentas of SGA infants with abnormal Doppler blood flow indices and found both a reduction of vascularization within the terminal villi and adverse diffusion conditions, suggesting insufficient functional maturity [66]. The SGA infants with normal Doppler indices or AGA controls did not have these pathological findings in their placentas. Locci et al. did a similar study comparing immunohistochemical evaluation of placentas from SGA infants with normal or abnormal Doppler indices and found histoimmunological abnormalities only in the SGA infants with abnormal Doppler studies [67]. Krebs et al. studied the morphology of the placentas of growth-restricted fetuses with absent end-diastolic flow velocity and found significant maldevelopment of the terminal villous compartment [57]. Giles et al. found significant reduction in nitric oxide synthase activity in the placentas from pregnancies with abnormal umbilical artery flow velocity waveforms, and coupled with their studies in the fetal sheep, suggest that this deficiency in nitric oxide synthase activity reflects inadequate placental function [57, 58]. These placental studies confirm the hypothesis that abnormal umbilical artery flow studies are a reflection of abnormal placental function.

Figure 18.2 shows a normal umbilical artery velocity study, whereas Fig. 18.3 shows absent end-diastolic flow in the umbilical artery of a significantly growth-restricted fetus. Figure 18.4 presents the fetal umbilical artery S/D ratio norms used at the author's institution.

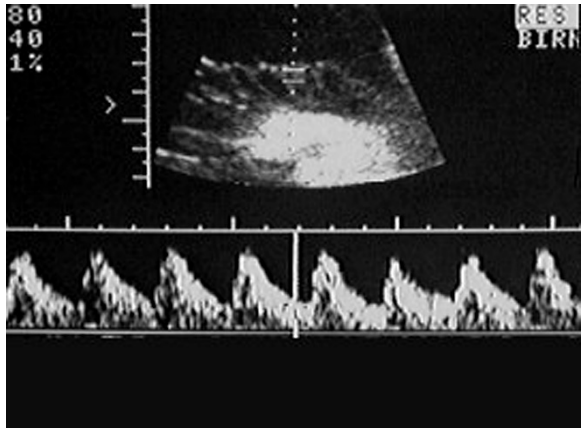

Fig. 18.2. Normal umbilical artery Doppler wave form at 34 weeks' gestation

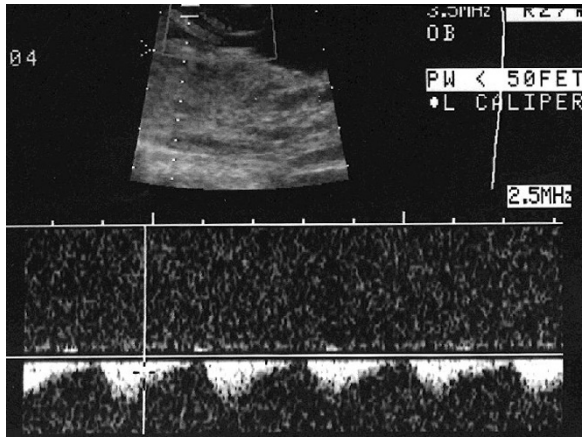

Fig. 18.3. Abnormal umbilical artery Doppler wave form with absent diastolic flow in a growth-restricted fetus at 34 weeks' gestation

In a study to evaluate the combined use of fetal weight estimation and Doppler ultrasound to better define true IUGR, Ott studied a series of 578 fetuses at risk for IUGR [68]. Fetuses were divided into four groups based on their weight estimation and umbilical artery Doppler studies:

1. Group 1: AGA with normal umbilical artery S/D ratios (normal Doppler)
2. Group 2: AGA fetuses with umbilical artery S/D ratios above the 90th percentile curve for gestational age (abnormal Doppler)
3. Group 3: SGA with normal Doppler
4. Group 4: SGA fetuses with abnormal Doppler

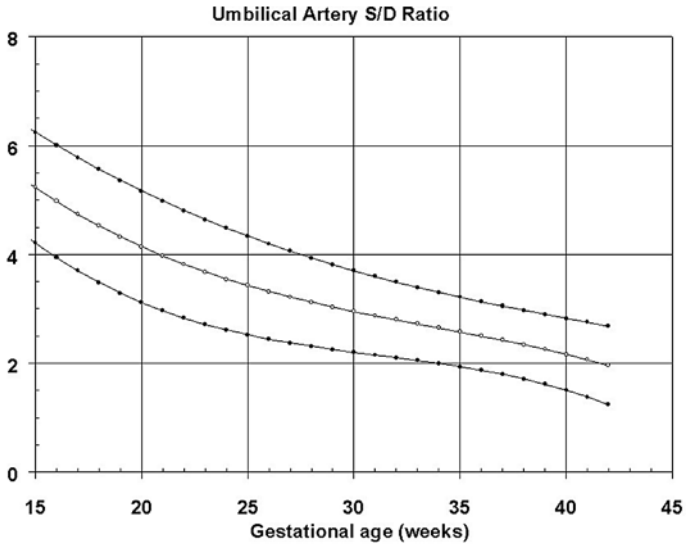

Fig. 18.4. Umbilical artery systolic/diastolic (*S/D*) ratio curve. Mean (*open symbols*) and 5th and 95th percentile values (*closed symbols*)

Table 18.3. Neonatal outcome based on weight and Doppler studies. *GA* gestational age, *NICU* neonatal intensive care, *NS* no significant difference between groups

	Group 1	Group 2	Group 3	Group 4	Significance
Number	231	215	37	95	
GA at delivery	33.9 (3.7)	34.1 (3.6)	33.6 (3.5)	34.0 (3.3)	NS
Birth weight (g)	2779 (757)	2543 (801)	1984 (635)	1916 (623)	1
Cesarean section for distress (%)	4.7	8.9	3.0	10.5	2
Days in the NICU	7.0 (14.8)	11.3 (20.5)	16.0 (25.1)	19.7 (29.7)	3

Group 1: average-for-gestational-age (AGA) fetuses with normal umbilical artery S/D ratios (normal Doppler); group 2: AGA fetuses with umbilical artery S/D ratios above the 90th percentile curve for gestational age (abnormal Doppler); group 3: small-for-gestational-age fetuses (SGA) with normal Doppler; group 4: SGA fetuses with abnormal Doppler Figures in parentheses are standard deviations.

1 No significant difference between categories 3 and 4; significant differences between categories 1–4 (combined); p=0.0241.

2 Abnormal Doppler (2 and 4) vs normal Doppler (1 and 3); $p = 0.034$. No other differences were significant.

3 Significant differences between category 4 vs category 2 or category 1; $p = 0.0001$. No significant differences between the other categories.

Table 18.3 lists the gestational age at delivery, birth weight, incidence of cesarean section for fetal distress, and length of stay in the NICU for the four study categories. There were no differences in gestational age at delivery between the four groups, and the expected differences in birth weight between the groups was seen. These findings did not change when the patients were analyzed by term or pre-term delivery. There were significant differences between the groups in cesarean section for fetal distress and in the length of stay in the NICU, both for the total patient population and when broken down into term or pre-term delivery. The presence of abnormal umbilical Doppler studies correlated better with cesarean section for distress or length of stay in the NICU than did fetal weight estimation.

There was a significant increase in neonatal morbidity in a combined group of patients with abnormal Doppler studies but not in the combined group of SGA infants. These differences became more apparent when the patients were analyzed by term or preterm delivery, with preterm infants having marked increased morbidity when Doppler studies were abnormal. Logistic regression analysis confirmed these findings. There were no differences in morbidity between AGA fetuses with normal blood flow studies or SGA fetuses with normal blood flow studies.

The results of this study suggest that categorizing fetuses at risk for poor perinatal outcome based on weight estimation and umbilical artery Doppler velocity flow studies has important prognostic significance. Neonatal outcome of SGA fetuses with normal Doppler studies was not significantly different from

their AGA cohorts. Both AGA and SGA infants with abnormal Doppler studies had increased neonatal morbidity, with the SGA infants in this subgroup having the worst prognosis.

Recent studies by Soothill et al. [69], and Holme and Soothill [70], and a study by Craigo et al. [71], using similar ultrasonic techniques, came to the same conclusions: namely, the combined use of fetal weight estimation and Doppler velocity studies better defines true IUGR. The current study seems to indicate that both fetal weight estimation and Doppler evaluation of the umbilical artery are useful in the prediction of neonatal morbidity in high-risk patients. Doppler ultrasound, however, appears to be a more sensitive indicator of potential fetal compromise than does weight estimation. Combining weight estimation (or abdominal circumference) with Doppler ultrasound is currently the best method for diagnosing IUGR.

Uterine Arteries

Since utero-placental dysfunction is a major cause of IUGR, evaluation of blood flow through the uterine arteries would logically seem to be an excellent method of identifying patients at risk for IUGR; however, controversy does exist as to the value of Doppler velocity studies of the uterine arteries [76]. Steel et al. evaluated 200 primiparous patients at 24 weeks' gestation with Doppler studies of the uterine arteries and found a low sensitivity for the prediction of hypertensive disease of pregnancy, but a very high sensitivity for predicting the development of IUGR associated with hypertension [72]. Vergani et al. found that abnormal uterine artery Doppler wave forms in IUGR fetuses in the third trimester were associated with a fourfold increase in adverse perinatal outcome [75]. Studies by North et al. [73] and Atkinson et al. [74], however, found only slight correlation between abnormal Doppler indices in the uterine arteries at 24 weeks' gestation and the later development of hypertensive disease, with or without IUGR, and both groups felt that uterine artery Doppler velocity studies were not a good method of screening for these complications of pregnancy.

More recent studies by Nicolaides et al. found that a one-stage color Doppler screening of the uterine arteries at 23–24 weeks of gestation was a highly sensitive method of identifying those patients that subsequently developed serious complications of impaired placentation (pregnancy-induced hypertension and/or IUGR) [76–80]. Calculation of the uterine artery pulsatility indices (which can be done as early as 14 weeks) [81] and evaluation of the presence or absence of uterine artery notches were highly predictive for the development of complications later in gestation. Other investigators have confirmed these findings

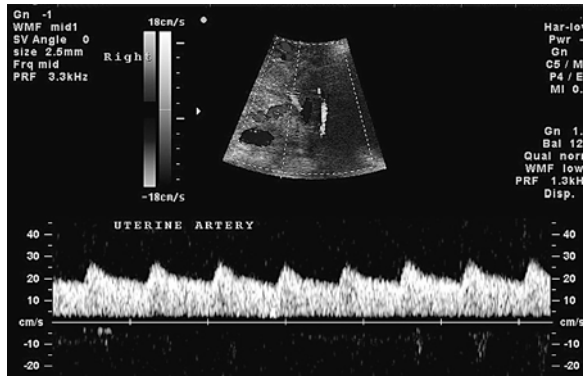

Fig. 18.5. Normal uterine Doppler wave form at 24 weeks' gestation

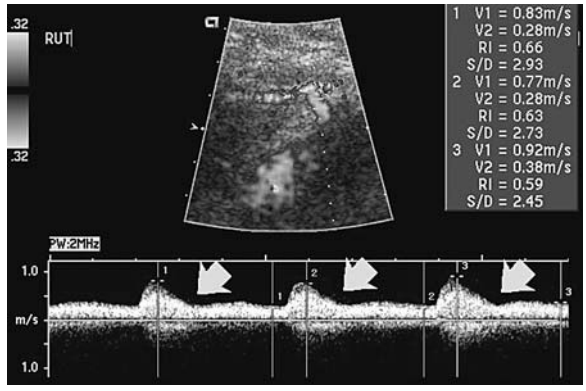

Fig. 18.6. An abnormal uterine artery Doppler wave form at 24 weeks' gestation in a hypertensive patient who later developed superimposed pregnancy-induced hypertension associated with IUGR. The *arrows* indicate uterine artery "notching"

Table 18.4. Predictive value of uterine artery Doppler studies for IUGR. *PPV* positive predictive value, *NPV* negative predictive value, *PI* pulsatility index

Criterion	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Reference
Bilateral notching	50	84	40	89	[83]
PI >1.44 or bilateral notching	13	96	25	93	[77]
PI >1.6	13	96	23	92	[78]
bilateral notching	20	92	19	92	[78]

[82, 83]. Table 18.4 shows the sensitivity, specificity, and predictive values of uterine artery Doppler studies at 23 weeks in predicting IUGR. Figure 18.5 illustrates normal uterine artery flow at 24 weeks, and Fig. 18.6 shows abnormal uterine artery flow with

diastolic notching in a chronic hypertensive patient at 24 weeks who later developed superimposed pregnancy-induced hypertension associated with IUGR.

Other Ultrasonic Methods of Diagnosing IUGR

Other ultrasonic methods of diagnosing IUGR have also been studied. Abramowicz et al. evaluated fetal subcutaneous adipose tissue by measuring cheek-to-cheek diameters from a coronal view of the fetal face at the level of the nostrils and lips [84]. Other measurements of fetal adipose tissues have been studied, such as subcutaneous tissue thickness at the level of the fetal mid-calf, mid-thigh, or abdominal wall; skin fold thickness; liver length; or other methods of fetal body composition [85–91]. Hill et al. [89] recently evaluated these measurements and felt that the degree of overlap in subcutaneous tissue thickness between normal, IUGR, and macrosomic fetuses was too great to be reliable in predicting abnormal growth, whereas Gardeil et al. [90] felt that measurements of subcutaneous fetal fat was as accurate in diagnosing IUGR as any other ultrasonic parameter. Further research in this area is needed to determine the utility of these measurements.

In summary, fetal weight estimation remains an important ultrasound parameter that can be used to diagnose IUGR. Combining fetal weight estimation with Doppler evaluation of the umbilical artery improves the accuracy of the diagnosis of IUGR. The other ultrasound parameters do not appear to add any additional accuracy to the diagnosis. Estimated fetal weight (or abdominal circumference), coupled with Doppler evaluation of the fetus, appears to be the best method of diagnosing and evaluating the fetus suspected of IUGR [52–55].

Evaluation and Follow-up of Suspected IUGR

Once the diagnosis of IUGR is made, the evaluation of the fetus and decision to effect delivery depends not only on the results of antenatal tests, but also the complete clinical situation. In addition, careful search for the cause of the IUGR should be undertaken. A detailed ultrasonic evaluation of the fetus for the presence of structural abnormalities should always be done. If any abnormalities are seen, the patient should be offered genetic amniocentesis or cordocentesis to rule out fetal chromosomal abnormalities. It is still somewhat controversial as to whether or not fetuses with isolated IUGR (no structural or other abnormalities seen on ultrasound examination) are at increased risk for chromosomal aneuploidy. The presence of intracranial or liver calcifications, or evidence of exposure to infectious agents, would indicate an increased risk for intrauterine infection as a cause of IUGR and the need for amniocentesis to rule out this cause. Figure 18.7 shows the flow chart recommended by Soothill et al. for the use of ultrasound and Doppler in the diagnosis of IUGR [53].

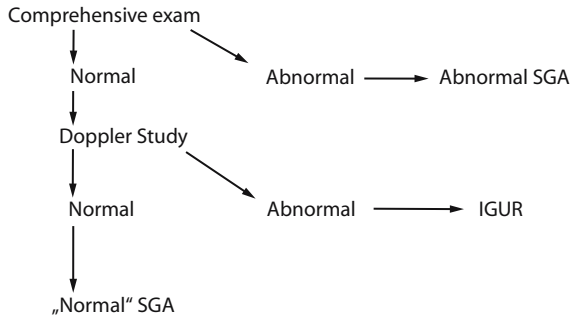

Fig. 18.7. Flow chart (after [53]) to differentiate true IUGR from a small but normal fetus. *SGA* small for gestational age

In those IUGR fetuses without structural or functional abnormalities, two major causes for the growth restriction should be considered: uteroplacental insufficiency (true IUGR) and a constitutionally small (SGA) but normal fetus. In the differentiation of these two conditions Doppler ultrasound plays an important role.

Umbilical Artery Doppler

There are a variety of antenatal tests available to evaluate and monitor the growth-restricted fetus. The fetal biophysical profile or modified biophysical profile (NST and fluid volume, only) are currently the gold standard for antenatal fetal evaluation and should be used to evaluate and monitor the IUGR fetus; however, Doppler velocity flow studies of the fetal umbilical artery play a critical role in the management of suspected IUGR.

Doppler ultrasound technology allows assessment of flow patterns and velocities in a number of fetal vessels, and the umbilical artery is the vessel most widely studied. Correlations have been observed between fetal outcome and various abnormal flow patterns, and data are accumulating that support the concept that the use of Doppler velocimetry in combination with other tests reduces the risk of antepartum fetal demise and improves neonatal outcome [92–94]. This is especially true in the IUGR fetus. Alfrevic and Neilson [92] performed a meta analysis of 12 randomized controlled trials of Doppler velocimetry and found:

"There is now compelling evidence that women with high-risk pregnancies, including preeclampsia and suspected intrauterine growth restriction, should have access to Doppler ultrasonographic study of umbilical artery waveforms."

There is significant agreement that markedly abnormal umbilical artery Doppler velocities (absent or reverse diastolic flow) are strongly correlated with poor perinatal outcome [95]. A high percentage of fetuses with absent or reverse umbilical artery diastolic flow require intervention because of fetal distress or acidemia [96, 97]. Recent prospective studies have confirmed this association [98, 99]. Gaziano et al. evaluated a group of 100 fetuses at risk for IUGR and found that umbilical artery velocity studies could distinguish a subgroup of SGA infants with normal velocity indices that had significantly better neonatal outcomes than SGA infants with abnormal indices [100]. Almstrom et al. published a prospective, randomized, controlled study comparing umbilical artery Doppler studies and non-stress tests for the evaluation of SGA infants and found a greater degree of intervention in the non-stress testing (NST) group without any improvement in perinatal outcome [101]. The authors felt that Doppler was a better modality for the evaluation of suspected IUGR than the NST. DeVore evaluated the clinical implications of umbilical artery Doppler velocity studies in the management of suspected intrauterine growth restriction by surveying maternal–fetal medicine subspecialists [102]. He found that the majority of subspecialists surveyed rely on Doppler studies in the clinical management of IUGR.

Work at the author's institution, and reports of other investigators, suggest that combining biophysical parameters with pulsed Doppler velocity flow wave analysis will provide further information concerning fetal status in IUGR and other high-risk situations [103–105]. Comparison of systolic/diastolic ratios (SD ratio) in the carotid or middle cerebral artery to the SD ratio in the umbilical artery (MC/UA ratio) appears to be an accurate method of prediction fetal outcome, especially in the growth-restricted fetus [106–110]. Arabin et al. proposed and evaluated a new fetal assessment score that included the NST, fetal breathing, fetal tone, response to vibroacoustic stimulation, and the umbilical and carotid artery resistance indices [111]. Baschat et al. [112] and Hecher et al. [113] performed serial evaluation of high-risk growth restricted fetuses using both biophysical parameters and Doppler blood flow studies and found, in general, that the abnormalities in the Doppler studies preceded deterioration in the biophysical parameters by about 1 week.

In a retrospective study combining the NST with Doppler blood flow studies of the middle cerebral and umbilical arteries, Ott was able to show that the addition of the MC/UA ratio improved the sensitivity for the prediction of poor perinatal outcome in a series of 447 high-risk patients [114]. The combination of the modified biophysical profile and Doppler ratios were then used in a prospective study of patients referred to the author's institution for antenatal surveillance [115]. Although the addition of Doppler studies to the modified biophysical profile did not improve neonatal outcome for the entire patient population studied, in a subgroup of fetuses at risk for IUGR there was a decreased utilization of cesarean section for delivery and an earlier identification of fetal compromise in the group of fetuses who had both modified biophysical profiles and Doppler studies used for antenatal testing (Table 18.5) [116]. A number of other studies have shown the value of Doppler velocity flow studies in the diagnosis and management of IUGR, and have suggested that the MC/UA ratio may be more sensitive in predicting neonatal outcome in IUGR fetuses [116–118]. The combined use of biophysical tests (non-stress test, biophysical profile) and Doppler ultrasound will better enable clinicians to monitor the IUGR infant and determine the optimal time for delivery.

Table 18.5. Neonatal morbidity: patients at risk for IUGR. *AFI* amniotic fluid index, *NST* non-stress testing

	Group 1[a]	Group 2[a]	*p* value
Number	56	63	
Maternal age (years)	30.0 (7.1)	31.0 (5.7)	0.4620
AFI at last exam (cm)	15.3 (5.9)	14.5 (5.2)	0.4969
Test to delivery (days)	14.2 (18.1)	6.2 (13.4)	0.0072
Non-reactive NST	8.9%	3.2%	0.1738
Gestational age at delivery	37.6 (2.7)	37.7 (2.3)	0.8388
Birth weight (g)	3057 (741)	3086 (771)	0.8129
Cesarean section for distress	10.7%	1.6%	0.0406
Admission to NICU	14	12	0.4328
Days in NICU	3.8 (10.4)	2.4 (7.0)	0.3973

[a] Group 1 = modified biophysical profile (MBPP) only; group 2 = MBPP plus Doppler studies.

Central Nervous System Blood Flow

Doppler velocity waveforms have been studied in a variety of other fetal vessels, but the most interest has been directed to the fetal cerebral circulation. The middle cerebral artery has been the most common fetal vessel studied. Middle cerebral artery peak systolic flow velocity has been shown to be of great value for monitoring fetuses with suspected anemia [119].

In other situations of fetal compromise, especially IUGR, there is frequently a redistribution of blood flow in the fetus with increasing flow to the cerebral

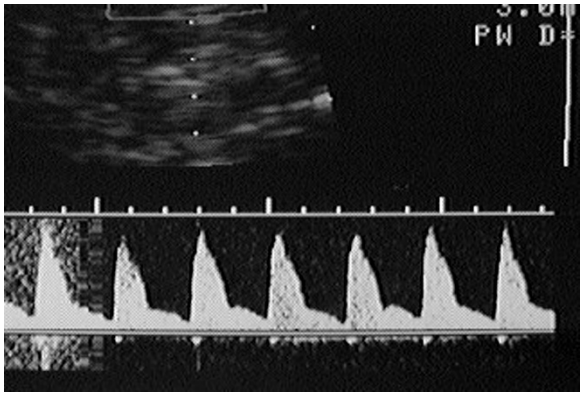

Fig. 18.8. Normal (high-resistance) Doppler wave form in the middle cerebral artery

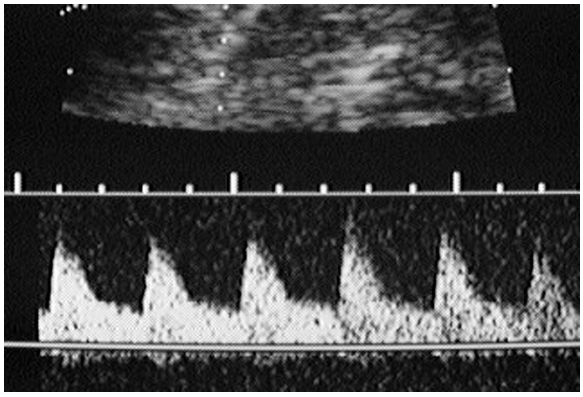

Fig. 18.9. Increased diastolic flow ("shunting") in the middle cerebral artery in a fetus with IUGR

circulation and a fall in resistance in the middle cerebral artery [120–122]. Figure 18.8 shows the normal, high-resistance flow in the fetal middle cerebral artery, whereas Fig. 18.9 shows increased diastolic flow ("shunting" or "brain sparing") in the middle cerebral artery of a fetus with significant IUGR. Serial Doppler flow studies of previable fetuses prior to fetal demise have shown progressive increased resistance in the umbilical artery with decreasing resistance in the middle cerebral artery until just prior to fetal demise, when resistance in the middle cerebral artery increases and signs of fetal heart failure (such as tricuspid regurgitation) develop [123, 124]. Of particular interest is the ratio of resistance indices of the middle cerebral artery and the umbilical artery. This ratio remains relatively constant throughout pregnancy but is significantly altered in fetuses with IUGR [125]. A number of studies involving fetal cerebral circulation suggest that there is an increase in cerebral flow in infants affected by uteroplacental insufficiency [126–129]. Studies at the author's institution of the ratio between carotid or middle cerebral and umbilical artery S/D ratio velocity waveforms (MC/UA) showed significant differences in neonatal outcome when these ratios were abnormal [130, 131]. A number of studies have shown the value of Doppler velocity flow studies in the diagnosis and management of IUGR, and have suggested that the MC/UA ratio may be more sensitive than other antenatal tests for the prediction of neonatal outcome in IUGR fetuses [130–134].

Growth-restricted fetuses, especially those that are delivered prematurely, are also at increased risk of intracranial hemorrhage or other CNS complications. The use of Doppler blood flow studies of the CNS in the fetus and neonate to identify those infants at increased risk for CNS complications may be an important tool; however, conflicting results have been obtained. Some investigators have shown a correlation between CNS complications and increased blood flow to the brain, whereas other investigators have shown a correlation between CNS complications and decreasing blood flow to the brain (increased resistance), or no correlation at all [135–140]. A recent study at the author's institution attempted to evaluate the ability of Doppler flow studies of the fetal CNS to predict CNS complications in the neonate.

Neonatal outcome of singleton pregnancies who delivered within 1 week of their final antenatal testing and had NST and fetal Doppler ultrasound (including measurements of blood flow in the fetal umbilical artery and middle cerebral artery [systolic/diastolic ratios (S/D)]) done at that time were studied. Since S/D ratios in both the umbilical and middle cerebral arteries decrease with advancing gestational age, these values were converted to multiples of the mean (MOM) derived from previously published norms [141, 142]. Both univariant and multivariant analyses were used to correlate the Doppler blood flow studies with the development of CNS complications. Correlations were also made for other tests of fetal well-being (NST and amniotic fluid volume), birth weight, and gestational age at delivery with the development of CNS complications.

Three hundred eighty-five patients were evaluated. The CNS complications occurred only in infants that were delivered at less than 37 weeks of gestation; therefore, the analysis was limited to the 131 patients that delivered at less than 37 weeks. Fourteen of the 131 patients (10.7%) developed CNS complications (IVH(1) 8; IVH(4) 1; encephalopathy 2; neonatal seizures 3), and Table 18.6 compares neonatal outcome parameters and results of antenatal testing between neonates with and without CNS complications. Univariant analysis showed that only birth weight, decreased amniotic fluid volume, and a non-reactive NST were statistically correlated with CNS complica-

Table 18.6. Central nervous system (*CNS*) complications: infants delivered at < 37 weeks gestation. *SGA* small for gestational age (< 10th percentile), *AFI* amniotic fluid index (sum of four-quadrant deepest pockets), *NST* non-reactive non-stress test, *Umb/MC ratio* ratio of the umbilical artery S/D to middle cerebral artery S/D, *MCmom* middle cerebral artery S/D ratio multiple of the mean, *UAmom* umbilical artery S/D ratio multiple of the mean, *High UA* umbilical artery S/D ratio multiple of the mean >1.5, *Low MC* middle cerebral artery S/D ratio multiple of the mean less than 0.7, *AbnUmb/MC* ratio of the umbilical artery S/D to middle cerebral artery S/D > 1.0

	CNS complications	No CNS complications	*P* [OR][a]
Number	14	117	
Maternal age	28.6 (6.8)	29.6 (5.9)	6365
Days scan to delivery	2.5 (3.6)	2.8 (2.4)	7807
Gestational age at delivery	32.9 (2.9)	33.9 (2.8)	2505
Birth weight (g)	1639 (729)	2142 (715)	0264
SGA	57.1%	34.5%	1718 [2.33 (0.71–9.45)]
AFI (cm)	9.2 (3.7)	13.9 (7.2)	0039
NST	64.3%	24.8%	0041 [5.46 (1.48–22.16)]
Umb/MC ratio	1.39 (0.81)	1.17 (1.30)	8425
MCmom	0.62 (0.32)	0.70 (0.34)	3773
UAmom	1.34 (0.51)	1.71 (4.24)	7611
High UA	42.9%	31.6%	2869 [1.62 (0.43–5.75)]
Low MC	57.1%	63.2%	8777 [0.77 (0.22–2.73)]
AbnUmb/MC	35.7%	23.9%	2551 [1.77 (0.43–6.43)]

[a] Chi-square or Fisher's exact test for distributional data; two-sample *t*-test for parametric data.
Figures in brackets are odds ratios, with confidence intervals in parentheses.
Figures in parentheses are standard deviations.

tions. Neither abnormal blood flow in the fetal umbilical artery or in the middle cerebral artery, nor evidence of "brain-sparing" (elevated umbilical artery/middle cerebral artery ratios), were found to be associated with CNS complications. Multivariant logistic regression analysis showed that a non-reactive NST had the strongest correlation with CNS complications, whereas there was a trend towards decreased CNS complications with increasing middle cerebral flow.

A number of investigators have evaluated the relationship between middle cerebral artery Doppler blood flow and the development of CNS complications in the neonate with conflicting results. Mullaart et al. [143], studying flow in the internal carotid artery, found a correlation between increased diastolic flow and CNS complications, but determined that fluctuations in flow, rather than the flow itself, was the significant correlate. VanBel et al. [144] evaluated the flow in the anterior cerebral artery and found similar results. Bada et al. [135] and Mires et al. [136] performed similar studies but came to the opposite conclusion: a correlation between CNS complications and increased resistance to flow in the CNS (decreased diastolic flow). Other investigators, however [138–140], could find no association between alterations in middle cerebral artery flow and CNS complications, whereas Mari et al. [145] found a lower risk of CNS complications in fetuses with increased middle cerebral artery blood flow.

These conflicting findings might be partially explained by the complex mechanisms that regulate fetal blood flow during developing uteroplacental insufficiency [144]. Akalin-Sel et al. studied Doppler flow in multiple fetal vessels and obtained umbilical venous blood gases in 32 severely growth-restricted fetuses [146]. They found that there are multiple mechanisms that regulate redistribution of blood flow in the fetus so that different clinical circumstances may result in difference changes in CNS blood flow. Investigators have also shown that just before fetal death, increased diastolic flow in the middle cerebral artery is lost, with a return to high resistance to flow, so that both the clinical cause of altered flow and the timing of the study may affect results [147].

In the author's study of CNS blood flow, neither abnormal umbilical artery nor middle cerebral artery blood flow were correlated with the development of CNS complications; but a non-reactive NST did show a strong correlation. Serial studies of high-risk patients with biophysical and Doppler tests have shown that the biophysical parameters (which include the NST) become abnormal only very late in the course of fetal deterioration, and this is consistent with the author's findings [148, 149]. This suggests that serial biophysical and Doppler studies could determine the time course of developing fetal anoxia and lead to a timely intervention.

Venous Doppler

Evaluation of the venous side of the circulation in fetuses suspected of IUGR also provides important in-

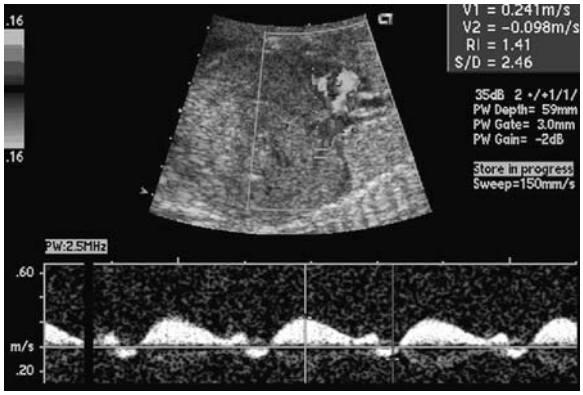

Fig. 18.10. Normal inferior vena cava flow at 30 weeks' gestation. Note the tri-phasic pattern with a small reverse A wave during atrial contraction

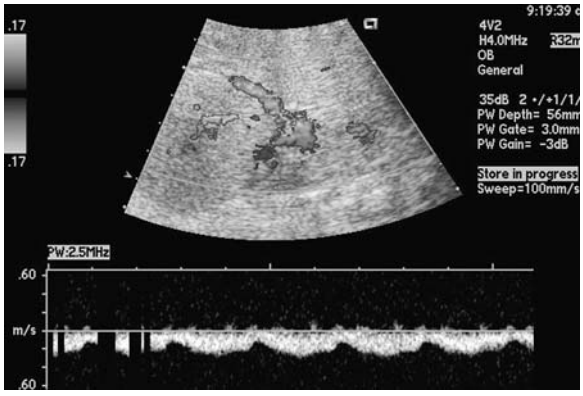

Fig. 18.11. Normal ductus venosus flow at 24 weeks. Note that there is always forward flow during the entire cardiac cycle

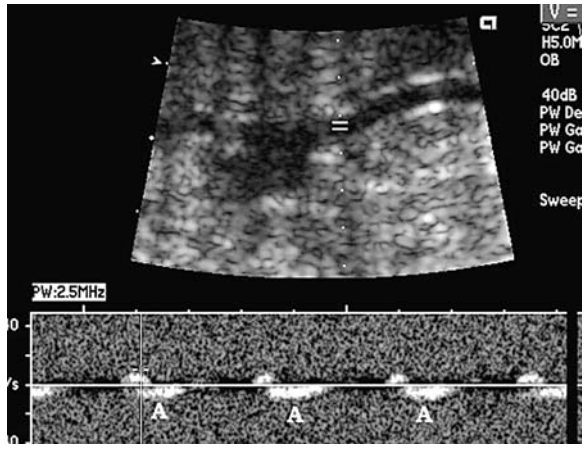

Fig. 18.12. Abnormal inferior vena cava waveform with a large A wave in a fetus at 22 weeks' gestation who died from placental abruption

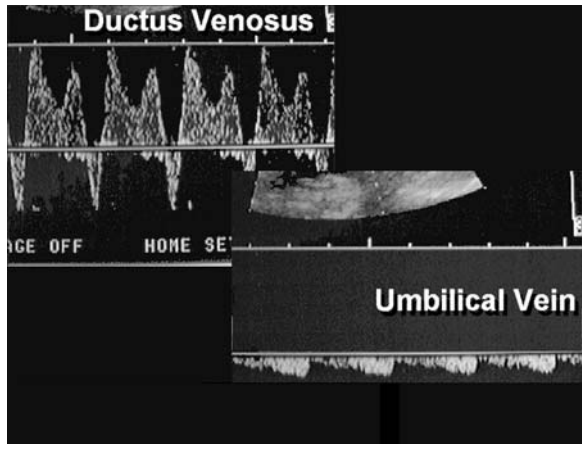

Fig. 18.13. Markedly abnormal ductus venosus flow with reverse flow during atrial contractions and transmitted venous pulsation in the umbilical vein in a severely growth-restricted fetus at 32 weeks' gestation

formation concerning fetal status [150–156]. Rizzo et al. evaluated numerous Doppler indices from the inferior vena cava and ductus venosus in a series of normal and growth-restricted fetuses prior to cordocentesis [157]. They found the inferior vena cava preload index (the peak velocity during atrial contraction divided by the peak velocity during systole) was the best index for predicting acidemia. Figures 18.10 and 18.11 show normal venous flow in the inferior vena cava and ductus venosus, respectively.

During pathological situations, transmission of increased reverse flow in the inferior vena cava and ductus venosus may result in venous pulsations in the umbilical vein. Indik et al. have postulated that it may be possible to distinguish subgroups of fetuses with abnormal umbilical artery S/D ratios by evaluating fetal vena cava flow [156]. Nakai et al. evaluated 209 patients and found 9 (4%) fetuses with umbilical venous pulsations, 7 of which (78%) had significant growth restriction [158]. Mitra followed seven singleton fetuses and two sets of twins with umbilical venous pulsations [159]. All fetuses showed tricuspid regurgitation and abnormal right-to-left ventricular diameter ratios – suggesting fetal heart failure. All seven of the singleton fetuses were significantly growth restricted, while the two twin pregnancies had twin–twin transfusion syndrome with the donor twin being growth restricted and the recipient twin being macrosomic. Studies in the fetal lamb have supported these clinical findings, suggesting that umbilical venous pulsations develop as a result of significant fetal venous pressure elevations [160]. In many clinical situations umbilical venous pulsations are a significant pathological event that require careful fetal evaluation, especially evaluation of the fetal cardiovascular

system; and fetal umbilical venous pulsations are related to very poor perinatal outcome. Figure 18.12 shows abnormal inferior vena cava blood flow; and Fig. 18.13 shows markedly abnormal ductus venosus flow with reverse flow during atrial contractions and transmitted venous pulsation in the umbilical vein in a severely growth-restricted fetus.

Ott evaluated 70 patients, over half of which were being followed for IUGR, to determine the value of the inferior vena cava flow as a tool to identify the very high risk fetus [161]. In addition to standard tests of fetal well-being the fetal inferior vena cava pre-load index (IVCPI) was also obtained. This value was calculated by placing the Doppler gate within the fetal inferior vena cava just proximal to its insertion into the right atria. The inferior vena cava pre-load index was calculated from the average of three consecutive cycles during a period of no fetal movement or respiration using the following formula: IVCPI=|A|/|S|, where A represents the peak velocity of reverse flow during atrial contraction and S represents the peak velocity of IVC flow during systole. The ability of the IVCPI to predict poor perinatal outcome was compared with three methods utilized in our laboratory to monitor fetal well-being: the NST; fetal umbilical artery S/D ratio (UAS/D); and the ratio of the fetal middle cerebral artery S/D ratio to the fetal umbilical artery S/D ratio (MCUA).

As shown in Table 18.7, the IVCPI had the highest odds ratios for predicting morbidity or prolonged stay in the NICU. Logistic regression analysis indicated that the combination of MCUA and IVCPI was the best predictor of neonatal outcome. When both tests were normal only 16% of these very high-risk fetuses had significant neonatal morbidity, whereas when both tests were abnormal 80% of the fetuses developed significant neonatal morbidity. Fetal IVC flow, therefore, gives additional important information concerning fetal status in suspected IUGR [162].

The fetal ductus venosus transmits well-oxygenated blood from the placenta to the right atria, and, via the anatomical and physiological mechanisms of the fetal heart, the majority of the ductus venosus blood is directed across the foramen ovale to the left heart [163, 164]. In normal pregnancies ductus venosus-pulsed Doppler waveforms show forward flow throughout the fetal cardiac cycle, and, unlike flow in the inferior vena cava, there is continued forward flow during atrial systole in the ductus venosus [165, 166].

Both DeVore and Horenstein [165] and Kiserud et al. [166] found that in seriously compromised fetuses, most of whom were also growth restricted, the lack of forward ductus venosus flow during atrial contractions was significantly associated with perinatal mortality or serious morbidity. Experience at the author's own institution and animal experimentation has also confirmed these findings [167]. Detailed reviews of the clinical value of blood flow studies of the ductus venosus by Sherer et al. [168] and Kiserud et al. [169] suggest that evaluation of this vessel provides important clinical information regarding both fetal welfare and the timing of pathological events related to fetal hypoxia. Lack of forward flow during diastole or, more significantly, reverse flow during diastole, is a sign of very significant fetal compromise.

Table 18.7. Neonatal outcome: univariant analysis. *NST* non-stress test, *UAS/D* umbilical artery systolic/diastolic ratio, *MCUA* middle cerebral artery/umbilical artery systolic/diastolic ratio, *IVCPI* inferior vena cava pre-load index

Significant morbidity when:	Test normal (%)	Test abnormal (%)	Odds ratio
NST	28 (17 of 60)	50 (5 of 10)	2.6 (0.4–14.6)
UAS/D	18 (8 of 45)	44 (11 of 25)	5.7 (1.7–18.8)
MCUA	19 (10 of 54)	56 (9 of 16)	3.6 (1.2–10.9)
IVCPI	16 (8 of 50)	55 (11 of 20)	6.4 (2.0–20.5)

Conclusion

The combined use of Doppler velocity wave form analysis of fetal vessels and the ultrasonic estimation of fetal weight (or abdominal circumference) appears to be the best method for both the identification and evaluation of IUGR (see Table 18.8). Once identified, the IUGR fetus should undergo serial evaluation on a weekly (or more frequent interval if the clinical situation warrants) basis with both Doppler velocity wave form studies and biophysical testing (the full or modified biophysical profile). Determination of the optimal time of delivery depends not only on the results of the antenatal testing, but also on the individual

Table 18.8. Role of Doppler studies in the diagnosis and management of IUGR

Diagnosis
Estimated fetal weight (or abdominal circumference) < 10th percentile = SGA fetus
Plus increased resistance in the fetal umbilical artery = IUGR fetus
Management
Serial biophysical testing and Doppler ultrasound
Absent or reversed diastolic flow in the umbilical artery or evidence of "brain sparing" (better diastolic flow in the middle cerebral artery than in the umbilical artery) = consider hospital admission for daily monitoring
Plus abnormal inferior vena cava or ductus venosus flow, and/or non-reactive NST = strongly consider delivery

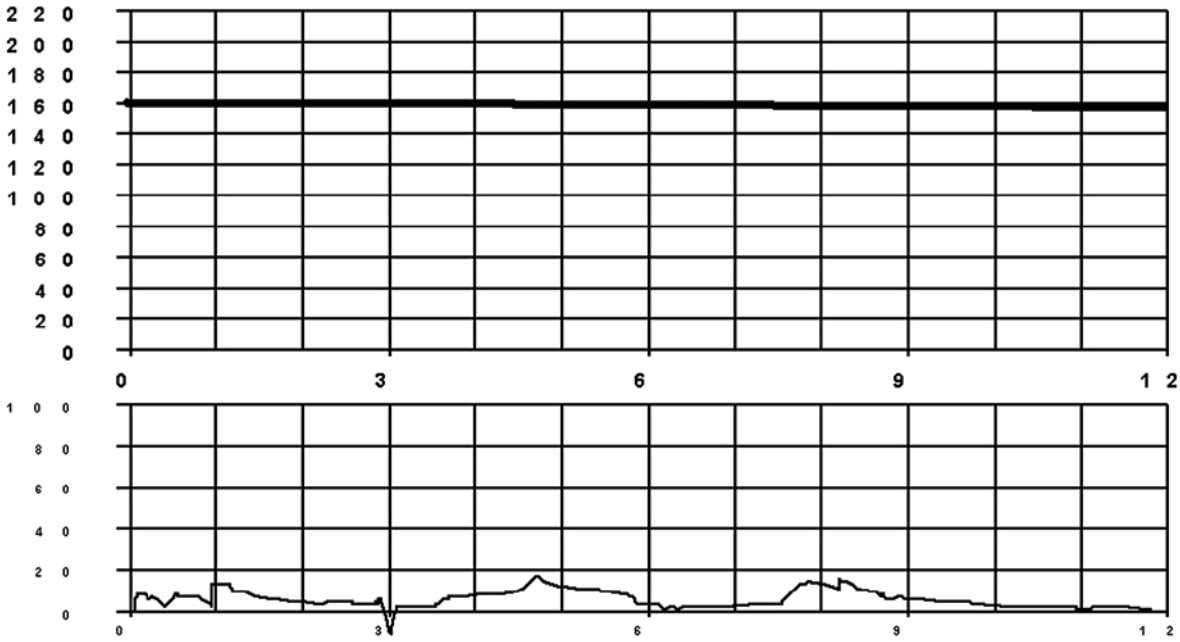

Fig. 18.14. Non-reactive non-stress testing with no acceleration and absent variability at 32 weeks' gestation

clinical situation [170]. In situations where the data is unclear, especially in the preterm fetus, the use of amniocentesis to determine lung maturity may be helpful. Growth-restricted fetuses will frequently have lungs that are more mature than would be expected for their gestational age. Fetal venous Doppler studies give additional information about the time frame and significance of the IUGR [134].

An aggressive approach to the management of IUGR would, hopefully, lead to a reduction in perinatal mortality and morbidity in these high-risk fetuses. A study from the UK showed that IUGR infants identified in the antenatal period (and managed aggressively) had a lower perinatal mortality and less severe 2-year neurodevelopmental, clinical, or growth morbidity than similar IUGR infants that were not identified antenatally [171].

Since approximately half of IUGR fetuses are found in otherwise low-risk pregnancies, a strong point could be made for routine screening for IUGR. At the author's institution it is recommended that an ultrasound examination to evaluate fetal growth in all patients be done at 32–34 weeks' gestation. If fetal weight estimation is below the 10th percentile of the fetal weight curve, additional evaluation is undertaken, which would include a detailed ultrasound examination to look for structural abnormalities and Doppler velocity flow studies of the fetal umbilical artery. If any abnormalities are found, then additional testing is done; if not, then the fetus is considered to be constitutionally SGA and not IUGR. A repeat scan may be done in 2–3 weeks if the clinical condition warrants and IUGR is still suspected. In those patients with the diagnosis of IUGR weekly (or more frequent) evaluation of the fetus should include both biophysical testing and Doppler studies of the umbilical artery and middle cerebral artery, and in many clinical situations venous Doppler studies are extremely helpful [172–174].

Once the fetus reaches 34 completed weeks of gestation, little is to be gained by prolonging the pregnancy, although in situations where the biophysical testing is normal and the Doppler studies are only minimally abnormal, waiting until 36 weeks may be permissible. In premature fetuses (< 32–34 weeks) with immature fetal lung studies, it may be difficult to determine the best time for delivery. Factors that might suggest the need for immediate delivery despite an early gestational age include:

1. Persistent non-reactive non-stress test; the presence of spontaneous late decelerations on the non-stress test; severe oligohydramnios
2. Evidence of "brain sparing" on Doppler ultrasound (lower resistance in the middle cerebral artery than in the umbilical artery)
3. Ominous Doppler studies: reverse diastolic flow in the umbilical artery; umbilical vein pulsatile flow
4. Maternal compromise.

Figures 18.14–18.16 illustrate the combined use of weight estimation, Doppler studies, and biophysical testing in a 32-week singleton gestation being evalu-

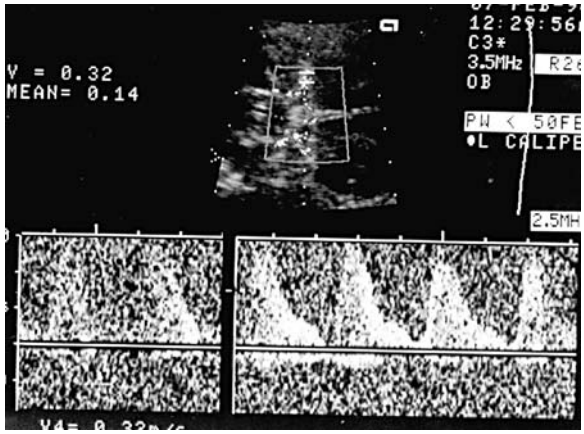

Fig. 18.15. Fetus from Fig. 18.14. High-resistance flow in the middle cerebral artery (loss of "shunting"?)

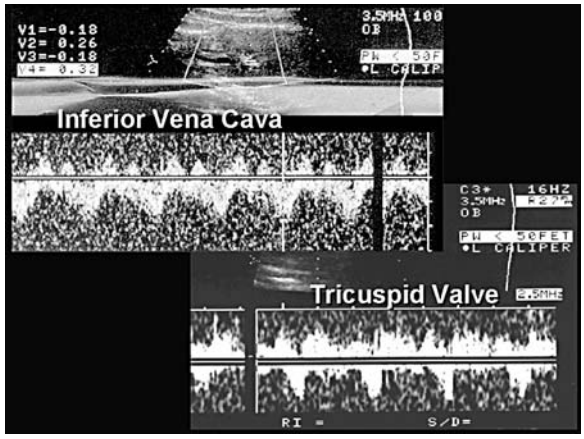

Fig. 18.16. Markedly increased A wave and tricuspid regurgitation in the fetus from Figs. 18.14 and 18.15

ated for IUGR. The estimated fetal weight was 1420 g (less than the 5th percentile) and there were no obvious anomalies seen on the ultrasound examination. The fetus had a non-reactive NST and received a score of 2 on the biophysical profile (only normal fluid). Doppler blood flow studies showed increased resistance in the umbilical artery but no CNS shunting, abnormal inferior vena cava flow, and tricuspid regurgitation. A viable male infant was delivered by cesarean section with Apgar scores of 2 and 6, an arterial pH of 7.15, and a pCO_2 of 61. Placental pathology showed hypoplasia with chronic infarction and decidual necrosis. No organisms were isolated. In this case significant uteroplacental dysfunction leading to IUGR and a compromised fetus was reflected in abnormal weight estimation, biophysical studies, and Doppler ultrasound. The combined use of these modalities enabled the clinicians to better evaluate the seriousness of the fetus' condition.

References

1. Hack M, Flannery DJ, Schluchter M, Cartar L, Borawski E et al (2002) Outcomes in young adulthood for very-low-birth infants. N Engl J Med 346:149–157
2. Taylor DJ (1984) Low birth weight and neurodevelopmental handicap. Clinics in Obstet Gynecol 11:525–531
3. Edouard L, Alberman E (1980) National trends in the identified causes of perinatal mortality 1960–1978. Br J Obstet Gynaecol 87:833–841
4. Simchen MJ, Beiner ME, Strauss-Livianthan N, Dulitsky M, Kuint J et al (2000) Neonatal outcome in growth-restricted versus appropriately grown preterm infants. Am J Perinatol 17:187–192
5. Tejani N, Mann LI (1977) Diagnosis and management of the small for gestational age fetus. Clin Obstet Gynecol 20:943–950
6. Hsieh HL, Lee KS, Khoshnood B et al (1997) Fetal death rate in the United States, 1979–1990: trend and racial disparity. Obstet Gynecol 89:33–39
7. Ahlenius I, Floberg J, Thomassen P (1995) Sixty-six cases of intrauterine fetal death: a prospective study with an extensive test protocol. Acta Obstet Gynecol Scand 74:109–117
8. Cefalo RC (1978) The hazards of labor and delivery for the intrauterine-growth-retarded fetus. J Reprod Med 21:300–314
9. Hediger ML, Overpeck MD, Ruan WJ, Troendle JF (2002) Birthweight and gestational age effects motor and social development. Paediatr Perinat Epidemiol 16:33–46
10. Doctor NA, O'Riordan MA, Kirchner HL, Shah D, Hack M (2001) Perinatal correlates and neonatal outcomes of small for gestational age infants born at term gestation. Am J Obstet Gynecol 185:652–659
11. Bernstein IM, Horbar JD, Badger GJ, Ohlsson A, Golan A (2000) Morbidity and mortality among very-low-birth-weight neonates with intrauterine growth restriction. Am J Obstet Gynecol 182:198–206
12. Keirse MJNC (1984) Epidemiology and aetiology of the growth retarded baby. Clin Obstet Gynaecol 11:415–422
13. Seeds JW (1984) Impaired fetal growth: definition and clinical diagnosis. Obstet Gynecol 64:303–330
14. Varma TR (1984) Low birth weight babies. The small for gestational age. A review of current management. Obstet Gynecol Surv 39:616–631
15. Ott WJ (1993) Intrauterine growth retardation and preterm delivery. Am J Obstet Gynecol 168:1710–1717
16. Zeitlin JA, Ancel P, Saurel-Cubizolles MJ, Papiernik E (2001) Are risk factors the same for small for gestational age versus other preterm births? Am J Obstet Gynecol 185:208–215
17. Ott WJ (1988) The diagnosis of altered fetal growth. Obstet Gynecol Clin North Am 15:237–263
18. Goldenberg AL, Cutter GR, Hoffman HJ et al (1989) Intrauterine growth retardation: standards for diagnosis. Am J Obstet Gynecol 161:271–277
19. Goldenberg RL, Nelson KG, Koski JF et al (1985) Low birth weight, intrauterine growth retardation, and preterm delivery. Am J Obstet Gynecol 152:980–984
20. Ott WJ (ed) (1999) Reference curves. Clinical obstetrical ultrasound. Wiley-Liss, New York, pp 353–384

21. Tamura RK, Sabbagha RE, Depp R et al (1984) Diminished growth in fetuses born preterm after spontaneous labor or rupture of membranes. Am J Obstet Gynecol 148:1105–1110
22. Alexander G, Himes JH, Kaufman RB et al (1997) A United States national reference for fetal growth. Obstet Gynecol 87:163–168
23. Anderson GD, Blidner IN, McClemont S et al (1984) Determinants of size at birth in a Canadian population. Am J Obstet Gynecol 150:236–245
24. Khoury MJ, Cohen BH (1987) Genetic heterogeneity of prematurity and intrauterine growth restriction: clues from the Old Order Amish. Am J Obstet Gynecol 157:400–409
25. Miller HC (1988) Prenatal factors affecting intrauterine growth retardation. Clin Perinatol 12:307–315
26. Peters TJ, Golding J, Butler NR et al (1983) Predictors of birth weight in two national studies. Br J Obstet Gynaecol 90:107–112
27. Raine T, Powell S, Krohn MA (1994) The rise of repeating low birth weight and the role of prenatal care. Obstet Gynecol 84:485–489
28. Hickey CA, Cliver SP, McNeal SF et al (1996) Prenatal weight gain patterns and birth weight among nonobese black and white women. Obstet Gynecol 88:490–496
29. Mittendorf R, Herschel M, Williams MA et al (1994) Reducing the frequency of low birth weight in the United States. Obstet Gynecol 83:1056–1059
30. Bakketeig LS, Hoffman HJ, Harley EE (1979) The tendency to repeat gestational age and birth weight in successive births. Am J Obstet Gynecol 135:1086–1099
31. Jones OW (1978) Genetic factors in the determination of fetal size. J Reprod Med 21:305–310
32. Bada HS, Das A, Bauer CR, Shankaran S, Lester B et al (2002) Gestational cocaine exposure and intrauterine growth: maternal lifestyle study. Obstet Gynecol 100: 916–924
33. Ounsted M, Moar VA, Scott A (1985) Risk factors associated with small-for-dates and large-for-dates infants. Br J Obstet Gynaecol 92:226–232
34. Visser GHA, Huisman A, Saathof PWF et al (1986) Early fetal growth retardation: obstetric background and recurrence rate. Obstet Gynecol 67:40–46
35. Wolfe HM, Gross TL, Sokol RJ (1987) Recurrent small for gestational age birth. Perinatal risks and outcomes. Am J Obstet Gynecol 157:288–297
36. Duverot JJ, Cheriex E, Pieters FAA et al (1995) Maternal volume homeostasis in early pregnancy in relation to fetal growth restriction. Obstet Gynecol 85:361–367
37. Salafia CM, Ernst LM, Pezzullo JC et al (1995) The very low birthweight infant: maternal complications leading to preterm birth, placental lesions, and intrauterine growth. Am J Perinatol 12:106–110
38. Benson CB, Doubilet PM, Saltzman DH (1986) Intrauterine growth retardation: predictive value of US criteria for antenatal diagnosis. Radiology 160:415–426
39. Brown HL, Miller JM, Gabert HA et al (1987) Ultrasonic recognition of the small-for-gestational-age fetus. Obstet Gynecol 69:631–647
40. Crane JP, Lopta MM, Welt SI et al (1977) Abnormal fetal growth patterns: ultrasonic diagnosis and management. Obstet Gynecol 50:205–209
41. Deter RL, Harrist RB, Hadlock FP et al (1982) The use of ultrasound in the detection of intrauterine growth retardation: a review. J Clin Ultrasound 10:9–22
42. Deter RL, Hadlock FP, Harrist RB (1983) Evaluation of normal fetal growth and the detection of intrauterine growth retardation. In: Callen PW (ed) Ultrasonography in obstetrics and gynecology. Saunders, Philadelphia, pp 113–140
43. Hadlock FP, Deter RL, Harrist RB et al (1983) Sonographic detection of fetal intrauterine growth retardation. Perinatol Neonatol 7:21–32
44. Little D, Campbell S (1982) Ultrasound evaluation of intrauterine growth retardation. Radiol Clin North Am 20:335–342
45. Ott WJ (1985) Fetal femur length, neonatal crown-heel length and screening for IUGR. Obstet Gynecol 65:460–465
46. Ott WJ (1985) The diagnosis of altered fetal growth. Obstet Gynecol Clin North Am 15:237–249
47. Benson CB, Doubilet PM, Saltzman DH (1986) Intrauterine growth retardation: predictive value of US criteria for antenatal diagnosis. Radiology 160:415–417
48. Schild RL, Fimmers R, Hansmann M (2000) Fetal weight estimation by three-dimensional ultrasound. Ultrasound Obstet Gynecol 16:445–452
49. Song TB, Moore TR, Lee JY, Kim YH, Kim EK (2000) Fetal weight prediction by thigh volume measurements with three-dimensional ultrasonography. Obstet Gynecol 69:157–161
50. Lee W, Comstock CH, Kirk JS, Smith RS, Monck JW et al (1997) Birthweight prediction by three-dimensional ultrasonographic volumes of the fetal thigh and abdomen. J Ultrasound Med 16:799–805
51. Ott WJ (2002) The diagnosis of intrauterine growth restriction: comparison of ultrasound parameters. Am J Perinatol 19:133–137
52. Ott WJ (1999) Altered fetal growth. In: Ott WJ (ed) Clinical obstetrical ultrasound. Wiley-Liss, New York, pp 229–262
53. Soothill PW, Bobrow CS, Holmes RP (1999) Small for gestational age is not a diagnosis. Ultrasound Obstet Gynecol 13:225–228
54. Craigo SD, Beach ML, Harvey-Wilkes KB, D'Alton ME (1996) Ultrasound predictors of neonatal outcome in intrauterine growth restriction. Am J Perinatol 13:465–471
55. Resnik R (2002) Intrauterine growth restriction. Obstet Gynecol 99:490–496
56. Krebs C, Macara LM, Leiser R et al (1996) Intrauterine growth restriction with absent end-diastolic flow velocity in the umbilical artery is associated with maldevelopment of the placental terminal villous tree. Am J Obstet Gynecol 175:1534–1542
57. Giles W, Ocallaghan S, Read M et al (1997) Placental nitric oxide synthase activity and abnormal umbilical artery flow velocity waveforms. Obstet Gynecol 89:49–52
58. Giles W, Falconer J, Read M et al (1997) Ovine fetal umbilical artery Doppler systolic diastolic ratios and nitric oxide synthase. Obstet Gynecol 89:53–56
59. MacLean M, Mathers A, Walker J et al (1992) The ultrasonic assessment of discordant growth in twin pregnancies. Ultrasound Obstet Gynecol 2:30–34

60. Reed K, Anderson C, Shenker L (1987) Changes in intracardiac Doppler blood flow velocities in fetuses with absent umbilical artery diastolic flow. Am J Obstet Gynecol 157:774–779
61. Chandran R, Serra-Serra V, Sellers S et al (1993) Fetal cerebral Doppler in the recognition of fetal compromise. Br J Obstet Gynaecol 100:139–144
62. Vyas S, Nicolaides K, Bower S et al (1990) Middle cerebral artery flow velocity waveforms in fetal hypoxemia. Br J Obstet Gynaecol 97:797–803
63. Trudinger BJ, Giles WB, Cook CM et al (1985) Fetal umbilical artery flow velocity waveforms and placental resistance: clinical significance. Br J Obstet Gynaecol 92:23–31
64. Erskin RLA, Ritchie JWK (1985) Umbilical artery blood flow characteristics in normal and growth-retarded fetuses. Br J Obstet Gynaecol 92:605–615
65. Giles WB, Trudinger BJ, Baird PJ (1985) Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. Br J Obstet Gynaecol 92:31–39
66. Hitschold T, Weiss E, Beck T et al (1993) Low target birth weight or growth retardation? Umbilical doppler flow velocity waveforms and histometric analysis of fetoplacental vascular tree. Am J Obstet Gynecol 168: 1260–1264
67. Locci M, Nazzaro G, DePlacido G et al (1993) Correlation of Doppler and placental immunohistochemical features in normal and intrauterine growth-retarded fetuses. Ultrasound Obstet Gynecol 3:240–245
68. Ott WJ (2000) Intrauterine growth restriction and Doppler ultrasound. J Ultrasound Med 19:661–668
69. Soothill PW, Bobrow CS, Holmes RP (1999) Small for gestational age is not a diagnosis. Ultrasound Obstet Gynecol 13:225–228
70. Holmes RP, Soothill PW (1999) Small fetuses with normal Dopplers are appropriately grown with normal pregnancy outcomes. J Obstet Gynecol 19 (Suppl 1):23
71. Craigo SD, Beach ML, Harvey-Wilkes KB, D'Alton ME (1996) Ultrasound predictors of neonatal outcome in intrauterine growth restriction. Am J Perinatol 13:465–471
72. Steel SA, Pearce M, Chamberlain GV (1988) Doppler ultrasound of the uteroplacental circulation as a screening test for severe pre-eclampsia with intrauterine growth retardation. Eur J Obstet Gynecol Reprod Biol 28:279–287
73. North RA, Ferrier C, Long D et al (1994) Uterine artery Doppler flow velocity waveforms in the second trimester for the prediction of preeclampsia and fetal growth retardation. Obstet Gynecol 83:378–386
74. Atkinson MW, Maher JE, Owen J et al (1994) The predictive value of umbilical artery doppler studies for preeclampsia or fetal growth retardation in a preeclampsia prevention trial. Obstet Gynecol 83:609–612
75. Vergani P, Roncaglia N, Andreotti C, Arreghini A, Teruzzi M et al (2002) Prognostic value of uterine artery Doppler velocimetry in growth-restricted fetuses delivered near term. Am J Obstet Gynecol 187:932–936
76. Chien PF, Arnott N, Gordon A, Owen P, Khon K (2000) How useful is uterine artery Doppler flow velocimetry in the prediction of pre-eclampsia, intrauterine growth retardation and perinatal death? Br J Obstet Gynaecol 107:196–208
77. Albaiges G, Missfelder-Lobos H, Lees C, Parra M, Nicolaides KH (2000) One-stage screening for pregnancy complications by color Doppler assessment of the uterine arteries at 23 weeks' gestation. Obstet Gynecol 96:559–564
78. Papageorghiou AT, Yu CKH, Bindra R, Pandis G, Nicolaides KH (2001) Multicenter screening for pre-eclampsia and fetal growth restriction by transvaginal uterine artery Doppler at 23 weeks of gestation. Ultrasound Obstet Gynecol 18:441–449
79. Lees C, Parra M, Missfelder-Lobos H, Morgans A, Fletcher O, Nicolaides KH (2001) Individualized risk assessment for adverse pregnancy outcome by uterine artery Doppler at 23 weeks. Obstet Gynecol 98:369–373
80. Missfelder-Lobos H, Teran E, Lees C, Albaiges G, Nicolaides KH (2002) Platelet changes and subsequent development of pre-eclampsia and fetal growth restriction in women with abnormal uterine artery Doppler screening. Ultrasound Obstet Gynecol 19:443–448
81. Martin AM, Bindra R, Curcio P, Cicero S, Nicolaides KH (2001) Screening for pre-eclampsia and fetal growth restriction by uterine artery Doppler at 11–14 weeks of gestation. Ultrasound Obstet Gynecol 18: 583–583
82. Hernandez-Andrade E, Brodszki J, Lingman G, Gudmundsson S, Molin J, Maršál K (2002) Uterine artery score and perinatal outcome. Ultrasound Obstet Gynecol 19:438–442
83. Venkat-Raman N, Backos M, Teoh TG, Lo WTS, Regan L (2001) Uterine artery Doppler in predicting pregnancy outcome in women with antiphospholipid syndrome. Obstet Gynecol 98:235–242
84. Abramowicz JS, Sherer DM, Bar-Tov E et al (1991) The cheek-to-cheek diameter in the ultrasonographic assessment of fetal growth. Am J Obstet Gynecol 165: 846–852
85. Hill LM, Guzick D, Thomas ML et al (1989) Thigh circumference in the detection of intrauterine growth retardation. Am J Perinatol 6:349–352
86. Catalano PM, Tyzbir ED, Allen SR et al (1992) Evaluation of fetal growth by estimation of neonatal body composition. Obstet Gynecol 79:46–50
87. Sumners JE, Findley GM, Ferguson KA (1990) Evaluation methods for intrauterine growth using neonatal fat stores instead of birth weight as outcome measures: fetal and neonatal measurements correlated with neonatal skinfold thickness. J Clin Ultrasound 18:9–14
88. Berstein IM, Goran MI, Amini SB et al (1997) Differential growth of fetal tissues during the second half of pregnancy. Am J Obstet Gynecol 176:28–32
89. Hill IM, Guzick D, Doyles D et al (1992) Subcutaneous tissue thickness cannot be used to distinguish abnormalities of fetal growth. Obstet Gynecol 80:268–271
90. Gardeil F, Greene R, Stuart B et al (1999) Subcutaneous fat in the fetal abdomen as a predictor of growth restriction. Obstet Gynecol 94:209–212
91. Gimondo P, Mirk P, LaBella A et al (1995) Sonographic estimation of fetal liver weight: an additional biometric parameter for assessment of fetal growth. J Ultrasound Med 14:327–333
92. Alfrevic Z, Neilson JP (1995) Doppler ultrasonography in high-risk pregnancies: systematic review with meta-analysis. Am J Obstet Gynecol 172:1379–1387

93. Divon MY (1995) Randomized controlled trials of umbilical artery Doppler velocimetry: How many are too many? Ultrasound Obstet Gynecol 6:377–379
94. Divon MY (1996) Umbilical artery Doppler velocimetry: clinical utility in high-risk pregnancies. Am J Obstet Gynecol 174:10–14
95. Wienerroither H, Steiner H, Tomaselli J, Lobendanz M, Thuyn-Hohenstein L (2001) Intrauterine blood flow and long term intellectual, neurologic, and social development. Obstet Gynecol 97:449–453
96. Rochelson B, Schulman H, Farmakides G et al (1987) The significance of absent end-diastolic velocity in umbilical artery waveforms. Am J Obstet Gynecol 156: 1213–1218
97. Divon MY, Girz BA, Lieblich R et al (1989) Clinical management of the fetus with markedly diminished umbilical artery end diastolic flow. Am J Obstet Gynecol 161:1523–1527
98. Karsdorp VHM, van Vugt JMG, van Geijn HP et al (1994) Clinical significance of absent or reverse end diastolic velocity waveforms in umbilical artery. Lancet 344:1664–1667
99. Valcomonico A, Danti L, Frusca T et al (1994) Absent end-diastolic velocity in umbilical artery: risk of neonatal morbidity and brain damage. Am J Obstet Gynecol 170:796–801
100. Gaziano EP, Knox H, Ferrera B et al (1994) Is it time to reassess the risk for the growth-retarded fetus with normal Doppler velocimetry of the umbilical artery? Am J Obstet Gynecol 170:1734–1743
101. Almstrom H, Axelsson O, Snattingius S et al (1992) Comparison of umbilical-artery velocimetry and cardiotocography for surveillance of small-for-gestational-age fetuses. Lance 340:936–941
102. DeVore GR (1994) The effect of an abnormal umbilical artery doppler on the management of fetal growth restriction: a survey of maternal-fetal medicine specialists who perform fetal ultrasound. Ultrasound Obstet Gynecol 4:294–303
103. Maršál K, Persson P (1988) Ultrasonic measurement of fetal blood velocity wave form as a secondary diagnostic test in screening for intrauterine growth retardation. J Clin Ultrasound 16:239–244
104. Yoon BH, Romero R, Roh CR et al (1993) Relationship between the fetal biophysical profile score, umbilical artery Doppler velocimetry, and fetal blood acid–base status determined by cordocentesis. Am J Obstet Gynecol 169:1586–1594
105. Johnstone FD, Prescott R, Hoskins P et al (1993) The effect of introduction of umbilical Doppler recordings to obstetric practice. Br J Obstet Gynaecol 100:733–741
106. Yoon BH, Lee CM, Kim SW (1994) An abnormal umbilical artery waveform: a strong and independent predictor of adverse perinatal outcome in patients with preeclampsia. Am J Obstet Gynecol 171:713–721
107. Wladimiroff JW, Wijngaard AGW, Degani S et al (1987) Cerebral and umbilical arterial blood flow velocity waveforms in normal and growth-retarded pregnancies. Obstet Gynecol 69:705–709
108. Gramellini D, Folli MC, Raboni S et al (1991) Cerebral–umbilical Doppler ratio as a predictor of adverse perinatal outcome. Obstet Gynecol 79:416–420
109. Devine PA, Bracero LA, Lysikiewicz A et al (1994) Middle cerebral to umbilical artery Doppler ratio in postdate pregnancies. Obstet Gynecol 84:856–860
110. Mari G (1994) Regional cerebral flow velocity waveforms in the human fetus. J Ultrasound Med 13:343–346
111. Arabin B, Snyjders R, Mohnhaupt A et al (1993) Evaluation of the fetal assessment score in pregnancies a risk for intrauterine hypoxia. Am J Obstet Gyneocl 169:549–554
112. Baschat AA, Gembruch U, Harman CR (2001) The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol 18:571–577
113. Hecher K, Bilardo CM, Stigter RH et al (2002) Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet Gynecol 19:564–570
114. Ott WJ (1999) Comparison of the non-stress test with the evaluation of centralization of blood flow by the prediction of neonatal compromise. Ultrasound Obstet Gynecol 14:38–41
115. Ott WJ, Mora G, Arias F et al (1998) Comparison of the modified biophysical profile to a "new" biophysical profile incorporating the middle cerebral artery to umbilical artery velocity flow systolic/diastolic ratio. Am J Obstet Gynecol 178:1346–1353
116. Rizzo G, Capponi A, Pietropolli A et al (1994) Fetal cardiac and extracardiac flows preceding intrauterine death. Ultrasound Obstet Gynecol 4:139–142
117. Akalin-Sel T, Nicolaides K, Peacock J et al (1994) Doppler dynamics and their complex interrelation with fetal oxygen pressure, carbon dioxide pressure, and pH in growth-retarded fetuses. Obstet Gynecol 84:439–444
118. Guzman E, Vintzileos A, Martins M (1995) Relationship between middle cerebral artery velocimetry, computer fetal heart rate assessment and degree of acidemia at birth in intrauterine growth restricted fetuses. Am J Obstet Gynecol 172:337
119. Detti L, Mari G, Akiyama M, Cosmi E, Moise KJ et al (2002) Longitudinal assessment of the middle cerebral artery peak systolic velocity in healthy fetuses and in fetuses at risk for anemia. Am J Obstet Gynecol 187: 937–939
120. Woo JK, Liang ST, Chan FY (1987) Middle cerebral artery Doppler flow velocity waveforms. Obstet Gynecol 70:613–616
121. Wladimiroff JW, Tonge HM, Sewart PA (1986) Doppler ultrasound assessment of cerebral blood flow in the human fetus. Br J Obstet Gynaecol 93:471–475
122. Vyas S, Nicolaides KH, Bower S et al (1990) Middle cerebral artery flow velocity waveforms in fetal hypoxemia. Br J Obstet Gynaecol 97:797–803
123. Huang SC, Chen CP, Chang FM et al (1993) Serial follow-up of abnormal flow velocity waveforms of dying fetus in case of chronic hypertension. J Clin Ultrasound 21:537–541
124. Rizzo G, Capponi A, Pietropolli LM et al (1994) Fetal cardiac and extracardiac flows preceding intrauterine death. Ultrasound Obstet Gynecol 4:139–142
125. Gramellini D, Folli MC, Raboni S et al (1992) Cerebral umbilical Doppler ratio as a predictor of adverse perinatal outcome. Obstet Gynecol 79:416–420

126. Simon NV, Levisky JS, Shearer DM et al (1988) Predictiveness of sonographic fetal weight estimation as a function of prior probability of intrauterine growth retardation. J Clin Ultrasound 16:285–298
127. Warsof SL, Cooper DJ, Little D et al (1986) Routine ultrasound screening for antenatal detection of intrauterine growth retardation. Obstet Gynecol 76:33–47
128. Medearis A (1988) The evaluation and interpretation of ultrasonic assessment of fetal growth. Semin Perinatol 12:31–58
129. Campbell S, Bewley S, Cohen-Overbeek (1987) Investigation of the uteroplacental circulation by Doppler ultrasound. Semin Perinatol 11:362–381
130. Ott WJ (1991) Value of fetal umbilical artery and carotid Doppler flow studies in the evaluation of suspected IUGR. J Matern Fetal Invest 1:185–190
131. Arias F (1994) Accuracy of the middle-cerebral-to-umbilical-artery resistance index ratio in the prediction of neonatal outcome in patients at high risk for fetal and neonatal complications. Am J Obstet Gynecol 171: 1541–1545
132. Sterne G, Shields LE, Dubinsky TJ (2001) Abnormal fetal cerebral and umbilical Doppler measurements in fetuses with intrauterine growth restriction predicts the severity of perinatal morbidity. J Clin Ultrasound 29:146–151
133. Akalin-Sel T, Nicolaides K, Peacock J et al (1994) Doppler dynamics and their complex interrelation with fetal oxygen pressure, carbon dioxide pressure, and pH in growth-retarded fetuses. Obstet Gynecol 84:439–444
134. Guzman E, Vintzileos A, Martins M (1995) Relationship between middle cerebral artery velocimetry, computer fetal heart rate assessment and degree of acidemia at birth in intrauterine growth restricted fetuses. Am J Obstet Gynecol 172:337
135. Bada HS, Miller JE, Menke JA, Menten TG, Bashiru M, Binstadt D, Sumner DS, Khanna NN (1982) Intracranial pressure and cerebral arterial pulsatile flow measurement in neonatal intraventricular hemorrhage. J Pediatr 100:291–296
136. Mires GJ, Patel NB, Forsyth JS, Howie PW (1994) Neonatal cerebral Doppler flow velocity waveforms in the pre-term infant with cerebral pathology. Early Hum Dev 36:213–222
137. Ilikkan B, Vural M, Yardimci D, Ozbek S, Perk Y, Ilter O (1998) Intraventricular hemorrhage in premature newborns. Turk J Pediatr 40:195–200
138. Baschat AA, Gembruch U, Viscardi RM, Gortner L, Harman CR (2002) Antenatal prediction of intraventricular hemorrhage in fetal growth restriction: What is the role of Doppler? Ultrasound Obstet Gynecol 19:334–339
139. Chan FY, Pun TC, Lam P, Lam C, Lee CP, Lam YH (1996) Fetal cerebral Doppler studies as a predictor of perinatal outcome and subsequent neurologic handicap. Obstet Gynecol 87:981–988
140. Scherjo SA, Oosting H, Smolders-DeHass H, Zondervan HA, Kok JH (1998) Neurodevelopmental outcome at three years of age after fetal 'brain-sparing'. Early Hum Dev 52:67–79
141. Woo JSK, Liang ST, Lo LS, Chan FY (1987) Middle cerebral artery Doppler flow velocity waveforms. Obstet Gynecol 70:613–616
142. Kurmanavicius J, Florio I, Wisser J, Hebisch G, Zimmermann R, Muller R, Huch R, Huch A (1997) Reference resistance indices of the umbilical, fetal middle cerebral and uterine arteries at 24–42 weeks' gestation. Ultrasound Obstet Gynecol 10:112–120
143. Mullaart RA, Hopman JC, Rotteveel JJ, Daniels O, Stoelinga GB, DeHaan AF (1994) Cerebral blood flow fluctuation in neonatal respiratory distress and periventricular haemorrhage. Early Hum Dev 37:179–185
144. VanBel F, VandeBor M, Stijnen T, Baan J, Ruys JH (1987) Aetiological role of cerebral blood-flow alterations in development and extension of peri-intraventricular haemorrhage. Dev Med Child Neurol 29:601–614
145. Mari G, Abuhamad AZ, Keller M, Verpairojkit B, Ment L, Copel JA (1996) Is the fetal brain-sparing effect a risk factor for the development of intraventricular hemorrhage in the preterm infant? Ultrasound Obstet Gynecol 8:329–332
146. Akalin-Sel T, Nicolaides KH, Peacock J, Campbell S (1994) Doppler dynamics and their complex interrelation with fetal oxygen pressure, carbon dioxide pressure, and pH in growth-retarded fetuses. Obstet Gynecol 84:439–444
147. Rizzo G, Capponi A, Pietropolli LM, Bufalino D, Romanini C (1994) Fetal cardiac and extracardiac flows preceding intrauterine death. Ultrasound Obstet Gynecol 4:139–142
148. Forouzan I, Zhi-Yun T (1996) Fetal middle cerebral artery blood flow velocities in pregnancies complicated by intrauterine growth restriction and extreme abnormality in umbilical artery Doppler velocity. Am J Perinatol 13:139–142
149. Baschat AA, Gembruch U, Harman CR (2001) The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol 18:571–577
150. Wladimiroff J, Huisman T, Stewart P (1991) Normal fetal arterial and venous flow-velocity waveforms in early and late gestation. In: Jaffe R, Warsof S (eds) Color Doppler imaging in obstetrics and gynecology. McGraw-Hill, New York, pp 155–173
151. Reed K (1991) Venous flow velocities in the fetus. In: Jaffe R, Warsof S (eds) Color Doppler imaging in obstetrics and gynecology. McGraw-Hill, New York, pp 175–181
152. Appleton C, Hatle L, Popp R (1987) Superior vena cava and hepatic vein doppler echocardiography in healthy adults. J Am Coll Cardiol 10:1032–1039
153. Reuss M, Rudolph A, Dae M (1993) Phasic blood flow patterns in the superior and inferior venae cavae and umbilical vein of fetal sheep. Am J Obstet Gynecol 145:70–78
154. Huisman T, van den Eijnde S, Stewart P et al (1993) Changes in inferior vena cava blood flow velocity and diameter during breathing movements in the human fetus. Ultrasound Obstet Gynecol 3:26–30
155. Reed K, Appleton C, Anderson C et al (1990) Doppler studies of vena cava flows in human fetuses. Circulation 81:498–505
156. Indik J, Chen V, Reed K (1991) Association of umbilical venous with inferior vena cava blood flow velocities. Obstet Gynecol 77:551–557

157. Rizzo G, Capponi A, Talone PE et al (1996) Doppler indices from inferior vena cava and ductus venosus in predicting pH and oxygen tension in umbilical blood at cordocentesis in growth-retarded fetuses. Ultrasound Obstet Gynecol 7:401–410
158. Nakai Y, Miyazaki Y, Masuoka Y (1992) Pulsatile umbilical venous flow and its clinical significance. Br J Obstet Gynaecol 99:977–980
159. Mitra SC (1995) Umbilical venous Doppler waveform without fetal breathing: its significance. Am J Perinatol 12:217–219
160. Reed KL, Chaffin DG, Anderson CF (1996) Umbilical venous Doppler velocity pulsations and inferior vena cava pressure elevations in fetal lambs. Obstet Gynecol 87:617–620
161. Ott WJ (1999) The value of fetal inferior vena cava blood flow analysis for prediction of neonatal outcome. Am J Perinatol 16:429–435
162. Ott WJ, Mora G, Arias F et al (1998) Comparison of the modified biophysical profile to a "new" biophysical profile incorporating the middle cerebral artery to umbilical artery velocity flow systolic/diastolic ratio. Am J Obstet Gynecol 178:1346–1353
163. Rizzo G, Capponi A, Talone PE, Ardunini D, Romanini C (1996) Doppler indices from inferior vena cava and ductus venosus in predicting pH and oxygen tension in umbilical blood at cordocentesis in growth-retarded fetuses. Ultrasound Obstet Gynecol 7:401–410
164. Rizzo G, Capponi A, Talone PE et al (1996) Doppler indices from inferior vena cava and ductus venosus in predicting pH and oxygen tension in umbilical blood at cordocentesis in growth-retarded fetuses. Ultrasound Obstet Gynecol 7:401–410
165. DeVore GR, Horenstein J (1993) Ductus venosus index: a method for evaluating right ventricular preload in the second-trimester fetus. Ultrasound Obstet Gynecol 3:338–342
166. Kiserud T, Eik-Nes SH, Blaas HGK et al (1991) Ultrasonographic velocimetry of the fetal ductus venosus. Lancet 338:1412–1414
167. Reed KL, Chaffin DG, Anderson CF (1996) Umbilical venous Doppler velocity pulsations and inferior vena cava pressure elevations in fetal lambs. Obstet Gynecol 87:617–620
168. Sherer DM, Fromberg RA, Divon MY (1996) Prenatal ultrasonographic assessment of the ductus venosus: a review. Obstet Gynecol 88:626–632
169. Kiserud T, Eik-Nes SH, Blaas HG et al (1994) Ductus venosus blood velocity and the umbilical circulation in the seriously growth-retarded fetus. Ultrasound Obstet Gynecol 4:109–114
170. Harrington KF (2000) Making best and appropriate use of fetal biophysical and Doppler ultrasound data in the management of the growth restricted fetus. Ultrasound Obstet Gynecol 16:399–401
171. Ogundipe EM, Wolfe CDA, Seed P et al (2000) Does the antenatal detection of small-for-gestational age babies influence their two-year outcomes? Am J Perinatol 17:73–81
172. Baschat AA, Gembruch U, Harman CR (2001) The sequence of changes in Doppler and biophysical parameters as severe fetal growth restriction worsens. Ultrasound Obstet Gynecol 18:571–577
173. Hecher K, Bilardo CM, Stigter RH, Ville Y, Hackeloer BJ et al (2002) Monitoring of fetuses with intrauterine growth restriction: a longitudinal study. Ultrasound Obstet Gynecol 19:564–570
174. Ferrazzi E, Bozzo M, Rigano S, Bellotti M, Morabito A, Pardi G et al (2002) Temporal sequence of abnormal Doppler changes in the peripheral and central circulatory systems of the severely growth-restricted fetus. Ultrasound Obstet Gynecol 19:140–146