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Jeffrey M. Dicke
Washington University School of Medicine in St. Louis
Phyllis Huettner
Washington University School of Medicine in St. Louis
Sida Yan
Washington University School of Medicine in St. Louis
Anthony Odibo
Washington University School of Medicine in St. Louis
Frederick T. Kraus
Washington University School of Medicine in St. Louis

Umbilical Artery Doppler Indices in Small for Gestational Age Fetuses

Correlation With Adverse Outcomes and Placental Abnormalities

Jeffrey M. Dicke, MD, Phyllis Huettner, MD, Sida Yan, Anthony Odibo, MD, Frederick T. Kraus, MD

Objective. The purpose of this study was to compare the screening efficiency of the umbilical artery systolic to diastolic ratio (S/D), pulsatility index (PI), and absent end-diastolic flow (AEDF) for adverse pregnancy outcomes and placental abnormalities in small for gestational age (SGA) fetuses. ***Methods.*** We conducted a retrospective cohort study of Doppler examinations of 161 nonanomalous SGA fetuses. The reliability of the S/D and PI were quantified by intraclass correlation coefficients. The association of the S/D, PI, and AEDF with adverse outcomes and placental abnormalities was compared by the χ^2 test. ***Results.*** There was a simple association of Doppler results with adverse outcomes, which was mitigated when controlled for gestational age. For all measures of adverse outcomes, the specificity of abnormal Doppler results exceeded the sensitivity, and the negative predictive value was greater than the positive predictive value. Comparing the S/D with the PI, there was no significant difference in the sensitivity; however, the specificity of the PI was at least 90% and exceeded that of the S/D for all outcomes. The intraclass correlation coefficients of the S/D and PI were similar, indicating no difference in reliability. Placental abnormalities were significantly more common in cases with abnormal Doppler values (positive predictive value, 94%) with no overlap in the types of placental lesions in most cases. ***Conclusions.*** As an initial screen for adverse outcomes in SGA fetuses, the umbilical artery Doppler S/D, PI, and AEDF were imprecise. However, these measures were all strongly and similarly predictive of placental abnormalities, especially lesions of maternal underperfusion and fetal vascular obstruction. ***Key words:*** placenta; small for gestational age; umbilical artery Doppler indices.

Abbreviations
AEDF, absent end-diastolic flow; IUGR, intrauterine growth restriction; LR, likelihood ratio; NICU, neonatal intensive care unit; NPV, negative predictive value; NRFS, nonreassuring fetal status; PI, pulsatility index; PPV, positive predictive value; S/D, systolic to diastolic ratio; SGA, small for gestational age

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Address correspondence to Jeffrey M. Dicke, MD, Department of Obstetrics and Gynecology, Division of Maternal-Fetal Medicine, Washington University School of Medicine, 4990 Children's Pl, Suite 1130, St Louis, MO 63110 USA.
E-mail: dickej@wustl.edu

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Doppler velocimetry of the umbilical artery is often used as the initial maneuver to distinguish small but normally growing fetuses from pathologically small fetuses due to aberrant uteroplacental perfusion.[1,2] This is accomplished by assessing impedance to blood flow in the umbilical artery with resistance indices, including the systolic to diastolic ratio (S/D) and pulsatility index (PI). Although both the S/D and PI have been used, there is little information as to which is the optimum measure.[3,4] In this study, the reliability and screening efficiency of the umbilical artery S/D and PI were compared with each other, and both were compared with absent end-diastolic flow (AEDF) as markers for adverse outcomes and placental abnormalities in a population of small for gestational age (SGA) fetuses.

Materials and Methods

This was a retrospective cohort study of sonographically dated nonanomalous singleton pregnancies greater than 27.0 weeks' gestation with estimated fetal weights below the 10th percentile based on growth curves formulated at this institution, which have been used for the last 20 years. This study was approved by the Human Research Protection Office at Washington University. Pregnancies were dated by menstrual age if corroborated by sonography at less than 22 weeks. If the menstrual age was uncertain or differed by greater than 7 days in the first trimester or greater than 10 days in the second trimester, the sonographic gestational age was used. Patients were scanned in the ultrasound units of the Department of Obstetrics and Gynecology, and all examinations were interpreted by the attending sonologists. The study period was from December 2003 to June 2007.

The Doppler results used were those obtained at the last sonographic examination performed before delivery. In cases in which the Doppler results were abnormal, Doppler studies were performed within 1 week of delivery. All waveforms were obtained from a free loop of umbilical cord during periods of fetal quiescence in the absence of breathing and movement. Color pulsed Doppler studies were performed with 3.5- and 5.0-MHz curved array probes (Sonoline Elegra and Acuson Sequoia; Siemens Medical Solutions, Mountain View, CA). At a minimum, 3 measurements were obtained, and the mean values were used. Doppler results were classified as follows: (1) normal (S/D <95th percentile or S/D and PI <95th percentile); (2) abnormal (S/D >95th percentile or S/D and PI >95th percentile)[5,6]; (3) discordant (S/D >95th percentile and PI <95th percentile; there were no cases where the PI was >95th percentile and the S/D was <95th percentile); and (4) AEDF. There were no cases with persistent reversed end-diastolic flow. Perinatal outcomes were grouped as follows: (1) composite morbidity (≥1 of the following: 5-minute Apgar score <7, umbilical artery PH <7.1, seizures, grade 3 or 4 intraventricular hemorrhage, hyaline membrane disease, bronchopulmonary dysplasia, need for respiratory therapy >48 hours, and perinatal death); (2) hypoxic morbidity (≥1 of the following: seizures, 5-minute Apgar score <7, umbilical artery PH <7.1, and perinatal death); (3) nonreassuring fetal status (NRFS) as an indication for delivery; and (4) neonatal intensive care unit (NICU) admission.

The reliability of the S/D and PI was compared by decomposition of variation into 2 parts: among repeated measurements within each patient and between operators. The intraclass correlation coefficient was used to quantify the reliability of S/D and PI measurements. The association of Doppler results with the above binary (yes and no) outcomes was determined in 2 ways. First, the difference in the proportion of adverse outcomes in each of the Doppler groups was compared by the χ^2 test for their statistical significance; $P < .05$ was considered statistically significant. Second, because gestational age is a known confounding factor, a logistic regression model was used to determine the association of umbilical artery Doppler results with perinatal outcomes, adjusting for gestational age at delivery.

Placental abnormalities were assessed by retrieving pathologic reports and microscope slides from departmental files. Placental weights and gross abnormalities were tabulated from reports. Microscope slides from each placenta were examined in random order by 2 pathologists blinded to the different clinical groups simultaneously and using a double-headed microscope. Histopathologic diagnoses were classified and tabulated according to standard nosologic criteria.[7–9] A diagnostic consensus was reached by the 2 pathologists as tabulations were made.

Placental abnormalities were grouped and collated into 6 categories: (1) lesions of maternal underperfusion, including infarcts, decidual vasculopathy (acute atherosis and poor vascular physiologic changes), distal villous hypoplasia, and increased syncytial knots (Figure 1); (2) fetal vascular obstructive lesions, including fetal thrombotic vasculopathy (large fetal vessel thrombi, avascular villi, intimal vascular fibrin "cushions," and villous stromal-vascular karyorrhexis) and chronic villitis with obliterative fetal vasculopathy (Figure 2); (3) lesions causing reduced placental reserve, including extensive perivillous fibrin and extensive chronic villitis (Figure 3); (4) dysmorphic villous changes, including mesenchymal increases, villous edema,

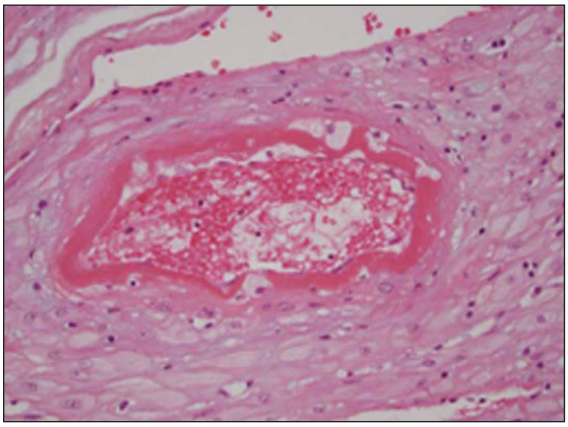


Figure 1. Decidual vasculopathy (acute atherosis) is characterized by fibrinoid necrosis of the vessel wall, a few foamy macrophages in the wall, and occlusion of the lumen by strands of fibrin (original magnification ×300).

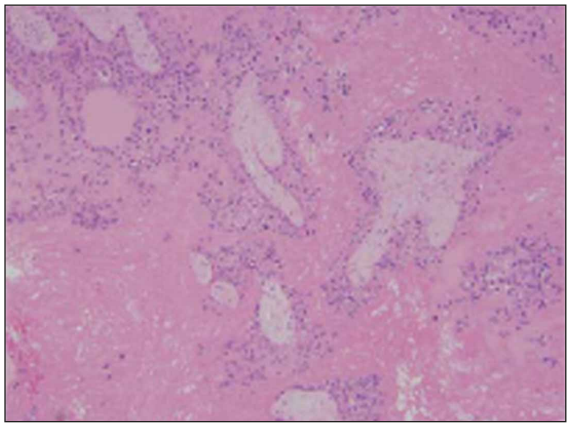


Figure 3. Massive perivillous fibrin. Degenerating villi are separated and surrounded by massive deposits of matrix-type fibrinoid. The syncytiotrophoblast layer has disappeared, and strands of cytotrophoblast cells migrate into the fibrinoid (original magnification ×150).

villous immaturity, villous maturation defects with reduced numbers of vasculo-syncytial membranes,[10] increased villous capillaries, and villous enlargement with markedly irregular villous shapes (Figures 4 and 5); (5) infections (acute chorioamnionitis); and (6) no abnormalities or minor abnormalities that appeared unimportant or insufficient to explain the occurrence of intrauterine growth restriction (IUGR).

Results

There were 161 fetuses meeting inclusion criteria, 80 of whom had both S/D and PI assessments. The number of patients in each group and pregnancy characteristics are listed in Table 1. Hypertensive disorders and preterm delivery (<32 weeks) were more common in pregnancies with an abnormal S/D, PI, and AEDF. All fetuses in these groups had birth weights of less than the 10th percentile versus 64% of fetuses with a normal S/D and PI.

The reliability of the umbilical artery S/D and PI were compared by intraclass correlation coefficients, which were 75.5% for the S/D and 75.8% for the PI. This indicates that the ratios of the between-subject variation over the total variation were similar for both the S/D and PI, and there was no difference in reliability. In 14 of the 80 cases (17.5%) with both the S/D and PI,

Figure 2. Fetal thrombotic vasculopathy. The cluster of avascular fibrotic villi at the left contrasts with the normal villi at the right margin. The larger-stem villus (center) shows obliterated vessels and extravasated red blood cells (original magnification ×150)

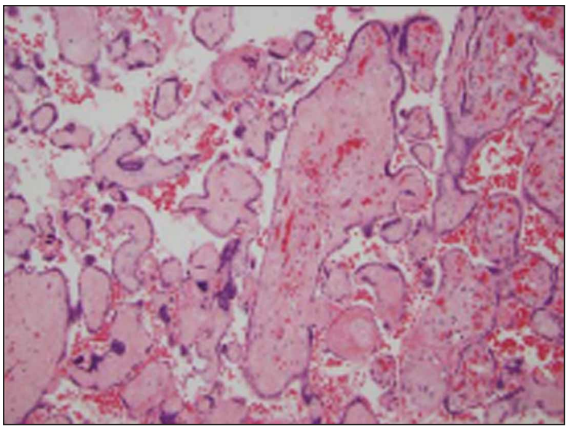
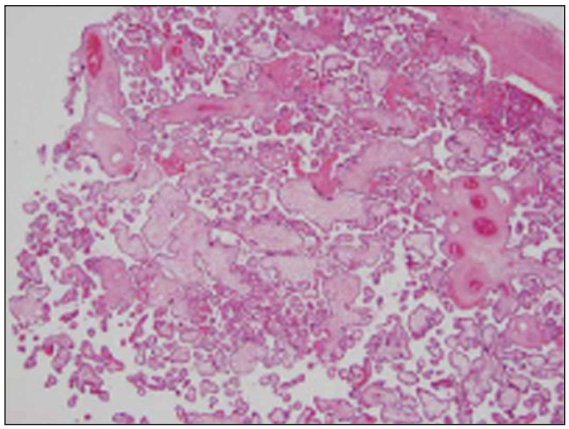


Figure 4. Dysmorphic villi greatly enlarged with abundant loose stroma and irregular bizarre outlines scattered throughout the field. The capillary vessels are scattered in the stroma, ineffective for gas and nutritional exchange (original magnification ×50).



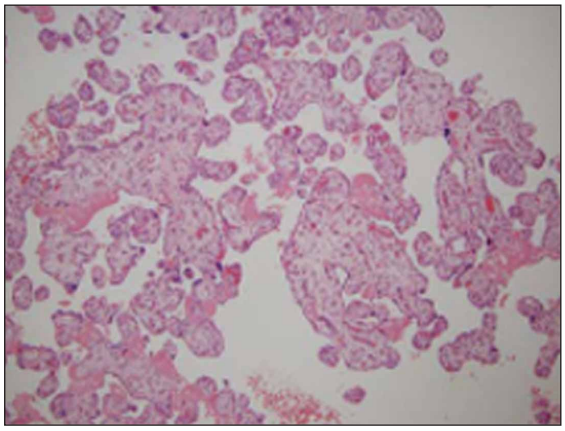


Figure 5. Placental maturation defect: higher magnification. The small vessels surrounded by edematous stroma are not capable of conducting nutritional or gas exchange (original magnification ×100).

the S/D was elevated, whereas the PI was normal. There were no cases in which the PI was elevated but the S/D was normal. The association of umbilical artery Doppler results with adverse outcomes is shown in Table 2. For all categories other than hypoxic morbidity, there was a significant trend toward adverse outcomes with worsening Doppler results. When Doppler results and outcomes were controlled for gestational age, however, there was no significant association with composite morbidity, hypoxic morbidity, or NICU admission. There remained a significant association between abnormal Doppler results and NRFS as an indication for delivery.

The screening efficiency of umbilical artery S/D and PI values above the 95th percentile and AEDF for adverse outcomes is shown in Tables 3 and 4. For all measures of adverse outcomes, there was no significant difference in the sensitivity of the S/D, PI, and AEDF. A post hoc power analysis showed that at an α level of .05, a sample size of 80 had a .95 power to detect a difference in the sensitivity between the groups. The specificity values of AEDF and the PI were similar and greater than the specificity of the S/D. The positive predictive value (PPV) and positive likelihood ratio (LR) of AEDF for composite morbidity and NICU admission were greater than those of the S/D and similar to those of the PI. The negative LR was not in a clinically useful range for any of the Doppler results.

A total of 146 cases had pathologic slides available for review. The types and frequencies of placental abnormalities are listed in Table 5. There were no significant differences in the frequencies of placental abnormalities between cases with S/D and PI values above the 95th percentile and AEDF; therefore, they were combined. Eleven cases with discordant Doppler results (S/D >95th percentile and PI <95th percentile) were not included because of an inability to classify them as normal or abnormal. Of these 11, 7 (64%) had placental abnormalities. The most common findings in both the normal and abnormal Doppler groups were lesions of maternal underperfusion and fetal vascular obstructive lesions, although these abnormalities were considerably more common in the cases with an abnormal S/D, PI, and AEDF. There were no differences in the frequencies of lesions causing reduced placental reserve and dysmorphic villous changes. In most cases (88%), there was a single pathologic process with no overlap in the lesions identified. Overlap was not more likely in cases with abnormal Doppler results than in cases with normal Doppler results. The screening umbilical artery Doppler parameters for placental abnormalities were as follows: sensitivity, 42.1%; specificity, 89.3%; PPV, 93.8%; negative predictive value (NPV), 28.7%; positive LR, 3.9; and negative LR, 0.65. Similar to the findings for adverse outcomes, the specificity was much higher than the sensitivity. Unlike application of the Doppler indices to adverse outcomes, the PPV of abnormal Doppler indices for placental lesions was much greater than the NPV.

Table 1. Study Population Characteristics

	Pregnancy Complications, n (%)			
Doppler Results	Hypertensive Disorders[a]	Diabetes Mellitus[b]	Delivery at <32 wk	Birth Weight <10%
Normal (n = 95)	31 (32.6)	7 (7.4)	13 (13.7)	61 (64.2)
Discordant (n = 14)	5 (35.7)	1 (7.1)	1 (7.1)	11 (78.6)
Abnormal (n = 18)	12 (66.7)	1 (5.6)	5 (27.8)	18 (100)
AEDF (n = 34)	19 (55.9)	4 (11.8)	21 (61.8)	34 (100)

Normal indicates S/D or S/D and PI less than 95th percentile; discordant, S/D greater than 95th percentile and PI less than 95th percentile; and abnormal, S/D or S/D and PI greater than 95th percentile.
[a]Preeclampsia and chronic hypertension.
[b]Gestational and insulin dependent.

Discussion

Umbilical artery Doppler assessment is used as a means of segregating small fetuses with abnor-

Table 2. Umbilical Artery Doppler Results and Adverse Outcomes

Doppler Results	Composite Morbidity, n (%)	Hypoxic Morbidity, n (%)	NRFS Indication for Delivery, n (%)	NICU Admission, n (%)
Normal (S/D or S/D and PI <95%)	24/95 (25.3)	6/95 (6.3)	21/95 (22.1)	19/95 (25.7)
Discordant (S/D >95%, PI <95%)	4/14 (28.6)	1/14 (7.1)	5/14 (35.7)	2/13 (15.4)
Abnormal (S/D or S/D and PI >95%)	7/18 (38.9)	2/18 (11.1)	8/18 (44.4)	6/18 (33.3)
AEDF	23/34 (67.7)	6/34 (17.7)	19/34 (55.9)	21/33 (63.6)
P	.0002	.2202	.0025	.0005

mal placentas from small fetuses with healthy placentas. Two commonly used measures of resistance to blood flow, the S/D and PI, were similarly reliable. The risk of adverse outcomes increased with worsening Doppler results. When controlled for gestational age, these trends became insignificant other than for NRFS as an indication for delivery. The major morbidities in this population were largely a function of prematurity and not consistently predicted by abnormal umbilical artery Doppler indices, regardless of whether end-diastolic flow was present or absent.

In a retrospective review of 56 pregnancies with absent or reversed end-diastolic flow, Zelop et al[11] reported that reversed end-diastolic flow and oligohydramnios were predictors of nonsurvival but that gestational ages at diagnosis and delivery were the major determinants of perinatal mortality. In a prospective multicenter study of 604 fetuses with placenta-based growth restriction delivered at less than 33 weeks' gestation, Baschat et al[12] reported that gestational age and birth weight were the best predictors of intact survival. Specifically, a gestational age of 29 weeks 2 days and a birth weight of 600 g were the thresholds beyond which only the presence or absence of forward flow in the ductus venosus was a significant determinant of intact survival among multiple perinatal variables. The presence of end-diastolic flow in the umbilical artery was significantly higher in those pregnancies with intact survival, although there were no differences in the percentages of patients with AEDF between intact and nonintact survivors.[12]

We found no significant differences between the umbilical artery S/D and PI with respect to

Table 3. Screening Efficiency of Umbilical Artery Doppler Results and Morbidity

Parameter	Composite Morbidity			Hypoxic Morbidity		
	AEDF	S/D >95%	PI >95%	AEDF	S/D >95%	PI >95%
Sensitivity, %	40 (27–53)	43 (22–66)	24 (8–47)	13 (16–68)	43 (10–82)	29 (4–71)
Specificity, %	89 (82–95)	76 (63–86)	93 (84–98)	81 (74–87)	73 (61–82)	90 (81–96)
PPV, %	68 (50–83)	39 (20–62)	56 (21–86)	18 (7–35)	13 (3–34)	22 (3–60)
NPV, %	72 (64–80)	79 (66–89)	78 (66–87)	93 (87–97)	93 (83–98)	93 (84–98)
LR+	3.7 (2.0–7.1)	1.8 (0.92–3.5)	3.5 (1.0–11.9)	2.1 (1.0–4.2)	1.6 (0.62–4.0)	3.0 (0.76–11.7)
LR–	0.67 (0.57–0.77)	0.75 (0.64–0.84)	0.94 (0.86–0.98)	0.74 (0.63–0.83)	0.63 (0.47–0.77)	0.79 (0.69–0.87)

Values are means (95% confidence intervals).

Table 4. Screening Efficiency of Umbilical Artery Doppler Results and NRFS or NICU Admission

Parameter	NRFS as Indication for Delivery			NICU Admission		
	AEDF	S/D >95%	PI >95%	AEDF	S/D >95%	PI >95%
Sensitivity, %	36 (23–50)	38 (10–59)	17 (5–37)	44 (30–59)	35 (14–62)	24 (7–50)
Specificity, %	86 (78–92)	75 (62–86)	91 (80–97)	87 (79–93)	69 (54–81)	90 (78–97)
PPV, %	56 (38–73)	39 (20–62)	44 (14–79)	64 (45–80)	27 (11–50)	44 (14–79)
NPV, %	73 (65–81)	74 (60–85)	72 (60–82)	75 (66–83)	76 (61–87)	78 (65–88)
LR+	2.6 (1.4–4.7)	1.5 (0.75–3.0)	1.9 (0.55–6.4)	3.4 (1.8–6.3)	1.1 (0.53–2.4)	2.4 (0.71–7.8)
LR–	0.74 (0.64–0.83)	0.84 (0.74–0.91)	0.91 (0.83–0.96)	0.65 (0.53–0.74)	0.94 (0.86–0.98)	0.84 (0.75–0.91)

Values are means (95% confidence intervals).

Table 5. Umbilical Artery Doppler Results and Placental Abnormalities

Abnormality	Normal (n = 87)	Abnormal (n = 48)
Lesions of maternal underperfusion, %	27.6 (18.5–38.2)	50.0 (35.2–64.8)
Fetal vascular lesions, %	14.9 (8.2–24.2)	27.1 (15.3–41.8)
Lesions causing reduced placental reserve, %	8.0 (3.3–15.9)	10.4 (3.5–22.6)
Dysmorphic villous changes, %	12.6 (6.5–21.5)	6.3 (1.3–17.2)
Chorioamnionitis, %	8.0 (3.3–15.9)	0
Total	71.3 (60.6–80.5)	93.8 (82.8–98.7)
None	28.7 (19.5–39.4)	6.2 (1.3–17.2)

Values in parentheses are 95% confidence intervals

screening efficiency other than specificity, which was significantly greater for the PI for all measures of adverse outcomes. This is reflected in the finding that in 18% of cases, the S/D was elevated but the PI was normal, whereas there were no cases in which the PI was elevated but the S/D was normal. The lower probability of misidentifying a fetus as at risk when using the PI is an argument for its use over the S/D as the preferred measure of resistance to blood flow in the umbilical artery. For AEDF and S/D and PI values above the 95th percentile, the absence of adverse outcomes was more reliably predicted than their occurrence. In this respect, umbilical artery Doppler indices mimic other tests of fetal well-being because we are more adept at identifying noncompromised fetuses than fetuses likely to have intrapartum or neonatal morbidity as a result of placental abnormalities.

Although abnormal Doppler indices were suboptimal measures of the fetal condition, they were strongly associated with placental abnormalities. Ninety-four percent of cases with either an S/D or a PI above the 95th percentile or AEDF had evidence of placental injury, the most common being vascular patterns characteristic of maternal underperfusion or fetal vascular obstruction. In most cases (88%), regardless of the Doppler results, there was a single pathologic process with no overlap of lesions.

A similar classification of placental lesions and their association with IUGR was described by Redline.[13] In his series of 66 cases, maternal vascular lesions were most common (47%), whereas patchy/diffuse villitis (20%) and perivillous fibrin deposition (17%) were both more common than fetal vascular obstruction (11%). These findings were not correlated with umbilical artery Doppler results. Madazli et al[14] reported the frequency of placental lesions in 47 IUGR fetuses, 28 of whom had a PI of greater than 2 SDs above the mean. There was a significant increase in the number of villous infarcts, cytotrophoblast proliferation, and thickening of the villous basement membrane in the abnormal Doppler group. However, multiple lesions were noted in most of these cases, and there was a higher percentage of maternal lesions and smaller number of fetal lesions than in our population. Viero et al[15] reported placental pathologic findings in 57 IUGR fetuses with absent or reversed end-diastolic flow. In 93% of their cases, 1 or more lesions were identified, and the frequency of fetal vasculopathy was only 5%.

Although gestational age is a more important determinate of the clinical outcome than umbilical artery Doppler results, Doppler interrogation provides valuable insights into the pathologic processes associated with many cases of abnormal fetal growth. Our results extend current knowledge of the relationship between small fetal size, placental abnormalities, and Doppler assessment of the umbilical artery. Compared with other studies, the number of cases examined in our series was larger and included both elevated S/D and PI values and AEDF. Most were associated with a single dominant lesion, with most of these being defects of maternal perfusion and fetal vascular obstruction. The placental lesions most commonly associated with abnormal Doppler values were those that could be expected to have a considerable impact on fetal growth. Additionally, 10% of our cases were associated with dysmorphic villous changes, abnormalities not described in other similar studies. Such changes may be underappreciated factors in suboptimal fetal growth (Figures 4 and 5). The cause and importance of the dysmorphic villous

patterns are unsettled at this time. Some of the villous abnormalities appear to correlate with stillbirth.[10] The pattern of enlarged irregular outlines resembles changes related to chromosomal abnormalities such as triploidy (Figure 4); the possibility of confined placental mosaicism deserves consideration. Large villi with increased edematous stroma and numerous vessels resemble some of the features of mesenchymal dysplasia. The pattern of a "maturation defect" has reportedly been associated with a marked increase in the risk of stillbirth[10] as well as extreme degrees of umbilical cord hypercoiling and increased nucleated red blood cell counts, suggestive of fetal hypoxia or ischemia.[16]

The observation that abnormal umbilical artery Doppler indices better reflect placental rather than fetal injury is not surprising because the elevated waveforms obtained reflect fetal placental vascular resistance. Although increased resistance to blood flow within the placenta along with its attendant consequences on nutrient provision to the fetus is the underlying pathologic condition in many fetal growth abnormalities, the mechanisms of such resistance vary. Fifty percent of our cases with abnormal Doppler indices had villous and intervillous lesions resulting in maternal underperfusion. Such insults are often secondary to aberrant trophoblastic infiltration and implantation. These abnormalities occur early in pregnancy, meaning that these placentas are destined to underachieve, often with demonstrable effects on fetal growth. Fetal vascular obstructive lesions were found in 27%. Placental lesions resulting in obstruction of the fetal circulation are caused by circulatory stasis, vascular injury, and hypercoagulability. Both of these abnormalities were strongly associated with an abnormal S/D, PI, and AEDF. They should alert the clinician to the existence of pathologic processes that can evolve as the pregnancy progresses, with effects not only on perinatal health but also on adult predisposition to chronic illnesses such as cardiovascular and metabolic disorders.

Appropriate additional evaluation and treatment of small fetuses with abnormal umbilical artery Doppler values is a subject of vigorous investigation. Doppler interrogation of other vessels, including the fetal middle cerebral artery, umbilical vein, ductus venosus, and maternal uterine artery, has been proposed in an attempt to reliably identify pathologically growth-restricted fetuses, standardize treatment, and predict outcomes. Tests of fetal well-being are also incorporated into assessment of SGA fetuses in an attempt to place abnormal umbilical artery Doppler values in the proper clinical context. However, the optimum combination of the above tests and the weight assigned to each remain to be determined.

In summary, as with other measures of the fetal status, umbilical artery Doppler indices are more likely to correctly identify noncompromised rather than at-risk fetuses, with gestational age being the key determinant of the outcome. Applied to SGA fetuses, the umbilical artery S/D and PI are equally reliable. Because of its greater specificity, the PI is arguably preferable to the S/D. Compared with both the S/D and PI, AEDF was not clearly superior in predicting adverse neonatal outcomes. Abnormal umbilical artery Doppler results, regardless of whether end-diastolic flow was present or absent, did reliably identify small fetuses whose placentas were abnormal. Although the Doppler changes usually occurred before overt fetal impairment, they should alert clinicians to the probability of an ongoing process of placental vascular changes with detrimental effects on fetal growth and well-being.

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