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UTEROPLACENTAL DOPPLER FLOW VELOCITY WAVEFORM INDICES IN NORMAL PREGNANCY: A STATISTICAL EXERCISE AND THE DEVELOPMENT OF APPROPRIATE REFERENCE VALUES

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ABSTRACT

In a prospective cross-sectional study, we examined 154 normal pregnant women and measured the systolic to diastolic (S/D) ratio and resistance index (RI) in the umbilical artery and both uterine arteries. Placental location with respect to laterality was determined by real-time ultrasound. In patients with unilateral placental location, each uterine artery was evaluated according to its relationship with the placenta. Doppler flow velocity waveforms were obtained by a continuous wave Doppler device. Kolmogorov D tests revealed that RI values follow gaussian distribution, but that S/D values were markedly skewed to the right. There was a significant negative linear relationship between gestational age and umbilical artery RI and a significant negative curvilinear relationship between gestational age and umbilical artery (S/D ($r = 0.83$, $p < 0.001$; and $r = -0.79$, $p < 0.001$, respectively). Confidence bands for umbilical artery RI were developed based on the linear model with gestational age (fitted umbilical artery RI = 0.97199 − 0.01045*gestational age). Confidence bands for umbilical artery S/D were derived from the corresponding RI values by means of the functional relationship S/D = 1/(1 − RI). The RI and S/D values of the uterine arteries declined until 24 to 25 weeks' gestation and remained unchanged thereafter. This relationship, however, was not statistically significant ($r = -0.10$, $p = 0.22$). The placental uterine artery is different from the nonplacental quantitatively and qualitatively. We suggest that properly derived reference values should be used when Doppler flow velocity waveform analysis is utilized in the management of high-risk pregnancies.

The value of Doppler flow velocity waveform (FVW) analysis in various clinical conditions has been under intense investigation during the past 8 years. A number of clinical protocols have been completed, and the reported results indicate the existence of significant associations between uteroplacenta FVWs and perinatal outcome in a spectrum of clinical problems.[1–6] Despite all the effort made to evaluate the clinical significance of this new methodology, very little attention has been given to the development of appropriate normal reference values throughout gestation. Most of the reports have presented data on the umbilical artery (UA) only, whereas some examined only the uterine artery and some others examined both vessels. Various vessels were called "uterine artery" by different investigators, leading to highly variable reference values.

From all the resistance indices that have been proposed, the systolic velocity (S) to diastolic velocity (D) ratio (S/D ratio) seems to be the most popular, primarily because of its mathematical simplicity. A less popular but equally simple index is the resistance index (RI), known also by the name Pourcelot index [RI = (S − D)/S]. S/D ratio is the only index used by most, if not all, American investigators. Normal UA and uterine artery S/D ratio reference values for American patients have been published based on mixed and cross-sectional data.[7–9] The statistical

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methodology used, however, was improper because it was based in the assumption that S/D ratios follow a gaussian distribution. This false assumption renders the calculation of 95% confidence intervals by the formula mean ± 1.96 SD inappropriate.

The purpose of this prospective study was to evaluate the mathematical relationship between the RI and the S/D ratio and to develop normal reference values of these indices for the UA and both uterine arteries with the use of appropriate statistical methodology on data collected from a sample of American patients with known placenta location, since uterine artery resistance depends on the location of the placenta in relation to the uterine arteries.[10]

MATERIAL AND METHODS

A total of 173 patients were studied. The study subjects were recruited from the low-risk clinics of the Wake Forest University Medical Center (Reynolds Health Center and the Department of Clinics of North Carolina Baptist Hospital, Winston-Salem, NC). Nineteen patients were excluded from the final analysis for the following reasons: two fetuses were diagnosed as having congenital anomalies (severe holoprosencephaly and multicystic kidney) four neonates were small for gestational age (SGA), four were born prematurely but appropriate for gestational age, and four were premature and SGA. Five patients were lost to follow-up and delivery data were not available. The study was approved by the Clinical Research Practices Committee and all patients gave written informed consent.

All patients were examined once during their pregnancy. The gestational age of the subjects during the Doppler examination ranged from 16 to 42 weeks. Gestational age was determined by accurate menstrual history or ultrasound prior to 24 weeks or both. Doppler FVWs were obtained by means of a continuous wave Doppler device operating at a frequency of 4 MHz equipped with a real-time spectrum analyzer (Vasoflo 3, Sonicaid-Oxford Medical, Clearwater, FL). The maximum acoustic power of the instrument is 15 mW/cm^2 and the high-pass filter was set at 200 Hz. During fetal apnea, UA, FVWs were obtained from four different abdominal sites to assure representation of the entire cord length. The mean of four measurements was obtained in order to minimize the effect of the fetal heart variability.[11] Waveforms from the uterine arteries were obtained by placing the transducer at the level of the anterior superior iliac spine and 2 to 3 cm medially with the transducer pointing toward the parametrial area. By this technique, waveforms originating from the ascending uterine artery or the proximal portion of major arcuate arteries can be easily and reproducibly obtained. Two waveforms of similar quality were measured and the transducer was lifted and placed again in the same area and another two waveforms of similar quality were measured. The same procedure was repeated for the opposite uterine artery. The average of all four measurements was labeled mean uterine artery. When the placenta was located unilaterally, one of the uterine arteries was labeled as placental uterine artery and the other as nonplacental uterine artery. Placental and nonplacental uterine arteries represent the average of the two measurements on the corresponding side. The S/D ratio and the Pourcelot index were calculated from the highest systolic and the lowest end-diastolic velocities. The intraobserver coefficients of variation for the two examiners (A.D.K. and M.P.) were 6% and 8% for umbilical artery and 7% and 10% for uterine artery FVWs, respectively. When the same patient was examined by both observers within a few minutes, with the observers being blinded, the mean umbilical and mean uterine artery values were not different (Table 1).

Placental location was determined by real-time ultrasound. The methodology was described previously.[10] The placenta was classified as right, left, or central regardless of its anteroposterior and fundal position. For the purpose of analysis, the patients with right or left placentas were classified as having unilaterally located placentas. Placental location was determined without prior knowledge of the FVWs. The interobserver error in assignment of placental location was 9% during this study. We attribute the difference from our first report to increased familiarity with the classification method.

STATISTICAL METHODS

Means and frequency distributions were used to describe the distributions of UA and mean uterine artery RI and S/D ratios. The relationship of these parameters with gestational age was examined using plots and regression analysis. Kolmogorov D tests[12] were used to examine the adequacy of normal (gaussian) approximations for the empirical distributions. Confidence bands and percentiles were computed based on this approximation relative to the normal

Table 1. Comparisons of Umbilical Artery and Uterine Artery S/D Ratios Between the Two Observers*†

	No.	*Observer A.D.K. (Mean ± SD)*	*Observer M.P. (Mean ± SD)*	*p Value*
Umbilical artery S/D	20	2.48 ± 0.14	2.59 ± 0.20	>0.10
Uterine artery S/D	20	1.96 ± 0.13	1.95 ± 0.19	>0.10

*Wilcoxon signed-rank test.
†S/D: systolic to diastolic.

approximations. Student's *t*-tests were used for comparisons of RI values and Wilcoxon signed-rank tests for comparisons of S/D ratios. The results were considered statistically significant when $p < 0.05$.

RESULTS

Analysis of data was limited to 154 patients who were found to have uncomplicated pregnancies with optimal perinatal outcome (5-minute Apgar score 7 or higher, birthweight appropriate for gestation, gestational age at delivery 37 or more weeks, no intensive care unit admissions). Table 2 shows the clinical characteristics of the study population. The number of patients studied for each gestational age is portrayed in Figure 1. Frequency distributions of the UA and mean uterine artery S/D ratio and RI are given in Figure 2. The distributions for UA and mean uterine artery RI appeared to be quite symmetrical; in contrast, the distributions of UA and mean uterine artery S/D ratios were markedly skewed to the right.

A plot of UA RI versus gestational age revealed a strong negative linear trend (Fig. 3, upper panel). Regression analyses indicated that this relationship was statistically significant ($r = -0.83$, $p < 0.001$). No significant improvement in fit was obtained by adding a quadratic term to the model ($p = 0.60$), which indicated that there was little evidence for any curvature in the relationship. The relationship of mean uterine artery RI with gestational age appeared to be very weak (Fig. 4, upper panel). Mean uterine artery RI appeared to decrease slightly until about 24 weeks, to just below 0.50, and then to remain fairly stable for the rest of the pregnancy. However, neither a linear model ($r = 0.10$, $p = 0.22$) nor the addition of a quadratic term ($p = 0.08$) was statistically significant.

S/D ratio is functionally related to RI via the equation $S/D = 1/(1 - RI)$. If UA RI is assumed to be linearly related with gestational age, the relationship of UA S/D would be curvilinear, as plotted in Figure 3, lower panel. Mean uterine artery S/D ratio was found to be significantly correlated with gestational age ($r = -0.13$, $p = 0.24$; Figure 4, lower panel).

Confidence bands for UA RI were developed based on the linear model with gestational age (fitted UA RI = 0.97199 − 0.01045*gestational age). Confidence bands for mean uterine artery were developed based on unadjusted values, but since the mean uterine artery seemed graphically to vary with gestational age before 24 weeks, these bands were limited to gestational ages greater than 24 weeks. Kolmogorov D tests indicated that neither the UA RI residuals nor the unadjusted mean uterine artery RI values differed significantly from normal (gaussian) distributions ($p > 0.05$). Confidence bands for S/D ratios were computed based on their functional relationship with RI. Table 3 gives the fitted 5th, 50th, and 95th percentiles for UA RI and S/D ratios from 16 to 42 weeks' gestation and Figures 5 and 6 portray these percentiles for UA RI and S/D ratio. Table 4 gives the 50th and 95th percentiles of the uterine artery RI and S/D ratio after 24 weeks' gestation.

When the placenta is unilaterally located, comparison of the placental and nonplacental uterine artery FVW indices revealed statistically significant differences between the two vessels. In patients with centrally located placenta, however, the right uterine artery and the left uterine artery FVW indices were not statistically different (Table 5). Figure 7 is a plot of the placental and nonplacental uterine artery RI and S/D ratio against the gestational age to demonstrate the consistent differences between the two

Table 2. Clinical Characteristics of the Study Sample

Characteristic	*Mean ± SD*	*Range*
Maternal age (yr)	22.5 ± 5.0	25
Gravidity	0.7 ± 0.9	5
Parity	1.3 ± 0.1	8
Systolic arterial pressure (mmHg)	110.0 ± 10	60
Diastolic arterial pressure (mmHg)	64.0 ± 7	40
Gestational age at delivery (weeks)	39.3 ± 1.2	5
Birthtweight (gm)	3354 ± 474	2116
5-minute Apgar score	9 ± 0.5	3

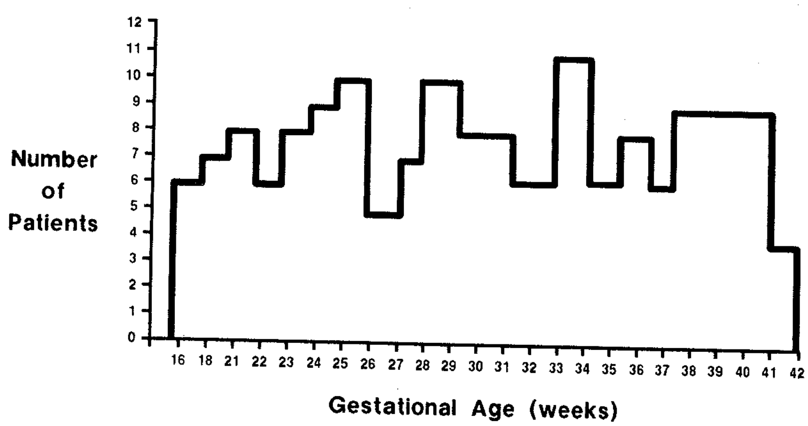

Figure 1. Frequency distribution of the 154 patients according to gestational age.

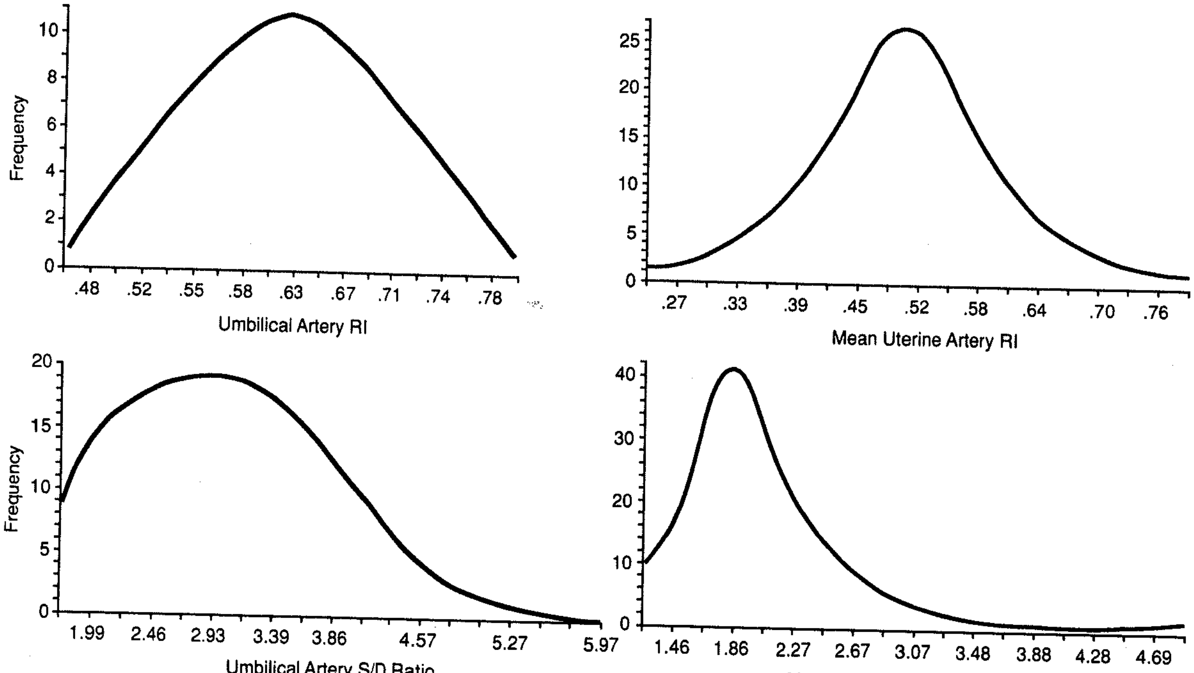

Figure 2. Frequency distribution of the umbilical and mean uterine artery resistance index (RI) and systolic to diastolic (S/D) ratio values derived from the 154 patients.

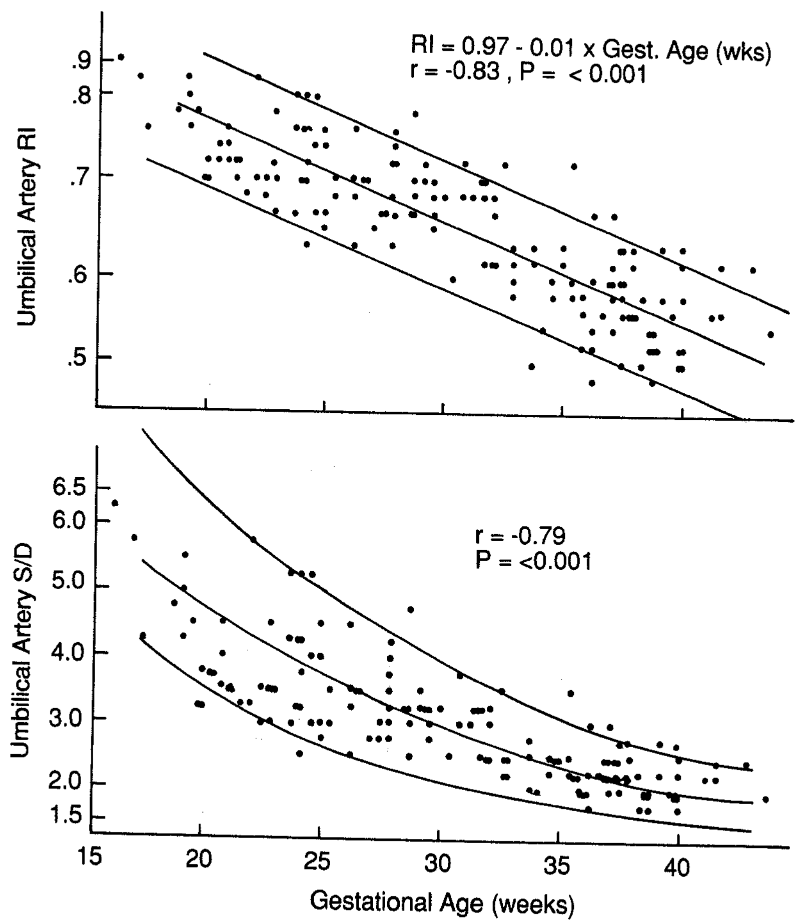

Figure 3. Regression analysis plots of the umbilical artery resistance index (RI) and systolic to diastolic (S/D) ratio against gestational age. Note the difference between the two indices in their relationship with gestational age.

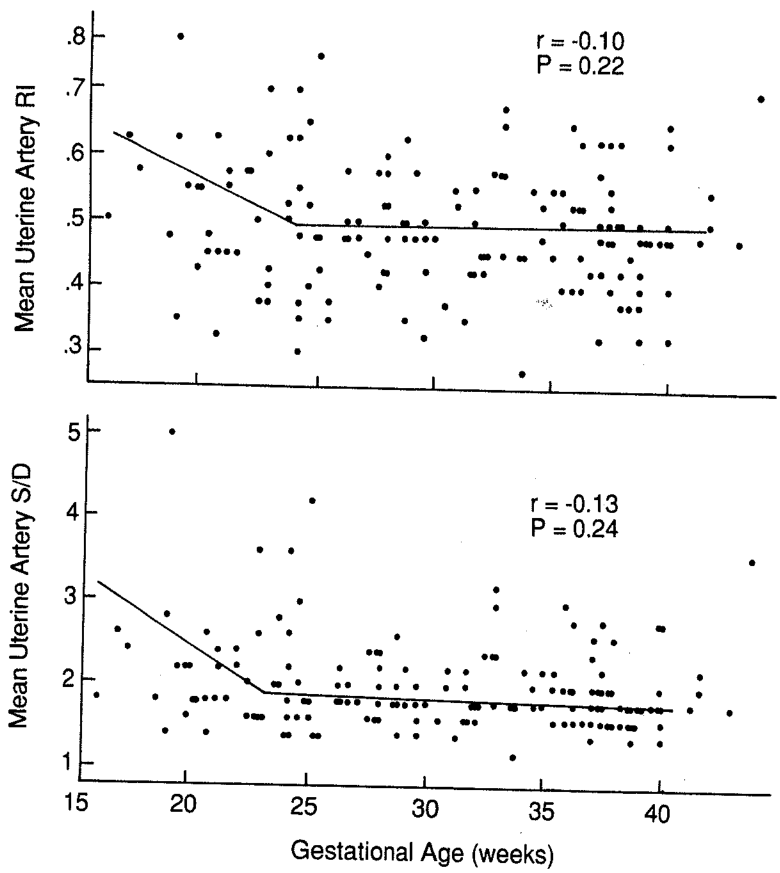

Figure 4. Regression analysis plots of the mean uterine artery resistance index (RI) and systolic to diastolic (S/D) ratio values against gestational age.

Table 3. Reference Values for Umbilical Artery RI and S/D Ratio from 16 to 42 Weeks Gestation

Gestational Age (Weeks)	*5th Percentile*		*50th Percentile*		*95th Percentile*	
	RI	*S/D*	*RI*	*S/D*	*RI*	*S/D*
16	0.70	3.33	0.80	5.00	0.90	10.00
17	0.69	3.23	0.79	4.76	0.89	9.09
18	0.68	3.13	0.78	4.55	0.88	8.33
19	0.67	3.03	0.77	4.35	0.87	7.69
20	0.66	2.94	0.76	4.17	0.86	7.14
21	0.65	2.86	0.75	4.00	0.85	6.67
22	0.64	2.78	0.74	3.85	0.84	6.25
23	0.63	2.70	0.73	3.70	0.83	5.88
24	0.62	2.63	0.72	3.57	0.82	5.56
25	0.61	2.56	0.71	3.45	0.81	5.26
26	0.60	2.50	0.70	3.33	0.80	5.00
27	0.59	2.44	0.69	3.23	0.79	4.76
28	0.58	2.38	0.68	3.13	0.78	4.55
29	0.57	2.33	0.67	3.03	0.77	4.35
30	0.56	2.27	0.66	2.94	0.76	4.17
31	0.55	2.22	0.65	2.86	0.75	4.00
32	0.54	2.17	0.64	2.78	0.74	3.85
33	0.53	2.13	0.63	2.70	0.73	3.70
34	0.52	2.08	0.62	2.63	0.72	3.57
35	0.51	2.04	0.61	2.56	0.71	3.45
36	0.50	2.00	0.60	2.50	0.70	3.33
37	0.49	1.96	0.59	2.44	0.69	3.23
38	0.47	1.89	0.57	2.33	0.67	3.03
39	0.46	1.85	0.56	2.27	0.66	2.94
40	0.45	1.82	0.55	2.22	0.65	2.86
41	0.44	1.79	0.54	2.17	0.64	2.78
42	0.43	1.75	0.53	2.13	0.63	2.70

RI: resistance index; S/D: systolic to diastolic.

uterine arteries, when the placenta is unilaterally located.

DISCUSSION

This report describes the first prospective cross-sectional study for the establishment of reference values for RI and S/D ratio of the UA and both uterine arteries in a sample of healthy pregnant American patients from 16 to 42 weeks' gestation. There exist two major differences between this report and the previous ones. First, the statistical methodology was appropriate for the data and, second, the two uterine arteries were examined separately from each other and in relation to placental location. Gundmundsson and Marsal[13] examined 125 Swedish women in a prospective cross-sectional study from the 20th to the 42nd week of gestation. Unlike others, they examined their data by obtaining two indices, the pulsatility index (PI) and the S/D ratio. Stuart et al[14] and Trudinger, et al[15] performed longitudinal studies and measured the S/D ratio, which they called the A/B ratio. Thompson et al[16] in a more recent report described the relationship among various Doppler indices; although they examined only patients during the last 10 weeks of pregnancy, they, too, found that only the RI values are normally distributed.

In all available studies[7-9,13-15] the reference values were obtained by grouping the patients in

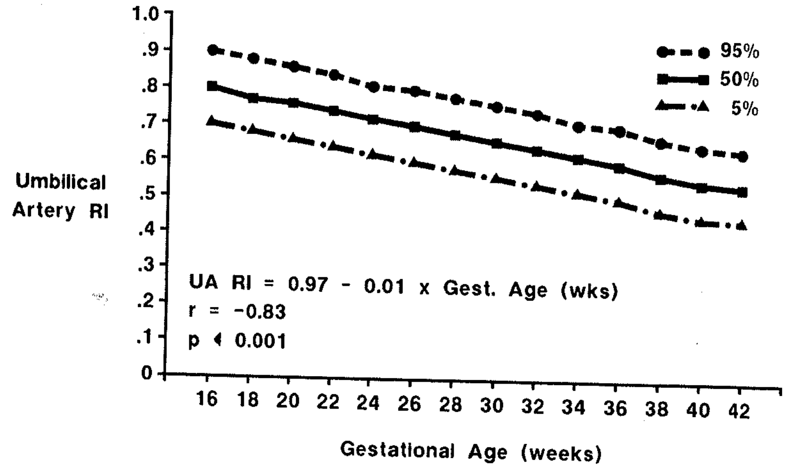

Figure 5. Graphic depiction of the 5th, 50th, and 95th percentiles of umbilical artery resistance index (RI) from 16 to 42 weeks' gestation.

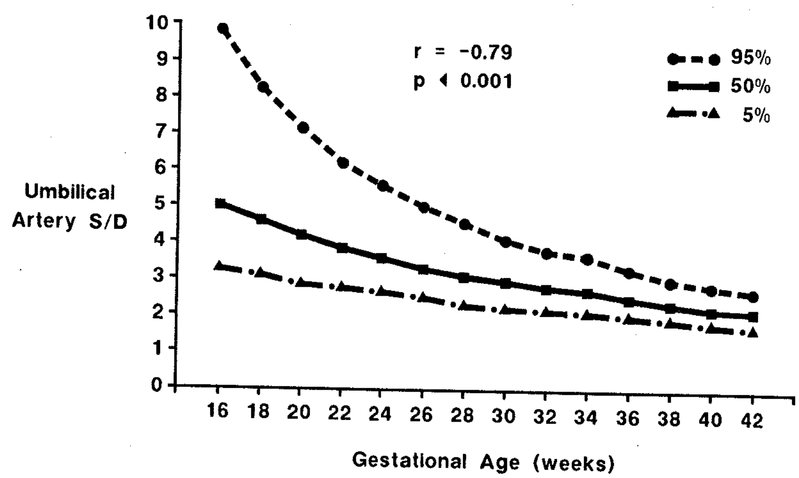

Figure 6. Graphic depiction of the 5th, 50th, and 95th percentiles of umbilical artery systolic to diastolic (S/D) ratio 16 to 42 weeks' gestation.

Table 4. 50th and 95th Percentiles of the RI and S/D Ratio After 24 Weeks for the Uterine Artery*

Vessel	*RI*		*S/D Ratio (Direct)*		*S/D Ratio Calculated from RI*†	
	50th%	*95th%*	*50th%*	*95th%*	*50th%*	*95th%*
MUtA	0.48	0.66	2.00	2.80	1.92	2.94
PUtA	0.41	0.60	1.74	2.30	1.69	2.50
NPUtA	0.52	0.77	2.34	3.70	2.08	4.35

*RI: resistance index; S/D: systolic to diastolic; MUtA: mean uterine artery; PUta: placental uterine artery; NPUtA: nonplacental uterine artery.

†Calculated by means of the formula S/D = 1/(1-RI).

Table 5. Comparisons of FVW Indices: Placental Versus Nonplacental Uterine Artery in Patients with Unilateral Placenta, and Right Versus Left in Patients with Centrally Located Placenta

Index	*Unilateral Placenta*			*Central Placenta*		
	PUta (Mean ± SD)	*NPUtA (Mean ± SD)*	*p Value*	*RUtA (Mean ± SD)*	*LUtA (Mean ± SD)*	*p Value*
S/D Ratio†	1.74 ± 0.30	2.34 ± 0.70	<0.0001	1.95 ± 0.53	2.00 ± 0.60	NS
RI‡	0.41 ± 0.10	0.54 ± 0.11	<0.0001	0.46 ± 0.11	0.48 ± 0.10	NS

*FVW: flow velocity waveform; PUtA: placental uterine artery; NPUtA: nonplacental artery; RUtA: right uterine artery; LUtA: left uterine artery; S/D: systolic to diastolic; RI: resistance index; NS: difference not significant.

†Wilcoxon signed-rank test.

‡Paired Student's *t*-test.

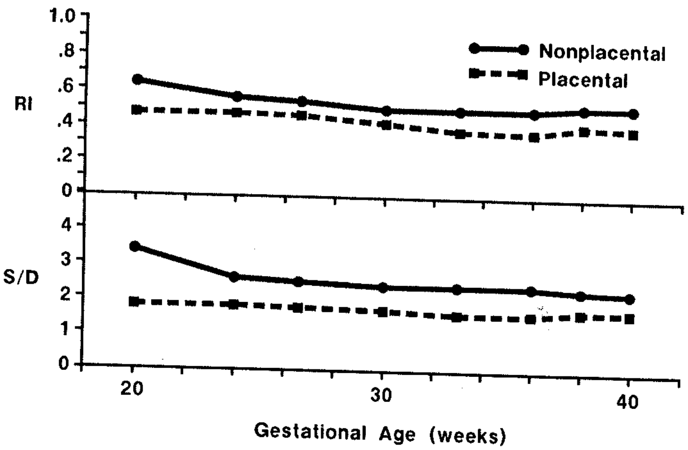

Figure 7. Placental and nonplacental uterine artery resistance index (RI) and systolic and diastolic (S/D) ratio against gestational age. Note the different compliance between the two vessels during pregnancy.

several gestational age subgroups and calculating the mean of the corresponding subgroup. Confidence bands were then calculated by adding or subtracting 2 SD to the mean of each particular subgroup. Confidence bands and fitted percentiles must reflect the underlying distribution of the data. For UA RI and mean uterine artery RI, this distribution could be assumed to be normal. This assumption leads to the traditional formula for a 95% confidence band: Mean ± 1.96 SD. If data do not follow a normal distribution, for example if they are markedly skewed, the above formula is incorrect. In the case of S/D ratio, this practice generates values that do not represent the reality and may affect the ability of the test to discriminate normal from abnormal patients. This effect is much more profound prior to 32 weeks of gestation: the true 95th percentile may be twice as high as the one generated by the addition of 1.96 SD to the mean value.

Regardless of the index used, it is quite evident that placental resistance in the umbilical vascular tree declines throughout pregnancy. The same is not true, however, for the uterine artery, which achieves the state of its lowest resistance at about 24 to 25 weeks' gestation and remains unchanged thereafter. This temporal relationship is in harmony with the completion of the trophoblastic invasion of the spiral arterioles around the 24th week of pregnancy. It is of interest, however, to notice that the placental uterine artery behaves differently than the nonplacental one. The resistance of the placental uterine artery becomes lowest at 18 to 20 weeks and remains unchanged throughout pregnancy. In contrast, the nonplacental uterine artery has significantly higher values earlier in pregnancy and declines continuously until the 25th week of pregnancy, remaining unchanged from that point on, and significantly higher than the placental uterine artery throughout the entire pregnancy.

In summary, this study evaluated the mathematical relationship between S/D ratio and RI. The data presented here demonstrate that S/D ratio is a quantity that does not follow a normal (gaussian) distribution and, if statistical analysis is performed that ignores this fact, the derived reference values will be incorrect and potentially harmful. Finally, this report represents reference values for the umbilical artery and for both uterine arteries derived from a prospective cross-sectional study. However, we would like to remind those who use FVW analysis for the management of high-risk pregnancies that the 95th percentile value is not necessarily the best cutoff point to discriminate between normal and abnormal.

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