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Changes in Placental Blood Flow in the Normal Human Fetus with Gestational Age

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ABSTRACT. We assessed fetoplacental blood volume flow and placental resistance prospectively with Doppler sonography in 74 normal human fetuses of 19 to 42 wk gestation to determine the changes in placental perfusion with gestational age. Placental blood volume flow was assessed from the umbilical vein as the product of the mean flow velocity integral and the cross-sectional area of the umbilical vein. Placental resistance was assessed as the ratio of maximum systolic and minimum diastolic blood flow velocities from an umbilical artery. Umbilical vein blood volume flow increased exponentially (r = 0.86) with gestational age from 19 wk to term, and did not decrease in postdate fetuses. Umbilical vein blood volume flow increased linearly with fetal weight (r = 0.77), although volume flow per unit body weight changed little with gestational age. Umbilical artery velocity ratio decreased progressively, indicating diminishing placental resistance with gestational age, but did not correlate closely with umbilical vein blood volume flow. We submit that fetoplacental blood volume flow can be readily calculated directly from the umbilical vein with Doppler ultrasound and may provide a better index of placental perfusion than the umbilical artery velocity ratio. (*Pediatr Res* 28: 383–387, 1990)

Normal fetal growth and viability depend directly upon the fetoplacental circulation for the supply of nutrients, gas, and metabolite exchange. Impaired placental blood flow has been shown to result in intrauterine growth retardation and increased perinatal mortality (1–4).

Since the initial observations that blood flow velocity in the umbilical cord could be measured in the human fetus (5–7), several attempts have been made to quantitate fetoplacental blood flow (8–16). These studies have assessed placental perfusion either as volume flow in the umbilical vein (8–11) or as a resistance to flow in one of the umbilical arteries (12–16). Previous estimates of volume flow have been calculated from Doppler velocity signals obtained with large or unknown angles between the ultrasound beam and the direction of blood flow. This results in underestimation of placental blood flow because Doppler estimates of velocity vary inversely with the cosine of this angle. Resistance to placental blood flow has traditionally been assessed as the ratio of systolic to diastolic blood flow velocity in the umbilical artery. Although this ratio appears to be useful clinically in differentiating fetuses with normal placental blood flow from those with placental insufficiency, its relation to placental blood volume flow has not been examined.

We assessed fetoplacental blood volume flow in 74 normal human fetuses using pulsed-wave Doppler. Our aims were 3-fold: *1*) to quantitate the changes in placental blood volume flow with gestational age and fetal body weight, *2*) to determine whether placental blood volume flow falls in postdate fetuses (greater than 40 wk), and *3*) to examine the relation between umbilical arterial velocity ratio and placental blood volume flow.

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MATERIALS AND METHODS

We studied 74 normal human fetuses ranging in age from 19 to 42 wk, whose mothers were referred for routine obstetric ultrasound examination to assess fetal gestational age and/or placental location. Mothers with diabetes, hypertension, preeclampsia, rhesus-incompatibility, multiple gestations, and previous fetuses with congenital malformations were excluded. Human fetuses were only included in this study if their biophysical profiles were normal for their gestational age and any congenital abnormalities involving the cardiovascular system or any other organ system were excluded. Each human fetus was studied only once to minimize any potential hazard from the Doppler ultrasound. Written informed consent was obtained from each mother, and the protocol was approved by the Brigham and Women's Hospital Human Subjects Committee.

Two-dimensional imaging and pulsed-wave Doppler flow studies were performed using a model 77020 AC/AR ultrasonoscope (Hewlett Packard Co., Palo Alto, CA) with either a 3.5-mHz or, more frequently, a 5.0-mHz transducer.

The transducer was placed on the maternal abdomen after the mother had rested semi-recumbent for 15 min, and each fetus was systematically scanned to insure that the heart, great vessels, umbilical cord, and placenta were normal and any congenital noncardiac anomaly was excluded. Fetal weight was estimated from measurements of biparietal diameter and abdominal diameter using a standard weight algorithm (17). Gestational age was assessed from the first day of the last menstrual period, and corroborated with measurements of biparietal diameter in the late 2nd or 3rd trimester.

The umbilical cord was located, and short axis images obtained in which the umbilical vein and both umbilical arteries were circular in cross-section (18) (Fig. 1). These images were recorded on videotape and later transferred onto the hard disc of a Franklin Quantic 1200 off-line analysis system, where umbilical vein diameter was measured from five to 10 cardiac cycles. Umbilical vein diameters were rounded off to the nearest mm and mean values were calculated. The reason that measurements of umbilical vein diameters were rounded off to the nearest mm is that the optimal axial resolution of a 5-mHz transducer is 0.7 mm, optimal lateral resolution is 1.6 mm, and optimal resolution in the elevation plane is similar. Thus, the maximum error introduced in umbilical vein diameter would be 0.5 mm, or 0.25 mm in radius. In the smallest fetus in our study (19 wk gestation), the umbilical vein diameter was 4 mm. A maximum error in diameter measurement of 0.5 mm would result in a 20.9% error in cross-sectional area and volume flow per min determinations. In a 40-wk gestation with an umbilical vein diameter of 10 mm, a maximum error in diameter measurement would result in a 10.1% error in cross-sectional area and volume flow per min. The minimum errors for these same fetuses at 19 and 40 wk would be 9.3 and 2.0%, respectively.

The umbilical vein was also imaged in its long axis and the Doppler pulsed-wave sample volume positioned within its lumen, where the diameter was measured, to sample the whole of the flow stream and not just the central core. We used pulsed-wave Doppler because it allowed us to visualize the umbilical vein and align the beam parallel to the direction of blood flow, and thus obtain accurate estimates of true velocity. The angle of incidence between the Doppler beam and the direction of blood flow was measured with the flow direction cursor, and recordings only analyzed when this angle was less than 20°. We chose 20° as a limit because this underestimates true velocity by no more than 8%. Velocity spectra with the maximum amplitude were recorded during periods of apnea because fetal respiratory movements may alter umbilical vein size and blood flow velocity (8, 10, 13). We used the microprocessor on the Hewlett Packard ultrasonoscope to display simultaneously the electronic maximum and mean blood flow velocities and the velocity spectral signal (Fig. 1). Mean velocity signals were digitized on the Franklin Quantic system to obtain flow velocity integrals for a minimum of 5 s in each fetus, and the mean value per s was calculated.

One of the umbilical arteries was imaged in its long axis, and the pulsed-wave Doppler sample volume positioned within its lumen, with the beam as close to parallel to the direction of blood flow as possible. The angle of incidence between the Doppler beam and the direction of blood flow was measured in each fetus, and recordings made only when it was less than 20° during fetal apnea. The highest velocities were obtained and the electronic maximum and mean and spectral signals were simultaneously recorded (Fig. 2). The velocity signals were digitized and the maximum systolic and the minimum diastolic velocities measured from 10 cardiac cycles, and their respective mean values calculated.

From the short axis two-dimensional echo images of the umbilical cord and the Doppler velocity signals from the umbilical vein and artery, the following values were calculated: *1*) cross-sectional area of the umbilical vein (CSAuv) (cm^2) from the umbilical vein diameter (D), CSAuv = (D/2); *2*) umbilical vein mean flow velocity integral (FVIuv) per s; *3*) placental blood volume flow (PBF) (mL/min) as the product of cross-sectional area of the umbilical vein and the flow velocity integral, PBF = CSAuv × FVIuv/s × 60; *4*) placental blood flow per unit fetal body weight (WT) (mL/min/kg), PBF/WT; and *5*) ratio of umbilical arterial (UA) maximum systolic (A) and minimum diastolic (B) velocities, UA(A/B).

Statistical analysis. The relations between umbilical vein diameter and gestational age, placental blood flow and gestational age, placental blood flow and fetal weight, and placental blood flow and umbilical arterial velocity ratio were assessed by regression analysis, and the correlation coefficients estimated by Pearson's method (19).

Interobserver and intraobserver variability of measurements of umbilical vein diameter in 25 fetuses was assessed by two observers. The regression equation of the comparison between measurements made by observer 1 and observer 2 demonstrated a correlation coefficient of 0.88, a regression equation, Y = 0.8271X + 0.104, and a standard error of the estimate of 0.068 cm. The regression equation for the comparison of intraobserver variability in 25 human fetuses was Y = 0.917X + 0.031. The correlation coefficient was 0.99 and the standard error of the estimate was 0.019 cm.

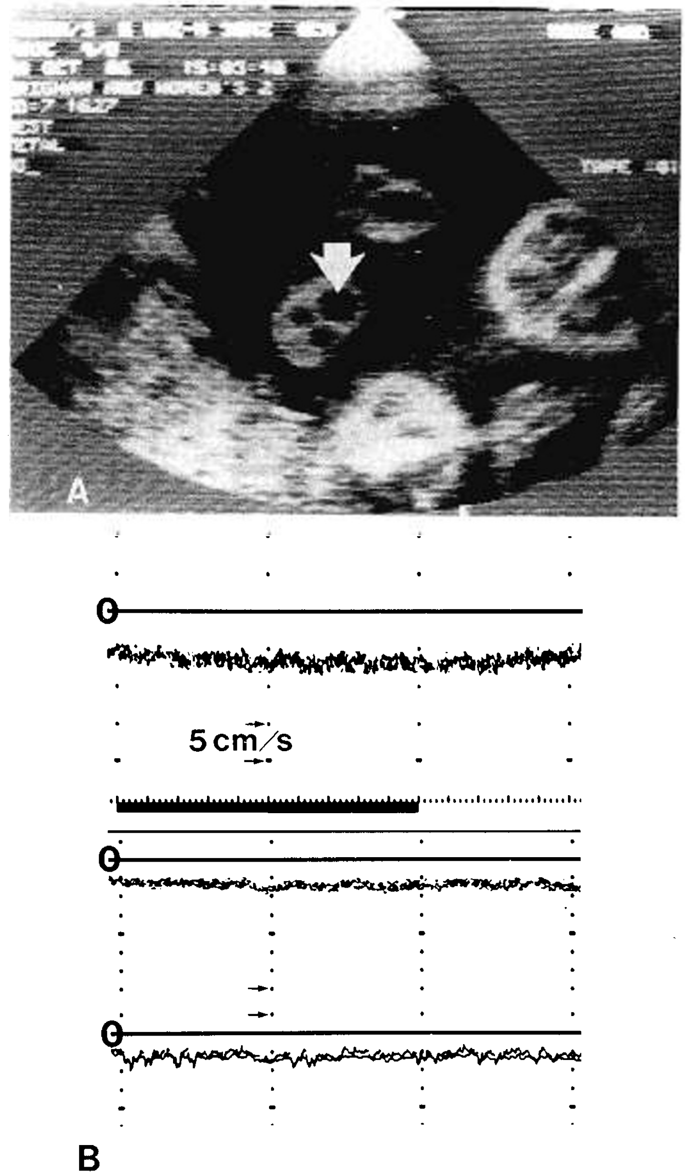

Fig. 1. *A*, ultrasound image of the short axis of the umbilical cord showing the umbilical vein (*white arrow*) and the two umbilical arteries, all three of which are circular in cross-section. *B*, the three tracings show the umbilical vein blood flow velocity spectral envelope, which is narrow and demonstrates laminar, nonpulsatile flow (*top*). Simultaneous recordings of spectral velocities (*middle tracing*) and the electronic maximum and mean flow velocities (*bottom tracings*). Note the electronic maximum and mean flow velocity amplitudes. The *black horizontal lines* represent zero (*0*) velocity. The velocity signals are all below the 0 line because the direction of blood flow is away from the transducer. The *calibration divisions* each represent 5 cm/s for all three tracings (*black arrows*).

RESULTS

Umbilical vein diameter increased linearly with age from 19 to 40 wk ($r = 0.83$) (Fig. 3). Fetal body weight was calculated only in fetuses older than 25 wk, because the algorithm used for weight determination is less reliable in younger fetuses (17), and increased linearly with gestational age ($r = 0.92$).

Umbilical vein blood flow velocity was low, the spectral velocity envelopes were narrow, and flow was nonpulsatile in all fetuses examined (Fig. 1). Umbilical vein peak velocity amplitude varied little with age, ranging from 7 to 23 cm/s. The narrow velocity spectral envelopes indicate that the range of velocities within the umbilical vein is small, such that the mean velocity and V_{max} are similar (Fig. 1). Previous studies have assumed that

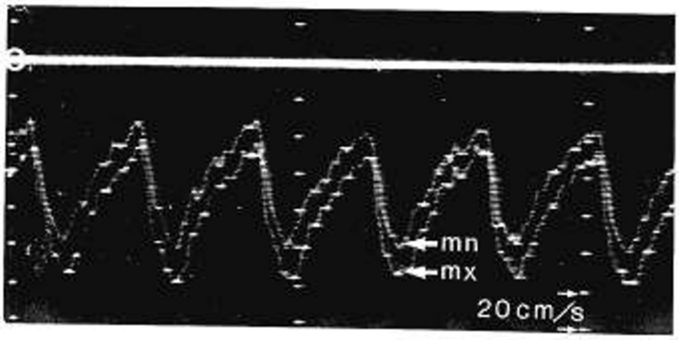

Fig. 2. The Doppler velocity recordings from the umbilical artery, with the electronic instantaneous maximum (*mx*) and mean (*mn*) velocities demonstrated. The *white horizontal lines* represent zero (*0*) velocity. *Each calibration division* represents 20 cm/s (*white arrows*).

mean flow velocity is 50% of maximum flow velocity (11), whereas in all the fetuses we examined, mean velocity was close to V_{max} and consistently greater than 50% of maximum (Fig. 1).

Placental blood volume flow per min increased exponentially with gestational age from 19 wk to term ($r = 0.86$) (Fig. 3). In contrast to previous studies in the human fetus, there was no tendency for placental blood flow to decrease near or after term. Some of the highest placental volume flows were recorded in the postdate fetuses (>40 wk). Placental blood flow increased linearly with fetal body weight ($r = 0.77$). However, when placental blood volume flow was normalized to unit fetal body weight, it was similar to mean placental flow per kg per min reported previously (1, 7, 20) (Table 1), and declined slightly with gestational age (Fig. 3 and 4).

The umbilical artery maximum systolic to minimum diastolic velocity ratio decreased with gestational age ($r = -0.53$) due to a relatively greater increase in diastolic than systolic velocity, indicating a small but progressive fall in resistance to placental blood flow (Fig. 4). However this velocity ratio did not correlate closely with placental blood volume flow per min ($r = -0.46$) (Fig. 4).

DISCUSSION

Placental blood flow in the human fetus increased exponentially from 19 wk to term. In contrast to previous studies (9, 20), there was no plateau or decrease in placental perfusion either before or after 40 wk. Some of the highest placental flows were observed in the postdate fetuses, providing little support for the assertion that their increased mortality is due to primary reduction in placental flow. The increase in placental blood flow with gestational age resulted more from the increase in cross-sectional area of the umbilical vein than any change in umbilical vein flow velocity, which varied over the same range throughout the period of gestation studied. Placental blood flow also increased with fetal body weight. When placental blood flow was normalized to unit body weight, there was little change or even a slight reduction with gestational age similar to that in the ovine fetus (21), and mean flow per unit body weight per min was similar to that reported previously (Table 1).

The velocity signals recorded from the umbilical vein provided important information regarding the flow characteristics of the oxygenated blood leaving the placenta. Flow in the umbilical vein was nonpulsatile, low velocity, and had a narrow velocity spectral envelope consistent with laminar flow in a large diameter conduit. The narrowness of the velocity spectral envelope reflects the narrow range of velocities in the umbilical vein at any instant in time. This is because the vast majority of blood in the umbilical vein travels at the same velocity, whereas blood close to the vessel wall travels at a lower velocity due to frictional resistance from the vessel wall. This type of velocity profile is referred to as "flat-fronted" or "plug" flow, and has relevance when volume flow is calculated from mean blood flow velocity. The mean velocity and V_{max} in flat-fronted flow are similar as demonstrated

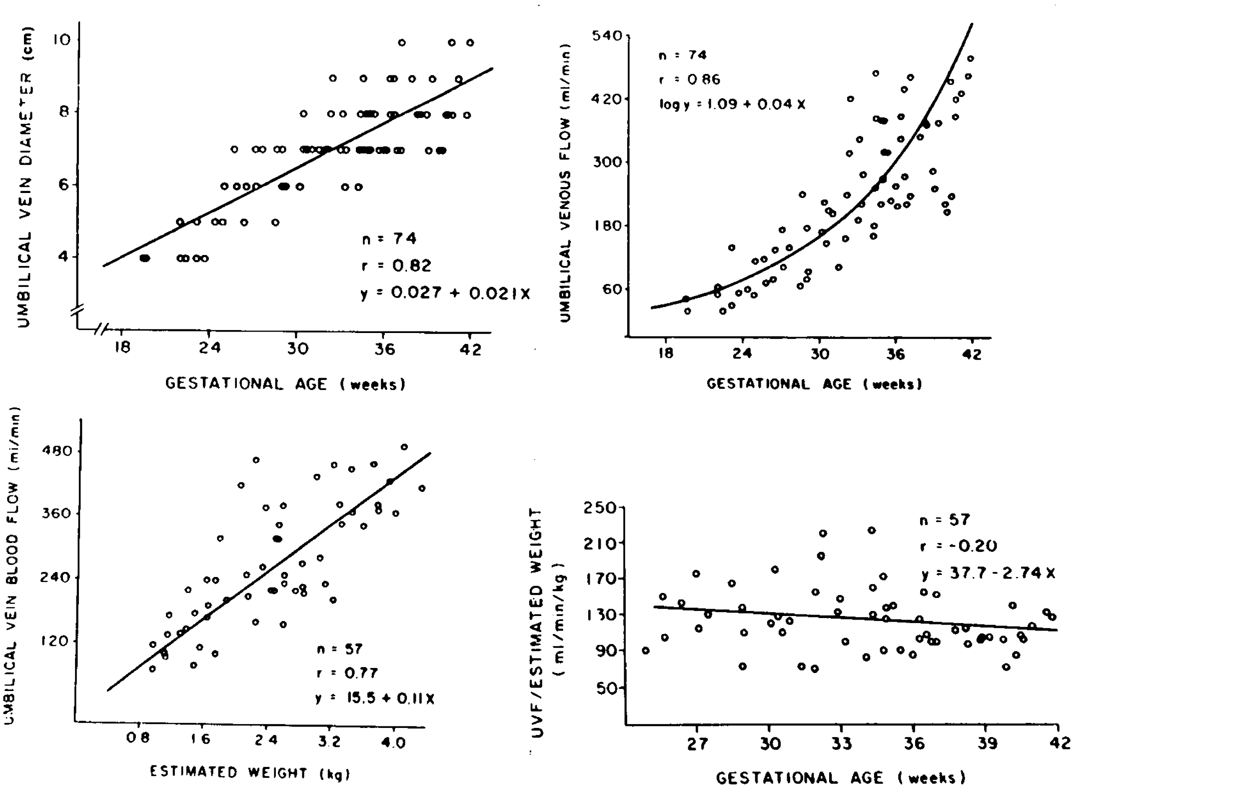

Fig. 3. Relationship between umbilical vein diameter (mm) and gestational age in wk (*top left*); umbilical venous flow (mL/min) *vs* gestational age (*top right*); umbilical vein blood flow (mL/min) *vs* fetal body weight (kg) (*bottom left*); and umbilical flow/unit fetal body weight (mL/min/kg) *vs* gestational age (*bottom right*).

Table 1. *Measurements of umbilical blood flow in normal human pregnancies*

Authors	Mean blood flow (mL/min/kg)
Eik-Nes *et al.*, 1980 (Ref. 7)	113
Gill *et al.*, 1981 (Ref. 6)	105–120
Jouppila *et al.*, 1984 (Ref. 4)	108–113
Kurjak *et al.*, 1982 (Ref. 1)	102–109
St. John Sutton *et al.*, 1990 (present study)	105–130

by our continuous velocity recordings from the umbilical vein, in which mean velocity was consistently greater than 50% of V_{max} (Fig. 1). Previous studies have assumed that mean velocity is 50% of V_{max} and thus have predictably underestimated true placental blood volume flow (11).

A further problem encountered in previous attempts to quantitate placental blood flow in the human fetus has been the inability to measure the angle of incidence between the direction of blood flow in the umbilical vein and the interrogating Doppler beam (22, 23). These difficulties have arisen largely because continuous wave Doppler has been used, with which the umbilical vein is never imaged. A prerequisite for accurate measurement of velocity using the Doppler equation is that the ultrasound beam is parallel to the direction of flow, because estimates of the true velocity vary inversely with the cosine of the angle between the ultrasound beam and the direction of flow. Accurate velocity determination is of paramount importance in quantitating placental flow because placental blood flow is calculated as the product of the area under the velocity signal and the cross-sectional area of the umbilical vein. When this angle has been recorded in previous studies, it has varied between 30 and 65° (9, 10, 22). These large angles predictably underestimate velocity, which in turn is translated into underestimation of placental blood volume flow (23). Our method of assessing umbilical vein blood flow afforded two major advantages. First, we could visualize the umbilical vein and therefore align the Doppler beam parallel to the direction of blood flow so as to minimize potential errors in velocity measurement. Second, we could display simultaneously Doppler mean, maximum, and spectral velocity signals. These two features enabled us to quantitate placental blood volume flow accurately.

An alternative to quantitating placental blood volume flow is to assess placental resistance to flow. Assessment of placental resistance is attractive because it does not require measurement of the angle between the ultrasound beam and the direction of blood flow, inasmuch as this does not change significantly from systole to diastole. A variety of different methods have been used to assess placental resistance from the umbilical arteries (12–16), some of which are based on observations initially made in the carotid arteries (24). These have included the ratio of the difference between umbilical arterial peak systolic and diastolic velocities and peak or mean systolic velocity (25, 26), or, more commonly, the ratio of maximum systolic to minimum diastolic flow velocities (5, 27).

We assessed the maximum systolic to minimum diastolic velocity ratio because it is the ratio that is most commonly used clinically and because it has been reported to discriminate between normal and abnormal placental perfusion. In addition, this velocity ratio has been shown to correlate with the microvascular anatomy of the placenta in terms of the number of arterioles in the tertiary stem villi, across which the major arterial pressure drop occurs (28). The precise relationship between the peak systolic to minimum diastolic placental velocity ratio and arterial resistance is complex, but the decrease with gestational age has been interpreted as indicating a reduction in arterial resistance (6, 7, 13–16) concordant with studies in the ovine fetus (21). The decrease in placental resistance is believed to result from an increase in placental size and a concomitant increase in the number of arterial channels in the tertiary stem villi. The reduction in the umbilical arterial velocity ratio with gestational age in our study was the result of a systematically greater increase in diastolic than in systolic blood flow velocity. Although the decrease in placental resistance with gestational age had a time course similar to that of the increase in placental blood volume flow, the umbilical arterial velocity ratio did not correlate closely with placental blood volume flow.

We could not confirm the fall in placental blood flow before term that has been reported previously (9, 20). Because blood volume flow is calculated as the product of the flow velocity time integral in the umbilical vein and the cross-sectional area of the umbilical vein, placental blood flow could only decrease if either the velocity or the size of the umbilical vein decreased. However, the umbilical vein diameter increased linearly with age (Fig. 3), and the umbilical vein velocity increased slowly but progressively with gestational age. Furthermore, the umbilical velocity ratio in this and all previous studies decreased with age, suggesting a fall in placental resistance. Thus, a fall in placental blood flow before term in the setting of increasing umbilical vein cross-sectional area, increasing blood flow velocity in the umbilical vein, and falling placental resistance is extremely unlikely. Support for this is provided by the constancy of the placental blood flow per unit fetal weight in the human fetus, inasmuch as fetal body weight continues to increase before term.

We have described the blood flow velocity characteristics in

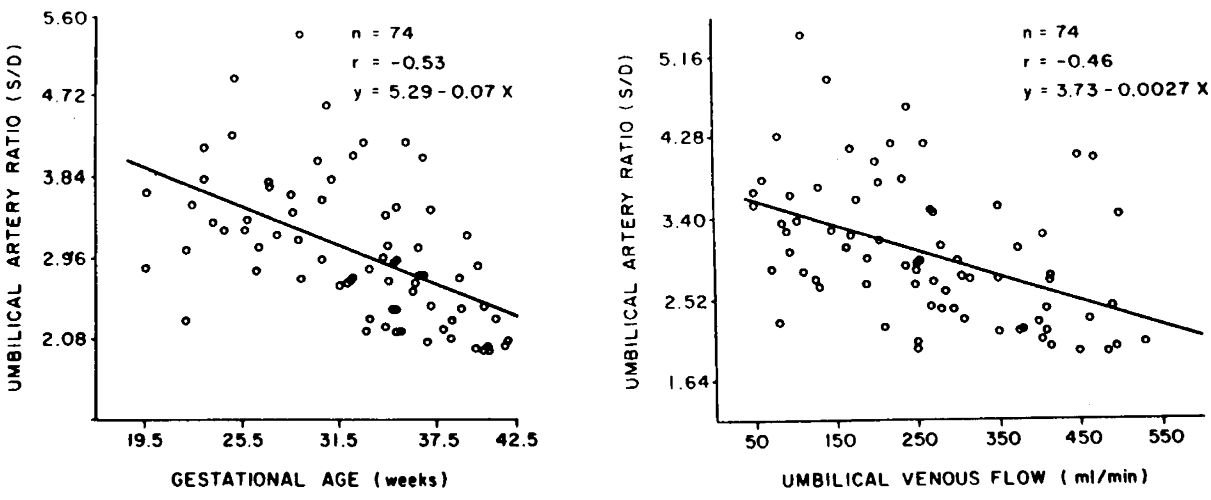

Fig. 4. Relationship between umbilical artery velocity ratio and gestational age (*left*), and between umbilical artery velocity ratio and umbilical vein blood flow (mL/min) (*right*).

the umbilical vein, quantitated placental perfusion in the normal human fetus from 19 wk to term, and prospectively examined the relationship between placental blood flow and placental resistance. We conclude that: *1*) fetoplacental blood volume flow increases exponentially from 19 wk to term; *2*) there is no decrease in placental flow in postdate fetuses; *3*) placental blood flow per unit fetal weight changes little with gestational age; and *4*) the umbilical arterial velocity ratio decreases with age, but does not correlate closely with placental blood volume flow. We submit that placental blood volume flow can be readily quantitated noninvasively, and provides more physiologic information regarding placental perfusion than measurement of umbilical arterial velocity ratio.

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