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Abbreviations

AC, abdominal circumference; AGA, appropriate for gestational age; CI, confidence interval; CPR, cerebroplacental ratio; EFW, estimated fetal weight; FGR, fetal growth restriction; FGR-D, FGR fetuses meeting Delphi criteria; IRB, Institutional Review Board; ISUOG, International Society of Ultrasound in Obstetrics and Gynecology; LOS, length of stay; MCAPI, middle cerebral artery pulsatility index; NICU, Newborn Intensive Care Unit; OR, odds ratio; SGA, small for gestational age; TAMAX, time-averaged maximum velocity; UAPI, umbilical artery pulsatility index; UVF, umbilical vein flow

Objectives—Umbilical vein flow (UVF) is reduced in fetal growth restriction (FGR). We compared absolute and size-adjusted UVF (estimated fetal weight [EFW] and abdominal circumference [AC]) and rates of abnormal UVF parameters (<10th percentile) among FGR fetuses meeting Delphi criteria (FGR-D) against small for gestational age (SGA) fetuses and appropriate for gestational age (AGA) controls.

Methods—Absolute UVF, UVF/EFW, and UVF/AC were compared between 73 FGR pregnancies (35 FGR-D, 38 SGA) and 108 AGA controls. Rates of abnormal UVF were compared to abnormal umbilical artery pulsatility index (UAPI). Independent samples *t*-tests, Mann–Whitney *U*, odds ratio (OR), chi-squared, and Fisher's exact tests were used as appropriate.

Results—Mean absolute UVF was significantly decreased in FGR-D compared to AGA ($P = .0147$), but not between SGA and AGA fetuses. The incidence of both abnormal absolute UVF and UVF/AC values (<10th centile) was higher among late-onset FGR fetuses versus AGA fetuses (UVF: OR 2.7, confidence interval [CI] 1.37–5.4; UVF/AC: OR 2.73, CI 1.37–5.4). UVF was more frequently abnormal than UAPI and in only two fetuses were both Doppler values abnormal.

Conclusion—Absolute UVF is altered in late-onset FGR, and most pronounced among FGR-D. UVF may provide additional insight into fetal compromise in those affected by growth restriction.

Key Words—fetal growth restriction; Doppler; intrauterine growth restriction; late-onset fetal growth restriction; placental blood flow; umbilical venous flow

Interest in umbilical vein flow (UVF) arose more than three decades ago when investigators began assessing flow in animal models and in normally grown and undergrown human fetuses with the idea of using this as a diagnostic tool in managing fetal growth restriction (FGR).[1–3] In a longitudinal study, there was evidence that UVF reduction, adjusted for fetal size, preceded biometric evidence of growth restriction by several weeks in the early third trimester.[4] Ferrazzi et al[5] found a correlation between reduction of UVF and abnormal umbilical artery pulsatility index (UAPI) in FGR fetuses with nonreactive fetal heart rate tracings. Para-Saavedra et al[6] found that employing UVF along with middle cerebral artery pulsatility index (MCAPI) in a stepwise diagnostic approach was useful in identifying pregnancies requiring cesarean delivery and was associated with a low umbilical cord blood pH. Most recently, Rizzo et al[7] found that abnormal UVF was a better predictor of adverse neonatal outcome in fetuses diagnosed with FGR than UAPI, uterine artery PI or MCAPI.

Since fetuses with EFW < 10th percentile (centile) encompasses fetuses that may have both low rates and very high rates of mortality and morbidity, it is important to identify those fetuses at greatest risk for adverse outcome so that appropriate fetal surveillance can be implemented to decrease the risk for adverse outcome. In an attempt to separate FGR from constitutionally small fetuses (small for gestational age [SGA]), a group of perinatal experts identified diagnostic criteria through a Delphi consensus procedure. These criteria allow for the delineation of fetuses with an EFW < 10th centile at greatest risk for adverse outcome (FGR fetuses meeting Delphi criteria [FGR-D]) from those SGA fetuses who are "constitutionally small."[8] The resulting Delphi definitions for FGR versus SGA were later incorporated into management guidelines for FGR published by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG).[8,9] Table 1 represents a condensed version of these criteria. UVF assessment has not been investigated in FGR pregnancies where the fetuses were stratified in to severe (FGR-D) and nonsevere (SGA) groups as suggested by the ISUOG guidelines. Using ISUOG guidelines, we hypothesized that those fetuses, defined by Delphi criteria as having late-onset growth restriction (FGR-D), would have decreased UVF compared to AGA controls and a similar reduction in absolute and size-adjusted UVF among FGR-D and SGA fetuses.

Therefore, the objectives of this study were as follows: 1) determine whether absolute UVF, UVF/EFW, and UVF/AC, using gestational age as the independent variable, were significantly decreased between late-onset FGR-D and SGA fetuses and AGA controls; 2) determine if differences in umbilical vein flow variables correlated with other outcome variables such as birth metrics, need for cesarean delivery, or presence of at least one adverse neonatal outcome; and 3) determine how often reduced UVF correlated with elevated UAPI, the most frequently used Doppler method for assessing fetal status in FGR.[10]

Table 1. Delphi Consensus-Based Definitions for Late Growth Restriction[8,9]

Late FGR: GA ≥ 32 Weeks With No Congenital Abnormalities
AC or EFW less than 3rd centile
Or at least two of the three:
1. AC or EFW less than 10th centile
2. AC or EFW crossing centiles greater than 2nd quartiles on growth centiles
3. CPR less than 5th centile or UAPI greater than 95th centile[a]

GA, gestational age; AC, fetal abdominal circumference; EFW, estimated fetal weight; PI, pulsatility index; UA, umbilical artery; CPR, cerebroplacental ratio.
[a]Growth centiles are noncustomized centiles.

Materials and Methods

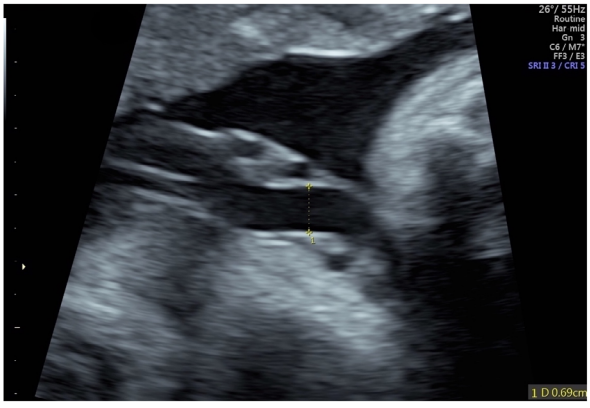
This was a prospective observational study of pregnancies affected by late-onset FGR recruited at a single ultrasound site in Denver, Colorado. Institutional Review Board (IRB) approval was obtained from the Colorado Multiple Institutional Review Board and informed consent was obtained from all study participants (IRB number 14-1360, date of approval May 29, 2015). Control data in patients with AGA fetuses in California were obtained as part of a study approved by the Pearl IRB (protocol #21-FEDC-101, Indianapolis, IN).[11] These AGA control data were taken from a large cohort of normal pregnancies in order to create a nomogram for umbilical vein flow.

The study cohort consisted of 73 subjects who were >18 years of age, had ultrasound gestational age assessment before 20 weeks, and whose ultrasounds showed no evidence of fetal anomalies. Inclusion required fetuses to have an EFW < 10th centile at the time of study enrollment. Ultrasound measurements from the last complete examination prior to delivery were used for analysis. Fetuses with a diagnosis of FGR at or beyond 32 weeks gestational age were included to examine only those fetuses with late-onset growth restriction. EFWs were based on measurements of the head circumference, biparietal diameter, AC, and femur length,[12] and centiles were assigned according to a population-based in-utero growth curve by Hadlock et al.[13]

Doppler waveforms were obtained from both umbilical arteries inside a free-floating loop of umbilical cord with the vessels running parallel to the ultrasound beam. The UAPIs from both arteries were averaged. Doppler waveforms from the middle cerebral artery (MCA) were obtained from the near-side vessel exiting the circle of Willis at an insonation angle as close as possible to 0°.

To measure UVF, a free-floating loop of umbilical cord was chosen for analysis. The vessel diameter was measured from a longitudinal 2D image obtained

Figure 1. Umbilical vein longitudinal view in which the diameter of the vein is measured in centimeters.



at 90° to the angle of insonation (Figure 1) and/or from a cross sectional image of the 3-vessel cord (Figure 2) as previously described.[1,5] Calipers were placed between the inner walls of the vein to measure the diameter (Figures 1 and 2). The time-averaged maximum velocity (TAMAX) was measured when the blood flow was parallel (0°) to the ultrasound beam (Figure 3). All 2D and Doppler images were obtained during fetal quiescence. UVF was calculated using the formula[14]:

$$\mathrm{UVF\,(mL/min)} = \mathrm{TAMAX} \times \left(0.5 \times \pi(\mathrm{D}/2)^2 \times 60\right)$$

UVF was normalized by kilogram fetal weight (UVF/EFW), and by the abdominal circumference in centimeters (UVF/AC). Centiles for absolute UVF, UVF/EFW, and UVF/AC were calculated based on *Z*-score analysis from control data from DeVore et al[11] and centiles for UAPI and cerebroplacental ratio (CPR) were based on previously published data.[15–18] The same UVF measurement technique was utilized for the study cohort and the separately obtained AGA controls.

The FGR cohort was divided into FGR-D (EFW < 10th centile with abnormal Doppler studies, UAPI >95th centile or CPR < 5th centile or an EFW or AC < 3rd centile) versus SGA (EFW between the 3rd and 10th centiles with a normal Doppler study of the UAPI and CPR) according to ISUOG guidelines.[8–10] Measures of adverse neonatal outcome were based on the study by Rizzo et al[7] and consisted of the following: need for admission to the Newborn Intensive Care Unit (NICU), need for emergency cesarean delivery due to fetal distress, and Apgar <7 at 5 minutes. Although other investigators have included umbilical artery pH less than 7.1 in their combined measure of adverse neonatal outcomes, we excluded this variable due to insufficient data.[7]

Figure 2. Umbilical vein cross-sectional view. D is the diameter of the vein in centimeters (cm); A is the area of the vein in cm^2. C is the circumference of the vein in cm. D2 is the diameter of the vein computed from the automated tracing of the area and circumference.

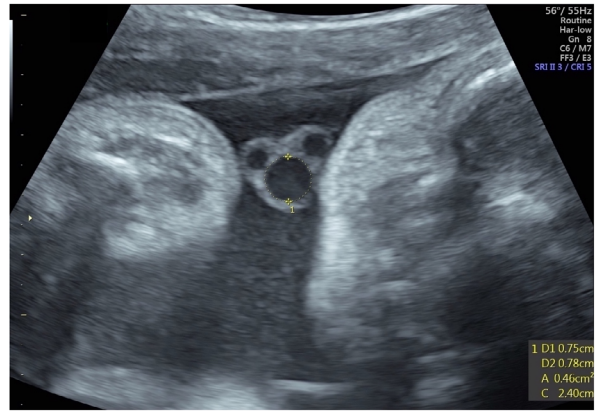
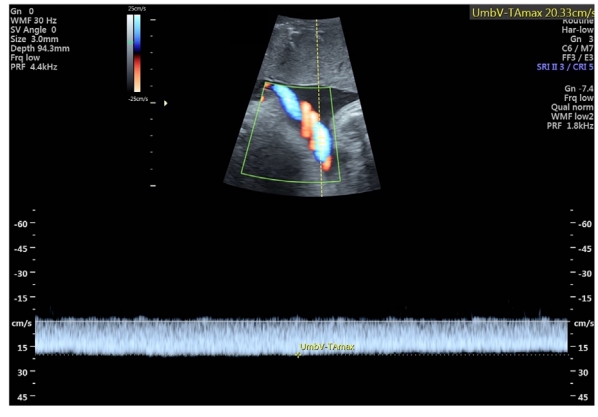


Figure 3. Umbilical vein time average maximal velocity (TAMX). UmbV-TAMX is the measured maximal velocity of umbilical vein flow in cm/s.



Statistical Analyses

SPSS Statistics version 28 software (IBM) was used for statistical analyses. Demographic and clinical characteristics were compared using independent samples *t*-tests. Mann–Whitney *U* tests and Chi-squared tests were used for continuous, non-normally distributed,

Table 2. Baseline Characteristics and Delivery Outcomes Among FGR-D and SGA

Variable	FGR-Delphi (FGR-D), $n = 35$	SGA, $n = 38$	*P* value
Maternal race	Asian, 1 (2.9%) Black, 2 (5.7%) White, 28 (80%) Mixed race, 1 (2.9%) Native American, 0 (0%) NR, 3 (8.6%)	Asian, 1 (2.6%) Black, 2 (5.3%) White, 30 (78.9%) Mixed race, 3 (7.9%) Native American, 0 (0%) NR, 2 (5.3%)	.887
Maternal age (years)	29.51 ± 5.06	28.26 ± 5.85	.334
Tobacco use in pregnancy	-	5 (13.2%)	.055
Chronic maternal hypertension	4 (11.4%)	2 (5.3%)	.418
Pregnancy-induced hypertension	2 (5.7%)	1 (2.6%)	.604
GDM, T1, T2 DM	-	-	1
UA Doppler PI > 95th percentile	7 (20%)	-	.004*
Gestational age at delivery (weeks)	37.26 ± .91	38.07 ± 1.23	.005*
Neonate birthweight (g)	2278.61 ± 295.42	2610.36 ± 291.13	<.001*
Gestational age at analysis (weeks)	35.59 ± 1.46	35.69 ± 1.64	.804

NR, no race indicated; GDM, gestational diabetes; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; UA, umbilical artery; EFW, estimated fetal weight; AC, abdominal circumference; UVF, umbilical vein flow.
*Indicates statistical significance ($P < .05$).

and categorical variables. Fisher's exact test was used for any categorical variables consisting of cells with an expected count less than 5. Data are presented as mean ± standard deviation, with a significance level of 95% (or *P* value of <.05). Odds ratios were computed using 5 and 95% reference intervals, and $P < .05$ was considered significant.

Results

Our cohort included 35 fetuses meeting criteria for FGR-D and 38 fetuses that were SGA. There were 108 fetuses that comprised the AGA control data base.[11] Baseline demographics are presented in Table 2. Mean gestational age at the time of analysis was similar between FGR-D and SGA fetuses (FGR-D: 35.59 ± 1.46, 35.69 ± 1.64; $P = .804$). The gestational age at delivery, EFW and AC at the time of ultrasound, and neonatal birthweight were different between FGR-D and SGA patients, reflecting the differences in definition and standard delivery criteria management of these groups (Tables 2 and 3).

Mean absolute UVF was significantly reduced in the FGR-D compared to AGA fetuses ($P = .0147$) (Table 3). There was no difference in absolute UVF between FGR-D and SGA, or SGA and AGA fetuses. When absolute UVF was adjusted by EFW, there were no differences found between groups. Similarly, when absolute UVF was adjusted by AC, there were no differences found between groups (Table 3).

However, when using odds ratio (OR) analysis based on abnormal UVF thresholds being <10th centile, additional significant differences were noted. All fetuses with late-onset FGR (combination of FGR-D and SGA together) had a higher likelihood of an abnormal UVF (OR 2.7, confidence interval [CI] 1.37–5.4) and abnormal UVF/AC (OR 2.73, CI 1.37–5.4) compared to AGA controls (Table 4). When FGR-D and SGA groups were examined separately, only the FGR-D group had a significantly increased number of fetuses with abnormal values <10th centile for UVF (OR 4.12, CI 1.8–9.5) and UVF/AC (OR 3.6, CI 1.6–8.3) compared to AGA controls (Table 4). The number of fetuses with an UVF/EFW < 10th centile was not different between study groups (Table 4).

Absolute UVF values below the 10th centile (*Z*-score < −1.28) were present in 31.4% FGR-D and 15.8% SGA fetuses (Table 4). UVF values adjusted by AC below the 10th centile were present in 28.6% of FGR-D and 18.4% of SGA fetuses (Table 4). When adjusted by EFW, the number of fetuses below the 10th centile fell to 17.1% FGR-D and 7.9% SGA fetuses (Table 4).

The clinical endpoints of NICU admissions and length of stay (LOS) as well as the need for cesarean delivery for fetal heart rate abnormality were similar

Table 3. Absolute and Adjusted Umbilical Vein Flows for FGR-D, SGA, and AGA Fetuses

Variable	FGR-Delphi (FGR-D), *n* = 35	SGA, *n* = 38	AGA, *n* = 108	*P* value
EFW (g)	2011.34 ± 328.48	2298.24 ± 368.35	2352.90 ± 375.30	FGR-D vs SGA = .001* FGR-D vs AGA = .0001* SGA vs AGA = .43
AC (cm)	27.95 ± 1.72	30.03 ± 1.92	29.70 ± 3.00	FGR-D vs SGA = .0001* FGR-D vs AGA = .0001* SGA vs AGA = .63
UVF (mL/min)	207.60 ± 83.32	244.90 ± 81.96	245.10 ± 76.28	FGR-D vs AGA = .0147* FGR-D vs SGA = .058 SGA vs AGA = .99
UVF/EFW (mL/min/kg)	105.65 ± 47.19	108.48 ± 37.07	105.54 ± 34.50	FGR-D vs AGA = .94 FGR-D vs SGA = .81 SGA vs AGA = .52
UVF/AC (mL/min/cm)	7.42 ± 2.95	8.16 ± 2.71	8.15 ± 2.50	FGR-D vs AGA = .19 FGR-D vs SGA = .98 SGA vs AGA = .26

EFW, estimated fetal weight; AC, abdominal circumference; UVF, umbilical vein flow; NS, not significant.
*Indicates statistical significance (*P* < .05).

Table 4. Odds Ratios of Rate of Absolute and Adjusted UVF <10th Percentile for Late-Onset FGR Grouped and Separately (FGR-D and SGA) Versus AGA Controls

UVF	FGR-D and SGA, *n* = 73	FGR-D, *n* = 35	SGA, *n* = 38
Absolute (mL/min)	17 (23.3%) OR = 2.7 95% CI 1.37–5.4 *P* = .004*	11 (31.4%) OR = 4.12 95% CI 1.8–9.5 *P* = .001*	6 (15.8%) OR = 1.68 95% CI 0.64–4.4 *P* = .28
Adjusted by EFW (mL/min/kg)	9 (12.3%) OR = 1.26 95% CI 0.56–2.9 *P* = .57	6 (17.1%) OR = 1.86 95% CI 0.7–4.9 *P* = .21	3 (7.9%) OR = .77 95% CI 0.2–2.7 *P* = .68
Adjusted by AC (mL/min/cm)	17 (23.3%) OR = 2.73 95% CI 1.37–5.4 *P* = .002*	10 (28.6%) OR = 3.6 95% CI 1.6–8.3 *P* = .003*	7 (18.4%) OR = 2.0 95% CI 0.8–5.1 *P* = .13

CI, confidence interval; EFW, estimated fetal weight; AC, abdominal circumference; UVF, umbilical vein flow.
*Indicates statistical significance (*P* < .05).

among the FGR-D and the SGA groups (Table 5). The presence of at least one adverse neonatal outcome was also similar between FGR-D and SGA groups (Table 5).

Among FGR-D and SGA fetuses, there were 17 cases of abnormal absolute UVF, and 7 cases of abnormal UAPI. In only two cases were both absolute UVF and UAPI abnormal (Table 6). Similarly, there were 16 cases of abnormal MCAPI, of which only three cases also had an abnormal absolute UVF (Table 6).

Comment: Principal findings:

1. Absolute UVF was significantly reduced in FGR-D fetuses compared to AGA controls (Table 3).
2. FGR-D and SGA fetuses had similar absolute UVF and EFW or AC-adjusted UVF (Table 3).
3. Late-onset FGR fetuses (FGR-D and SGA) had a significantly higher incidence of abnormal absolute UVF and UVF/AC (values less than the 10th centile) compared to AGA controls (Table 4).

Table 5. Neonatal Outcomes Among FGR-D and SGA Groups

	FGR-D	SGA	*P* value
Apgar <7 at 5 minutes	0	0	1
Emergency c-section for fetal distress	2 (7.69%)	1 (3.33%)	.592
NICU admission	8 (33.33%)	7 (26.92%)	.621
Presence of at least one adverse neonatal outcome[a]	9 (36.00%)	7 (26.92%)	.485
NICU LOS (days)	6.25 ± 5.52	3.00 ± 3.27	.189
NICU LOS ≥3 days	6 (75.00%)	2 (28.57%)	.132

c-section, cesarean section; UA, umbilical artery; NICU, neonatal intensive care unit; LOS, length of stay.
[a]Presence of one adverse neonatal outcome includes the following: Apgar score <7 after 5 minutes, need for emergency c-section for fetal distress, and admission to the NICU.

Table 6. Rates of Normal and Abnormal Absolute UVF Versus UA and MCA

	UVF Normal	UVF Abnormal
UA normal	51	15
UA abnormal	5	2
MCA normal	43	14
MCA abnormal	13	3

Abnormal values were defined respectively as absolute UVF < 10th centile, MCA-PI < 10th centile UA-PI > 95th centile.
UVF, umbilical vein flow; UA, umbilical artery; MCA, middle cerebral artery; PI, pulsatility index.

4. Rates of adverse neonatal outcomes were similar among the FGR-D and SGA groups (Table 5).
5. Absolute UVF was more frequently abnormal than UAPI in the 73 study fetuses (FGR-D and SGA). In only two cases were both UAPI and UVF abnormal (Table 6).

Discussion

Comparison with Other Studies

It is difficult to compare this study's findings with those of other studies because of differences in study design and the makeup of the published study populations. The patients in the current study had fetuses with late-onset growth restriction that had a low rate of neonatal morbidity, which is typical for this gestational age. None of the fetuses in this study sample had absent/reversed flow in the UA and all fetuses survived. Aside from the rate of NICU admissions for both groups (which is subject to provider bias and thereby can skew a variable representing adverse neonatal outcomes), these fetuses in the short term were less severely compromised than those in the earlier published studies. For example, in the 2002 study from Boito et al,[19] the average birthweight and age at delivery were 1089 g and 32 weeks versus 1247 g and 32 weeks in those with abnormal and normal UVF/kg, respectively. Both groups had a 25% mortality. In comparison, in our study the FGR-Ds and SGAs, respectively, had average birth weights of 2279 and 2610 g and the average gestational age at delivery was 37 and 38 weeks for each group. A literature search showed a limited number of other studies on UVF in late-onset FGR.[7,20]

Although the patient population in the study by Rizzo et al[7] was similar regarding gestational age, the acuity was different because only fetuses were entered who were already defined as having FGR by Delphi definitions (eg, constitutionally small or SGA fetuses were excluded). This would also explain the higher rates of cesarean delivery for fetal distress and abnormal neonatal blood gases recorded in Rizzo et al.[7] Our rate of NICU admission likely reflected an institutional bias rather than the degree of neonatal compromise. The objective of the study by Rizzo et al[7] was to concentrate on the potential clinical value of UVF/AC versus other Doppler methods of surveillance (uterine artery PIs, CPRs, MCAPIs) in this high-risk group of FGR fetuses. The UVF adjusted by EFW had the highest calculated Z-score area under the curve for prediction of the composite adverse neonatal outcome.

In another study of UVF in growth restriction, Zhu et al[20] examined 14 growth restricted fetuses versus 26 AGA fetuses and found lower UVF by MRI in growth-restricted fetuses. This study had slightly different definitions of growth restriction than our study and only examined UVF by MRI measurements without any biometric adjustments, thus limiting its comparability.

In a stepwise decision-tree approach, Para-Saavedra et al[6] explored the use of UVF adjusted by EFW, together with a measure of brain sparing, MCAPI, to predict outcome. In a two-step process applied to growth restricted fetuses, the authors used a set level of UVF/EFW (<68 mL/s/kg) and MCAPI (<1.46) as initial screening thresholds. Fetuses below these values were then re-appraised for MCAPIs below a second, more stringent level of <1.23. This more strictly categorized group of fetuses had a substantially higher risk for emergency cesarean delivery and lower arterial umbilical cord pH at birth.

Our study was designed to determine whether fetuses diagnosed with EFWs <10th centile after 32 weeks who were assigned to be at higher risk for adverse outcomes by Delphi definitions (FGR-D) had low absolute and adjusted UVFs more frequently than those fetuses designated to be constitutionally small (SGA). Our goal was to establish whether UVF differed between these two groups as a way to better understand its potential role in current algorithms for the characterization and care of growth restricted fetuses.

Absolute UVF Versus "Corrected" UVF

It is easy to assume that a fetus genetically programmed to be small would have an UVF to be commensurate with its size. Therefore, the UVF is adjusted to the EFW or AC to determine if the flow is reduced even more than expected for a given fetus' size. To counter this, many small fetuses with intrauterine deprivation attempt to counter placental insufficiency by decreasing their energy demands to meet the reduction in oxygen and nutrient supply.[21]

The AC is the most affected biometric measurement since it reflects the size of the liver, an organ whose growth is curtailed in FGR as the fetus redistributes its blood flow to other organs.[14] Therefore, a reassuring normal UVF/AC ratio may not identify fetuses who, while matching their size to the level of the already restricted flow, could still be severely growth restricted. Since the AC plays a major role in the calculation of the EFW, correction with this variable carries the same misleading possibilities. In these cases, the absolute UVF could be more predictive of severity by its deviation from gestational age expectations.

Another problem with correcting for UVF by fetal size is that it is unknown what degree of hypoxemia will cause later neurological or cardiovascular disorders. Some small fetuses with a Delphi designation of SGA with normal UVF/EFW or AC could still have an abnormal absolute UVF (for gestational age) suggesting a modest, but possibly detrimental level of hypoxemia.

The reason for using a comprehensive approach to the diagnosis and surveillance of FGR is to make sure fetuses do not escape the safety net of fetal surveillance, and absolute UVF may be more inclusive, yet at least as predictive as corrected flow (UVF/EFW, UVF/AC). Its use in clinical application to reduce adverse neonatal outcome will require continued study.

Relationship of UVF to UAPI

In normal pregnancies, small arterioles and venules within the secondary and tertiary villi are closely related in number and proximity. In FGR pregnancies, there are fewer terminal villi and often micro-thrombi form in the small villus arteries.[22] This causes increased downstream resistance and an increased afterload. For years, clinicians have depended upon the UAPI to reflect the status of the placental arterial bed. However, less is known about the diffusion activities of the venules and capillaries in the terminal and stem villi. At present, the only available way to monitor these activities is by assessing the flow though the vehicle distributing the blood to the fetus, the umbilical vein; however, this has been an infrequent target of investigation.

The differences between absolute UVF and UAPI results were striking. Using the 95th and 5th centile thresholds for the 73 fetuses in the study, 7 (9.6%) had abnormal UAPIs and 17 (23.3%) had abnormal UVFs. Surprisingly, in only two patients were both UAPI and UVF abnormal. Both patients were FGR-D fetuses. Trudinger et al[23] showed that at least 60 to 70% of the placental fetal arterial circulation needs to be obliterated to create an umbilical artery waveform with a PI above the 95th centile. It is uncertain how flow from the venous side of the placenta was maintained in the seven cases where circulation in the arterial bed of the placenta was so significantly compromised. This suggests that abnormalities in both the umbilical artery and vein may be independent risk factors for fetal morbidity in the setting of growth restriction, and thus, may function as independent screening tools.

The lack of correlation among UVF, UA, and MCA is also notable (Table 6). Elevated UAPI occurs when there is significant placenta-related hypoxemia

often seen in more severe growth restriction. MCAPI is decreased when hypoxemia has reached a point to necessitate adaptive circulatory redistribution. The higher rate of abnormal UVF in our overall less severe late-onset FGR cohort compared with MCA and UAPI could underscore its potential value as a more sensitive pre-brain sparing marker of hypoxemia.

Clinical Implications

It has been postulated that in the face of placental compromise at the terminal villus level, there is a mechanism to shunt essential activities away from infarcted or poorly perfused areas to other areas within the placenta.[24] The oxygen and nutrient content of blood in the umbilical vein is dependent upon diffusion at the level of the terminal villi but it is unclear what factors control the flow of blood out of the placenta and the possible role the diameter of the umbilical vein lumen plays as a flow-limiting factor.[25] Whatever mechanisms are involved, the UVF should not only provide information about the adequacy of the venous delivery system but also overall villus function.

In this study group of patients with late-onset growth restriction, the overall rate of absolute UVF < 10th centile is 17/73 (23%) (Table 4). Although the difference in UVF between FGR-D and SGA was not significant, there were more abnormal UVFs among the FGR-D (11) than SGA fetuses (6), which also reflects the average differences in flow between these groups (FGR-D: 207.60 mL/min, SGA: 244.90 mL/min) (Tables 3 and 4).

The overall 9.5% of abnormal UAPIs and a 23% rate of abnormal UVF flow may be representative of a study group that has a heavy proportion of late-onset growth restriction—not unlike that of many high-risk referral centers in the United States. In particular for the UAPI, several studies have shown that the Doppler waveform in late-onset FGR is normal in a large percent of cases. Fortunately, these late-onset FGR fetuses have lower rates of perinatal mortality, but they are not immune to morbidities emerging in childhood or adulthood.[26–28] The fact that even SGAs can have later morbidities[26,28,29] suggests that the lines between SGA and FGR-D are blurred.

After three decades of sporadic investigation, it is hoped that UVF may be adjunctively useful as a predictor of later cardiac and neurobehavioral morbidities, some of which can be prevented by multi-pronged proactive approaches in childhood.[30–33]

Research Implications

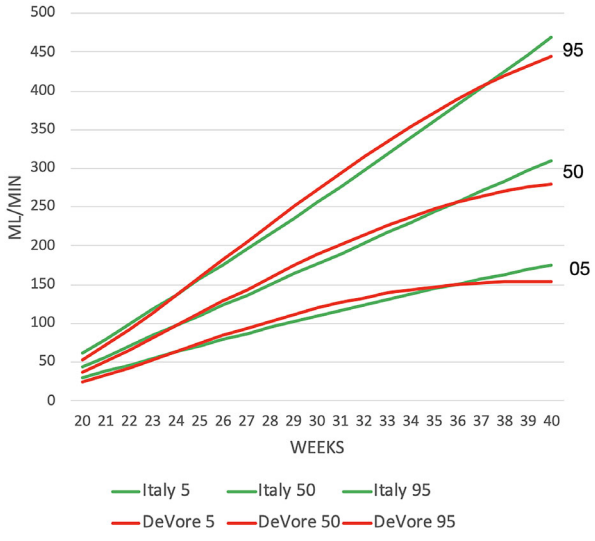
Today, different fetal testing tools have been used to detect fetuses at risk for fetal death and/or immediate neonatal morbidity. However, it is unknown how much hypoxemia the fetal heart can withstand before becoming remodeled or the brain can tolerate before cognitive impairment ensues. Late-onset FGR encompasses a heterogeneous group of fetuses who, along with being exposed to varying degrees of oxygen and nutrient deprivation, may be epigenetically destined to have different types of later morbidities. The availability of in utero diagnostic clues might enable more specific predictions for these future morbidities. For example, if further studies confirm adjusted UVF to be associated with adverse neonatal outcomes, this information might be combined with MCA Doppler in the setting of normal UA Doppler to assess the risk for later neurobehavioral abnormalities.[34] Similarly, UVF could be combined with ultrasound measures of fetal cardiac size, shape, and ventricular contractility to identify those at greater risk for childhood and adult cardiovascular disease.[26–28]

As noted by the authors of the Delphi consensus criteria,[8] a limitation of studying late-onset FGR is that the usual adverse neonatal outcome endpoints (eg, respiratory distress syndrome, intraventricular hemorrhage, and necrotizing enterocolitis) seen frequently in early-onset FGR are uncommon or rare in late-onset FGR. This leaves the softer endpoints of NICU admissions and LOS to be used for late-onset FGR as in prior reports[7,12] (Table 5). However, even these are imprecise in excluding future morbidities, and the only way to link in utero findings in these fetuses is to carry investigations out long past their discharge from the nursery. These studies are underway at our institution.

Strengths and Limitations

Strengths of this study include a large AGA cohort to validate the overall FGR group's UVF measurements and add to the growing body of literature examining the role of UVF in growth restriction. A limitation of our study is that our subgroups of FGR-D and SGA were relatively small ($n = 35$ and $n = 38$, respectively). Additionally, most of those meeting the FGR-D definitions were based on EFW or AC < 3rd centile alone and thus we were unable to stratify the UVF findings by other Doppler abnormalities such as UAPI or CPR.

Figure 4. Comparison of DeVore versus Italian control curves for absolute umbilical vein flow in mL/min. The graph displays the 5th, 50th, and 95th reference interval centiles.



An additional limitation inherent to any study of UVF is the difficulty with UVF measurement precision. A particularly vulnerable part of this measurement is the cross-sectional area as the radius calculation is squared and thus any small variations are further amplified. We minimized this by using reproducible, previously established methodology for measuring UVF as described above.[35]

The Search for AGA Control Data

Another possible limitation was our use of control data from a nonindigenous source due to difficulties recruiting an AGA cohort locally. We turned initially to colleagues in Italy with whom we have collaborated in the past. Using their data and equations, we began analyzing our SGA and FGR study data. However, because of the concern regarding the validity of applying European normative data to American fetuses, we ultimately chose to use a control population from the United States that provided data for UVF, UVF/AC, and UVF/EFW for AGA fetuses.[11] The DeVore study provided a calculator that allowed for the computation of *Z*-scores and centiles for the above variables of flow used in the current study.

Population differences in fetal biometrics have garnered substantial attention in their application to the diagnosis of FGR. Controversy about the transferability of growth charts between populations stimulated the WHO to create a fetal growth curve to address this issue.[36] With this in mind, we compared the curves by DeVore et al[11] and our Italian colleagues and found the means and reference intervals to be highly concordant for absolute UVF (Figure 4).

Lastly, while our study cohort included a population living at 5000 feet above sea level and the control curves for umbilical vein flow were constructed at 1000 feet, previous research has shown that there is not a significant effect of this altitude on Doppler parameters.[37] However, higher altitudes of >10,000 feet can have a modest effect on both birth weight and umbilical vein volume flow largely related to the diameter of the vessel.[38]

Conclusions

In FGR fetuses categorized by Delphi criteria to be at higher risk of adverse outcome, absolute UVF is significantly reduced when compared to controls. No differences were found when UVF was corrected for EFW. Additionally, the number of fetuses with an absolute UVF (for gestational age) and UVF/AC below the 10th centile is increased when compared with control fetuses, in contrast to those labeled as SGA. Prospective studies of both corrected and uncorrected absolute flow may determine their potential utility as adjunctive screening measures for predicting adverse outcomes in growth restriction.

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