2018

Three-dimensional power Doppler evaluation of cerebral vascular blood flow: A novel tool in the assessment of fetal growth restriction

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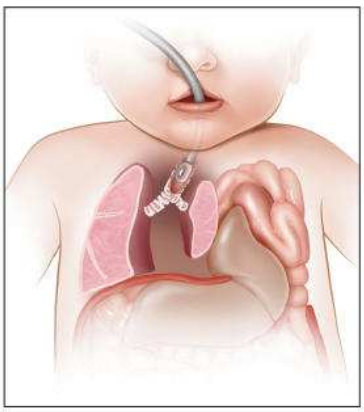

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Three-Dimensional Power Doppler Evaluation of Cerebral Vascular Blood Flow

A Novel Tool in the Assessment of Fetal Growth Restriction

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Received November 3, 2016, from the Department of Obstetrics, Gynecology, and Reproductive Sciences, University of Maryland, Baltimore, Maryland USA (K.R.G.); Department of Obstetrics and Gynecology, Washington University, St Louis, Missouri USA (A.G.C., G.A.M.); and Department of Obstetrics and Gynecology, University of South Florida, Tampa, Florida USA (L.O., A.O.O). Manuscript accepted for publication April 2, 2017.

This research was supported in part by the American College of Obstetricians and Gynecologists Kenneth Gottesfeld-Charles Hohler Memorial Foundation Research Award in Ultrasound. This work was presented in part as an oral presentation at the American Institute of Ultrasound in Medicine 2014 Annual Convention; March 29–April 2, 2014; Las Vegas, Nevada.

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Abbreviations

AGA, appropriate for gestational age; BMI, body mass index; FGR, fetal growth restriction; FI, flow index; GA, gestational age; PI, pulsatility index; 3D, 3-dimensional; 2D, 2-dimensional; VFI, vascularization-flow index; VI, vascularization index; VOCAL, Virtual Organ computer-aided analysis

doi:10.1002/jum.14323

Objectives—To determine whether fetuses with fetal growth restriction (FGR) are more likely to have abnormal cerebral vascular flow patterns compared to fetuses who are appropriate for gestational age (AGA) when quantified by using 3-dimensional (3D) power Doppler ultrasound.

Methods—We conducted a prospective cohort study of singleton gestations presenting for growth ultrasound examination between 24 and 36 weeks' gestation. Patients with FGR (estimated fetal weight < 10th percentile) were enrolled and matched 1:1 for gestational age (±7 days) with AGA fetuses. A standardized 3D power Doppler image of the middle cerebral artery territory was obtained from each patient. The vascularization index (VI), flow index (FI), and vascularization-flow index (VFI) were calculated by the Virtual Organ computer-aided analysis technique (GE Healthcare, Milwaukee, WI). These indices were compared between FGR and AGA fetuses and correlated with 2-dimensional Doppler parameters. Neonatal outcomes were also compared with respect to the 3D parameters.

Results—Of 306 patients, there were 151 cases of FGR. There was no difference in the VI (6.0 versus 5.7; $P = .65$) or VFI (2.0 versus 1.8; $P = .31$) between the groups; however, the FI was significantly higher in FGR fetuses compared to AGA controls (33.9 versus 32.3; $P = .009$). There was a weak, but significant, negative correlation between the FI and both the middle cerebral artery pulsatility index ($r = -0.34$; $P < .001$) and cerebroplacental ratio ($r = -0.29$; $P < .001$). Within the FGR group, there was no difference in any of the 3D vascular indices with regard to neonatal outcomes.

Conclusions—Three-dimensional power Doppler measurement of cerebral blood flow, but not the vascularization pattern, is significantly altered in FGR. This measurement may play a future role in distinguishing pathologic FGR from constitutionally small growth.

Key Words—fetal growth restriction; flow index; middle cerebral artery; obstetrics; 3-dimensional power Doppler; 3-dimensional ultrasound; vascularization-flow index; vascularization index

Fetal growth restriction (FGR) is a major contributor to perinatal morbidity and mortality, affecting 4% to 8% of pregnancies.[1–4] Although FGR is suspected in all fetuses with an ultrasound-estimated weight below the 10th percentile, this definition alone is unable to differentiate those fetuses who are constitutionally small versus those with a pathologic condition. In pathologic cases of

growth restriction, fetuses have a preferential redistribution of blood flow to the brain as an adaptive response to preserve cerebral oxygenation in the presence of chronic hypoxia, known as the "brain-sparing" response.[5] These alterations in the fetal brain circulation in response to chronic hypoxia are associated with long-term neurodevelopmental dysfunction in affected neonates.[6–9]

The current clinical standard used to assess the fetal brain circulation is 2-dimensional (2D) pulsed Doppler evaluation of the middle cerebral artery.[10,11] This approach has both technical limitations and practical concerns, including its inability to accurately detect subtle changes in blood flow in small vessels and its assumption that redistribution of blood flow to all regions of the brain is symmetric. With the advent of 3-dimensional (3D) power Doppler techniques, it has been possible to actually quantify blood flow in fetal organs, including the kidney, liver, and placenta, by assessing both vascularization and flow indices.[12–14] Prior studies have attempted to extrapolate these techniques to the fetal cerebral circulation in normal gestations; however, there are extremely limited data on how this method of blood flow assessment performs in fetuses with FGR.[15–19]

The objective of this study was to use 3D power Doppler ultrasound to compare cerebral vascular flow indices between normally grown and FGR fetuses to determine whether alterations of cerebral perfusion in FGR fetuses can be detected by this technology. We hypothesized that FGR fetuses would be more likely to have elevated cerebral vascular flow indices compared to normally grown fetuses and that these changes might be detectable in FGR fetuses who have no evidence of other abnormal 2D pulsed Doppler findings.

Materials and Methods

This work was a prospective cohort study of women presenting to Washington University for fetal growth ultrasound examinations between 2011 and 2013. Women with viable ongoing singleton pregnancies between gestational ages (GAs) of 24 weeks and 36 weeks 6 days carrying a fetus with an estimated fetal weight below the 10th percentile were approached for study participation. These women were matched 1:1 by GA (±7 days) with women carrying fetuses who were appropriate for gestational age (AGA), defined as an estimated fetal weight between the 10th and 90th percentiles. The GA limit of 36 weeks 6 days was chosen because the standard of care at our institution at the time of the study was to deliver all fetuses with an estimated fetal weight below the 10th percentile at 37 weeks' gestation. All pregnancy dating was confirmed by a prior ultrasound examination in either the first or second trimester. Pregnancies were redated if a discrepancy between ultrasound dating and the last menstrual period was greater than 5 days in the first trimester or greater than 7 days in the second trimester. Exclusion criteria included multiple gestations, major congenital anomalies, and chromosomal abnormalities. Institutional Review Board approval was obtained from Washington University (No. 10-1318), and written informed consent was provided by all study participants at enrollment.

Ultrasound study data were collected at the time of enrollment. Participants were not followed with serial ultrasound examinations for study purposes only. For each study participant, the estimated fetal weight was calculated from biometric measurements using the growth formula of Hadlock et al.[20] Umbilical artery Doppler studies were performed on a free-floating umbilical cord loop for each fetus. The pulsatility index (PI) was calculated and averaged over at least 3 consecutive measurements. Umbilical artery PI values above the 95th percentile were considered abnormal.[21] Middle cerebral artery Doppler studies were also performed for all fetuses. The middle cerebral artery measurement was obtained in the transverse plane of the fetal head at the base of the skull at the proximal portion of the vessel immediately after its origin from the circle of Willis. The angle of insonation was kept as close to 0° as possible for all measurements. Pulsatility index values were averaged over at least 3 consecutive measurements. Middle cerebral artery PI values below the 5th percentile were considered abnormal.[22] The cerebroplacental ratio was calculated as a ratio of the middle cerebral artery PI divided by the umbilical artery PI, and values of less than 1.08 were considered abnormal.[23] Given that the cerebroplacental ratio incorporates information regarding the placental status and subsequent fetal response, it has the potential to be able to indicate redistribution of fetal blood flow earlier than would be evident with independent interrogation of either vessel alone.

After all 2D measurements were complete, the volume box was adjusted to obtain an image of the complete circle of Willis. The 3D power Doppler mode was

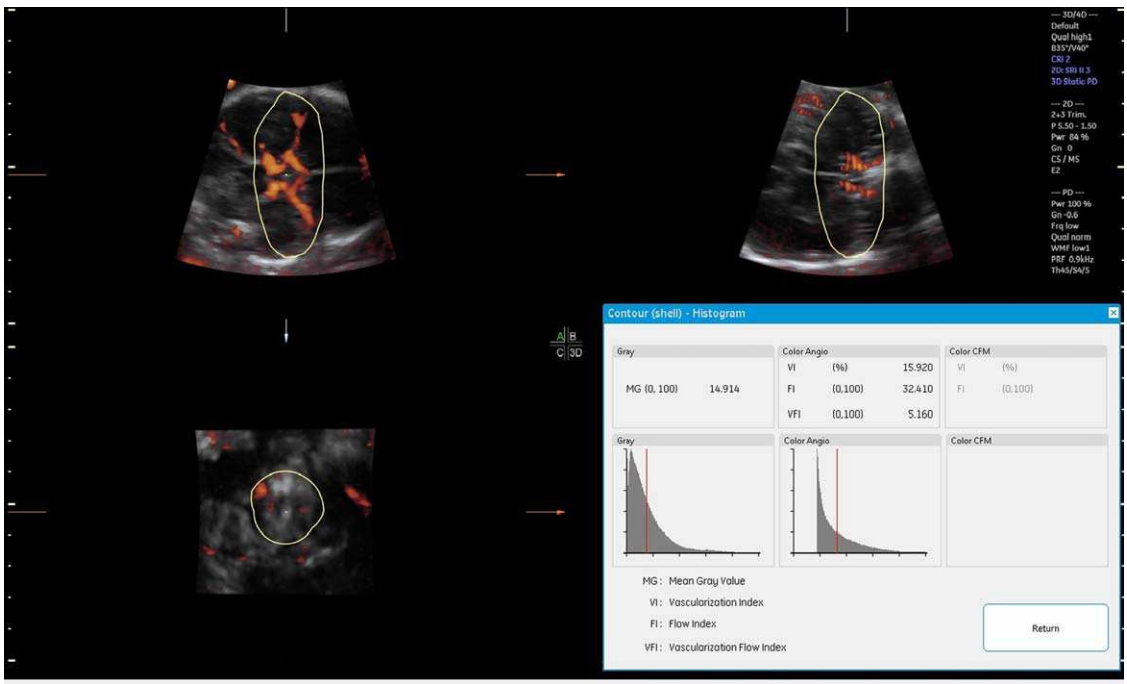
then activated, and a 3D sweep of the region of interest was taken and stored for subsequent offline analysis. The angle of volume acquisition was 90°, and the duration of image acquisition lasted from 10 to 15 seconds. All images were acquired by trained obstetric sonographers using preestablished instrument power settings on Voluson 730 Expert ultrasound machines equipped with 4–8-MHz transducers (GE Healthcare, Milwaukee, WI; angio mode, cent; smooth, 4/5; FRQ, low; quality, 16; density, 6; enhance, 16; balance, GO150; filter, 2; actual power, 2 dB; and pulse repetition frequency, 0.9) All study sonographers showed proficiency in obtaining 3D study images, as assessed by the investigators before the start of the study.

Offline analysis was performed by a single operator using Virtual Organ computer-aided analysis (VOCAL) software (3D SonoView; GE Healthcare). At the beginning of the VOCAL analysis, the image was oriented in the standard biparietal diameter biometric plane. With the use of the rotational technique, the acquired image was then rotated at 30° intervals, and the region of interest was outlined in each rotation by the trace method. The region of interest was defined as the middle cerebral artery territory and was outlined by tracing the entire circle of Willis in an ovoid fashion, including both emanating middle cerebral arteries from the inner aspect of the anterior and posterior parietal bones. The vascularization index (VI), flow index (FI), and vascularization-flow index (VFI) were then automatically calculated by the histogram in the VOCAL program for each image (Figure 1). The VI measures the ratio of color voxels to the total number of voxels and represents the density of blood vessels in the region of interest. The FI is the average value of all color voxels and represents the intensity of blood flow in the region. The VFI is the sum of weighted color voxels divided by the total number of voxels in the region and represents both blood flow and vascularization.

To determine the reliability of the measurements, a reproducibility study was performed on 20 randomly selected patients within the cohort. From the stored images, the 3D vascular indices were acquired twice by 2 independent operators who were blinded to their first and the other's measurements. Intraobserver and interobserver variability was expressed by intraclass correlation coefficients.

Maternal demographic information, the medical history, and the obstetric history were obtained from a routine questionnaire administered to all patients at the

Figure 1. Three-dimensional power Doppler evaluation of the middle cerebral artery territory using the VOCAL trace method with histogram analysis of the VI, FI, and VFI.



time of enrollment. Obstetric and neonatal outcomes were abstracted from the medical record at the time of delivery. The primary outcome was all 3D vascular indices. Secondary outcomes included neonatal intensive care unit admission, umbilical cord pH of less than 7.2, 5-minute Apgar score of less than 7, cesarean delivery for nonreassuring fetal status, and the composite adverse neonatal outcome of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolits, and hypoglycemia. Baseline demographic characteristics, 2D Doppler parameters, and 3D vascular indices were compared between FGR and AGA fetuses. Three dimensional vascular indices were also compared between FGR fetuses with and without the secondary neonatal outcomes listed above. Categorical variables were compared by χ^2 statistics, and continuous variables were compared by the Student t test and Mann-Whitney U statistics, as appropriate. The normality of the distribution was tested by the Kolmogorov-Smirnov test. Given the potential for the maternal body mass index (BMI) to attenuate the 3D Doppler signal, a linear regression analysis was used to adjust for this potential confounder. Subgroup analyses were performed in FGR fetuses with and without abnormal umbilical artery Doppler studies as well as in fetuses with confirmed FGR by birth weight. Correlation coefficients were calculated for each 2D Doppler parameter in relation to each 3D vascular index. All statistical analysis was performed with Stata SE version 12.0 software (StataCorp, College Station, TX). $P < .05$ was considered statistically significant.

As there are no known validated reference ranges for the 3D cerebral vascular indices, the power calculation was based on previously published data by Bartha et al.[19] Varying sample sizes were estimated by reducing the difference in means as well as expanding the standard deviations using these baseline data, comparing each vascular index between AGA and FGR fetuses. Given the exploratory nature of these data, the largest sample size was chosen. With a 2-sided α error of .05 and a β error of .20, we estimated that we would need 150 patients in each group to have 80% power to detect a 0.5 difference in the mean VI, a 2.0 difference in the mean FI, and a 0.2 difference in the mean VFI.

Results

A total of 336 patients were enrolled in the study. Twenty-one patients either withdrew from the study or were lost to follow-up. Eight patients were excluded because of inadequate 3D image quality, and 1 patient was excluded after postnatal diagnosis of a chromosomal abnormality. Of the 306 remaining patients, 151 had an estimated fetal weight below the 10th percentile and were compared to 155 AGA controls. On average, women with FGR fetuses were significantly younger, had a lower BMI, and were of lower gravidity and parity compared to the AGA controls. As expected, women with FGR fetuses delivered at a significantly earlier GA and had lower birth weights compared to women with AGA fetuses. There was no significant difference in race, tobacco use, alcohol use, chronic hypertension, and pregestational diabetes between the groups (Table 1).

With regard to 2D Doppler parameters, there was no significant difference in the proportion of fetuses with abnormal umbilical and middle cerebral artery Doppler findings between FGR and AGA fetuses; however, there was a higher proportion of fetuses with an abnormal cerebroplacental ratio in the FGR group. When comparing the 3D vascular indices, there was no significant difference in the VI or VFI between the groups; however, the FI was significantly higher in the FGR fetuses compared to controls (Table 2). This difference remained significant even after adjusting for the maternal BMI. On evaluation of neonatal outcomes, there was no significant difference in any of the 3D vascular indices between FGR fetuses with and without any of the secondary neonatal outcomes (Table 3).

Subgroup analyses were then performed in the FGR group, comparing those with and without abnormal umbilical artery Doppler findings and those with

Table 1. Maternal Demographics and Pregnancy Characteristics Compared Between FGR and AGA Fetuses

Characteristic	FGR (n = 151)	AGA (n = 155)	*P*
Maternal age, y	26.7 ± 6.2	28.9 ± 5.5	<.001
GA at enrollment, wk	31.2 ± 3.4	31.3 ± 3.3	.84
GA at delivery, wk	36.6 ± 3.4	38.3 ± 1.8	<.001
Birth weight, g	2598 ± 2259	3216 ± 538	.001
BMI, kg/m^2	27.1 ± 8.8	28.6 ± 8.5	.14
Gravidity	2.4 ± 1.8	2.9 ± 2.0	.02
Parity	0.8 ± 1.4	1.2 ± 1.6	.01
African American race, %	53.0	46.4	.25
Tobacco use, %	15.9	9.0	.09
Alcohol exposure, %	2	1.9	.97
Chronic hypertension, %	15.9	18.1	.61
Pregestational diabetes, %	4.6	7.7	.26

Data expressed as mean ± SD where applicable.

and without actual birth weights below the 10th percentile for GA. These subgroups were thought to represent those fetuses with true pathologic growth restriction as opposed to constitutional smallness. There was no difference in the proportion of abnormal middle cerebral artery Doppler findings in either subgroup. With regard to the 3D vascular indices, the FI again was significantly higher in those fetuses with abnormal umbilical artery Doppler findings and in those with both an estimated fetal weight and a birth weight below the 10th percentile. There was no significant difference in the VI or VFI in either subgroup (Table 4).

Correlation coefficients between 2D Doppler parameters and each 3D vascular index were then calculated. There was a weak, but significant, negative correlation between the FI and middle cerebral artery PI ($r = -0.34$; $P < .001$). Similarly, the FI and cerebroplacental ratio also showed a weak, but significant, negative correlation ($r = -0.29$, $P < .001$; Figure 2). There was no significant correlation between the VI and VFI and any of the 2D Doppler parameters. With regard to the reproducibility analysis, intraobserver intraclass correlation coefficients were 0.93, 0.98, and 0.87 for the VI, FI, and VFI, respectively. Interobserver intraclass correlation coefficients were 0.89, 0.91, and 0.83 for the VI, FI, and VFI, respectively.

Table 2. Two-Dimensional Doppler Parameters and 3D Vascular Indices Compared Between FGR and AGA Fetuses

Parameter	FGR (n = 151)	AGA (n = 155)	*P*
UA PI > 95th percentile, %	10.6	7.7	.39
MCA PI < 5th percentile, %	5.3	1.9	.11
CPR < 1.08, %	6.0	0.6	.009
VI	6.0 (4.1–9.1)	5.7 (3.7–9.1)	.65
FI	33.9 (29.7–38.1)	32.3 (29.3–35.6)	.009
VFI	2.0 (1.3–3.4)	1.8 (1.1–3.2)	.31

Data are expressed as median (range) where applicable. CPR indicates cerebroplacental ratio; MCA, middle cerebral artery; and UA, umbilical artery.

Table 3. Comparison of 3D Vascular Indices in Relation to Neonatal Outcomes in FGR Fetuses

	3D Vascular Index		
Parameter	Yes	No	*P*
Neonatal intensive care unit admission (n = 17)			
VI	7.2 (5.1–9.6)	5.9 (3.8–9.0)	.13
FI	32.5 (30.6–36.6)	34.1 (29.7–38.2)	.41
VFI	2.1 (1.7–3.3)	1.9 (1.2–3.4)	.24
Arterial cord pH < 7.2 (n = 11)			
VI	5.8 (4.6–11.9)	6 (4.1–9.1)	.54
FI	36.6 (31.3–38.4)	33.7 (29.7–38.1)	.28
VFI	2.1 (1.5–4.0)	2.0 (1.2–3.3)	.43
5-min Apgar < 7 (n = 6)			
VI	7.9 (5.8–11.7)	5.9 (4.0–9.0)	.18
FI	34.4 (27.1–36.6)	33.9 (29.9–38.1)	.62
VFI	2.6 (2.0–4.7)	1.9 (1.3–3.3)	.23
Cesarean delivery for nonreassuring fetal status (n = 15)			
VI	5.8 (3.4–9.20)	6.0 (4.2–9.0)	.76
FI	33.8 (29.7–36.6)	34.1 (29.8–38.1)	.80
VFI	2.0 (1.1–4.0)	2.0 (1.3–3.3)	.86
Composite adverse neonatal outcome (n = 96)[a]			
VI	6.4 (4.2–10.1)	5.8 (3.8–7.7)	.14
FI	34.5 (29.7–38.5)	33.3 (29.9–37.6)	.43
VFI	2.1 (1.4–3.5)	1.8 (1.1–2.8)	.14

Data expressed as median (range).
[a]Respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and hypoglycemia.

Discussion

Our study demonstrates that the FI, as quantified by 3D power Doppler ultrasound, is significantly higher in FGR compared to their AGA controls. This same increase in the FI also was observed in subanalyses evaluating only FGR fetuses with abnormal umbilical artery Doppler findings and fetuses with confirmed birth weights below the 10th percentile. This finding was in contrast to the other 3D vascular indices, VI and VFI, which did not differ significantly between the groups. Despite this observed increase in the FI in the FGR fetuses, there was no significant difference in the proportion of abnormal middle cerebral artery Doppler PI values between the FGR and AGA fetuses. This finding suggests that changes in the FI may be more subtle signs of brain blood flow redistribution, which may be evident before changes in conventional 2D pulsed wave Doppler measurements of the middle cerebral artery are measurable. Finally, there was no difference in any of the 3D vascular indices with regard to neonatal outcomes in the FGR fetuses; however, our study was not powered to fully evaluate these rare secondary outcomes.

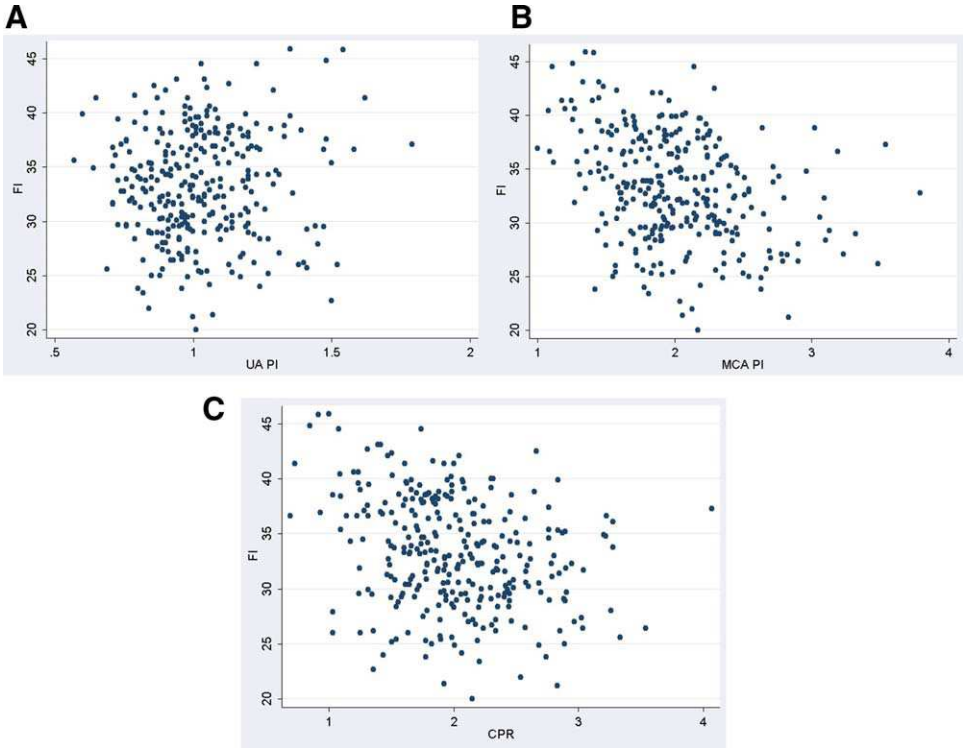
The normal physiologic response to a hypoxic insult, such as occurs in FGR, is for the fetus to preferentially redistribute blood flow to vital organs such as the brain, heart, and adrenal glands at the expense of other less vital organs such as the splanchnic circulation. This

Table 4. Subgroup Analysis of 2D Doppler Parameters and 3D Vascular Indices by Abnormal Doppler Findings and by Persistent Versus Resolved FGR

FGR With and Without UA Doppler Abnormalities			
Parameter	**FGR + Abnormal UA Doppler (n = 16)**	**FGR + Normal UA Doppler (n = 135)**	***P***
MCA PI < 5th percentile, %	12.5	4.4	.17
CPR < 1.08, %	43.7	1.5	<.001
VI	6.8 (4.8–9.3)	5.9 (4.1–9.1)	.50
FI	38.1 (32.6–43.3)	33.6 (29.7–37.9)	.03
VFI	2.6 (1.6–3.7)	1.9 (1.2–3.3)	.21
Persistent Versus Resolved FGR at Delivery			
Parameter	**Persistent FGR (n = 77)**	**Resolved FGR (n = 74)**	***P***
UA PI > 95th percentile, %	15.6	5.4	.04
MCA PI < 5th percentile, %	3.9	6.8	.43
CPR < 1.08, %	9.1	2.7	.10
VI	6.3 (4.5–9.1)	5.9 (3.7–8.8)	.45
FI	34.9 (32.2–38.5)	32.3 (29.5–37.1)	.005
VFI	2.1 (1.5–3.4)	1.8 (1.1–3.3)	.17

Data are expressed as median (range) where applicable. CPR indicates cerebroplacental ratio; MCA, middle cerebral artery; and UA, umbilical artery.

Figure 2. Scatterplots of 2D Doppler parameters versus FI. **A**, Umbilical artery (UA) PI. **B**, Middle cerebral artery (MCA) PI. **C**, Cerebroplacental ratio (CPR).



response results in vasodilatation of the middle cerebral artery, with increasing cerebral blood flow to supply oxygen and nutrients to support the brain metabolism.[5,24] This vasodilatation is reflected in a decreased PI in the middle cerebral artery, as assessed by 2D pulsed Doppler ultrasound.[10,11] Given that the FI is representative of the intensity of blood flow in a given region, our finding of a higher FI in FGR fetuses may be reflective of this increasing cerebral blood flow, which may be identified before observed 2D changes in the middle cerebral artery PI. The fact that we did not observe a difference in the VI and VFI may suggest that the flow intensity, and not the density of blood vessels, is the driving force behind this brain-sparing response. Although this brain-sparing response was once thought to be a protective mechanism, more recent studies suggest that this incremental increase in cerebral blood flow may lead to both short- and long-term neurodevelopmental dysfunction.[7–9,25] The ability to detect this brain-sparing response earlier in its course could have implications on pregnancy surveillance and delivery timing.

An advantage of 3D power Doppler ultrasound over conventional 2D pulsed Doppler ultrasound is its ability to evaluate an entire region of perfusion as opposed to flow within a single vessel. In addition, 3D power Doppler ultrasound is more sensitive in detecting low-velocity blood flow in small, low-resistance vessels such as those in the fetal brain. Finally, 3D power Doppler ultrasound is not dependent on the angle of insonation, thereby removing that factor as a technical limitation to assessing cerebral perfusion.[26,27] Multiple prior studies have assessed the feasibility of the application of 3D power Doppler ultrasound in quantifying cerebral perfusion in normal gestations.[11–18] Chang et al[15] evaluated 155 normal singleton gestations between 21 and 40 weeks and noticed a significant positive correlation between each 3D vascular index and GA. In contrast, Milani et al[18] conducted a cross-sectional study on 111 normal pregnancies between 26 and 34 weeks and noted a low correlation between the vascular indices and GA. To remove this factor as a source of bias from our study, we chose to match FGR fetuses with AGA controls based on GA. Additionally, we observed a high level of intraobserver and interobserver reproducibility in the application of this method to the fetal brain circulation, consistent with prior study results.[19]

To date, there was only 1 study that applied 3D power Doppler quantification of cerebral perfusion to FGR fetuses. That study demonstrated that all vascular indices were increased in 25 growth-restricted fetuses compared to 100 normally grown fetuses. In addition, a larger proportion of growth-restricted fetuses had cerebral redistribution of blood flow when defined by increased vascular indices versus the conventional measure of a low middle cerebral artery PI (52% versus 20%).[19] Of note, all growth-restricted fetuses in that study had abnormal umbilical artery Doppler findings at the time of evaluation. Recent studies have demonstrated that signs of brain vasodilatation may be present even in the setting of normal umbilical artery blood flow.[28,29] Furthermore, long-term neurodevelopmental dysfunction also has been demonstrated in FGR fetuses with normal umbilical artery Doppler indices. These findings suggest that more sensitive parameters for detecting true pathologic growth restriction are needed.[30–32] By limiting the FGR population to only those with abnormal umbilical artery Doppler indices, a proportion of pathologically growth-restricted fetuses will be missed. It is these fetuses who may benefit the most from investigation of other more sensitive measures of perfusion.

Strengths of our study included its prospective study design as well as our rigorous evaluation of both maternal and neonatal covariates. In addition, we had a very low loss-to-follow-up rate, allowing for the collection of very complete outcome information in addition to the 2D and 3D Doppler parameters. We also were able to perform subgroup analyses in FGR fetuses with and without abnormal umbilical artery Doppler findings as well as those with confirmed birth weights below the 10th percentile. The reproducibility of our results in these subgroups supports the overall robustness of our findings.

Our study was not without limitations, including the lack of serial ultrasound data to evaluate temporal trends in Doppler parameters. In addition, we were not powered to evaluate many of the rare neonatal outcomes that can be associated with pathologic growth restriction, nor were we able to evaluate both short- and long-term neurodevelopmental dysfunction, which may be more related to aberrations in cerebral blood flow than the short-term neonatal outcomes evaluated in this study. Finally, the number of patients with both estimated fetal weights below the 10th percentile and abnormal umbilical artery Doppler indices was low in our study population. Despite these small numbers, the difference in the

FI remained significant. This finding suggests that the observed difference in the FI may actually be an underestimation of the true effect size and may even be magnified in a more enriched population of truly growth-restricted fetuses.

In conclusion, 3D power Doppler quantification of cerebral blood flow is significantly altered in FGR compared to AGA fetuses and may actually be a more sensitive marker of blood flow centralization than 2D middle cerebral artery pulsed Doppler findings. The novel application of this technique in the assessment of FGR may have the potential to identify fetuses with brain-sparing pathophysiologic states earlier in the course of gestation, which could have implications for fetal surveillance strategies and the timing of delivery. Future studies in a cohort of FGR fetuses stratified by abnormal umbilical artery and middle cerebral artery Doppler indices are warranted for validation.

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