Evaluation of Umbilical Vein Blood Volume Flow in Preeclampsia by Angle-Independent 3D Sonography

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Objectives—To investigate the association between umbilical vein blood volume flow and the condition of preeclampsia in an at-risk maternal patient cohort. Umbilical vein volume flow was quantified by a 3-dimensional (3D) sonographic technique that overcomes several limitations of standard sonographic flow measurement methods.

Methods—A total of 35 patients, each with a singleton pregnancy, were recruited to provide 5 patients with preeclampsia, derived as a subset from a 26-patient at-risk group, and 9 patients with normal pregnancies. An ultrasound system equipped with a 2.0–8.0-MHz transducer was used to acquire multivolume 3D color flow and power mode data sets to compute the mean umbilical vein volume flow in patients with normal pregnancies and preeclampsia.

Results—The gestational ages of the pregnancies ranged from 29.7 to 34.3 weeks in the patients with preeclampsia and from 25.9 to 34.7 weeks in the patients with normal pregnancies. Comparisons between patients with normal pregnancies and those with preeclampsia showed weight-normalized flow with a moderately high separation between groups ($P = .11$) and depth-corrected, weight-normalized flow with a statistically significant difference between groups ($P = .035$). Umbilical vein volume flow measurements were highly reproducible in the mean estimate, with an intrapatient relative SE of 12.1% ± 5.9% and an intrameasurement relative SE of 5.6% ± 1.9 %. In patients who developed pregnancy-induced hypertension or severe pregnancy-induced hypertension, umbilical vein volume flow suggested gestational hypertensive disorder before clinical diagnosis.

Conclusions—Results indicate that mean depth-corrected, weight-normalized umbilical vein volume flow is reduced in pregnancies complicated by preeclampsia and that volume flow may indicate hypertensive disorder earlier in gestation. Volume flow measurements are highly reproducible, and further study in a larger clinical population is encouraged to determine whether 3D volume flow can complement the management of preeclampsia and, in general, at-risk pregnancy.

Key Words—basic science; color flow; c-surface imaging; Doppler (obstetrics); Doppler (techniques/physics); high-risk pregnancy; obstetrics; power mode; preeclampsia; 3-dimensional sonography; umbilical vein blood flow; vascular sonography; volume flow

Received April 18, 2017, from the Departments of Radiology (S.Z.P., O.D.K., J.B.F., J.M.R.) and Obstetrics and Gynecology (M.C.T., A.W.K.), University of Michigan, Ann Arbor, Michigan USA. Manuscript accepted for publication September 24, 2017.

Partial funding support was provided by the American Institute of Ultrasound in Medicine Endowment for Education and Research. Equipment support was provided by GE Healthcare.

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Abbreviations
3D, 3-dimensional

doi:10.1002/jum.14507

Umbilical cord blood flow is critical to fetal development, and its importance cannot be overstated. An editorial in *Ultrasound in Obstetrics and Gynecology* by Ferrazzi, entitled "Measurement of Venous Blood Flow in the Human Fetus: a Dream Comes True, but Now for Some Standardization",[1] tells it all.

Umbilical cord flow is among the highly desired parameters for monitoring fetal well-being, since cord flow is directly related to placental volume flow, a parameter considered as important in the fetus as cardiac output and lung perfusion in adults.[2] An accurate, reliable, and rapid method for measuring umbilical cord volume flow would help the obstetric provider identify fetuses with abnormal flow, such as decreased flow in intrauterine growth restriction[3] and potentially those at increased risk for an adverse outcome.

Currently, there are well-known problems with standard sonographic volume flow measurement techniques in terms of the required assumptions: cylindrically symmetric flow velocity profile, circular vessel cross section, and a mean velocity estimate that requires angle correction.[4] Each supposition is tenuous in umbilical cords where vessel paths are helical. Helical geometry generally invalidates the assumption of a cylindrically symmetric flow profile.[5] Angle correction is difficult given the constant change in vessel geometry. In addition, the umbilical vein, which some consider the preferred vessel for analysis,[6,7] is often not circular in cross section. In general, standard volume flow methods are rarely used in clinical practice. Despite these limitations, many investigators have evaluated umbilical cord blood flow in fetal populations and showed that flow is relevant when assessing fetal well-being and placental function.[2,3,8–15]

Our group has been developing and evaluating a 3-dimensional (3D) sonographic method for measuring blood volume flow that overcomes nearly all limitations of standard techniques and is independent of the flow velocity profile, vessel geometry, and vessel angle, as long as there is detectable color signal.[16–19] With this 3D approach, umbilical vein blood volume flow is quantified in a small cohort of patients, and measurements are compared between at-risk pregnancies diagnosed with preeclampsia and normal pregnancies. Gestational timelines for patients with preeclampsia are used to determine whether 3D volume flow can indicate gestational hypertensive disorder before clinical diagnosis. In addition, umbilical vein volume flow measurements are evaluated in terms of intrapatient and intrameasurement variability. Overall, if the 3D method is viable, the approach could simplify umbilical cord volume flow measurement and may provide a new and valuable clinical parameter to assess fetal well-being.

Materials and Methods

Clinical Cohort

A total of 35 patients, each with a singleton pregnancy, were recruited from the University of Michigan Medical Center Maternal-Fetal Medicine Clinics and consecutively enrolled in this prospective study. Each patient provided fully informed written consent to an Institutional Review Board–approved protocol involving transcutaneous measurement of fetal blood volume flow with sonography. The study was Health Insurance Portability and Accountability Act compliant.

Patients were recruited from a population known to be at an increased risk of preeclampsia (risk factors included hypertension, obesity, diabetes, and advanced maternal age). A preeclampsia group was derived as a subset from the at-risk group and consisted of patients who either had preeclampsia at the time of enrollment or who went on to develop preeclampsia. An additional subset of patients without risk factors for preeclampsia or growth abnormalities was also recruited. Overall, the 35-patient cohort could be classified into 3 groups: 21 at-risk patients, 5 patients with preeclampsia, and 9 patients with normal pregnancies.

In utero fetal weight at the time of sonography was estimated on the basis of a spline interpolation of 50th percentile weight data.[20] Patients were followed to full term, and final outcomes were verified in medical records.

Sonographic Data Acquisition

A LOGIQ E9 ultrasound system (GE Healthcare, Milwaukee, WI) equipped with a 2.0–8.0-MHz bandwidth convex array transducer (RAB6-D) was used to acquire multivolume 3D color flow and power mode data sets. A custom imaging preset with scanner parameters optimized for acquiring volume flow data was stored on the system and used in all scans. Each multivolume data set consisted of 30 (nominal) individual volumes. An individual volume acquisition would occasionally be discarded because of fetal or maternal movement during the sweep, but volumes would continue to be acquired sequentially until the multivolume data set was complete. Approximately 5 to 10 minutes were required to collect a multivolume data set.

Two examiners highly skilled in obstetric sonography performed the imaging (M.C.T. and J.M.R.). Each individual imaging study was performed by a single

examiner. Examiners were completely blinded to the volume flow measurement results, since calculations were performed offline.

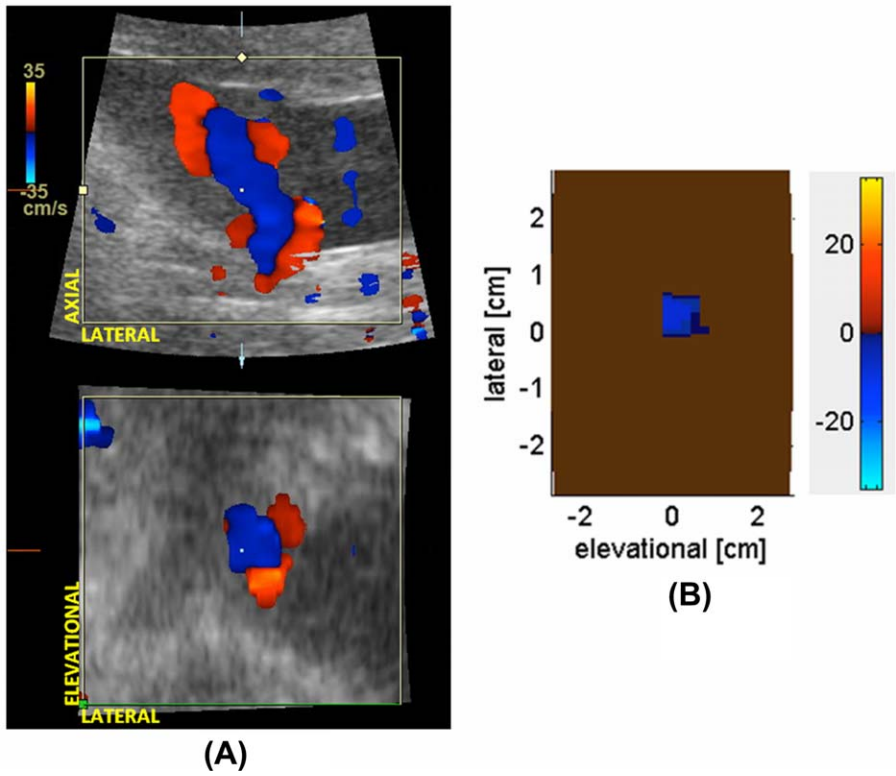
Umbilical vessels of a free cord loop were visualized in the lateral-elevational imaging plane (c-surface) by adjusting the position and tilt angle of the transducer until the c-surface fully intersected the vein and both arteries with a sufficient margin. For the duration of each multivolume scan, the transducer was held primarily in said position unless there was fetal or maternal movement; the transducer would then be repositioned to maintain vessels in the c-surface. The color flow axial focus was aligned directly with, or as near as possible to, the c-surface depth. Umbilical cord imaging depths ranged from 3.3 to 11.0 cm. Glancing exposure to the fetus was largely avoided.

For each patient, mean umbilical vein volume flow was assessed at 3 different free loop positions along the length of the umbilical cord. In 5 patients, volume flow was assessed at only 2 positions, and in 1 patient, volume flow was assessed at only 1 position, for reasons that included poor color flow image quality, patient having to leave the study early, and lack of study time due to a highly active fetus (ie, substantial cord movement).

Volume Flow Analysis

Multivolume 3D data sets were exported as duplex-mode Digital Imaging and Communications in Medicine files, along with the corresponding scanner acquisition settings, for offline processing and prospective analysis. Volume flow for each multivolume data set was computed (S.Z.P.) by custom algorithms implemented in MATLAB (The MathWorks, Natick, MA) through a user-specified c-surface by the method of surface integration of color flow–measured velocity vectors.[21,22] Power mode data were used to correct for the partial volume effect.[16–19]

Figure 1. Color flow image planes of the umbilical cord from an at-risk patient (gestation, 30 weeks 3 days). **A**, Axial-lateral and elevational-lateral (c-surface) views on the GE LOGIQ E9 system. Both views coincide at the marked center point (white dot), which also corresponds to the color flow focal depth of 8.86 cm. The center point is positioned directly over the umbilical vein (blue), and 2 umbilical arteries (red) are shown surrounding the vein. **B**, Elevational-lateral view from **A** shown in the offline analysis after segmenting the vein from the arteries and any adjacent vasculature and color flow artifacts. Color bars indicate velocity in centimeters per second.



Mean volume flow in the umbilical vein is computed by the summation of flow in all voxels that intersect the vessel. Volume flow in each voxel is computed by $Q = v \times (A \times w)$, where v is the mean local color flow–measured velocity; A is the area of the local surface element; and w $(0 \leq w \leq 1)$ is a local weighting factor computed in reference to the power in voxels that contain 100% blood and indicates the voxel area fraction that intersects the vessel. The above equation is only applicable when velocity is normal to the c-surface area element, a condition satisfied by the transducer's scan geometry. Prior articles[16–19] provide further review on power-weighted surface integration of color flow–measured velocity vectors.

Umbilical vein volume flow was computed on an image volume-by-volume basis for each multivolume data set, and overall flow was recorded as the mean of individual flow estimates. Image volume-by-volume flow computation is necessary for the umbilical application because it permits movement of the cord within the imaging volume of interest between subsequent sweeps by the 3D transducer. To compute flow only in the umbilical vein, the vessel was isolated from adjacent arteries by directional criteria and from the local color flow artifact by broad manual segmentation (S.Z.P.), since partial volume correction is ultimately used to determine the vessel's boundary.

Results

The gestational ages of the pregnancies ranged from 22.0 to 37.0 weeks in all 35 patients, from 22.0 to 37.0 weeks in the at-risk patients, from 29.7 to 34.3 weeks in the patients with preeclampsia, and from 25.9 to 34.7 weeks in the patients with normal pregnancies. Figure 1 shows a representative color flow image obtained from a single 3D sweep in an at-risk patient with umbilical vessels in a free cord loop visualized in the axial-lateral and lateral-elevational (c-surface) imaging planes. The umbilical vein and arteries fully intersect the c-surface with an adequate margin. A cross-sectional orientation of the cord in the c-surface (as shown in Figure 1) is the required view for 3D flow measurement and was achieved with all scans performed in this study.

Figure 2 shows the gestational age dependence of umbilical vein volume flow measurement. The mean absolute flow increases with gestational age, and there appears to be a lack of flow separation between patients with normal pregnancies and those with preeclampsia, although several preeclampsia data points are lower in comparison. Note that these flow measurements are not weight normalized.

Figure 3 shows the depth dependence of umbilical vein volume flow measurement. Linear regression analyses show that the mean absolute flow increases with

Figure 2. Umbilical vein volume flow (absolute flow) as a function of gestational age for patients with normal pregnancies and those with preeclampsia. Each data point indicates the mean of a patient's 3 (nominal) free-loop flow measurements. Error bars indicate standard error of the mean.

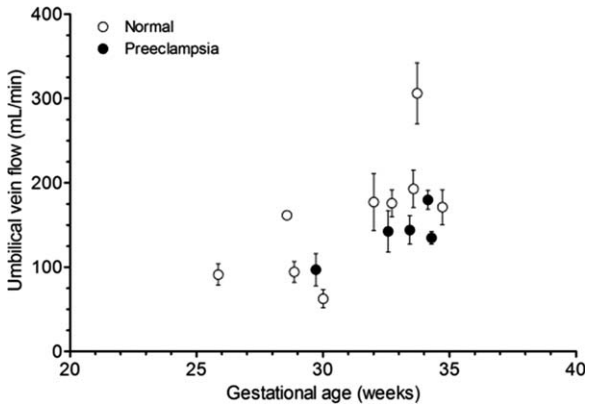
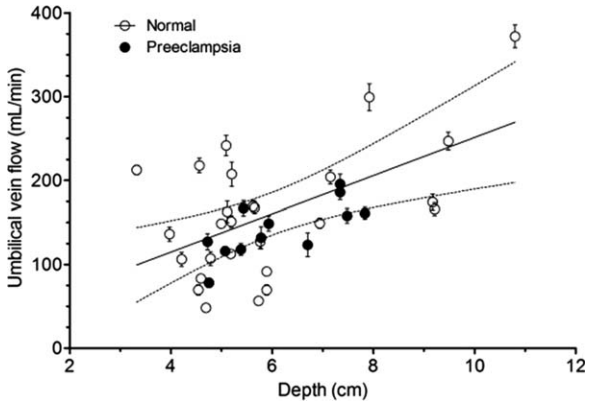


Figure 3. Umbilical vein volume flow (absolute flow) as a function of vessel imaging depth for patients with normal pregnancies and those with preeclampsia. Each data point indicates the mean of 30 (nominal) individual flow measurements at each free loop position. Error bars indicate standard error of the mean. A linear regression with the 95% confidence interval is shown only for the normal group. Linear regression slopes (95% confidence interval; r^2) for the normal and preeclampsia groups were 22.73 (8.85–36.62; 0.31) and 21.16 (7.02–35.30; 0.53) mL/min/cm, respectively.



vessel depth for both patients with normal pregnancies and those with preeclampsia. Figure 3 depicts the linear regression only for the normal group. Details on the linear regressions for both the normal and preeclampsia groups are provided in the legend. A comparison of linear regressions indicated that the difference between slopes for the groups was not significant ($P = .92$).

A variability analysis of umbilical vein volume flow is given in Table 1, where intrapatient variability is based on a patient's free loop flow estimates, and intrameasurement variability is based on the multivolume data set acquired at a free loop position. Multivolume data sets consisted of 28.3 ± 3.3 (mean ± SD) individual volumes. Relative standard deviation (ie, coefficient of variation), and relative standard error values reported in Table 1 were computed by using absolute flow estimates and were averaged over the entire cohort of patients.

Figure 4 provides comparisons between mean umbilical vein volume flow in patients with normal pregnancies and those with preeclampsia based on the following metrics: absolute flow, depth-corrected flow, weight-normalized flow, and depth-corrected, weight-normalized flow. Depth-corrected refers to an adjustment based on the linear regression slope of the patients with normal pregnancies (22.73 mL/min/cm; Figure 3), which accounts for the depth dependence of the elevational beam width when away from the elevational focus. Absolute flow (Figure 4A) and depth-corrected flow (Figure 4B) show moderate separation between groups ($P = .58$ and .41, respectively). Weight-normalized flow (Figure 4C) shows a moderately high separation between groups ($P = .11$). Depth-corrected, weight-normalized flow (Figure 4D) shows a statistically significant difference between groups ($P = .035$).

Table 2 shows the sonographic volume flow scan, gestational diagnosis, and delivery timelines for the patients with preeclampsia. Note that for patients with pregnancy-induced hypertension or severe pregnancy-induced hypertension, the clinical diagnosis was made on delivery.

Table 1. Volume Flow Estimate Variability (All Patients, Absolute Flow)

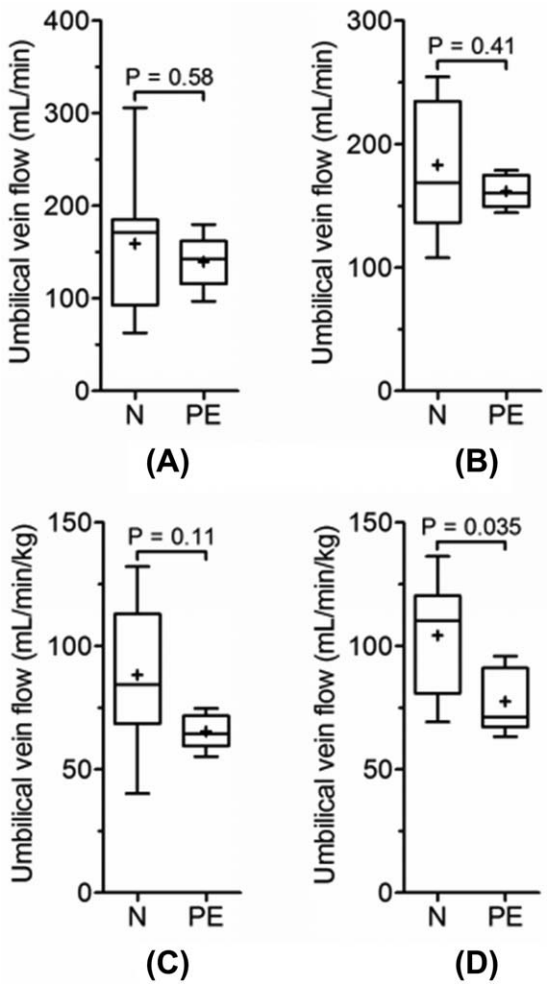
Statistic	Value
Intrapatient relative SD (CV), %	20.3 ± 10.1
Intrameasurement relative SD (CV), %	29.6 ± 9.6
Intrapatient relative SE, %	12.1 ± 5.9
Intrameasurement relative SE, %	5.6 ± 1.9

Data are presented as mean ± SD. CV indicates coefficient of variation.

Discussion

Standard sonographic evaluation of umbilical cord blood flow is not uncommon. Umbilical artery waveform analyses use surrogate flow parameters (eg, systolic-to-diastolic ratios), but such parameters fail to directly

Figure 4. Comparisons of umbilical vein volume flow between patients with normal pregnancies (N) and those with preeclampsia (PE) based on absolute flow (**A**), depth-corrected flow (**B**), weight-normalized flow (**C**), and depth-corrected, weight-normalized flow (**D**). Data points used in each group indicate the mean of a patient's 3 (nominal) free-loop flow measurements. *P* values (2 tailed) are from an unpaired *t* test of independent samples. In the box-and-whisker plots, the box extends from 25th to 75th percentiles; whiskers extend from minimum to maximum values; line is median; and + is mean.



reflect placental-fetal blood flow, and changes often occur too late for use as a screening tool in low-risk pregnancies.[12,23] Furthermore, recent work has shown that umbilical artery velocity indices are generally insensitive for distinguishing many small-for-gestational-age fetuses from those with intrauterine growth restriction.[24] Such indices are typically derived from flow velocity estimates that are acquired by standard pulsed wave techniques, and their values are only related to umbilical cord flow; thus, the indices fail to indicate true flow. Also, the indices are often difficult to interpret and can vary depending on the measurement location in the umbilical cord.[25]

Volume flow estimation is a considerably different approach. Volume flow changes in the umbilical vein have been shown to occur before umbilical artery flow indices become abnormal.[10] Volume flow also has the attractive property of being a parameter that directly reflects placental blood volume flow, the pathophysiologic parameter of interest.[2] Furthermore, because of conservation of mass, volume flow should be equivalent everywhere along the length of the cord, and the average flow in umbilical arteries must equal that in the vein. Therefore, volume flow measurements should be independent of the position where they are acquired along the cord.

Fetal volume flow has been a target of serious investigation since the early 1980s; however, the measure has had continual technical problems such as large measurement variability and the requirement for considerable operator skill.[1] In fact, it has been explicitly stated that volume flow measures are presently too inaccurate and too difficult to reproduce to be clinically relevant.[7] Nevertheless, placental-fetal blood flow is considered such a valued parameter that recent studies have continued to focus on umbilical vein volume flow despite the limitations.[6,7] One group of observers indicated that umbilical vein volume flow estimation is tractable and can be performed by a nonexpert operator,[1] although the ultimate reality seems to be that volume flow estimation using standard pulsed wave techniques, as performed presently, is highly variable and difficult to perform.[1,7,12,24]

Our approach for blood volume flow measurement uses 3D sonography, which overcomes several technical limitations of standard flow methods.[16–18] In theory, this 3D method is independent of the flow velocity profile, vessel geometry, and vessel angle, as long as there is a detectable color signal. Our intention is for blood volume flow estimation in the umbilical vein to be as straightforward as standard color flow imaging. In this study, the 3D method was used to measure umbilical vein volume flow in a small cohort of patients, and results were compared between at-risk pregnancies diagnosed with preeclampsia and normal pregnancies.

Preeclampsia is a condition defined by maternal hypertension and proteinuria and can evolve into eclampsia when seizures develop.[26] Preeclampsia is one of the leading causes of maternal and fetal mortality, although the cause of the condition is still under investigation.[26] A general consensus is that the cause of preeclampsia is placenta based; however, beyond that idea, there are multiple theories and risk factors, which include a history of preeclampsia, nulliparity, multiple pregnancy, a high body mass index, more than 10 years since prior pregnancy, and hypertension.[27] Other associations include low dietary calcium intake and undernutrition.[28–30] Multiple genetic factors have also been associated with preeclampsia.[26] If the onset of preeclampsia could potentially be predicted on the basis of decreased umbilical cord volume flow, it may provide an avenue for investigating and understanding this serious and mysterious condition. In this regard, this study detected a statistically significant difference in mean depth-corrected, weight-normalized umbilical vein blood

Table 2. Study Gestational Timelines for Patients With Preeclampsia

Patient	Volume Flow Scan	Diagnosis (Gestational Age)	Delivery
13	29 wk 5 d	Severe pregnancy-induced hypertension (34 wk 5 d)	34 wk 5 d
16	32 wk 4 d	Mild pregnancy-induced hypertension (32 wk 4 d) Severe pregnancy-induced hypertension (35 wk 1 d)	35 wk 1 d
18	34 wk 1 d	Gestational hypertension (31 wk 0 d) Severe pregnancy-induced hypertension (34 wk 4 d)	34 wk 4 d
19	33 wk 3 d	Pregnancy-induced hypertension (36 wk 5 d)	36 wk 5 d
22	34 wk 2 d	Gestational hypertension (39 wk 0 d)	39 wk 0 d

volume flow between normal pregnancies and those complicated by preeclampsia ($P = .035$).

Based on the study timelines for patients with preeclampsia (Table 2), umbilical vein volume flow suggested gestational hypertensive disorder at or before the clinical diagnosis in 4 of 5 patients (13, 16, 19, and 22). In patients which developed pregnancy-induced hypertension or severe pregnancy-induced hypertension (13, 16, 18, and 19), volume flow suggested the disorder before the clinical diagnosis in all 4 cases. An earlier scheduled sonographic volume flow scan could potentially improve the detection time and lead to earlier intervention. Furthermore, although the analysis in Table 1 showed an elevated estimate variability (relative standard deviation), the relative standard error showed that the estimate precision for mean volume flow approached reasonable values when acquiring a practical number of repeated samples. Implementation of the 3D volume flow method on a 2-dimensional–array transducer could provide repeated samples within seconds, which would substantially reduce the time required to acquire a multivolume data set and to sample multiple free loop positions.

The preliminary results presented here encourage further investigation, but there were some limitations with the current study. First, the size of the recruited population was limited; therefore, these results should be confirmed in a larger population. A sole objective diagnostic judgment is not recommended on the basis of the reported results, given the small sample size. Currently, this proposed application of 3D volume flow in preeclampsia should be regarded as a complementary or additive diagnostic criterion until the conclusions are validated in a larger study. Although preeclampsia was the condition under investigation, in such a small sample size, it was possible that the detected difference in umbilical vein volume flow was more generally suggestive of hypertensive disorder. In a larger study, one could investigate umbilical vein volume flow across a spectrum of hypertensive disorders and determine for which the method would be most sensitive and specific.

Second, multivolume data sets were collected with a mechanically swept 3D ultrasound transducer, which requires several seconds to sweep a volume (ie, to acquire a c-surface) through the umbilical cord. If the fetus moves the cord during this time-consuming step, the flow data, and thus the measurement, are invalid, and additional volume scans are required. Third, the mechanically swept 3D transducer has a fixed elevational focus where the c-surface is best defined. Outside this focal depth, the beam broadens, and a 100% reference blood measurement for partial volume correction may not exist. We had to compensate for imaging depth in flow estimates likely because of this fixed elevational focus. This effect should be reduced with a 2-dimensional–array transducer, for which the elevational focus can be controlled electronically to provide a more tightly focused elevational beam.

Three-dimensional volume flow is currently under development by the Quantitative Imaging Biomarkers Alliance in an effort to evaluate measurement variability across users and systems. Based on these Quantitative Imaging Biomarkers Alliance outcomes, we will be able to determine the degree of variability expected between users for 3D volume flow measurements in the umbilical vein.

In conclusion, with the use of a 3D sonographic method to measure umbilical vein blood volume flow in a small cohort of patients, a difference in flow was detected between normal pregnancies and those complicated by preeclampsia. If this result remains consistent with further investigation, the proposed 3D method could provide a quantitative and robust flow metric to help predict pregnancies that will develop hypertension and proteinuria before signs and symptoms arise.

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