Umbilical Venous Doppler Velocimetry to Supplement Conventional Arterial Doppler to Assess Third Trimester Fetal Growth Restriction

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Objectives:
To evaluate whether the use of umbilical venous Doppler velocimetry and volume flow measurements in near-term pregnancies with suspected fetal growth restriction (FGR) are predictive of immediate perinatal outcome.

Methods:
Consecutive cases with suspected FGR after 28 weeks of gestation were prospectively recruited over 12 months. The fetuses with and without confirmed FGR, as well as normally growing controls, were compared. Fetuses with significant congenital abnormalities were excluded from the analysis.

Results:
A total of 62 confirmed FGR fetuses were compared with a control group of 58 normally growing fetuses. Total umbilical venous flow (TUVF) was significantly lower in the fetuses confirmed to have FGR (198.6 ml/min; standard deviation [SD], 35.3 ml/min) as compared to those without (263.9 ml/min; SD, 50.8 ml/min; p<0.001), but the TUVF per unit birth weight did not differ between the two groups (87.6 ml/min/kg vs 83.1 ml/min/kg). However, the mean TUVF per unit weight was significantly lower (73.2 ml/min vs 87.9 ml/min) for those with a positive composite neonatal morbidity score as compared to those with a negative score.

Conclusion:
Umbilical venous volume flow studies could supplement prediction of immediate morbidity in growth-restricted fetuses.
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Keywords: Blood flow velocity; Fetal growth retardation; Ultrasonography, Doppler, color; Ultrasonography, prenatal

Introduction

Fetuses born with significant growth restriction have an increased risk of adverse perinatal outcomes[1]. Moreover, increased perinatal morbidity and mortality was often associated with the presence of abnormal Doppler waveforms in the umbilical arteries (UAs), either in the form of absent or reversed end-diastolic flow[2,3]. In fetuses with abnormal umbilical arterial Doppler findings, a brain-sparing effect with blood flow redistribution to the brain can often be shown as an increase in diastolic flow to cerebral vessels[4], so that an umbilical-cerebral or placental-cerebral index might be predictive of neonatal outcome[5]. Umbilical venous flow volume has been shown to reflect total cardiac output of the fetus[6]. Possible myocardial dysfunction in fetuses with severe growth restriction may give rise to increased reverse flow in the inferior vena cava, leading to abnormal umbilical venous pulsations[7] and

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an increased distribution of flow to the ductus venosus rather than the fetal liver[8]. However, there was little data to indicate whether umbilical venous Doppler velocimetry and volume flow measurements are useful for fetal assessment, and whether they reflect the degree of compromise. This study was designed to evaluate whether the use of umbilical venous Doppler velocimetry and total umbilical venous flow (TUVF) were predictive of fetal growth restriction (FGR), and immediate perinatal outcomes.

Methods

Consecutive cases with suspected FGR after 28 weeks of gestation were prospectively recruited from the antenatal clinic of a regional obstetric service over a 12-month period. Ultrasound examination for fetal biometry was performed for clinical indications, such as uterus small-for-gestational-age (SGA), or for high-risk patients (e.g. with previous SGA babies or gestational hypertension). The diagnosis of FGR was suspected when fetal biometry and estimated gestational fetal weight fell below the 10th percentile, and such patients were recruited into the study. The subsequent diagnosis of FGR was confirmed if the birth weight fell below the 10th percentile according to local growth charts[9], and these constituted the study group. The remainder in which FGR was not confirmed at birth were regarded as controls. An additional control group of normally growing fetuses were also recruited during that period when they were scanned (between 28 and 40 weeks) for non–growth-related indications, such as placental localisation or assessment of fetal presentations. These were usually consecutive suitable cases that scanned after the index cases in the same clinic session. Fetuses with significant congenital abnormalities were excluded from analysis.

Fetal biometry findings and umbilical arterial and cerebral Doppler findings were routinely provided to the managing obstetric team, but corresponding umbilical venous Doppler findings were not revealed. In this study, the results of fetal biometry and Doppler measurements performed within 10 days of delivery were used for subsequent analysis. The entire study was approved by the local Cluster Research Ethics Review Board.

All ultrasound measurements were performed with a Philips / Advanced Technology Laboratories 5000 machine (Philips ATL Bothwell, WA, USA) using a curvilinear transabdominal broadband probe of 2-5 MHz. The following measurements were recorded: the pulsatility index (PI) of the UAs and middle cerebral arteries (MCAs), the peak systolic velocity in the MCAs, the diameter of the umbilical vein (UV), and the mean average velocity of umbilical venous flow.

Measurements of MCAs were taken from a transverse plane of the fetal head visualising the Circle of Willis; the Doppler gate was placed on a segment of the vessel distal to where it arose from this Circle. All impedance measurements and MCA peak systolic velocity were an average of three or more consecutive regular waveforms on screen in the absence of fetal movements or fetal breathing movements, and with insonation angles of less than 30 degrees. A free umbilical cord loop was chosen for umbilical arterial and venous measurements, and the diameter of the UV was measured as the true 'inner-to-inner' internal diameter of the vessel. The mean cross-sectional area of the UV was calculated from the vessel diameter assuming the cross-section of the vessel to be a perfect circle. The mean flow volume was thus the time-averaged mean flow velocity (intensity weighed) x the vessel cross-sectional area. The velocity measurement was taken from a stable Doppler shift signal for a time-sequence of 10 seconds or more, with an incident angle of less than 30 degrees. A placental/cerebral ratio of the corresponding UA and MCA Doppler indexes was calculated using the UA index as the numerator and the MCA index as the denominator.

Pregnancy outcome was obtained from a comprehensive perinatal database and from a review of individual patient records. Pregnancy complications (including pre-eclampsia, placental abruption, meconium-stained liquor in labour, perinatal mortality) and perinatal outcome parameters (birth weight, gestation and mode of delivery, Apgar scores) were also logged. The birth weight of the babies were stratified into appropriate-for-gestational-age (AGA) or SGA, using local growth chart percentiles with the cut-off for SGA being below the 10th percentile. Those who were SGA were considered to constitute the FGR group, while AGA subjects were regarded as controls. A composite neonatal morbidity score was also recorded. A baby was considered positive for neonatal morbidity if one or more of the following

Table 1. Demographic data and pregnancy outcomes in the presence and absence of fetal growth restriction (FGR)*

Demographic data / pregnancy outcomes	FGR (n=62)	Non-FGR (n=58)	p Value; mean difference (95% confidence interval)
Mean (SD) maternal age (years)	33 (4)	33 (5)	0.76; 0.25 (-1.36 to 1.86)
Parity			
Nulliparous	36 (58%)	30 (52%)	NS
Multiparous	26 (42%)	28 (48%)	
Previous caesarean section	8 (13%)	6 (10%)	NS
Gestational hypertension	5 (8%)	4 (7%)	NS
Antepartum haemorrhage	1 (2%)	1 (2%)	NS
Gestational diabetes/IGT	6 (10%)	8 (14%)	NS
Mean (SD) gestation (weeks)	37.1 (1.7)	38.5 (1.5)	<0.001; -1.33 (-1.97 to -0.99)
Induction of labour	14 (23%)	8 (14%)	
Mode of delivery			
Normal spontaneous delivery	34 (55%)	37 (64%)	NS
Instrumental	9 (15%)	8 (14%)	
Caesarean	19 (31%)	13 (22%)	
Caesarean for fetal distress	5 (8%)	3 (5%)	NS
Mean (SD) birth weight (g)	2292 (276)	3235 (542)	<0.001; -942 (-1097 to -788)
Adjusted birth weight (g) [at 40-week gestation]	2718 (106)	3447 (478)	0.001; -728 (-852 to -605)
Positive for composite neonatal morbidity score	16 (26%)	4 (7%)	NS
Meconium-stained liquor in labour	11 (18%)	8 (14%)	NS
Apgar score			
1 min <4	1	2	NS
5 min <7	1	2	
Shoulder dystocia	0	2 (3%)	NS
Stillbirth / neonatal death	0	0	-

* SD = standard deviation, IGT = impaired glucose tolerance, NS = non-significant

were present: active neonatal resuscitation immediately after birth, any form of ventilatory support, care in the special neonatal unit for over 24 hours, significant metabolic disturbances (hypoglycaemia, electrolyte imbalance), neonatal jaundice requiring treatment, and confirmed neonatal infection given antibiotic therapy. Data analysis was performed using the Statistical Package for the Social Sciences (Windows version 13.0; SPSS Inc, Chicago [IL], US), and Student's *t*-test, Chi-square tests and ANOVA with post-hoc multiple comparisons by the Bonferroni method were used for comparison of the different groups as appropriate.

Results

Of 80 patients recruited based on antenatal ultrasound findings of suspected FGR, the diagnosis was confirmed after birth in 62 (78%). The mean and standard deviation (SD) birth weight of the FGR group was 2292 g and 276 g, respectively. The 18 AGA fetuses in which FGR was not confirmed were regarded as controls and considered together with 40 other AGA fetuses to form the entire control group. Their mean and SD birth weight (3235 g and 542 g) differed from the FGR group (p<0.001). There were no stillbirths or neonatal deaths in this cohort. The mean gestational age

Table 2. Doppler parameters associated with fetal growth restriction (FGR) and non-FGR pregnancies

Parameter*	Mean (SD)		p Value; mean difference (95% confidence interval)
	FGR (n=62)	Non-FGR (n=58)	
UA PI	0.86 (0.19)	0.98 (0.20)	0.001; -0.12 (-0.19 to -0.005)
MCA PI	1.61 (0.33)	1.57 (0.28)	0.58; 0.03 (-0.08 to 0.14)
UA/MCA PI ratio	0.54 (0.22)	0.63 (0.23)	0.039; -0.088 (-0.17 to -0.004)
MCA PSV (cm/s)	0.47 (0.08)	0.46 (0.09)	0.58; 0.006 (-0.015 to 0.028)
UV diameter (mm)	7.94 (0.61)	8.10 (0.57)	0.12; -0.16 (-0.38 to 0.047)
Umbilical venous mean flow velocity (cm/s)	6.82 (1.74)	8.63 (1.99)	<0.001; -1.80 (-2.48 to -1.13)
Mean TUVF (ml/min)	198.60 (35.30)	263.90 (50.80)	<0.001; -65.3 (-81 to -49.5)
Mean TUVF/birth weight (ml/min/kg)	87.60 (17.0)	83.10 (18.2)	0.16; 4.49 (-1.8 to 1.08)

* UA = umbilical artery, PI = pulsatility index, MCA = middle cerebral artery, PSV = peak systolic velocity, UV = umbilical vein. TUVF = total umbilical venous flow, SD = standard deviation

at delivery was earlier for the FGR group than the non-FGR controls (37.1 vs 38.5 weeks; p<0.001); when birth weight adjusted for gestation was used, the difference was still significant (Table 1). There were no differences between the two groups in terms of maternal age, parity, incidence of antenatal complications, mode of delivery, or proportion of Caesarean sections carried out for fetal distress.

Abnormal cerebral/placental ratio (MCA/UA index <1) was demonstrable in six of the FGR cases, of which four had transient or complete absent end diastolic flow. The PI values were used for comparison in the analysis. The umbilical venous waveform was normal with no pathological pulsations in all the fetuses examined. To test the consistency of the time-averaged velocity measurements, a set of preliminary validation data for the first 25 cases was evaluated. When measurements were repeated 3 times for each patient in similar settings, the coefficient of variation as calculated was 5.6%. The mean umbilical flow velocity (6.82 cm/s vs 8.63 cm/s; p<0.001) and TUVF (198.6 ml/min vs 263.9 ml/min, p<0.001) at birth was significantly lower in confirmed FGR fetuses than in the controls. However, the TUVF per unit birth weight did not differ between the two groups (87.6 ml/min/kg vs 83.1 ml/min/kg) [Table 2]. Within the FGR group, 26% (n=16) were positive for the composite neonatal score, compared to only four (7%) in the non-FGR group, though this difference was not statistically significant (Table 1).

When all the fetuses were re-stratified into confirmed FGR, suspected-but-unconfirmed FGR, and the normally growing controls, the suspected FGR group did have significantly lower birth weights than the normally growing controls (ANOVA, p<0.001; Table 3). However, the differences in Doppler indices persisted and were consistent when the confirmed FGR group was compared to the other two groups, while there was little difference between the suspected FGR group and normally growing controls.

A comparison of those with positive neonatal morbidity scores (16/62 in the FGR group and 4/58 in the non-FGR group) and those with zero scores showed that the former had lower actual and adjusted birth weights (2741 g vs 3136 g, p=0.001) as well as higher mean TUVF and TUVF values per unit birth weight

Table 3. Doppler indexes for different birth weight categories in all pregnancies

Parameter*	Mean (SD)		
	I	II	III
	Confirmed FGR (n=62)	Suspected-but-unconfirmed FGR (n=18)	Controls (n=40)
Birth weight (g)	2292 (276)	2893 (292)	3389 (560)
Adjusted birth weight (g)	2718 (106)	3160 (282)	3576 (492)
Gestation (weeks)	37.1 (1.7)	38.1 (1.45)	38.7 (1.51)
UA PI	0.86 (0.19)	0.98 (0.18)	0.98 (0.21)
MCA PI	1.61 (0.33)	1.64 (0.24)	1.54 (0.30)
UA/MCA PI ratio	0.54 (0.22)	0.60 (0.13)	0.64 (0.27)
MCA PSV (cm/s)	0.47 (0.064)	0.48 (0.074)	0.46 (0.045)
UV diameter (mm)	7.94 (0.61)	7.93 (0.62)	8.18 (0.53)
UV flow velocity (cm/s)	6.82 (1.74)	8.38 (1.30)	8.75 (2.24)
Mean TUVF (ml/min)	198 (35.3)	245 (10.7)	272 (59)
Mean TUVF/birth weight (ml/min/kg)	87.6 (17)	85.6 (10.2)	82.1 (20.9)

* UA = umbilical artery, PI = pulsatility index, MCA = middle cerebral artery, PSV = peak systolic velocity, UV = umbilical vein. TUVF = total umbilical venous flow, SD = standard deviation

Table 4. Comparison of Doppler parameters in neonates with positive or negative composite morbidity scores

Parameter*	Positive neonatal morbidity score (n= 20)	Zero neonatal morbidity score (n=100)	p Value; mean difference (95% confidence interval)
Mean (SD) birth weight (g)	2483 (253)	2800 (675)	0.04; -317 (-621 to -13)
Adjusted mean (SD) birth weight (g)	2741 (146)	3136 (518)	0.001; -395 (-627 to -163)
UA/MCA PI ratio	0.57 (0.15)	0.63 (0.24)	0.25; -6.45 (-0.176 to 0.047)
Absent / reversed EDF in UA	4 (20%)	0	NS
MCA PSV (cm/s)	0.46 (0.04)	0.47 (0.06)	0.65; -0.006 (-0.036 to 0.022)
UV diameter (mm)	7.9 (0.58)	8.0 (0.60)	0.40; -0.12 (-0.41 to 0.16)
UV mean (SD) flow velocity (cm/s)	6.25 (1.28)	7.99 (2.08)	0.001; -1.74 (-2.70 to -0.78)
Mean (SD) TUVF (ml/min)	181 (21)	239 (53)	0.001; -58.4 (-82.7 to -34.2)
Mean (SD) TUVF/birth weight (ml/min/kg)	73.2 (7.3)	87.9 (18.1)	0.001; -14.6 (-22.9 to- 6.47)

* UA = umbilical artery, MCA = middle cerebral artery, PI = pulsatility index, EDF = end diastolic flow, PSV = peak systolic velocity, UV = umbilical vein, TUVF = total umbilical venous flow, SD = standard deviation, NS = not significant

ANOVA		p Value; mean difference (95% confidence interval)		
F	p Value	I vs II	I vs III	II vs III
94.5	0.001	0.001; -601 (-750 to -451)	0.001; -1096 (-1262 to -931)	<0.001; -495 (-777 to -214)
91.1	0.001	0.001; -441 (-529 to -352)	0.001; -858 (-986 to -729)	0.002; -416 (-667 to -165)
11.7	0.001	0.02; -0.98 (-1.86 to -0.10)	0.001; -1.57 (-2.23 to -0.90)	0.18; -0.58 (-1.46 to 0.28)
0.303	0.73	0.27; -0.12 (-0.22 to -0.019)	0.29; -0.12 (-0.20 to 0.04)	0.97; 0.004 (-0.11 to 0.11)
0.791	0.45	0.65; -0.038 (-0.20 to 0.13)	0.34; 0.062 (-0.068 to 0.19)	0.22; 0.10 (-0.06 to 0.26)
2.39	0.09	0.29; -0.057 (-0.16 to 0.052)	0.04; -0.10 (-0.20 to -0.003)	0.19; 0.02 (-0.18 to 0.093)
0.87	0.42	0.65; -0.008 (-0.04 to 0.027)	0.29; 0.012 (-0.01 to 0.036)	0.52; -0.044 (-0.11 to 0.052)
2.28	0.10	0.98; 0.002 (-0.32 to 0.33)	0.04; -0.24 (-0.48 to -0.008)	0.12; -0.24 (-0.56 to 0.073)
14.2	0.001	0.001; -1.55 (-2.44 to -0.67)	0.001; -1.92 (-2.71 to -1.13)	0.52; -0.36 (-1.5 to 0.77)
37.46	0.001	0.001; -46.4 (-63.3 to -29.5)	0.001; -73.8 (-92.3 to-55.2)	0.05; -27.4 (-55 to 0.79)
1.21	0.30	0.62; 2.07 (-6.34 to 10.4)	0.14; 5.58 (-1.9 to 13)	0.50; 3.5 (-6.92 to 1.39)

Table 5. Logistic regression using presence or absence of composite neonatal morbidity as the dependent variable

Variable*	B (regression coefficient)	Standard error	Wald	p Value
Constant	43.41	11.5	14.25	0.002
Adjusted birth weight	-0.0076	0.0024	9.746	0.001
UA/MCA PI ratios	-1.307	2.154	0.368	0.540
MCA PSV value	-10.55	8.30	1.61	0.610
Mean umbilical venous flow velocity	0.244	0.316	0.597	0.430
Mean TUVF	-202.5	64.3	9.92	0.001

* UA = umbilical artery, MCA = middle cerebral artery, PI = pulsatility index, PSV = peak systolic velocity, UV = umbilical vein, TUVF = total umbilical venous flow

(73.2 vs 87.9 ml/min/kg, p=0.001) values (Table 4). A logistic regression model using presence or absence of composite morbidity as the dependent variable showed that the adjusted birth weight and the total mean TUVF remained as significant factors predictive of perinatal morbidity (Table 5).

Discussion

Our findings confirmed the utility of conventional umbilical arterial Doppler waveforms for the assessment of FGR; the highest-risk fetuses with abnormal UA Doppler waveforms were associated with significant neonatal morbidity. There was also a slight but significant difference between umbilical/cerebral Doppler ratios between the FGR and non-FGR groups, again confirming that severe FGR was associated with blood flow redistribution that signified possible fetal compromise. While the data showed a significant difference in the umbilical flow velocities and the TUVF volume between FGR and non-FGR fetuses, it was not evident when the mean umbilical flow volume per unit birth weight was compared. In addition, fetuses with significant immediate neonatal morbidity had lower mean umbilical venous flow velocity and flow volumes than the controls, indicating that this parameter was an independent parameter for predicting immediate

neonatal outcome.

The underlying aetiology of FGR has been largely ascribed to placental insufficiency, and a wide variety of fetal responses to placental insufficiency involving many different organ systems have been described[9]. Examination of the vascular flow patterns and waveforms using Doppler measurements have permitted detailed studies of the cardiovascular response of such fetuses. Blood flow in individual organ vascular beds downstream of the cardiac output (arterial Doppler), as well as forward function of the heart (venous Doppler) can be assessed[10]. Umbilical and cerebral arterial Doppler have quite commonly been adopted for surveillance of FGR fetuses[11], and recently ductus venosus flow waveforms have also come into common use[12]. However, determination of venous volume flow has yet to become part of the routine assessment tool, and the relationship between flow volumes and perinatal outcome has not yet been established.

In previous studies, mean TUVF has been shown to reflect the total cardiac output of the fetus[9], such that the larger fetus with higher cardiac outputs have higher flow volumes. Thus, not surprisingly normal larger fetuses had significantly higher TUVF values than smaller FGR fetuses. Thus, it was expected that when controlled for birth weight, the mean TUVF differences between those with and without FGR would be greatly attenuated. However, despite such a proportional relationship, a weight-specific reduction in TUVF was demonstrated whenever there was severe FGR[12]. The main parameter leading to such reductions in flow volume has been ascribed to a reduction of the mean flow velocity in compromised fetuses, probably related to progressive myocardial dysfunction persisting for several weeks before delivery[13].

Our data also revealed a significantly lower umbilical venous flow velocity in FGR fetuses than controls, which was consistent with previously published findings. Apart from the lower umbilical flow velocity in these growth-restricted fetuses, there was preferential distribution of umbilical venous flow to the ductus venosus rather than via the fetal liver that may be part of the blood flow redistribution process[8]. Reference values for the differential flow in the ductus venosus, inferior vena cava, and hepatic veins have been reported[14]. It is possible that the more growth-restricted fetuses exhibit more severe venous shunting, such that those subsequently suffering significant neonatal morbidity may have significantly lower mean UV flow volumes and ductus venosus flow[15]. However, compared to the relatively more straightforward UV measurements, the measurement of ductus flow volume was technically more demanding due to its anatomical site and proneness to measurement errors. Whether the demonstration of such shunting could be an independent or better indicator of fetal compromise requires further evaluation.

There were several limitations to this study. While our data showed good reproducibility, there is as yet no established data to validate this method of volume measurement. The assumption that the diameter of the UV in a free cord loop reflects cross-sectional area or unit flow could also be over-simplistic. There is also a need to establish an appropriate Doppler sample volume size proportional to the inner diameter of the vessel to assume laminar flow, but unfortunately such references are not available in the literature. Thus, the umbilical flow velocities and volumes we describe could be biased by these possible sources of error, and further large-scale validation studies are needed for verification.

Various studies have evaluated the progression of Doppler abnormalities in FGR[16,17], fetuses and attempted to use various parameters to predict adverse outcome and the optimal time for delivery[18,19]. With reference to venous Doppler, the current practice is largely based on qualitative assessment of the ductus venosus waveform[19], and a direct relationship between the TUVF and perinatal morbidity has yet to be established. While our preliminary data support such an association, a larger cohort is required. As we have not included routine DV waveform measurements for direct comparison with the UV flow, further research is needed to compare the use of these two venous parameters in the surveillance of growth-restricted fetuses.

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