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Fetal Umbilical Vein Flow in the Classification of Fetuses with Growth Restriction

Daniele Farsetti [1,2,*], Francesca Pometti [1,2], Grazia Maria Tiralongo [2], Damiano Lo Presti [2], Ilaria Pisani [2], Giulia Gagliardi [2], Barbara Vasapollo [2], Gian Paolo Novelli [3] and Herbert Valensise [1,2]

1 Department of Surgery, Tor Vergata University, 00133 Rome, Italy; francescapometti@hotmail.it (F.P.); valensise@med.uniroma2.it (H.V.)
2 Division of Obstetrics and Gynecology, Policlinico Casilino Hospital, 00169 Rome, Italy; grazia.tiralongo@hotmail.it (G.M.T.); dam.lopresti@gmail.com (D.L.P.); ilaria_pisani@hotmail.it (I.P.); giuly2v@hotmail.it (G.G.); barbara.vasapollo@hotmail.it (B.V.)
3 Department of Integrated Care Processes, Fondazione Policlinico Tor Vergata, 00133 Rome, Italy; gp.novelli@hotmail.com
* Correspondence: dan.farsetti@gmail.com; Tel.: +39-3395238927

Abstract: Objectives: To assess umbilical vein (UV) blood flow in fetal growth restriction (FGR) and in pregnancy with small for gestational age (SGA) fetus. To evaluate the predictive capacity of UV blood flow (QUV) in the discrimination of SGA fetuses from FGR before and after 32 weeks of pregnancy. Methods: Sixty-five women with a recent diagnosis of FGR or SGA fetuses were enrolled and underwent a complete fetal Doppler examination comprehending QUV. We collected SGA (n = 34), early-FGR (n = 9), and late-FGR (n = 22) fetuses. Results: UV diameter was lower in early and late-FGR compared to SGA, while time-averaged maximum velocity (TAMXV) was lower only in early-FGR. UV blood flow (QUV) and QUV corrected for estimated fetal weight (cQUV) were significantly lower in early-FGR and late-FGR compared to SGA. The receiver operating characteristic (ROC) curves analysis of cQUV showed a significant predictive capacity for SGA diagnosis before and after 32 weeks. Conclusions: The evaluation of UV blood flow allows distinguishing SGA fetuses from FGR. The assessment of UV flow should be taken into consideration in future research of new parameters to differentiate SGA from FGR.

Keywords: fetal growth restriction; early-FGR; late-FGR; small for gestational age; umbilical vein blood flow

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1. Introduction

Fetal growth restriction (FGR) occurs when a fetus does not reach its biological potential growth as a consequence of impaired placental function [1]. A fetus is considered small for gestational age (SGA) when its estimated weight or abdominal circumference (AC) fall below the 10th centile of given reference ranges. An SGA fetus is not at increased risk of adverse perinatal outcome, while impaired fetal growth is associated with an increased risk of perinatal mortality and morbidity [2–4].

To differentiate SGA from FGR in the fetuses whose size is below the 10th centile, several methods have been proposed: evaluation of fetal growth velocity, fetal Doppler assessment, and use of biomarkers [2]. An international team of experts established consensus-based definitions for FGR that include biometric and functional parameters [1]. Current research is searching for new parameters to discriminate FGR. Recently, researchers have shown the fundamental role of maternal hemodynamics in pregnancy, and it has been assessed in several obstetric conditions [5–8]. In particular, it plays a key role in the pathophysiological process of fetal growth impairment and the cardiovascular assessment could help to distinguish SGA and FGR fetuses [9–12].

The umbilical vein (UV) blood flow could be considered a surrogate parameter of quantity of oxygen and nutrients reaching the fetus and therefore a measurement of vascu-

lar placental function [13]. In recent years, the advent of advanced ultrasound technology and pulsed Doppler allowed reliable measurements of UV blood flow [14]. Several studies have shown an important role in the prediction of adverse outcome in SGA fetuses and a correlation between fetal growth restriction and reduced UV blood flow [13,15].

The aim of this study is to assess UV blood flow in different forms of fetal growth restriction (early and late) and in pregnancy with SGA fetus, and to evaluate the predictive capacity of UV blood flow in the discrimination of SGA fetuses from FGR before and after 32 weeks of pregnancy.

2. Materials and Methods

This was an observational study performed at the Department of Obstetrics and Gynaecology, Policlinico Casilino Hospital, Rome. During the period between November 2019 and October 2020, we enrolled 65 women with a recent diagnosis of FGR or SGA fetus during the second half of pregnancy. According to the fetal ultrasonographic features and to the gestational age at diagnosis, we collected SGA (n = 34), early-onset FGR (n = 9), and late-onset FGR (n = 22) fetuses.

Diagnosis of FGR fetuses was established according to Gordijn et al. 2016 criteria [1].

Definition of early onset FGR (<32 weeks of gestation):

1. AC below the 3rd centile or estimated fetal weight (EFW) below the 3rd centile or absent end diastolic flow in the umbilical artery

   or

2. Both of the following
   - EFW or AC circumference below the 10th centile and
   - Pulsatility index (PI) of the uterine artery above the 95th centile or pulsatility index in the umbilical artery (UA PI) above the 95th centile.

Definition of late onset FGR (≥32 weeks of gestation):

1. AC below the 3rd centile, or EFW below the 3rd centile

   or

2. At least two of the following:
   - AC below the 10th centile or EFW below the 10th centile
   - AC or EFW crossing centiles >2 quartiles
   - Cerebro–placental ratio (CPR) below the 5th centile or UA PI above the 95th centile.

SGA fetuses are defined by an estimated fetal weight or abdominal circumference less than the 10th centile [2].

The inclusion criteria were singleton pregnancy with a viable fetus at ≥ 20 weeks' gestation, with SGA detected on antenatal ultrasound assessment (EFW < 10th centile) and confirmed at delivery (birth weight < 10th centile).

The exclusion criteria were multiple pregnancy, chromosomal abnormalities, genetic syndrome or major structural fetal abnormality, preterm rupture of membranes, intrauterine infection, undetermined gestational age, and/or pre-existing chronic maternal medical problems.

For the ultrasound examinations, a 2-8 MHz volumetric probe (GE Healthcare, Milan, Italy) was used. Fetal biometry and Doppler parameters were assessed according to local reference values [16–18]. Doppler measurements were obtained from the umbilical artery (UA), middle cerebral artery (MCA), and uterine artery, according to the most modern standard protocol [19]. The CPR was calculated by dividing the pulsatility indices of the MCA by the UA.

The UV Doppler evaluation has been performed at the time diagnosis of SGA or FGR fetuses. The UV was sampled in a free loop along the cord. The UV blood flow (QUV) obtained at the free loop has been shown to be reproducible with a good degree of reliability [14]. The internal vein diameter was measured in a longitudinal plane where the vessel walls were perpendicular to the direction of the beam. The average of three

consecutive diameters (measured by the caliper placement at the inner edge of the vessel) was recorded in centimeters. The UV mean velocity, assuming that the velocity has a parabolic profile, was calculated by the formula:

$$\text{UV mean velocity} = \text{time-averaged maximum velocity (TAMXV)} \times 0.5. \quad (1)$$

The TAMXV was measured during fetal quiescence, with an insonation angle close to zero and below 15 degrees, with the sample volume covering the entire lumen of the vessel and the high-pass filter set at minimum. The TAMXV was obtained by the mean of three different measurements.

The formula used to calculate the QUV was:

$$\text{QUV} = \pi \times (\text{D}/2)^2 \times 0.5 \times \text{TAMXV} \times 60, \quad (2)$$

where QUV is the volume flow (mL/min), D is the diameter of the vein (cm), and TAMXV is the time-averaged maximum flow velocity (cm/s).

The QUV corrected for EFW (cQUV) is obtained dividing QUV by EFW and is expressed in mL/min/kg. The UV diameter, TAMXV, QUV, and cQUV centile were calculated using reference values [20].

Fetal biometry and Doppler measurements were obtained by a single specially trained examiner, using a Voluson E8®, GE Healthcare (Milan, Italy).

Statistical Analysis

Continuous variables were expressed as median (interquartile range), categorical variables were expressed as number and percentage. Comparisons among groups were performed with one-way analysis of variance with Student–Newman–Keuls correction for multiple comparisons and with Kruskall–Wallis test where appropriate. The comparison between proportions was performed using the chi-square test.

Receiver operating characteristic (ROC) curve analysis was performed for cQUV centile and hemodynamic parameters to test the predictive capacity of these variables in identifying SGA fetuses before and after 32 weeks of pregnancy.

3. Results

Table 1 reports the maternal and fetal features of the three groups at the time of enrollment. No significant differences were found in maternal age, body mass index (BMI), and proportions of nulliparous. The percentile of estimated fetal weight (EFW) was higher in SGA compared to early-FGR and late-FGR ($p < 0.001$). As expected, we found significant differences in fetal Doppler velocimetry; in particular, the proportion of patients with UA PI above the 95th centile was higher in early and late-FGR (33% and 18%, respectively) compared to SGA. Moreover, the proportion of patients with CPR below the 5th centile was higher in early- and late-FGR (22% and 14%, respectively).

Table 1. Maternal and fetal features at the enrollment.

	Early FGR (*n* = 9)	**Late FGR (*n* = 22)**	**SGA (*n* = 34)**	***p*-Value ***	
Age (years)	33.00 (33.00 to 34.00)	31.50 (25.25 to 37.00)	32.00 (29.00 to 35.5)	0.29	
BMI (kg/m^2)	24.50 (23.30 to 28.70)	25.89 (24.30 to 27.00)	23.50 (22.25 to 26.54)	0.19	
Nulliparous	6 (67%)	17 (77%)	24 (71%)	0.79	
Gestational age (days)	203 (176 to 209)	244 (234 to 250)	228 (217 to 239)	<0.00001	§ † ‡
AC (mm)	210 (193 to 229)	271 (260 to 284)	262 (248 to 277)		
AC centile	1.00 (1.00 to 2.00)	2.00 (1.00 to 2.00)	5.00 (4.00 to 8.75)	<0.000001	† ‡
EFW (g)	912 (660 to 1080)	1896 (1555 to 1994)	1668 (1414 to 1942)		
EFW centile	2.00 (1.00 to 3.00)	2.00 (1.00 to 3,75)	6.50 (5.00 to 8.75)	<0.001	† ‡
UA PI	1.30 (1.10 to 1.40)	0.96 (0.83 to 1.14)	1.02 (0.86 to 1.10)		
UA PI centile	88.00 (64.00 to 97.00)	66.00 (20.25 to 90.00)	63.00 (29.25 to 73.75)	0.14	

Table 1. *Cont.*

	Early FGR (*n* = 9)	Late FGR (*n* = 22)	SGA (*n* = 34)	*p*-Value *	
UA PI > 95th centile	3 (33%)	4 (18%)	0 (0%)	0.01	† ‡
MCA PI	1.81 (1.70 to 1.98)	1.73 (1.60 to 1.98)	1.95 (1.83 to 2.09)		
MCA PI centile	52.00 (49.00 to 81.00)	38.00 (18.75 to 65.00)	61.50 (52.50 to 76.00)	0.06	
MCA PI < 5th centile	1 (11%)	3 (14%)	0 (0%)	0.09	
CPR	1.52 (1.29 to 1.61)	1.79 (1.55 to 2.26)	1.93 (1.75 to 2.32)		
CPR centile	38.00 (15.00 to 42.00)	30.50 (13.00 to 74.00)	52.00 (34.75 to 77.75)	0.12	
CPR < 5th centile	2 (22%)	3 (14%)	0 (0%)	0.04	† ‡

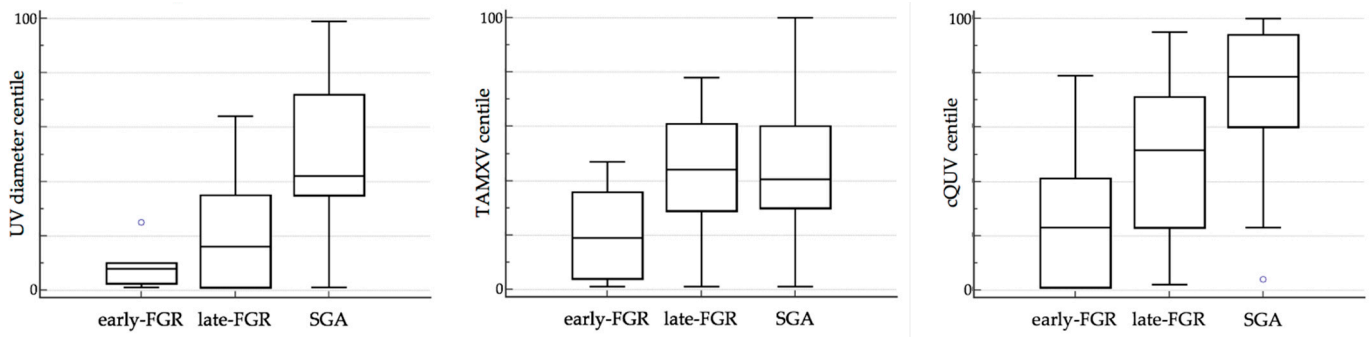
Data are presented as median (interquartile range) or *n* (%). Fetal growth restriction (FGR); small for gestational age (SGA); body mass index (BMI); abdominal circumference (AC); estimated fetal weight (EFW), umbilical artery pulsatility index (UA PI); middle cerebral artery pulsatility index (MCA PI); cerebro-placental ratio (CPR). * Pairwise comparison of group ($p < 0.05$): † early-FGR vs. SGA, ‡ late-FGR vs. SGA, § early-FGR vs. late-FGR.

Table 2 summarized the UV features assessment at the time of enrollment in three groups. The UV diameter centile was significantly lower in early-FGR and late-FGR compared to SGA ($p < 0.00001$). TAMXV centile was significantly lower in early-FGR compared to late-FGR and SGA ($p = 0.04$). The QUV centile values in early-FGR and late-FGR, which were 2.00 (1.00 to 5.00) and 11.52 (1.00 to 24.63) respectively, were significantly lower than SGA with $p < 0.000001$. The cQUV centile was higher in SGA compared to early-FGR and late-FGR ($p < 0.001$). Figure 1 reports the box plot of the UV diameter centile, TAMXV centile, and cQUV centile. The percentage of patients with a cQUV below the 10th centile was higher in early-FGR (38%) and in late-FGR (21%) compared to SGA (3%) ($p = 0.01$).

Table 2. Umbilical vein features at the enrollment.

	Early FGR (*n* = 9)	Late FGR (*n* = 22)	SGA (*n* = 34)	*p*-Value *	
UV diameter (cm)	0.52 (0.46 to 0.56)	0.63 (0.56 to 0.67)	0.68 (0.65 to 0.73)		
UV diameter centile	8.00 (3.00 to 10.00)	16.00 (1.50 to 33.75)	42.00 (35.00 to 71.75)	<0.00001	† ‡
TAMXV (cm/s)	13.00 (11.54 to 13.66)	16.30 (15.05 to 17.11)	15.35 (14.28 to 17.30)		
TAMXV centile	18.90 (5.00 to 34.04)	44.44 (29.02 to 59.49)	40.82 (30.07 to 60.13)	0.04	§ †
QUV (mL/min)	67 (63 to 96)	152 (106 to 173)	177 (153 to 197)		
QUV centile	2.00 (1.00 to 5.00)	11.52 (1.00 to 24.63)	47.52 (28.27 to 66.01)	<0.000001	† ‡
cQUV (mL/min/kg)	81 (60 to 89)	81 (69 to 92)	105 (93 to 131)		
cQUV centile	23.12 (1.00 to 40.30)	51.68 (24.58 to 69.44)	78.82 (60.28 to 93.72)	<0.001	§ † ‡
cQUV < 10th centile	3 (33%)	5 (23%)	1 (3%)	0.02	† ‡

Data are presented as median (interquartile range) or *n* (%). Fetal growth restriction (FGR); small for gestational age (SGA); umbilical vein (UV); time-averaged maximum velocity (TAMXV); umbilical vein blood flow (QUV); umbilical vein blood flow corrected for estimated fetal weight (cQUV). * Pairwise comparison of group ($p < 0.05$): † early-FGR vs. SGA, ‡ late-FGR vs. SGA, § early-FGR vs. late-FGR.



(**a**) (**b**) (**c**)

Figure 1. Multiple comparison graphs (box plot) of UV mean diameter centile (**a**), TAMXV centile (**b**), and corrected for estimated fetal weight (cQUV) centile (**c**) in early-FGR, late-FGR, and SGA.

Table 3 summarizes the predictive performance of cQUV centile in the identification of SGA fetuses before and after 32 weeks of pregnancy. The ROC curve analysis was performed on 16 SGA with gestational age <32 weeks and 18 SGA with gestational age ≥32 weeks.

Table 3. Summary of predictive performance for SGA diagnosis of optimal cut-off value for cQUV, derived from receiver operating characteristics curve analysis.

	Cut Off	AUC (CI 95%)	*p*-Value	Sensibility	Specificity
<32 weeks					
cQUV centile	>45	0.93 (0.75-0.99)	<0.0001	93.75	87.50
≥32 weeks					
cQUV centile	>50	0.72 (0.56-0.85)	<0.01	94.40	50.00

Area under curve (AUC); umbilical vein blood flow corrected for estimated fetal weight (cQUV).

4. Discussion

FGR fetuses present reduced umbilical vein blood flow, as evidenced by lower cQUV, compared to SGA fetuses.

Most of the knowledge about FGR is focused on fetal weight and artery Doppler that become altered as a consequence of placental damage. In this study, we focused on the pathophysiological mechanisms underlying the FGR. In particular, the alterations concern the umbilical vein flow that provides nutrients, oxygen, and promotes the fetal growth.

The QUV and cQUV values are significantly reduced in FGR compared to SGA, regardless of gestational age. The FGR is characterized by the inability to grow in compliance with its genetic perspectives due to a placental damage, which involves a restriction in oxygen and nutrients supply to the fetus and reflects in reduced UV flow. On the contrary, SGA are constitutionally small fetuses that are otherwise healthy. In this case, the materno-fetal hemodynamics is normal and the UV carries an adequate quantity of oxygen and nutrients for fetal well-being.

Similar evidence of significant QUV reduction in FGR fetuses was shown in several previous studies on this topic [13,15,21,22]. Rigano et al. [21] selected an early-FGR population with severe artery Doppler alterations. In this study, the QUV was extremely reduced in FGR, and the mean values of UV features were in line with our results in the early-FGR population.

The correct diagnosis of SGA fetus is fundamental to distinguish fetuses at risk of perinatal and neonatal morbidity and mortality. Modern diagnostic criteria risk being ineffective for the identification of a group of fetuses with growth restriction, especially when artery Doppler values are not yet altered [2,23].

The modern Doppler technology allows obtaining accurate measurements of UV blood flow [14,24]. The UV blood flow is obviously related to the size of the fetus that it supplies, and for this reason, normalized parameters should be used to compare different populations. For this purpose, we selected cQUV, and we founded significant reduced values in early- and late-onset FGR compared to SGA; and the ROC curves analysis identify cut-off values that could differentiate SGA fetuses from FGR with a high degree of certainty. The predictive capacity of UV flow measurements in discrimination of SGA fetuses from early- and late-FGR has not previously been evaluated.

Our results suggest a promising role of cQUV assessment in the diagnosis of SGA fetuses from FGR. We can speculate that the strength of this parameter is largely because it is a surrogate of placental function and it has been demonstrated to be already reduced in FGR fetuses even before the artery Doppler alterations and diagnosis of FGR [21].

One of the strengths of this study is the inclusion of a well-defined cohort of SGA, early-FGR, and late-FGR fetuses, according to current definition of FGR.

The most important limitation is the small number of early-FGR, and further studies with a larger population should be conducted to confirm the high predictive capacity of

UV flow before 32 weeks. Furthermore, this study uses cross-sectional data and a future longitudinal study should be performed.

5. Conclusions

In conclusion, evaluation of UV blood flow can help distinguish SGA fetuses from FGR. We can speculate that the assessment of cQUV could increase the capacity to exclude a FGR diagnosis in a fetus with biometry below 10th centile. The modern knowledge about the pathophysiologic mechanisms causing FGR should be taken into consideration in the future research of new parameters to differentiate SGA from FGR.

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