

Association of umbilical vein flow with abnormal fetal growth and adverse perinatal outcome in low-risk population: multicenter prospective study

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KEYWORDS: Doppler ultrasound; fetal growth restriction; fetal hypoxia; placental insufficiency; umbilical vein

CONTRIBUTION

What are the novel findings of this work?

Reduced umbilical vein flow close to term is associated with stunted fetal growth and adverse perinatal outcome in a low-risk pregnant population. However, the predictive value was moderate to rule out and poor to rule in these outcomes.

What are the clinical implications of this work?

Umbilical vein flow may help in the identification of fetuses at high risk of placental insufficiency, but given its moderate predictive value, it cannot be used as a standalone parameter. Further studies should evaluate its role in multivariable prediction models.

ABSTRACT

Objective To investigate the relationship of umbilical vein flow (UVF) measured close to term with abnormal fetal growth and adverse perinatal outcome in a cohort of pregnancies at low risk of placental insufficiency.

Methods This was a prospective multicenter observational study conducted across two tertiary maternity units. Patients with a singleton appropriate-for-gestational-age fetus between 35 and 38 weeks' gestation were included. Pregnancies at higher risk of placental insufficiency or with fetal anomalies were excluded. At ultrasound examination, the abdominal circumference (AC), umbilical vein diameter and peak velocity of the umbilical vein were measured, and, using these variables, a new variable, UVF/AC, was calculated. The primary outcome was the occurrence of severely stunted fetal growth, defined as a

greater than 40-percentile drop between estimated fetal weight at the third-trimester ultrasound and birth weight. The occurrence of adverse perinatal outcome (defined as one of the following: neonatal acidosis (umbilical artery pH < 7.15 and/or base excess > 12 mmol/L) at birth, 5-min Apgar score < 7, neonatal resuscitation or neonatal intensive care unit admission) was analyzed as a secondary outcome.

Results Between April 2021 and March 2023, 365 women were included in the study. The mean UVF/AC at enrolment was 6.4 ± 2.6 mL/min/cm, and 35 (9.6%) cases were affected by severely stunted fetal growth. Severely stunted fetal growth was associated with a lower mean UVF/AC (5.4 ± 2.6 vs 6.5 ± 2.6 mL/min/cm; $P = 0.02$) and a higher frequency of UVF/AC < 10th percentile (8/35 (22.9%) vs 28/330 (8.5%); $P = 0.01$). Moreover, UVF/AC showed an area under the receiver-operating-characteristics curve (AUC) of 0.65 (95% CI, 0.55–0.75; $P = 0.004$) in predicting the occurrence of severely stunted fetal growth, and the optimal cut-off value of UVF/AC for discriminating between normal and severely stunted fetal growth was 7.2 mL/min/cm. This value was associated with a sensitivity and specificity of 0.77 (95% CI, 0.60–0.90) and 0.33 (95% CI, 0.28–0.39), and positive and negative predictive values of 0.11 (95% CI, 0.07–0.15) and 0.93 (95% CI, 0.87–0.97), respectively. Regarding the occurrence of adverse perinatal outcome, this was associated independently with maternal age (adjusted odds ratio (aOR), 0.93 (95% CI, 0.87–0.99); $P = 0.04$), UVF/AC Z-score (aOR, 0.53 (95% CI, 0.30–0.87); $P = 0.01$) and augmentation of labor (aOR, 2.69 (95% CI, 1.28–5.69); $P = 0.009$). UVF/AC showed an AUC of 0.65 (95% CI, 0.56–0.73;

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Accepted: 8 November 2023

$P = 0.005$) in predicting the occurrence of adverse perinatal outcome, and the optimal cut-off value of UVF/AC for discriminating between normal and adverse perinatal outcome was 6.7 mL/min/cm. This value was associated with a sensitivity and specificity of 0.70 (95% CI, 0.54–0.83) and 0.40 (95% CI, 0.34–0.45), and positive and negative predictive values of 0.14 (95% CI, 0.09–0.19) and 0.91 (95% CI, 0.85–0.95), respectively.

Conclusions Our data demonstrate an association between reduced UVF close to term, severely stunted fetal growth and adverse perinatal outcome in a cohort of low-risk pregnant women, with a moderate ability to rule out and a poor ability to rule in either outcome. Further studies are needed to establish whether the assessment of UVF can improve the identification of fetuses at risk of subclinical placental insufficiency and adverse perinatal outcome. © 2023 The Authors. *Ultrasound in Obstetrics & Gynecology* published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.

INTRODUCTION

Normal fetal growth is the result of a combination of genetic-related growth potential and placental function^{1,2}. Placental insufficiency is the most common cause of fetal growth impairment and is associated with an increased risk of adverse perinatal outcomes, including stillbirth^{3,4}. Close to term, fetuses affected by placental insufficiency slow their growth trajectory, often without falling below the 10th percentile of estimated fetal weight (EFW), and this results in stunted fetal growth⁵. These fetuses, which are at higher risk for adverse perinatal outcome^{6,7}, often remain undetected because the sonographic diagnosis of fetal growth restriction is based mostly upon the detection of fetal smallness rather than stunted fetal growth^{8,9}.

Umbilical vein flow (UVF) is the main determinant of oxygen and nutrient transport from the placenta to the fetus and has been shown to impact on intrauterine fetal growth^{1,2,10,11}. Recently, the assessment of UVF has been suggested for the identification of subclinical placental insufficiency in fetuses considered appropriate-for-gestational age (AGA). In a cohort of low-risk pregnancies at term, Stampalija *et al.*¹² reported that lower values of UVF were associated with a significant abdominal-circumference (AC) drop of over 20 percentiles between the second trimester and delivery. In another study, Prior *et al.*¹³ reported an association between abnormal UVF and intrapartum fetal compromise. However, it is worth noting that there are limited available data assessing UVF in low-risk pregnancies.

The aim of this study was to investigate the correlation of UVF measured close to term with stunted fetal growth and adverse perinatal outcome in singleton pregnancies considered at low risk of placental insufficiency.

METHODS

This was a prospective multicenter observational cohort study conducted across two tertiary maternity units in Italy (University Hospital of Parma, Parma and IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan). The study protocol was approved by the local ethics committee of each of the two participating centers (949/2019/OSS/UNIPR and 3094/2021).

Women were approached during their routine obstetric evaluation near term at the antenatal clinic and provided written informed consent prior to enrolment in the study. The inclusion criteria were uncomplicated singleton pregnancy between 35 and 38 weeks' gestation. Gestational age was calculated based on the crown–rump length measurement performed between 11 + 0 and 13 + 6 weeks. The exclusion criteria were: known hypertensive disorders, gestational or pregestational diabetes, autoimmune disease, body mass index (BMI) > 35 kg/m², drug addiction and fetal structural or chromosomal abnormality. More importantly, patients were not considered eligible for the study if EFW and/or AC fell below the 10th percentile at the routine ultrasound scan, which is performed at 28–32 weeks among low-risk pregnancies in accordance with the Italian protocol of antenatal care. Recruitment was non-consecutive and depended upon the availability of the research team to perform the measurements of the included patients.

All included patients underwent a sonographic examination for the assessment of UVF at the time of enrolment. The umbilical vein diameter was measured on a free loop along the umbilical cord during fetal rest, and the image resolution was optimized to the largest magnification. In order to reduce sampling bias, five consecutive measurements of the umbilical vein diameter between internal-to-internal wall in a B-mode view were performed, with the ultrasound beam perpendicular to the longest axis of the vessel (Figure 1a)¹⁴. The final umbilical vein diameter was calculated as the average of the five measurements. The peak velocity measurement was also performed during fetal rest, in the absence of fetal breathing and body movements, on a longitudinal section of a free loop of the vessel. The time-averaged maximum velocity of the blood flow was reported as the mean of three consecutive measurements obtained with an angle of insonation below 30°, as close as possible to 0° (Figure 1b). The UVF was then calculated using the following equation¹⁵:

$$\text{UVF (mL/min)} = \pi \times (\text{umbilical vein diameter}/2)^2 \times (\text{time-averaged maximum velocity of the umbilical vein} \times 0.5) \times 60.$$

Given that our population was not considered at high risk for placental insufficiency during the enrolment ultrasound scan, only the fetal AC was measured and the corresponding percentile, according to the INTERGROWTH-21st curve, was calculated¹⁶. If the AC was below the 10th percentile, this case would be

excluded from the analysis due to possible late-onset fetal growth restriction. We adjusted UVF for fetal size, dividing UVF by AC, and the new variable obtained, i.e. UVF/AC, was expressed in mL/min/cm. The UVF/AC value that selected the lowest 10% of the observed values was chosen as the 10th percentile, and reduced UVF/AC was defined based on the UVF/AC below this threshold. To reduce interobserver variability of our results, all measurements were performed by only two members of each research team (C.D.I. and B.V. (Parma); F.G. and I.F.C. (Milan)).

On admission to the labor ward, we reassessed the eligibility of the patients, and if they had developed hypertensive disorders of pregnancy, they were excluded from the final analysis. Labor was managed according to the local protocols of each collaborating center. Obstetricians and midwives in charge of intrapartum care were blinded to the results of the Doppler evaluation, in order to avoid bias in their clinical management.

Maternal, pregnancy and perinatal data were retrieved from the medical records. Maternal data included ethnicity, age, parity, first-trimester BMI, weight gain during pregnancy and gestational age at inclusion. Labor data included induction and augmentation of labor, epidural use and mode of delivery. Perinatal outcomes included gestational age at delivery, birth weight, birth-weight percentile (corrected for gender and calculated using the Italian Neonatal Study (INeS) charts¹⁷), 5-min Apgar score, umbilical artery pH, base excess, neonatal primary resuscitation and neonatal intensive care unit (NICU) admission. Data were recorded and stored in a Microsoft Excel (Microsoft Corp., Redmond, WA, USA) secured pseudonymized database, which was accessible only by the members of the research team.

The main outcome of the study was the occurrence of severely stunted fetal growth, defined as a drop of over 40 fetal-weight percentiles between the routine third-trimester ultrasound, performed at 28–32 weeks' gestation, and delivery. The secondary outcomes were

(1) adverse perinatal outcome, defined as one of the following: neonatal acidosis (umbilical artery pH < 7.15 and/or base excess > 12 mmol/L) at birth, 5-min Apgar score < 7, neonatal resuscitation or NICU admission, and (2) operative delivery due to suspected intrapartum fetal compromise.

Statistical analysis

Power sample size calculation was attempted by estimating the incidence of low-risk fetuses with a drop of over 40 fetal-weight percentiles in the late-third trimester. This estimation was based on previous studies, which, in contrast to our work, reported a 30-percentile drop^{7,18}. We estimated the incidence to be between 8% and 10%. Thus, under the assumption of 80% power and an alpha error of 0.05, we calculated we would need 356 patients to demonstrate that reduced UVF/AC might result in a 50% increase (from 9% to 13.5%) in the incidence of the primary outcome (severely stunted fetal growth) in the study population.

Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) version 22 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov test was used to assess the normality of the distribution of the data. Statistical analysis was performed using the chi-square test for categorical variables and the Student's *t*-test or the Mann–Whitney *U*-test as appropriate for continuous variables, and the results are presented as *n* (%), mean $\pm$ SD or median (interquartile range). For subgroup analysis between groups and continuous variables, we performed one-way ANOVA. Within-group comparison was performed with planned contrasts. For subgroup analysis between groups and categorical variables, we performed chi-square test. Multivariable regression analysis was used to control for potential confounding variables. If the variables were not linear, they were converted into Z-scores before entering them into the multivariable model. The prediction of primary outcome was determined by

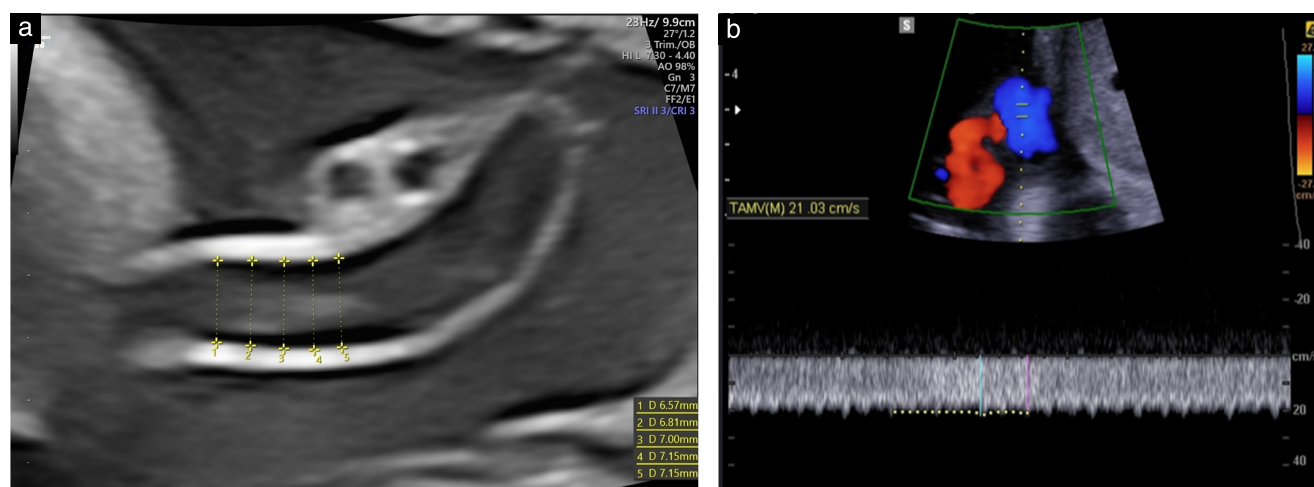


Figure 1 Sonographic measurement of: (a) umbilical vein diameter, whereby final umbilical vein diameter was calculated as average of five measurements (calipers), and (b) umbilical vein peak velocity, using color and pulsed-wave Doppler. TAMV(M), mean time-averaged maximum velocity.

receiver-operating-characteristics (ROC) curve analysis. P -values < 0.05 were considered statistically significant.

This study was conducted following the STROBE guidelines¹⁹.

RESULTS

Between April 2021 and March 2023, 378 women were eligible for this study. Among these, five patients developed pre-eclampsia and eight delivered in a different hospital, and were excluded, leaving 365 women for data analysis (Figure 2). In our population, the mean UVF and UVF/AC at enrolment were 215.6 ± 91.0 mL/min and 6.4 ± 2.6 mL/min/cm, respectively. Gestational age at delivery and birth weight were $39 + 5 \pm 1 + 0$ weeks and 3428 ± 399 g, respectively, with 35 (9.6%) cases affected by severely stunted fetal growth (Table 1).

Table 2 summarizes the demographic and ultrasound characteristics of the study population, according to the presence of severely stunted fetal growth. Severely stunted fetal growth was associated with a lower mean UVF (179.1 ± 92.8 vs 219.5 ± 90.1 mL/min; $P = 0.01$) and mean UVF/AC (5.4 ± 2.6 vs 6.5 ± 2.6 mL/min/cm; $P = 0.02$). Furthermore, there was a higher frequency of UVF/AC $< 10^{\text{th}}$ percentile (8/35 (22.9%) vs 28/330 (8.5%); $P = 0.01$) among fetuses with severely stunted fetal growth. The diagnostic accuracy of the UVF/AC for the prediction of severely stunted fetal growth, showed an area under the ROC (AUC) of 0.65 (95% CI, 0.55–0.75); $P = 0.004$). The optimal cut-off value of the UVF/AC for discriminating between normal and severely stunted fetal growth was 7.2 mL/min/cm. This value was associated with a sensitivity of 0.77 (95% CI, 0.60–0.90) and a specificity of 0.33 (95% CI, 0.28–0.39), a positive and negative predictive value of 0.11 (95% CI, 0.07–0.15) and 0.93 (95% CI, 0.87–0.97), and a positive and negative likelihood ratio of 1.15 (95% CI, 0.94–1.39) and 0.70 (95% CI, 0.37–1.31), respectively.

To explore further the relationship between UVF and stunted fetal growth, we divided our population into three subgroups, based on the percentile difference between

EFW at the third-trimester ultrasound and birth weight: severely stunted fetal growth (fetal-weight drop > 40 percentiles), moderately stunted fetal growth (fetal-weight drop between 20 and 40 percentiles) and normal fetal growth (fetal-weight drop < 20 percentiles). UVF/AC showed a significant direct linear trend (5.4 ± 2.6 vs 5.9 ± 2.2 vs 6.7 ± 2.8 mL/min/cm; $P = 0.002$), according to fetal growth, indicating that the lower the UVF/AC value the more stunted was fetal growth. Planned contrasts analysis within subgroups revealed that the mean UVF/AC in the severely stunted ($t = 2.87$; $P = 0.004$) and in the moderately stunted ($t = 2.65$; $P = 0.008$) fetal-growth groups was significantly lower compared with the normal fetal-growth group (Figure 3). Moreover, the incidence of UVF/AC $< 10^{\text{th}}$ percentile was highest in the severely stunted fetal-growth group, intermediate in the moderately stunted and lowest in the normal group, and this difference was statistically significant (8/35 (22.9%) vs 11/86 (12.8%) vs 17/244 (7.0%); $P = 0.008$) (Table 3).

For the evaluation of the secondary outcomes, we excluded a further five patients from the analysis because they underwent elective Cesarean section for breech presentation. Table 4 summarizes maternal, ultrasound and delivery characteristics of the study population, according to the occurrence of adverse perinatal outcome. Significantly lower maternal age (30.2 ± 5.6 vs 32.3 ± 4.9 years; $P = 0.02$), mean UVF (179.2 ± 55.9 vs 221.6 ± 94.5 mL/min; $P = 0.01$) and mean UVF/AC (5.3 ± 1.6 vs 6.6 ± 2.7 mL/min/cm; $P = 0.006$) were found in fetuses with adverse perinatal outcome. Furthermore, there was a higher frequency of smokers (6/34 (17.6%) vs 17/326 (5.2%); $P = 0.005$) and augmentation of labor

Table 1 Demographic, ultrasound and delivery characteristics of 365 term singleton pregnancies at low risk of placental insufficiency

Characteristic	Value
Maternal age (years)	32.4 ± 5.2
Ethnicity	
Caucasian	306 (83.8)
Sub-Saharan African	29 (7.9)
Mediterranean African	10 (2.7)
Other	20 (5.5)
First-trimester BMI (kg/m^2)*	22.5 ± 3.6
Weight gain during pregnancy (kg)	11.6 ± 3.8
Nulliparous	212 (58.1)
Smoker	24 (6.6)
GA at inclusion (weeks)	$36 + 6 \pm 0 + 5$
Abdominal circumference (mm)	336.5 ± 17.0
UVF (mL/min)	215.6 ± 91.0
UVF/AC (mL/min/cm)	6.4 ± 2.6
UVF/AC $< 10^{\text{th}}$ percentile	36 (9.9)
Severely stunted fetal growth†	35 (9.6)
GA at delivery (weeks)	$39 + 5 \pm 1 + 0$
Birth weight (g)	3428 ± 399
Birth-weight percentile	53.8 ± 27.9
Birth weight $< 10^{\text{th}}$ percentile	17 (4.7)

Data are given as mean $\pm$ SD or n (%). *At presentation. †Defined as greater than 40-percentile drop between estimated fetal weight at third-trimester ultrasound and birth weight. AC, abdominal circumference; BMI, body mass index; GA, gestational age; UVF, umbilical vein flow.

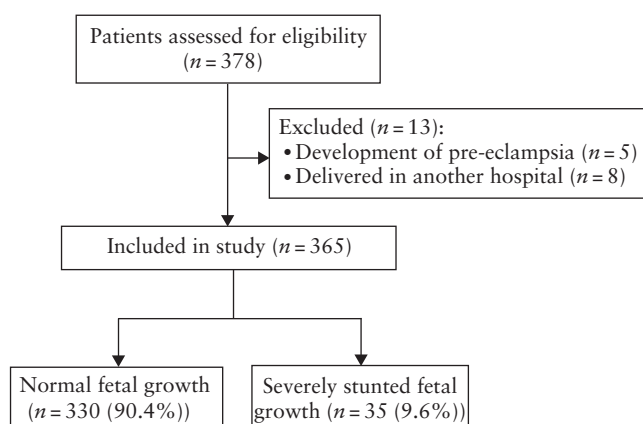


Figure 2 STROBE flowchart summarizing inclusion of singleton pregnancies at low risk of placental insufficiency between 35 and 38 weeks' gestation.

(20/34 (58.8%) vs 116/326 (35.6%); $P = 0.009$) in fetuses with adverse perinatal outcome.

Multivariable logistic regression was used to analyze the relationship between the variables which were significant on univariate analysis and adverse perinatal outcome. We entered the variables in two blocks (the first did not include UVF/AC) in order to assess the effect of UVF/AC on the final model. We found that UVF/AC significantly improved our ability to predict adverse perinatal outcome ($X^2 = 7586$; $P = 0.006$). The final model showed that maternal age (adjusted odds ratio (aOR), 0.93 (95% CI, 0.87–0.99); $P = 0.04$), UVF/AC Z-score (aOR, 0.53 (95% CI, 0.30–0.87); $P = 0.01$) and augmentation of labor (aOR, 2.69 (95% CI, 1.28–5.69); $P = 0.009$) were associated independently with the occurrence of adverse perinatal outcome (Table 5).

When evaluating the diagnostic accuracy of UVF/AC for the prediction of adverse perinatal outcome, UVF/AC showed an AUC of 0.65 (95% CI, 0.56–0.73); $P = 0.005$. The optimal cut-off value of UVF/AC in discriminating between normal and the occurrence of adverse perinatal outcome was 6.7 mL/min/cm. This value was associated with a sensitivity and specificity of 0.70 (95% CI, 0.54–0.83) and 0.40 (95% CI, 0.34–0.45), positive and negative predictive values of 0.14 (95% CI, 0.09–0.19) and 0.91 (95% CI, 0.85–0.95) and positive and negative likelihood ratios of 1.16 (95% CI, 0.93–1.44) and 0.76 (95% CI, 0.47–1.22), respectively.

Finally, there was no significant difference in UVF/AC (6.4 ± 2.6 vs 6.4 ± 2.7 mL/min/cm; $P = 0.99$) or incidence of UVF/AC below the 10th percentile (2/29 (6.9%) vs 34/331 (10.3%); $P = 0.56$) between fetuses that underwent operative delivery due to suspected intrapartum compromise and those that did not (Table S1).

DISCUSSION

This study suggests that reduced UVF, adjusted for AC (UVF/AC), was associated with stunted fetal growth.

Moreover, lower values of UVF/AC were also associated with the occurrence of adverse perinatal outcome, but not with the likelihood of operative delivery due to suspected intrapartum fetal compromise.

The UVF determines the rate of oxygen delivery and nutrient transport to the fetus^{10,11,20}. To secure normal fetal growth, the UVF should be proportional to the amount of tissue and organs to be perfused. Therefore, if UVF/AC is lower than expected for a given fetus, this indicates placental insufficiency, which might result in tissue underperfusion and constrained fetal growth. When this occurs, fetuses deviate from their normal expected

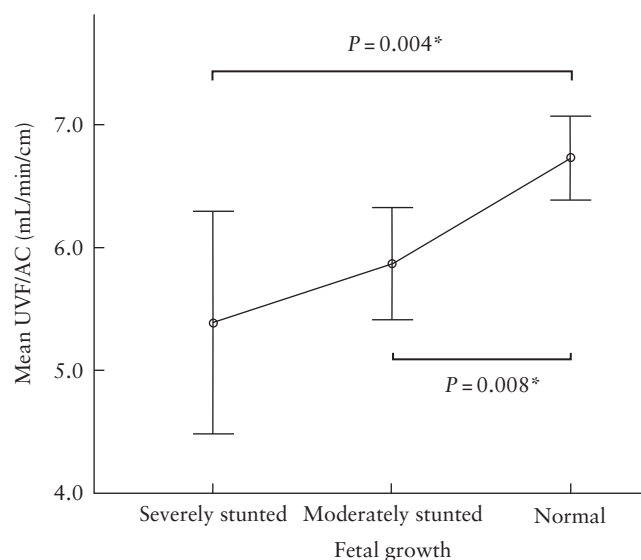


Figure 3 Error bars showing mean with corresponding standard error of umbilical vein flow (UVF) adjusted for abdominal circumference (AC) in cohort of 365 pregnancies at low risk of placental insufficiency, according to fetal growth: severely stunted (fetal-weight drop > 40 percentiles), moderately stunted (fetal-weight drop between 20 and 40 percentiles) and normal (fetal-weight drop < 20 percentiles). *Comparison performed using one-way ANOVA and planned contrasts analysis.

Table 2 Demographic and ultrasound characteristics of 365 term singleton pregnancies at low risk of placental insufficiency, according to percentile drop between estimated fetal weight at third-trimester ultrasound and birth weight

Characteristic	Weight drop		P
	> 40 percentiles (n = 35)	≤ 40 percentiles (n = 330)	
Maternal age (years)	31.7 ± 5.8	32.4 ± 5.1	0.40
Ethnicity			0.19
Caucasian	26 (74.3)	280 (84.8)	
Sub-Saharan African	3 (8.6)	26 (7.9)	
Mediterranean African	2 (5.7)	8 (2.4)	
Other	4 (11.4)	16 (4.8)	
First-trimester BMI (kg/m ²)*	22.9 ± 3.9	22.5 ± 3.6	0.57
Weight gain during pregnancy (kg)	10.8 ± 3.7	11.7 ± 3.8	0.22
Nulliparous	19 (54.3)	193 (58.5)	0.63
Smoker	4 (11.4)	20 (6.1)	0.22
GA at inclusion (weeks)	36 + 5 ± 0 + 4	37 + 0 ± 0 + 5	0.16
UVF (mL/min)	179.1 ± 92.8	219.5 ± 90.1	0.01
UVF/AC (mL/min/cm)	5.4 ± 2.6	6.5 ± 2.6	0.02
UVF/AC < 10 th percentile	8 (22.9)	28 (8.5)	0.01

Data are given as mean ± SD or n (%). *At presentation. AC, abdominal circumference; BMI, body mass index; GA, gestational age; UVF, umbilical vein flow.

growth trajectory, which is identified clinically as a drop in fetal-weight percentile during a time interval. Of note, placental insufficiency is to be considered also when, despite the growth drop, the actual fetal size (EFW and AC) falls within the normal range (i.e. subclinical placental insufficiency).

In this study, we confirmed that lower UVF/AC values are indeed associated with a flattening fetal growth curve. Of note, we chose a different cut-off than the one usually used to define fetal growth restriction (fetal-weight drop over 50 percentiles from the 20-week scan to the last scan)²¹, as the time interval in this study

was shorter (from 28–32-week scan to delivery) and there is no standardized definition of abnormal fetal growth during the third trimester of pregnancy. This is supported by the literature, as some studies have shown that a smaller fetal-weight drop (e.g. > 30 percentiles) is associated with adverse perinatal outcome in AGA fetuses⁷. Interestingly, UVF/AC also appears significantly lower in fetuses affected by moderate degrees of abnormal fetal growth (defined as fetal-weight drop between 20 and 40 percentiles) compared with normally grown fetuses. This is important, because although these fetuses are even farther from meeting the full criteria of growth restriction, they might be still affected by some degree of subclinical placental insufficiency and may therefore be at increased risk of adverse outcome⁶.

Our results are in line with the only previous study that explored the relationship between UVF and fetal growth in a low-risk population¹². That prospective

Table 3 Umbilical vein flow (UVF) adjusted for abdominal circumference (AC) measurements in 365 term singleton pregnancies at low risk of placental insufficiency, according to fetal growth based on percentile difference between estimated fetal weight at third-trimester ultrasound and birth weight

Parameter	Fetal growth			P§
	Severely stunted* (n = 35)	Moderately stunted† (n = 86)	Normal‡ (n = 244)	
UVF/AC (mL/min/cm)	5.4 ± 2.6	5.9 ± 2.2	6.7 ± 2.8	0.002
UVF/AC < 10 th percentile	8 (22.9)	11 (12.8)	17 (7.0)	0.008

Data are given as mean ± SD or *n* (%). *Fetal-weight drop > 40 percentiles. †Fetal-weight drop between 20 and 40 percentiles. ‡Fetal-weight drop < 20 percentiles. §Multiple comparisons among birth-weight-percentile groups performed using one-way ANOVA or chi-square test.

Table 5 Multivariable logistic regression analysis for prediction of adverse perinatal outcome in 360* term singleton pregnancies at low risk of placental insufficiency, from demographic, ultrasound and delivery characteristics

Variable	aOR (95% CI)	P
Maternal age (in years)	0.93 (0.87–0.99)	0.04
Smoker (yes/no)	2.90 (0.97–8.68)	0.06
UVF/AC Z-score	0.53 (0.30–0.87)	0.01
Augmentation of labor (yes/no)	2.69 (1.28–5.69)	0.009

*Five patients excluded due to elective Cesarean section for breech presentation. AC, abdominal circumference; aOR, adjusted odds ratio; UVF, umbilical vein flow.

Table 4 Demographic, ultrasound and delivery characteristics of 360* term singleton pregnancies at low risk of placental insufficiency, according to occurrence of adverse perinatal outcome

Variable	Adverse perinatal outcome (n = 34)†	No adverse perinatal outcome (n = 326)‡	P
Maternal age (years)	30.2 ± 5.6	32.3 ± 4.9	0.02
Ethnicity			0.74
Caucasian	30 (88.2)	273 (83.7)	
Sub-Saharan African	3 (8.8)	24 (7.4)	
Mediterranean African	0 (0)	10 (3.1)	
Other	1 (2.9)	19 (5.8)	
First-trimester BMI (kg/m ²)‡	22.8 ± 3.4	22.4 ± 3.6	0.49
Weight gain during pregnancy (kg)	10.9 ± 4.9	11.7 ± 3.7	0.26
Nulliparous	24 (70.6)	183 (56.1)	0.11
Smoker	6 (17.6)	17 (5.2)	0.005
GA at inclusion (weeks)	37 + 0 ± 0 + 5	37 + 0 ± 0 + 6	0.94
UVF (mL/min)	179.2 ± 55.9	221.6 ± 94.5	0.01
UVF/AC (mL/min/cm)	5.3 ± 1.6	6.6 ± 2.7	0.006
UVF/AC < 10 th percentile	5 (14.7)	31 (9.5)	0.34
Induction of labor	16 (47.1)	113 (34.7)	0.15
Augmentation of labor	20 (58.8)	116 (35.6)	0.009
Epidural use	20 (58.8)	169 (51.8)	0.46
Birth weight (g)	3347 ± 393	3452 ± 399	0.14
Birth-weight percentile	48.6 ± 27.8	54.9 ± 28.1	0.21
Birth weight < 10 th percentile	1 (2.9)	13 (4.0)	0.74

Data are given as mean ± SD or *n* (%). *Five patients excluded due to elective Cesarean section for breech presentation. †Adverse perinatal outcome defined as at least one of the following: neonatal acidosis (umbilical artery pH < 7.15 and/or base excess > 12 mmol/L) at birth, 5-min Apgar score < 7, neonatal resuscitation and neonatal intensive care unit admission. ‡At presentation. AC, abdominal circumference; BMI, body mass index; GA, gestational age; UVF, umbilical vein flow.

study, conducted on 200 low-risk pregnant women, reported an association between lower values of UVF adjusted for EFW at 36 weeks' gestation and abnormal fetal growth (defined as a fetal AC drop ≥ 20 percentiles from 20 weeks' gestation to term). Although our findings confirm these results, we are the first to show that the association between UVF and abnormal fetal growth follows a linear trend from moderate to the most severe degrees of stunting.

Placental insufficiency is also associated with a higher incidence of intrapartum hypoxia, which may lead to increased operative delivery to prevent adverse perinatal outcome^{22,23}. Prior *et al.*¹³ conducted a study on 589 low-risk women and reported that a lower UVF was associated with an increased incidence of Cesarean section due to intrapartum fetal compromise. However, the authors failed to find any significant association with adverse perinatal outcome. Stampalija *et al.*¹² conducted another study on 200 low-risk pregnant women and found no significant association between the UVF and the occurrence of adverse perinatal outcome. To our knowledge, this study is the first to demonstrate that even in low-risk pregnancies, a reduction of the UVF may lead to an increased incidence of adverse perinatal outcome. Notably, this study did not find any association between a reduced UVF/AC and the need for operative delivery due to suspected intrapartum fetal compromise. One possible explanation for this finding is that adverse perinatal outcome, compared with the occurrence of operative delivery, is a more objective and reliable measure for quantifying the unfavorable impact of reduced UVF. Contrarily, the need for obstetric intervention due to suspected intrapartum fetal compromise relies on the subjective assessment of the electronic fetal heart rate monitoring, which has high intra- and interobserver variability^{24,25}.

Recent studies have reported that Doppler parameters, such as cerebroplacental ratio and uterine artery pulsatility index, obtained at late gestation or in active labor are more accurate in the prediction of intrapartum compromise and composite adverse perinatal outcome compared with ultrasound biometric measurements, albeit with poor predictive values^{26–30}. Given the direct correlation between UVF and the amount of oxygen and nutrients transported to the fetus, a reduced UVF may anticipate the deterioration of fetal arterial Doppler in heralding a subclinical placental insufficiency. In such context, the use of the UVF in the low-risk population may become the earliest tool to identify fetuses with subclinical placental insufficiency, and which may benefit from increased ante- and intrapartum surveillance.

Indeed, according to our data, a lower UVF/AC is associated with a significantly higher risk of adverse perinatal outcome, but with a limited positive predictive value. Thus, we believe that the UVF/AC should not be considered as a standalone parameter to identify antenatally those fetuses which are candidates for a more intensive surveillance. Further studies are needed to clarify if the routine assessment of UVF close to term, as a part of multivariable models, may alter the obstetric management

of low-risk populations and lead to improved perinatal outcome.

The main strength of this study is represented by its original and prospective design. The main limitation is the lack of data on fetal arterial Doppler. Given the low-risk nature of our population, we did not measure any of these variables and, therefore, could not exclude any abnormalities. Another limitation is that we did not measure EFW at enrolment, as it is not common practice in our hospitals to perform biometry in low-risk populations close to term. Therefore, we calculated the fetal-growth trajectory by comparing EFW percentile at 28–32 weeks' gestation with the actual birth-weight percentile, which may have introduced bias.

In conclusion, our data demonstrate an association of reduced UVF close to term with stunted fetal growth and adverse perinatal outcome in low-risk pregnant women. Further studies are needed to establish whether the routine assessment of UVF close to term can improve the identification of fetuses with subclinical placental impairment.

ACKNOWLEDGMENT

This study was supported financially in part by The Italian Ministry of Health, Bando Ricerca Corrente, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:



Table S1 Demographic, ultrasound and delivery characteristics of 360* term singleton pregnancies at low risk of placental insufficiency, according to operative delivery for suspected intrapartum fetal compromise (IFC)