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Late-term fetuses with reduced umbilical vein blood flow volume: An under-recognized population at increased risk of growth restriction

Tamara Stampalija [a,b,*], Lorenzo Monasta [c], Moira Barbieri [a,e], Antonella Chiodo [a,d], Mariachiara Quadrifoglio [a], Ilaria Fantasia [a], Leila Lo Bello [a], Valentina Barresi [a], Chiara Ottaviani [a], Daniela Denis Di Martino [e], Eleonora Marangon [a], Laura Travan [f], Maria Bernardon [a], Enrico Maria Ferrazzi [e,g]

[a] Unit of Fetal Medicine and Prenatal Diagnosis, Institute for Maternal and Child Health IRCCS "Burlo Garofolo", Trieste, Italy
[b] Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy
[c] Clinical Epidemiology and Public Health Research Unit, Institute for Maternal and Child Health IRCCS "Burlo Garofolo", Trieste, Italy
[d] Department of Obstetrics and Gynecology, Policlinico Universitario Duilio Casula, University of Cagliari, Monserrato, Cagliari, Italy
[e] Department of Mother, Child and Neonate, Fondazione IRCCS Ca' Granda Ospedale Policlinico di Milano, Milan, Italy
[f] Neonatology Division, Institute for Maternal and Child Health IRCCS "Burlo Garofolo", Trieste, Italy
[g] Department of Clinical and Community Sciences, University of Milan, Milan, Italy

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ABSTRACT

Objectives: To investigate the umbilical vein and uterine arteries blood flow volume (UV-Q, UtA-Q) in late-term pregnancies.
Study design: This was a prospective observational cohort study of singleton pregnancies ≥40 + 0 weeks in which UV-Q and UtA-Q, both absolute and normalized for estimated fetal weight (EFW) values, were evaluated in relation to AC drop of ≥20 percentiles from 20 weeks to term, Doppler signs of fetal cerebral blood flow redistribution and composite adverse perinatal outcome. The presence of neonatal hypoglycaemia and the need of formula milk supplementation were also examined.
Results: The study population comprised 200 women. Fetuses with AC drop (n = 34) had a significantly lower UV-Q and UV-Q/EFW than fetuses without AC drop (n = 166): median UV-Q 184 ml/min (IQR 143–225) vs 233 ml/min (IQR 181–277), p = 0.0006; median UV-Q/EFW 55 ml/min/kg (IQR 42–66) vs 63 ml/min/kg (IQR 48–74), p = 0.03. Fetuses with cerebral blood flow redistribution (n = 48) had a significantly lower UV-Q and UV-Q/EFW than those without (n = 134): median UV-Q 210 ml/min (IQR 155–263) vs 236 ml/min (IQR 184–278), p = 0.04; median UV-Q/EFV 58 ml/min/kg (IQR 45–70) vs 65 ml/min/kg (IQR 50–76), p = 0.04. There was a significant moderate correlation between middle cerebral artery pulsatility index (MCA-PI) and UV-Q and UV-Q/EFW (Spearman Rho −0.20 and −0.20; p = 0.008 and p = 0.006).
Conclusions: The umbilical vein blood flow volume might have a potential role to identify fetuses with stunted growth in late-term pregnancies.

Introduction

Late-term and post-term pregnancies are at higher risk of adverse outcome even in women without identified antenatal risk factors and with fetuses with an appropriate growth for gestational age (AGA) [1]. The majority of stillbirths at term occur in fetuses that are not small-for-gestational age (SGA) or growth restricted fetuses (FGR), and 63% of cases of intrapartum hypoxia occur in pregnancies without detectable risk factors [2]. There is still no agreement on the best biophysical tool able to predict which pregnancy, with an apparently physiological course, is at higher risk of complications. Some evidence suggests that cerebral blood flow redistribution in AGA fetuses is associated with higher incidence of fetal distress during labor [3,4], thus, even AGA fetuses at term might suffer some degree of hypoxemia [5].

* Corresponding author at: Unit of Fetal Medicine and Prenatal Diagnosis, Institute for Maternal and Child Health IRCCS "Burlo Garofolo", Via dell'Istria, 65/1, 34137 Trieste, TS, Italy.
E-mail address: tamara.stampalija@burlo.trieste.it (T. Stampalija).

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Adequate umbilical vein blood flow (UV-Q) is essential to support fetal growth and its oxidative metabolism [6]. Studies on UV-Q have demonstrated reduced blood flow in early and late FGR [7–9] but only few have examined UV-Q in fetuses at term, AGA or unselected, in relation to perinatal outcome [10,11]. Even fewer studies investigated the uterine arteries blood flow volume (UtA-Q) [12,13].

The aim of the study was to investigate UV-Q and UtA-Q in late-term pregnancies with longitudinal fetal growth follow-up in relation to abdominal circumference (AC) drop from 20 weeks to term, Doppler signs of cerebral blood flow redistribution and adverse perinatal outcome.

Materials and methods

This was a prospective observational cohort study conducted between June 2017 to December 2019 in a single tertiary referral centre. The study protocol was approved by the Ethics Committee (CEUR-2019-EM-225). Pregnant women with singleton term pregnancy $\geq$ 40 + 0 weeks were included. Inclusion criteria were: (1) first-trimester dating based on crown rump length measurement, and (2) compliance with the routine ultrasound examinations at 19–21 weeks and at 30–32 weeks of gestation. Twin pregnancies, pregnancies complicated by fetal structural or chromosomal abnormalities or by infections were excluded.

As per local protocol, pregnant women $\geq$ 40 + 0 weeks underwent a complete assessment of maternal and fetal wellbeing. Fetal examination included: biometry (head circumference [HC], biparietal diameter [BPD], abdominal circumference [AC], femur length [LF], and estimated fetal weight [EFW]), amniotic fluid index (AFI), Doppler velocimetry (UtA, umbilical artery [UA] and middle cerebral artery [MCA]) and computerized cardiotocography (cCTG). Fetal biometry and Doppler velocimetry were performed following the ISUOG guidelines [14,15]. The EFW was calculated by using the Hadlock formula [16]. For the purpose of this study, UtA-Q and UV-Q were calculated.

In the absence of any abnormal maternal and/or fetal finding or complications, an expectant management was adopted until 41^{+3}-41^{+4} weeks. If a spontaneous onset of labour did not occur, an induction of labour was planned.

UtA-Q calculation

The UtA were sampled at the level of the common trunk of the uterine artery. The image was optimized to the largest magnification. The diameters were measured on a perpendicular B-mode view of the longitudinal vessel section [6,15,16]. The lumen of the vessels was measured as the average of three successive measurements between the internal-internal wall. The time-averaged maximum velocity (TAMXV) of the blood flow was measured by rotating the probe to align the insonation slope to the vessel, always as close to zero as possible and never above 30°, correcting for the soundproofing angle [6,17,18]. The UtA in the tract between its origin usually shows a pulsatile and laminar flow [18]. Thus, the blood flow calculation can be done applying a correction coefficient (h) to the formula. The coefficient h was calculated according to the fluid dynamic model developed by *Rigano et al* [18]. UtA-Q was calculated based on the following formula:

$$UtAQ = \pi * (D/2)^2 * TAMXV * h$$

where Q is the blood flow volume per minute, D/2 is the radius of the vessel and TAMVX is the average space velocity through the vessel section in a given time t.

The mean of left and right UtA-Q was calculated and expressed in mL/min for the absolute value, and in mL/min/kg for the value normalized for EFW.

UV-Q calculation

The UV was sampled and measured at a free loop along the umbilical cord in the absence of fetal movements and respiratory acts. The image of the vessel was optimized to the largest magnification. The average of three consecutive diameter measurements in B-mode of the vascular lumen between the internal-internal wall was recorded with the insonation slope perpendicular to the vessel [7,17–18] (Fig. 1a). The TAMXV was measured on a steady-state venous velocity profile by rotating the probe to align the insonation slope to the vessel, always as close to zero and never above 30°, correcting for the soundproofing angle [6,17]. Velocity values were reported as the mean of three different measurements of the TAMAX (Fig. 1b). The UV blood flow on straight portion of the vessel was assumed to be a parabolic flow, thus, blood flow volume calculation was done by applying a correction factor equal of 0.5 to the TAMXV [17]. UV-Q was calculated according to the following equation [7]:

$$\mathrm{UVQ} = \pi * (\mathrm{D}/2)^2 * \text{mean TAMXV} * 0.5 * 60$$

The UV-Q was expressed in mL/min for the absolute value, and in mL/min/kg for the value normalized for EFW.

Definitions

The cerebral blood flow redistribution was defined as MCA-PI < 5th percentile. To define an abnormal value of MCA-PI, reference charts by *Arduini et al.* were adopted [19]. The Delphi consensus criteria were adopted to define FGR [20]. Neonatal hypoglycaemia was defined as blood glucose concentration < 45 mg/dL.

Outcomes

A composite abnormal condition at birth was defined as the presence of at least one of the following [21,22]: (1) need for an operative emergency delivery due to non-reassuring fetal status (NRFS); (2) umbilical artery pH < 7.15 or base excess $\geq$ 12 mEq/L; (3) Apgar score at 5 min < 7; and/or (4) admission to neonatal intensive care unit (NICU).

Analysis

The following analysis, a priori decided, were performed:

1. UV-Q and UtA-Q, both absolute and normalized for EFW, were explored in relation to:
   a. fetal AC drop from 20 weeks to the last scan, defined as $\geq$20 percentiles drop, taking into account a 15% of error in ultrasound measurements [23] and similarly to MacDonald et al. [24];
   b. cerebral blood flow redistribution;
   c. composite abnormal condition at birth;
   d. neonatal hypoglycaemia and need of formula milk supplementation;
2. the UV-Q cut-off value of 68 ml/min/kg was evaed for the prediction of composite adverse outcome, as proposed by *Parra-Saavedra et al.* for the prediction of emergency delivery for NRFS and neonatal metabolic acidosis in SGA fetuses [21].

Statistical methods

Continuous data were described by parametric and non-parametric analysis (mean and standard deviation [SD] or median and interquartile range [IQR]) according to the distribution of the variables, verified by the Shapiro-Wilk normality test. In case of data not normally distributed, a log transformation was applied. Categorical data were reported as absolute frequencies and percentages. The Mann-Whitney Rank-sum test was used to assess significant differences between

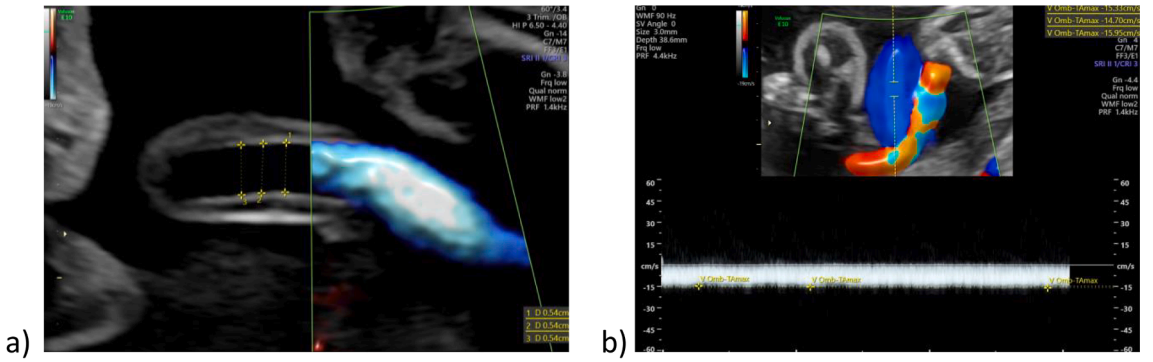

Fig. 1. Ultrasound measurements of: a) umbilical vein diameter, and b) umbilical vein blood flow velocity, for the calculation of the umbilical vein blood flow volume. The measurement of the three diameters is represented and the average value is used for formula calculation.

groups. An exact two-tailed Fisher test was used to assess the association between two dichotomous variables. The correlation between the variables was evaluated with Pearson or Spearman's rank correlation coefficient. A p-value < 0.05 was considered statistically significant. All analyses were conducted with Stata/IC 14.2 for Windows (StataCorp LLC, College Station, USA).

Results

Two-hundred women fulfilling the inclusion criteria were recruited. Maternal characteristics, ultrasound parameters and perinatal outcome data are shown in Table 1. Overall, 190 (95%) fetuses were AGA, 9 (4.5%) fetuses were SGA and one (0.5%) fetus was FGR. Thirty-four (17%) fetuses showed an AC drop of at least 20 percentiles from 20 weeks scan till term. In 18 (9%) cases the MCA was not assessed due to low-lying position of the fetal head. In the remaining 182 cases, 48 (26.4%) fetuses showed signs of cerebral blood flow redistribution. Fourteen women (7%) delivered elsewhere, thus the outcome data were available for 186 mothers and their neonates. Forty-three (23.1%) fetuses had a composite abnormal outcome at birth, 8 (4.3%) had hypoglycaemia, and 43 (23.1%) needed formula milk supplementation.

The mean weight at birth of fetuses with AC drop was significantly lower than that of fetuses without AC drop (3327 ± 356 gr vs 3622 ± 353 gr; $p = 0.0002$). The fetuses without AC drop and without cerebral blood flow redistribution ($n = 131$) had a median UV-Q 234 ml/min (IQR 184–278) and UV-Q/EFW 64 ml/min/kg (IQR 50–75), respectively. The fetuses with the AC drop of at least 20 percentiles had a significantly lower UV-Q and UV-Q/EFW than those without AC drop, while there were no significant differences in UtA-Q and UtA-Q/EFW (Table 2). The same was true for the fetuses with cerebral blood flow redistribution compared to those without cerebral blood flow redistribution (Table 2). There was a moderate statistically significant correlation between the MCA-PI and both UV-Q and UV-Q/EFW (Rho −0.20 and −0.20, $p = 0.008$ and $p = 0.006$, respectively, Fig. 2).

There were no significant differences in UV-Q and UV-Q/EFW between fetuses that experienced a composite abnormal outcome at birth and those that did not (Table 3). However, fetuses that were delivered by an instrumental delivery due to NRFS had a lower UV-Q and UV-Q/EFW than those that were not although this difference did not reach statistical significance for UV-Q: UV-Q median 203 ml/min (IQR 161–260) vs 233 ml/min (IQR 178–274), $p = 0.07$; and UV-Q/EFW median 56 ml/min/kg (IQR 44–68) vs 62 ml/min/kg (IQR 48–75), $p = 0.03$. Fetuses that needed milk formula supplementation had a significantly lower UV-Q than those that were exclusively breastfeed (Table 3). In our cohort, UV-Q/EFW of 68 ml/min/kg was not significantly associated with composite abnormal outcome at birth ($p = 1.0$).

Table 1
Maternal characteristics, ultrasound parameters and perinatal outcome data. Data are represented as number and percentage, mean ± standard deviation or median with interquartile range, as appropriate.

	Late-term pregnancies (n = 200)
Maternal age (years)	32 (29 – 35)
Non-caucasian ethnicity	1 (0.5%)
Maternal pre-pregnancy BMI (kg/m^2)	21.3 (19.7–23.4)
Smoking status, non-smoker	196 (98%)
Nulliparous	127 (63.5%)
Pregnancy conceived by ART	9 (4.5%)
Pregnancy complications	
Gestational hypertension	4 (2%)
Pre-eclampsia	3 (1.5%)
Gestational diabetes	5 (2.5%)
Fetal growth restriction	1 (0.5%)
Small for gestational age fetuses	9 (4.5%)
Ultrasound data	
GA at last ultrasound (weeks)	40.9 (40.8 – 41.0)
EFW at last ultrasound (g)	3653 (3472 – 3837)
EFW percentile	42 (30 – 50)
Abdominal circumference drop ≥ 20 percentiles from 20 weeks to term	34 (17%)
*Cerebral blood flow redistribution**	48/182 (26.4%)
Delivery and outcome data	**(n = 186)****
GA at delivery (weeks)	41.2 (41.1 – 41.6)
BW at last ultrasound (g)	3550 (3340 – 3820)
Induction of labour	44 (23.6%)
Elective cesarean section	11 (5.9%)
Birthweight (gr)	3578 (3340 – 3820)
Composite abnormal outcome at birth	43 (23.1%)
• *Instrumental vaginal or emergency caesarean section delivery for NRFS*	22 (11.8%)
• *Apgar score < 7 at 5′*	0
• *pH < 7.15****	16/155 (10.3%)
• *BE ≥ 12 mEq****	0
• *NICU admission*	10 (5.4%)
Time in NICU (days)	4.4 (2 – 4)
Hypoglycaemia	8 (4.3%)
Exclusive breast feeding	143 (76.8%)
Formula milk supplementation	43 (23.1%)

ART, assisted reproductive technology; BMI, body mass index; EFW, estimated fetal weight; GA, gestational age; MCA, middle cerebral artery; PI, pulsatility index; BE, base excess; GA, gestational age; NICU, neonatal intensive care unit; NRFS, non-reassuring fetal status.
*The middle cerebral artery assessment was not performed in 18 cases.
**Fourteen women delivered elsewhere, thus, outcome and delivery data are missing.
***Neonatal pH or base excess testing was not performed in 31 (16.7%) of the 186 cases, respectively.

Table 2
Umbilical vein and uterine arteries blood flow volume in fetuses with at least 20 percentiles abdominal circumference drop from 20 weeks to term and in foetuses with cerebral blood flow redistribution. Data are represented as median with interquartile range.

	Abdominal circumference ≥ 20 percentiles drop			Cerebral blood flow redistribution		
	No (n = 166)	Yes (n = 34)	p	No (n = 134)	Yes (n = 48)	p
UV-Q (ml/min)	233 (181–277)	184 (143–225)	0.0006	236 (184–278)	210 (155–263)	0.04
UV-Q/EFW (ml/min/kg)	63 (48–74)	55 (42–66)	0.03	65 (50–76)	58 (45–70)	0.04
UtA-Q (ml/min)	216 (130–272)	182 (111–250)	0.2	203 (128–268)	197 (112–252)	0.8
UtA-Q/EFW (ml/min/kg)	58 (35–74)	54 (33–76)	0.7	56 (35–74)	54 (31–69)	0.8

EFW, estimated fetal weight; UtA-Q, uterine arteries blood flow volume; UtA-Q/EFW, uterine arteries blood flow volume normalized for EFW; UV-Q, umbilical vein blood flow volume; UV-Q/EFW, umbilical vein blood flow volume normalized for EFW.

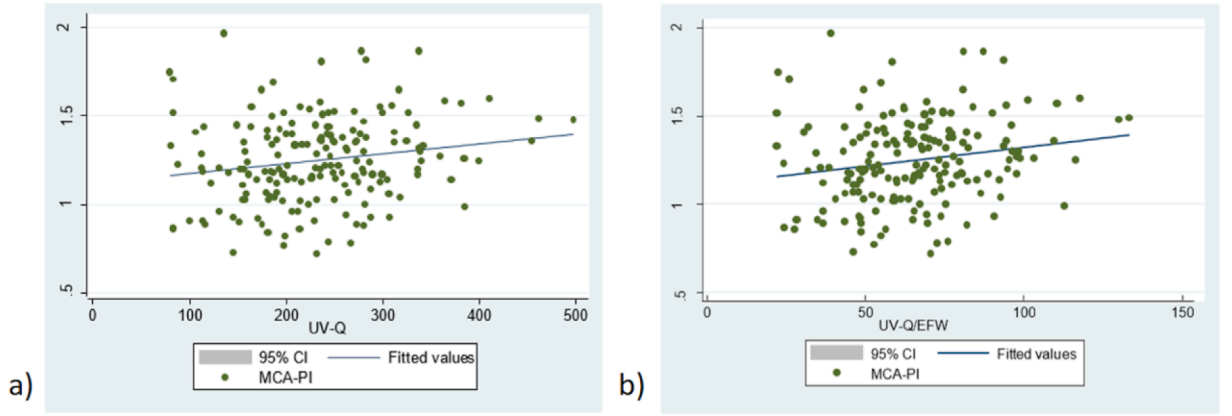

Fig. 2. Correlation between umbilical vein blood flow volume and middle cerebral artery pulsatility index: a) umbilical vein blood flow; b) umbilical vein blood flow normalized for estimated fetal weight. EFW, estimated fetal weight; MCA-PI, middle cerebral artery pulsatility index; UV-Q, umbilical vein blood flow volume; UV-Q/EFW, umbilical vein blood flow volume normalized for EFW.

Table 3
Umbilical vein and uterine arteries blood flow volume in relation to perinatal outcome, hypoglycaemia and need of formula milk supplementation. Data are represented as median with interquartile range.

	Composite abnormal outcome at birth			Hypoglycaemia			Milk formula supplementation		
	No (n = 143)	Yes (n = 43)	p	No (n = 178)	Yes (n = 8)	p	No (n = 143)	Yes (n = 43)	p
UV-Q (ml/min)	233 (175–272)	224 (175–272)	0.9	223 (172–271)	238 (169–264)	0.9	230 (178–277)	203 (154–240)	0.03
UV-Q/EFW (ml/min/kg)	61 (47–74)	59 (42–74)	0.4	61 (46–73)	65 (47–75)	0.6	62 (47–74)	56.0 (44–66)	0.05
UtA-Q (ml/min)	213 (131–268)	188 (109–249)	0.3	207 (123–268)	203 (137–279)	0.8	202 (121–263)	224 (14–305)	0.2
UtA-Q/EFW (ml/min/kg)	59 (36–76)	50 (30–67)	0.1	56 (35–74)	56 (35–74)	0.6	55 (33–71)	62 (40–83)	0.1

EFW, estimated fetal weight; UtA-Q, uterine arteries blood flow volume; UtA-Q/EFW, uterine arteries blood flow volume normalized for EFW; UV-Q, umbilical vein blood flow volume; UV-Q/EFW, umbilical vein blood flow volume normalized for EFW.

Discussion

Our study shows that the UV-Q and UV-Q/EFW are lower in late-term fetuses that experienced a growth drop of at least 20 percentiles and/or with cerebral blood flow redistribution than in those without growth drop or cerebral blood flow redistribution. Fetuses that were delivered by emergency operative delivery during labor due to NRFS had a significantly lower UV-Q. These data underline the potential role of the UV-Q in identifying fetuses at risk of stunted growth and hypoxemia at term and late term.

While the absolute value of UV-Q increases during pregnancy (from 53 ml/min at 20 weeks to 250 ml/min at term), its normalized value for EFW decreases (from 110 ml/min/kg at 20 weeks to 68 ml/min/kg at term), indicating a progressive miss-match between the increasing fetal requests to maintain intrauterine growth and metabolism and the placental availability and function [25]. Several groups explored the UV-Q in early and late FGR [7,9,21], while there is a paucity of studies that explored its value in term AGA or unselected fetal population. *Prior et al.* performed UV-Q measurements in term low-risk pregnancies, observing that fetuses with UV-Q below the 20th percentile were at increased risk of intrapartum fetal compromise [11]. Fetuses that presented normal CTG recordings had a mean UV-Q of 222.4 ml/min, while those with suspicious and abnormal CTG recordings had a mean UV-Q of 210.1 and 201.2 ml/min.

In our cohort, fetuses without AC drop and without cerebral blood flow redistribution had a median UV-Q 234 ml/min (UV-Q/EFW 64 ml/min/kg), and we observed progressively decreasing values of UV-Q and UV-Q/EFW in fetuses with cerebral blood flow redistribution and fetuses with AC drop, that showed the lowest values (UV-Q 210 ml/min-UV-Q/EFW 58 ml/min/kg and UV-Q 184 ml/min-UV-Q/EFW 55 ml/min/kg, respectively).

These findings seem to be in line with the observation that in the early stages of pregnancy fetal nutritional requirements grow exponentially and a placental dysfunction will have a greater impact on fetal

growth. Towards the term of pregnancy placental dysfunction impacts more metabolic requests resulting in persistent hypoxemia without significant detectable impact on fetal growth [26]. In fact, most stillbirths at term occur in AGA fetuses [2]. Therefore, a possible miss-match toward the term between fetal request and placental availability might be the result of an absolute reduction of the UV-Q (inadequate placental perfusion) or a relative reduction of the UV-Q (exaggerated fetal requests), or both. Certainly, an argument against our interpretation might be that most of the decrease in UV-Q is physiological, due to the different fetal weight distribution. Conversely, it is our opinion that the reduced absolute UV-Q indicates an inadequate placental perfusion to which the fetus is forced to adapt.

MacDonald et al. performed a cohort study in fetuses born with a normal birthweight and found that reduced growth velocity of at least 30–35 percentiles was associated with cerebral blood flow redistribution, pH < 7.15 at birth and lower fetal body fat mass [24]. Similarly, our data suggest that there is a proportion of term fetuses that slow their growth trajectory and/or that present signs of cerebral blood flow redistribution, but that do not fulfil the criteria for FGR, in which the UV-Q is reduced.

In line with data of *Prior et al.* [11] in our cohort there were no significant differences in UV-Q between fetuses that experienced a composite adverse outcome and those that did not. One possible explanation might be that our study was not powered enough to show these differences, although it might also be that the rate of instrumental deliveries and delivery management differs largely among centres. Similarly to *Prior et al*, we observed a lower UV-Q in fetuses that were delivered by emergency operative delivery during labour due to NRFS. The median UV-Q in this group of fetuses was 202.9 ml/min, quite similar to the reported value in abnormal CTG group (201.2 ml/min) by Prior et al [11].

Finally, UV-Q was significantly lower in fetuses that required formula milk supplementation at birth. In fact, the new-borns' requests must face the onset of respiratory activity, the maintenance of thermoregulation and, also, metabolic changes and growth processes. Lower nutrient and oxygen delivery may lead to decreased fetal energy reserves as such to require nutrition reinforced by complementary feeding in the immediate post-natal life.

We found no differences in UtA-Q or UtA-Q/EFW, suggesting that the same amount of maternal blood flow supplies the placenta both in fetuses with and without growth drop (mean birthweight 3333gr and 3600gr, respectively). This finding supports studies that minimize the importance of the UtA flow in late-onset growth disorders [27].

The advantages of the study are that this was a prospective cohort in which the UV-Q measurements were blinded to the physician and a longitudinal follow up was available. The main limitation is that the sample size was not powered enough to explore differences in adverse perinatal outcomes. Generally, the main criticism to the UV-Q evaluation is that there are many sources of error making this measure non-reproducible. Nevertheless, the adherence to methodological recommendations resulted in accurate measurements [28,29,30] and our UV-Q values are in accordance with available literature suggesting a reproducible methodology [11]. Finally, it has to be addressed that we did not evaluate the histopathological placental findings, representing this another limitation of the study.

Conclusions

Our data show a lower UV-Q in fetuses at term with a growth drop and/or with cerebral blood flow redistribution. In association with other Doppler parameters, the quantitative assessment of UV-Q may have a potential clinical application in the risk stratification of pregnancies at or near term, allowing for more tailored decision making regarding the timing of delivery as well as the approach to peripartum electronic monitoring. The effectiveness of such approach remains to be determined in larger multicentric and appropriately powered studies.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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