OBSTETRICS

Reduced fetal growth velocity and weight loss are associated with adverse perinatal outcome in fetuses at risk of growth restriction

Tamara Stampalija, MD; Hans Wolf, MD; Bronacha Mylrea-Foley, MD; Neil Marlow, MD; Katie J. Stephens, MD; Caroline J. Shaw, PhD; Christoph C. Lees, MD; On behalf of TRUFFLE-2 Feasibility Study authors

BACKGROUND: Although fetal size is associated with adverse perinatal outcome, the relationship between fetal growth velocity and adverse perinatal outcome is unclear.

OBJECTIVE: This study aimed to evaluate the relationship between fetal growth velocity and signs of cerebral blood flow redistribution, and their association with birthweight and adverse perinatal outcome.

STUDY DESIGN: This study was a secondary analysis of the TRUFFLE-2 multicenter observational prospective feasibility study of fetuses at risk of fetal growth restriction between 32^{+0} and 36^{+6} weeks of gestation (n=856), evaluated by ultrasound biometry and umbilical and middle cerebral artery Doppler. Individual fetal growth velocity was calculated from the difference of birthweight and estimated fetal weight at 3, 2, and 1 week before delivery, and by linear regression of all available estimated fetal weight measurements. Fetal estimated weight and birthweight were expressed as absolute value and as multiple of the median for statistical calculation. The coefficients of the individual linear regression of estimated fetal weight measurements (growth velocity; g/wk) were plotted against the last umbilical-cerebral ratio with subclassification for perinatal outcome. The association of these measurements with adverse perinatal outcome was assessed. The adverse perinatal outcome was a composite of abnormal condition at birth or major neonatal morbidity.

RESULTS: Adverse perinatal outcome was more frequent among fetuses whose antenatal growth was <100 g/wk, irrespective of signs of cerebral blood flow redistribution. Infants with birthweight <0.65 multiple of the median were enrolled earlier, had the lowest fetal growth velocity, higher umbilical-cerebral ratio, and were more likely to have adverse perinatal outcome. A decreasing fetal growth velocity was observed in 163 (19%) women in whom the estimated fetal weight multiple of the median regression coefficient was <−0.025, and who had higher umbilical-cerebral ratio values and more frequent adverse perinatal outcome; 67 (41%; 8% of total group) of these women had negative growth velocity. Estimated fetal weight and umbilical-cerebral ratio at admission and fetal growth velocity combined by logistic regression had a higher association with adverse perinatal outcome than any of those parameters separately (relative risk, 3.3; 95% confidence interval, 2.3−4.8).

CONCLUSION: In fetuses at risk of late preterm fetal growth restriction, reduced growth velocity is associated with an increased risk of adverse perinatal outcome, irrespective of signs of cerebral blood flow redistribution. Some fetuses showed negative growth velocity, suggesting catabolic metabolism.

Key words: adverse outcome, brain sparing, catabolism, cerebral blood flow redistribution, cerebro-placental ratio, Doppler, fetal growth restriction, growth velocity, hypoxemia, middle cerebral artery, small for gestational age, umbilical-cerebral ratio

Introduction

Birthweight (BW) for gestational age is a key risk factor for perinatal mortality, which is lowest for births between the 80th and 84th percentile and highest below the 2.3rd percentile.[1] The attainment of optimal fetal growth velocity, in contrast, is rarely studied in relation to mortality or perinatal outcome.[2−5] Determination of fetal growth velocity requires serial ultrasound biometric assessments, from which estimated fetal weight (EFW) is derived, which has a close, although imperfect, relationship with BW.[6] Differences are frequently ascribed to the derivation algorithm or inaccuracy in biometric measures, but may be also related to divergent growth between ultrasound estimation of fetal weight and birth.[6]

Neonatal weight loss is common after birth because of a range of factors, primarily water loss during perinatal adaptation and slow establishment of nutritional intake.[7] In utero weight loss has recently been reported.[8,9] In a cohort of 885 term singletons with fetal biometry within 2 weeks of delivery, fetal weight gain, defined as a discrepancy between EFW and BW, ranged from −26 g/d for BW <10th percentile, through positive gain in all other groups, to +48 g/d for those >90th percentile.[9] Apparent weight loss was associated with evidence of fetal compromise, namely cerebral blood flow redistribution, and may represent a fetal catabolic state.[9] Thus, fetal growth velocity estimation provides different information from that of a single EFW measurement.

To investigate this further, we performed an analysis of a large prospective cohort of fetuses at risk of late preterm fetal growth restriction (FGR) who had well characterized Doppler velocimetry. We evaluated fetal growth velocity in relation to umbilical and cerebral Doppler indices, BW, and adverse perinatal outcome.

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AJOG at a Glance

Why was this study conducted?

This study aimed to evaluate the growth velocity in fetuses at risk of growth restriction and assess the association of fetal growth velocity with adverse perinatal outcome and signs of cerebral blood flow redistribution.

Key findings

In the last week before delivery, the fetuses with lowest growth velocity showed no growth, and in some cases negative growth. Fetal growth velocity <100 g/wk was associated with adverse perinatal outcome, irrespective of signs of cerebral blood flow redistribution.

What does this add to what is known?

Fetal growth velocity is an important parameter that might identify fetuses at risk of adverse outcome irrespective of signs of cerebral blood flow redistribution, and might differentiate from constitutionally small fetuses.

Materials and Methods

Study population

This was a secondary analysis from a prospective multicenter observational study conducted between April 1, 2017 and July 1, 2018 in 33 European perinatal centers with fetal medicine and specialized neonatal intensive care services, the TRUFFLE-2 Feasibility Study.[11] Briefly, women with singleton pregnancy at 32^{+0} to 36^{+6} weeks of gestation were eligible if the fetus was considered at risk for growth restriction. This was defined as EFW or abdominal circumference (AC) <10th percentile, an abnormal arterial Doppler, or an AC growth velocity drop from the 20-week scan of >40 percentile points, and an expected date of delivery verified by ultrasound before 20 weeks of gestation. The references for EFW, AC, and Doppler parameters were based on local charts. Fetuses with absent diastolic flow in the umbilical artery, an abnormal cardiotocography (CTG), an immediate indication for delivery, or structural abnormalities were not eligible. Delivery timing was based on the local protocol. The study protocol advised the use of computerized CTG or absent or reversed umbilical artery flow to decide if delivery was needed; although not specified as a criterion for delivery, the umbilical-to-cerebral-artery (UCR) ratio was calculated for each fetus as part of the feasibility study.

Study endpoint

The primary adverse perinatal outcome was a composite of abnormal condition at birth or major neonatal morbidity or neonatal death. Abnormal condition at birth was defined as at least 1 of the following: Apgar score <7 at 5 minutes, umbilical artery pH <7.0 or vein pH <7.1, resuscitation with intubation, chest compressions or medication, or stillbirth. Major neonatal morbidity was defined as at least 1 of the following: neurologic abnormality (intracerebral hemorrhage grade 3 or 4, periventricular leukomalacia grade 2 or 3, encephalopathy, or seizures necessitating antiepileptic drug treatment); cardiovascular abnormality (hypotensive treatment, ductus arteriosus treatment, or disseminated coagulopathy); respiratory morbidity (respiratory support for >1 week, or mechanical ventilation, meconium aspiration, persistent pulmonary hypertension); or sepsis (clinical sepsis with positive blood culture, necrotizing enterocolitis [Bell's stage ≥2], or meningitis).

Data analysis

Preeclampsia was defined as hypertension and proteinuria, or hypertension and clinical signs of preeclampsia.[12] UCR was categorized as normal (<0.9) or abnormal (≥0.9), corresponding to a cerebroplacental ratio (CPR) of 1.1. This threshold was used because it is most closely associated with adverse birth and neonatal outcome,[13] and a single threshold was used because reference charts of UCR or CPR show very little variation in the gestational age window of 32 to 37 weeks.[13] The association of abnormal UCR with fetal growth and composite adverse outcome was assessed by crosstab test. EFW was calculated using the Hadlock algorithm.[14] BW multiple of the median (MoM) and EFW MoM were calculated by dividing measured weight by the median expected weight for the gestational age derived from the Hadlock fetal growth chart.[15] We preferred MoM values over percentiles because these require a normal distribution, whereas MoM values do not. Moreover, the advantage of the MoM is that it expresses the measured weight to the expected median weight as a proportion and thereby gives an exact figure of the growth deficit. Perinatal details were specified for BW MoM <0.65, ≥0.65 to <0.75, and ≥0.75. These BW MoM categories represent the 10th and the 50th percentile of BW in the study population, and correspond to the 0.3rd percentile and the 3rd percentile of Hadlock fetal growth chart.[15]

Fetal growth velocity was assessed by 3 methods:

1. A classification was made for completed weeks 1 to 3 before delivery, that is, 7 to 13, 14 to 20, and 21 to 27 days, using only the last measurement made in each week for each woman. Data from the last week (0−6 days) before delivery (week 0) were not used. Fetal growth velocity was calculated as the difference between BW and EFW, divided by the interval to delivery in weeks (in double precision) and expressed as g/wk for each of the 3 weeks studied. Fetal growth velocity calculated by this method was assessed for each category of BW MoM (<0.65, ≥0.65 to <0.75, and ≥0.75).
2. A linear regression of all EFW measurements and BW was computed for each woman, with gestational age in weeks as the independent variable. The coefficient of the regression represented

individual fetal growth velocity in g/wk, and was plotted against the last UCR measured within 3 weeks (ie, 20 days) of delivery. The plot was divided in 4 quadrants separated at UCR ≥0.9 vs <0.9, and fetal growth ≥100 g/wk vs <100 g/wk, to determine differences in BW MoM, gestational age at delivery, and adverse perinatal outcome between these categories. In addition, the association of adverse perinatal outcome with fetal growth velocity, UCR, or both was assessed by logistic regression analysis. We chose a threshold of 100 g/wk, corresponding to growth below the 3rd percentile according to the Hadlock EFW growth charts in the period between 32 and 36 weeks,[15] and it represented approximately the lower quartile of the study population.

3. Individual linear regressions of all EFW MoM values with gestational age in weeks as the independent variable were computed. The EFW MoM coefficients were plotted against BW MoM. This plot was divided in 3 areas at EFW MoM regression coefficients of −0.025 and 0.025. These areas were compared by UCR at inclusion, BW, gestational age at birth, and adverse perinatal outcome. The reason for this approach was that a linear analysis of MoM values could better show a change in growth velocity than absolute weight values because the MoM values show the difference from median normal weight, and a change represents a change in severity of FGR.

Statistical methods

Data were presented as number with percentage or median with interquartile range (IQR). Groups were compared by Kruskal−Wallis, median, or chi square tests, as appropriate. Two-sided statistical significance was calculated at $P<.05$. Logistic regression analysis was performed using a backward procedure, with P to remove at.1. Calculations were made with IBM SPSS Statistics software (version 25; IBM Corp, New York, NY).

Ethical approval

The study was observational and practice (monitoring, delivery, steroid administration) was based on existing local guidance. Data were recorded and anonymized after delivery outcomes were obtained. In 6 countries (19 centers), ethical approval was required and obtained, and participating women gave informed signed consent. In the remaining 5 countries this was not required.

Results

Complete delivery and outcome data were recorded for 873 women. Seventeen women were excluded because of major fetal congenital abnormality, leaving 856 women and their fetuses for the final cohort analysis. Demographic, obstetrical, and fetal Doppler velocimetry data are shown in Table 1. There were 2770 measurements of UCR and EFW performed (median, 3 [IQR, 2−4]/woman). In 696 (81%) women with >1 measurement of UCR the median interval between measurements was 7 (IQR, 5−10) days; 160 (19%) women had only 1 measurement. At enrolment, median gestational age was 34 weeks (IQR, 33−35), 63 (7%) women had a UCR ≥0.9, and EFW MoM was 0.79 (IQR, 0.73−0.83).

Median gestational age at delivery was 38 weeks (IQR, 37−39), and BW MoM was 0.76 (IQR, 0.70−0.82). Adverse perinatal outcome was present in 93 (11%) births (Table 2).

Evaluation of the relationship between BW and study parameters is shown in Table 3. Infants with the lowest BW MoM were enrolled at an earlier gestational age, and had lower EFW MoM at inclusion and lower fetal growth velocity than infants in higher BW MoM categories. This lowest-BW group also had higher UCR values, both at inclusion and at last measurement within 3 weeks of delivery. They were delivered at an earlier gestational age, more frequently by cesarean delivery, and had a higher proportion of adverse perinatal outcomes.

Fetal growth velocity was lowest in the category of BW MoM <0.65, and in this group the median fetal growth velocity was not different from 0 at 1 week before delivery (10 g/wk; IQR, −61 to 73; 1 sample Wilcoxon signed-rank test) (Figure 1). In the 2 lowest BW categories, fetal growth velocity reduced from week 3 to week 1, whereas in the group with BW MoM ≥0.75, fetal growth velocity did not change. In the last group, fetal growth velocity was close to normal (152 g/wk [IQR, 95−203] vs 200 g/wk).[15]

Compared with those with higher growth velocity, infants with fetal growth <100 g per week had a significantly lower BW MoM and gestational age at delivery, as a sign of more severe FGR (Figure 2). Adverse perinatal outcomes were more frequent in infants with fetal growth <100 g/wk (20% vs 9%; $P<.001$). When specified for normal vs abnormal UCR, this difference reached statistical significance only in those with normal UCR. In both fetal growth categories (fetal growth <100 g/wk vs ≥100 g/wk), gestational age at delivery was lower when UCR was abnormal vs normal. When fetal growth was <100 g/wk, BW MoM and adverse perinatal outcome were not associated with UCR. In those with higher growth velocity, BW MoM and gestational age at delivery were significantly lower following abnormal UCR (Figure 2). Fetal growth velocity was lower in infants with abnormal UCR (Table 4), either at any time or at the last measurement, and lower in those with adverse perinatal outcome. Among those with consistently normal UCR, growth was similar between those with adverse and those with normal outcomes.

For 612 (72%) women, the EFW MoM linear regression coefficient was between −0.025 and 0.025, indicating little change in growth velocity after study inclusion (Figure 3). Compared with these women, 163 (19%) women who had an EFW MoM regression coefficient <−0.025, indicating a reduction of fetal growth velocity, had higher UCR at inclusion, lower BW MoM, and more frequent adverse perinatal outcomes; 67 (41%; 8% of total group) of these women had negative growth velocity.

TABLE 1
Demographic and obstetrical characteristics of the study population

Variable	Women (n=856)
Maternal age	31 (28–35)
Nulliparity	524 (61)
Body mass index (kg/m^2)	22.5 (20.3–26.0)
Smoking	68 (8)
Diabetes mellitus type 1, 2, or gestational	70 (8)
Chronic hypertension	19 (2)
At inclusion	
Gestational age (wk)	34.1 (32.9–35.4)
Inclusion indication[a]	
EFW or AC <10°pc	792 (93)
AC growth velocity drop ≥40° pc	50 (6)
Doppler abnormality	98 (11)
EFW (g)	1894 (1624–2145)
EFW MoM	0.79 (0.73–0.83)
Umbilical artery PI	1.00 (0.86–1.14)
Umbilical artery PI ≥95° pc	141 (17)
Middle cerebral artery PI	1.75 (1.51–2.01)
Middle cerebral artery PI <5° pc	91 (11)
UCR	0.56 (0.47–0.69)
CPR	1.79 (1.45–2.14)
UCR ≥0.9 or CPR <1.1	63 (7)
Before delivery	
Preeclampsia or HELLP syndrome	79 (9)
Any hypertensive disorder of pregnancy	119 (14)
Corticosteroids for fetal lung maturation (>24 h before delivery)	97 (11)
Arterial Doppler measurements—number	2770
Arterial Doppler measurements—per women	3 (2–4)
Interval from inclusion to delivery (d)	27 (14–38)
Umbilical artery PI[b]	0.94 (0.82–1.11)
Umbilical artery PI ≥95° pc[b]	158 (21)
Middle cerebral artery PI[b]	1.47 (1.30–1.70)
Middle cerebral artery PI <5° pc[b]	122 (16)
UCR[b]	0.63 (0.52–0.79)
CPR[b]	1.59 (1.27–1.92)
UCR ≥0.9[b]	164 (22)
Delivery	
Prelabor CD	
Indication	219 (26)
Fetal condition (CTG or Doppler)	155 (71)
Fetal growth/EFW	25 (11)

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The different thresholds that were discussed earlier (UCR ≥0.9, EFW <10th percentile, fetal growth <100 g/wk and EFW MoM change <−0.025) were assessed for their association with adverse perinatal outcome, first by univariable analysis, and then combined with logistic regression analysis. Table 5 shows that the highest association with adverse perinatal outcome was by multivariable analysis, using UCR, EFW, and fetal growth (risk ratio, 3.3; 95% confidence interval, 2.3–4.8).

Comment

Principal findings

In this prospective study of closely monitored fetuses at risk of late preterm FGR, we observed that adverse perinatal outcomes were more prevalent with decreased fetal growth velocity (<100 g/wk). Individual growth velocities varied greatly, and 67 (8%) fetuses showed negative growth. Those with reduced fetal growth velocity showed signs of cerebral blood flow redistribution more frequently than those with higher growth velocity. However, in the reduced growth velocity group, abnormal UCR on its own was not associated with adverse perinatal outcome. Importantly, although poor fetal growth and fetal smallness are to some extent related, fetal growth velocity was a better independent predictor of adverse perinatal outcome than EFW at inclusion. When both were combined with a raised UCR, the predictive value was further improved.

Results in the context of what is known

Fetal nutritional (growth) and oxidative metabolism depends on the balance between fetoplacental demands and maternoplacental availability of oxygen and nutritional substrates. Whenever there is a mismatch, irrespective of the underlying cause, compensatory fetal adaptive mechanisms are necessary to preserve fetal condition.[16] The oxygen and nutrient requirements for tissue growth are substantial and increase with higher fetal weight during the course of pregnancy.[16,17] The fetal response to impaired oxygen and nutrient delivery drives redistribution of fetal cardiac

TABLE 1
Demographic and obstetrical characteristics of the study population
(continued)

Variable	Women (n=856)
Maternal condition	39 (18)
Induction of labor	
Indication	369 (43)
Fetal condition (CTG or Doppler)	112 (30)
Fetal growth/EFW	213 (58)
Maternal condition	44 (12)
Spontaneous onset of labor	268 (31)
CD after onset of labor	117 (14)
Fetal condition	65 (56)
Other indication	52 (44)

Data are presented as number (percentage) or median (interquartile range).

AC, abdominal circumference; *CD*, cesarean delivery; *CPR*, cerebro-placental ratio; *CTG*, cardiotocography; *EFW*, estimated fetal weight; *HELLP*, hemolysis, elevated liver enzymes, and low platelets; *MoM*, multiple of the median; *pc*, percentile; *PI*, pulsatility index; *UCR*, umbilical-cerebral ratio.

[a] Multiple indications possible; [b] Last Doppler measurement within 3 weeks before delivery, n=753.

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TABLE 2
Neonatal outcomes

Variable	Infants (n=856)
Gestational age at delivery, wk	38.1 (37.0–39.1)
Birthweight, g	2478 (2140–2790)
Birthweight MoM[a]	0.76 (0.70–0.82)
Birthweight <10° pc[a]	596 (70)
Birthweight <50 pc[a]	826 (93)
Male sex	372 (43)
Composite adverse outcome (abnormal condition at birth or major neonatal morbidity)	93 (11)
Abnormal condition at birth[b]	27 (3)
• Fetal death	2 (0)
• pH art <7.0 or pH ven <7.1 (17% missing data)	7 (1)
• Apgar score at 5 min <7	15 (2)
• Resuscitation with intubation or medication	10 (1)
Major neonatal morbidity[b]	77 (9)
• Cerebral	7 (1)
• Cardiovascular	7 (1)
• Respiratory	53 (6)[c]
• Infection	17 (2)
Neonatal death	0

Data are presented as number (percentage) or median (interquartile range).

art, arterial; *MoM*, multiple of the median; *pc*, percentile; *ven*, venous.

[a] Reference chart for calculation by Hadlock[14]; [b] Multiple conditions possible; [c] 39/53 (74%) had only some respiratory support of short duration in the first week.

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output in favor of brain, heart, and adrenal glands, the so-called "brain-sparing" effect,[18] with subsequent growth restriction of the remaining parts of the body including the liver and limbs.[19,20] The association of lower fetal growth velocity with abnormal UCR reflects this process.[9]

Using umbilical cord sampling in hypoxemic fetuses with FGR, plasma concentrations of essential amino acids were decreased and the ratio of nonessential to essential amino acids was increased compared with normally growing fetuses, suggesting that intrauterine starvation was occuring.[21] Alongside this there is an impaired process of gluconeogenesis.[21–23] Glucose is the major metabolic substrate capable of sustaining 50% to 70% of oxidative metabolism.[24] Thus, impaired gluconeogenesis, together with shortage of substrates, may explain the finding of reduced fetal growth velocity.

Reduced fetal growth velocity represents not only a consequence of a shortage of nutrient and oxygen substrates, but also an adaptive "saving" mechanism in an attempt to reduce substrate demands.[16,25] Indeed, an ovine model with prolonged oxygen starvation was associated with reduced total oxygen and substrate consumption.[26–28] In some cases, this reduction in fetal growth, and thus in fetal demands, will be sufficient to normalize the balance between demands and supply, and restore fetal normoxia.[16] However, the long-term impact of restricted growth, even in the absence of cerebral blood flow redistribution, on fetal organs and systems is still not well understood.

Clinical and research implications

Late preterm FGR is associated with poor neurodevelopmental outcome and school achievement.[29–32] Thus, a standardized definition of the condition is central to identifying pregnancies that are at highest risk.[3] In our cohort, fetuses with reduced fetal growth (<100 g/wk) more commonly had adverse perinatal outcome than those with normal fetal growth, irrespective of signs of cerebral blood flow redistribution. We selected growth <100 g/wk as "poor weight gain"

TABLE 3
Comparison of birthweight multiple of the median categories

	Birthweight MoM (n)		
	<0.65 (100=12%)	≥0.65 and <0.75 (275=32%)	≥0.75 (481=56%)
Inclusion			
Gestational age (wk)[a]	33.1 (32.4–34.3)[b]	34.0 (32.7–35.6)	34.3 (33.1–35.6)
EFW (g)[a]	1464 (1324–1775)[b]	1800 (1584–2039)[b]	1978 (1738–2216)
EFW MoM[a]	0.69 (0.63–0.73)[b]	0.76 (0.72–0.80)[b]	0.81 (0.78–0.85)
Umbilical artery PI[a]	1.11 (0.99–1.33)[b]	1.03 (0.90–1.16)[b]	0.96 (0.84–1.08)
Middle cerebral artery PI	1.69 (1.44–1.89)	1.73 (1.50–1.99)	1.77 (1.53–2.05)
UCR[a]	0.70 (0.55–0.85)[b]	0.59 (0.49–0.71)[b]	0.53 (0.45–0.63)
Fetal growth (g/wk)[c]	61 (13–103)[b]	117 (66–151)[b]	177 (147–209)
Last week before delivery[d]			
Umbilical artery PI[a]	1.13 (0.98–1.38)[b]	0.98 (0.85–1.16)[b]	0.90 (0.79–1.02)
Middle cerebral artery PI	1.51 (1.31–1.75)	1.46 (1.27–1.67)	1.46 (1.31–1.72)
UCR[a]	0.74 (0.61–1.00)[b]	0.67 (0.55–0.83)[b]	0.59 (0.50–0.72)
Delivery			
Gestational age (wk)[a]	36.8 (35.1–37.7)[b]	37.7 (36.9–38.7)[b]	38.6 (37.3–39.7)
Delivery indicated[a, e]	86 (86%)[f]	221 (80%)[f]	269 (56%)
Cesarean delivery (prim or sec)[a]	72 (72%)	114 (42%)	150 (31%)
Birthweight (g)[a]	1768 (1520–1948)[b]	2260 (2070–2410)[b]	2745 (2543–2938)
Birthweight MoM[a]	0.61 (0.58–0.63)[b]	0.71 (0.68–0.73)[b]	0.82 (0.78–0.86)
Adverse outcome	31 (31%)[b]	32 (12%)[b]	30 (6%)

EFW, estimated fetal weight; *MoM*, multiple of the median; *PI*, pulsatility index; *prim*, rimary; *sec*, secondary; *UCR*, umbilical-cerebral ratio.

[a] The distribution differs across the categories of first abnormal UCR (Kruskal–Wallis or chi square test). Pairwise comparison by Kruskal–Wallis or chi square test with adjustment by Bonferroni correction for multiple tests; [b] Significant difference compared with all column(s) with higher birthweight MoM; [c] Fetal growth calculated by linear regression of individual EFW and birthweight; [d] 753 women with a last UCR measurement within 3 weeks before delivery; [e] Delivery indicated either by induction of labor or cesarean delivery before onset of labor; [f] Significant difference compared with last column.

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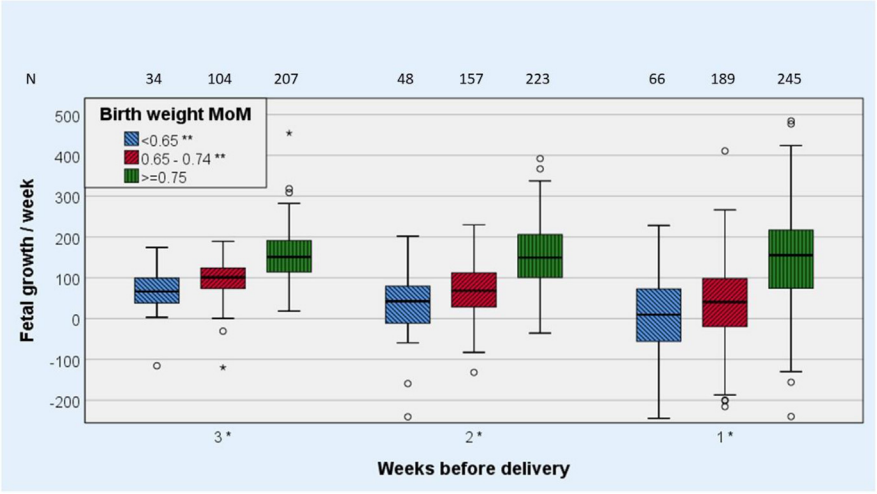
on the basis of a very conservative weight gain (third percentile) from the Hadlock EFW model. This finding is of clinical importance because it suggests that decreased fetal growth velocity, even in the presence of normal Doppler findings, may be associated with short-term adverse outcome. Although it is not possible to infer that fetuses that grow most slowly or negatively are likely to suffer later developmental concerns, this hypothesis cannot be excluded on the basis of current data.

Detection of FGR during routine prenatal care is known to be low.[33] Prenatal differentiation between the constitutionally small but healthy fetus and true FGR poses further difficulties.[5] Ultrasound evaluation of EFW has been shown to be a poor predictor of BW in small-for-gestational-age neonates because of an apparent EFW overestimation in the context of reduced fetal growth velocity,[8,9] although other studies found EFW to be the only ultrasound parameter independently associated with adverse perinatal outcome in late FGR.[34] In 2021, Deter et al,[35] using data from the PORTO study,[36] observed a large heterogeneity in individual fetal growth velocity. Approximately 30% of infants with normal BW (>10th percentile) had an abnormal growth pattern, whereas nearly 40% of infants with a BW <10th percentile had a normal growth pattern. As can be observed from the confidence intervals presented in the results section, individual variation in growth velocity was also large in our population. A small subgroup (17%) had BW >10th percentile with fetal growth velocity of 216 g/wk (IQR, 189–255); thus, 25% of these fetuses had fetal growth velocity <189 g/wk. Conversely, in those with a BW <10th percentile, 15% had fetal growth velocity >189 g/wk (data not shown). Part of these inconsistencies might have been caused by measurement error.

A recent study that assessed the efficacy of biometry for the diagnosis of FGR concluded that AC growth was more effective than a single EFW measurement for the prediction of adverse

FIGURE 1
Fetal growth by birthweight MoM categories and weeks before delivery



Fetal growth in grams per week. The *asterisk* denotes fetal growth differs between the categories of birthweight MoM (Kruskal–Wallis). The *double asterisks* denote fetal growth differs between the categories of weeks before delivery (Kruskal–Wallis). The median of fetal growth in week 1 for the category of birthweight MoM <0.65 does not differ from 0.

MoM, multiple of the median.

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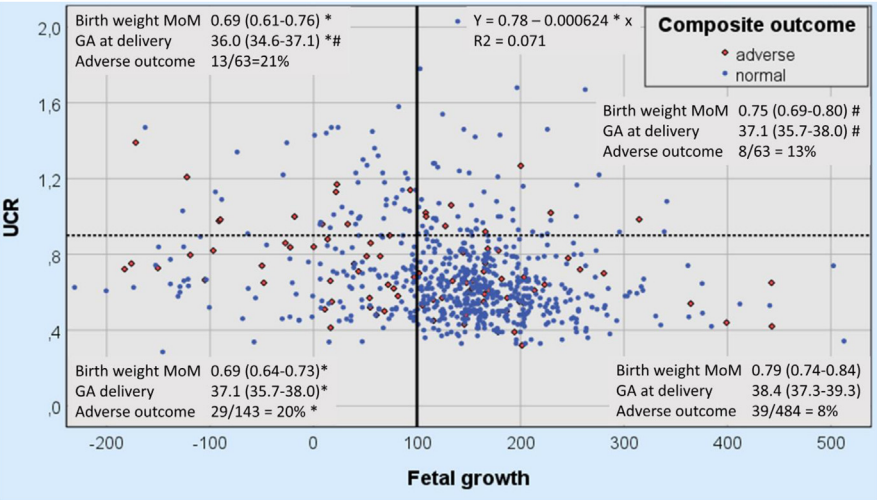
FIGURE 2
UCR 3 weeks before delivery and fetal growth per week



Scatterplot of the last UCR measured within 3 weeks before delivery and fetal growth per week, calculated by individual linear regression analysis (n=753). A linear regression line is shown for all measurements. The quadrants are divided by a line at fetal growth larger or less than 100 g/wk (*bold vertical line*) and UCR ≥0.9 vs <0.9 (*intermittent line*). The *asterisk* denotes significant difference between growth <100 g/wk vs ≥100 g/wk. The *hashtag* denotes significant difference between UCR ≥0.9 vs <0.9.
(Chi square or Kruskal–Wallis tests.)

EFW, estimated fetal weight; *GA*, gestational age; *MoM*, multiple of the median; *UCR*, umbilical-to-cerebral-artery ratio.

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perinatal outcome.[37] This supports our finding that measurement of fetal growth velocity is more relevant in this respect than a single measurement. During normal near-term growth, the fetal liver is large because of glycogen storage, which is necessary to maintain blood glucose levels during the first week when nutrient supply may be insufficient.[38] In FGR, liver volume may be reduced by the reduced deposit of glycogen owing to insufficient nutrients. This study supports the hypothesis that the growth pattern might differentiate between constitutionally small-for-gestational-age newborns and those with growth restriction because of insufficient placental supply.

Strengths and limitations

A weakness of all studies of EFW, including our study, is the large inter- and intraobserver error of EFW estimation; a random error of ±15% is reported.[6] In this study we used the Hadlock formula for EFW calculation; this has the closest correlation to BW, especially between 1500 and 3500 g,[10] which mirrors that of our cohort. The Hadlock formula for EFW has also been shown to outperform that of INTERGROWTH-21st, particularly at the extreme percentiles.[39] Multiple measurements and calculation of fetal growth velocity may further improve detection of FGR.[40,41] In our study, biweekly biometry facilitated accurate prediction of low BW, using a combination of EFW MoM and gestational age at first measurement, and of fetal growth velocity. Our data also support the hypothesis that the prediction of BW by EFW might be affected by a progressive reduction in fetal growth in a proportion of fetuses, and not by systematic or random errors of ultrasound measurements or algorithm calculation issues. Indeed, in a randomized study of induction vs expectant management in term FGR, there were significantly more infants born with BW <third percentile in the expectant management group where there was delayed delivery (31% vs 13%), suggesting a falling of growth velocity after randomization.[42] Thus, an overestimation of EFW in FGR might be

TABLE 4
Comparison of fetal growth, calculated by linear regression analysis, between women with adverse outcome and those with normal outcome

Umbilical-cerebral ratio	Fetal growth (g/wk)	Outcome	N	Fetal growth (g/wk)
UCR never abnormal	153 (110–196)	Adverse outcome	67/689 (10%)	146 (44–187)
		Normal outcome	622/689 (90%)	155 (114–197)
UCR abnormal anytime after inclusion	114 (44–166)[a]	Adverse outcome	26/167 (16%)	53 (−32 to 136)[b]
		Normal outcome	141/167 (84%)	117 (62–167)
Last UCR normal <3 wk predelivery	153 (106–195)	Adverse outcome	68/627 (11%)	129 (40–185)[b]
		Normal outcome	559/627 (89%)	154 (111–196)
Last UCR abnormal <3 wk predelivery	100 (37–157)[a]	Adverse outcome	21/126 (17%)	33 (−81 to 130)[b]
		Normal outcome	105/126 (83%)	103 (44–158)

Comparison specified for UCR at any time after study inclusion (n=856) or for a last UCR within 3 weeks before delivery (n=753).

UCR, umbilical-cerebral ratio.

[a] Statistically significant difference of fetal growth between never abnormal and abnormal UCR (Kruskal–Wallis test); [b] Statistically significant difference of fetal growth between adverse and normal outcome (Kruskal–Wallis test).

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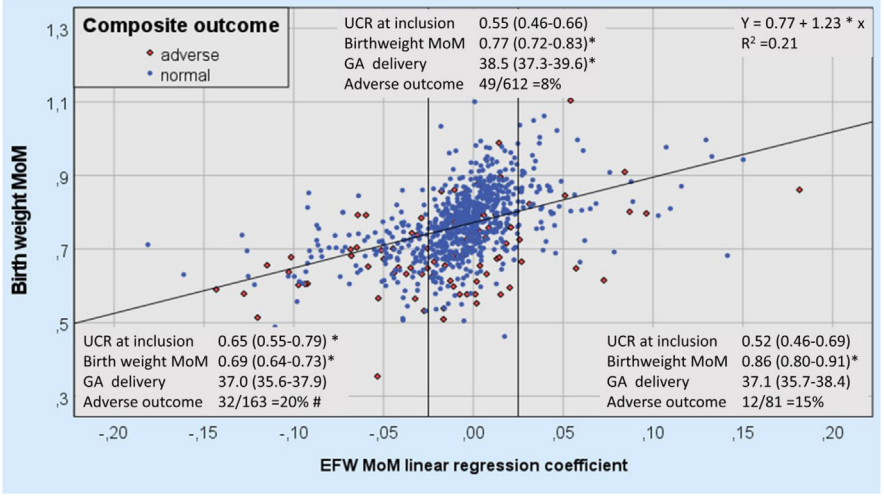
explained by arrested or negative fetal growth and not by measurement error.

The study was performed in 33 centers in 10 different European countries, and although differences in management and definition might have affected results, this is unlikely. The results of a multilevel logistic regression analysis with an unconditional mean model, using the participating centers and composite adverse outcome, showed that 6% of the chance of having an abnormal composite endpoint was explained by differences between centers.[11]

FIGURE 3
Birthweight MoM and the linear regression coefficient of EFW MoM



Scatterplot of birthweight MoM and the linear regression coefficient of EFW MoM, n=753. The plot is divided in 3 areas at EFW MoM regression coefficients of −0.025 and 0.025. The *asterisk* denotes significant difference from other categories ($P<.001$; Kruskal–Wallis). The *hashtag* denotes significant difference from middle category ($P<.001$; Kruskal–Wallis).

EFW, estimated fetal weight; *GA*, gestational age; *MoM*, multiple of the median; *UCR*, umbilical-to-cerebral-artery ratio.

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A characteristic of all observational studies, including this one, is that obstetrical management is frequently based on the parameters that are studied. The association between abnormal fetal growth or UCR and adverse perinatal outcome is clear, but whether perinatal outcome can be improved by using these parameters to determine delivery timing remains unproven. This can only be assessed by a randomized trial, and given the low incidence of adverse perinatal outcome after 32 weeks, such a trial would need a large sample size.[43]

Conclusions

In fetuses at risk of late preterm FGR, reduced fetal growth velocity is associated with increased risk of adverse perinatal outcome. In a proportion of fetuses, it is plausible to consider that fetal growth is negative and associated with in utero catabolism. The clinical observation of reduced fetal growth velocity based on ultrasound findings should not be assumed to be because of ultrasound measurement error, but instead should warrant further assessment of fetal condition and whether delivery or additional monitoring is indicated. ■

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TRUFFLE-2 feasibility study authors:

Bine Arabin, MD; Astrid Berger, MD; Eva Bergman, MD; Amarnath Bhide, MD; Caterina

TABLE 5
Adverse perinatal outcomes with the different thresholds specified in the manuscript

	Adverse outcome/total (%)		Prediction of adverse outcome				
Test	Threshold abnormal	Threshold normal	RR (95% CI)	Sens	Spec	LR+	LR-
Inclusion UCR ≥0.9	19/63 (30%)	74/793 (9%)	3.2 (2.1−5.0)	20%	94%	3.5	0.8
Inclusion EFW <10° pc	80/687 (12%)	13/169 (8%)	1.5 (0.9−2.7)	86%	20%	1.1	0.7
Fetal growth <100 g/wk	43/219 (20%)	50/637 (8%)	2.5 (1.7−3.6)	46%	77%	2.0	0.7
EFW MoM change <−0.025	32/163 (20%)	61/693 (9%)	2.2 (1.5−3.3)	34%	83%	2.0	0.8
Regression using all[a]	51/248 (21%)	42/608 (7%)	3.3 (2.3−4.8)	55%	74%	2.5	0.6

Logistic regression analysis of all parameters together in the bottom line.

CI, confidence interval; *EFW*, estimated fetal weight; *LR-*, likelihood after a negative test; *LR+*, likelihood after a positive test; *MoM*, multiple of the median; *pc*, percentile; *RR*, relative risk; *Sens*, sensitivity; *Spec*, specificity; *UCR*, umbilical-cerebral ratio.

[a] Area under the receiver operating characteristic curve, 0.67; 95% CI, 0.61−0.73; EFW MoM change ejected because of *P*>.1.

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M. Bilardo, MD; Andrew C. Breeze, MD; Jana Brodszki, MD; Pavel Calda, MD; Elena Cesari, MD; Irene Cetin, MD; Jan B. Derks, MD; Catherine Ebbing, MD; Enrico Ferrazzi, MD; Tiziana Frusca, MD; Wessel Ganzevoort, MD; Sanne J. Gordijn, MD; Wilfried Gyselaers, MD; Kurt Hecher, MD; Philipp Klaritsch, MD; Ladislav Krofta, MD; Peter Lindgren, MD; Silvia M. Lobmaier, MD; Gisuseppe M. Maruotti, MD; Federico Mecacci, MD; Kirsti Myklestad, MD; Rafaele. Napolitano, MD; Federico Prefumo, MD; Luigi Raio, MD; Jute Richter, MD; Ragnar K. Sande, MD; Jim Thornton, MD; Herbert Valensise, MD; Gerry H.A. Visser, MD; Ling Wee, MD.

We would like to acknowledge the TRUFFLE-2 Feasibility Study collaborating authors:

Christoph Brezinka, MD, Department of Obstetrics and Gynecology, Medical University of Innsbruck, Innsbruck, Austria; Davide Casagrandi, MD, University College London Hospitals National Health Service (NHS) Foundation Trust, London, United Kingdom; Andrej Cerny, MD, Department of Obstetrics and Gynaecology, General University Hospital and First Faculty of Medicine, Charles University, Prague, Czech Republic; Andrea Dall'Asta, MD, Department of Obstetrics and Gynecology, University of Parma, Parma, Italy; Roland Devlieger, MD, Department of Gynecology and Obstetrics, Universitair Ziekenhuis Leuven, Leuven and Department of Regeneration and Development, Katholieke Universiteit Leuven, Leuven, Belgium; Johannes Duvekot, MD, Erasmus Centre Rotterdam, Rotterdam, The Netherlands; Torbjorn Eggebo, MD, St Olav's Hospital, Trondheim, Norway; Ilaria Fantasia, MD, Unit of Fetal Medicine and Prenatal Diagnosis, Institute for Maternal and Child Health, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Burlo Garofolo, Trieste, Italy; Francesca Ferrari, MD, Obstetrics and Gynecology, Policlinico University Hospital of Modena, Modena, Italy; Nicola Fratelli, MD, Department of Obstetrics and Gynecology, Aziende Socio Sanitarie Territoriali (ASST) Spedali Civili di Brescia and University of Brescia, Brescia, Italy; Tullio Ghi, MD, Department of Obstetrics and Gynecology, University of Parma, Parma, Italy; Oliver Graupner, MD, Department of Obstetrics and Gynecology, Klinikum Rechts Der Isar, Technical University of Munich, Munich, Germany; Patrick Greimel, MD, Department of Obstetrics and Gynecology, Medical University of Graz, Graz, Austria; Cornelia Hofstaetter, MD, Department of Obstetrics and Gynecology, University Hospital of Bern, Bern, Switzerland; Damiano Le Presti, MD, Department of Surgery, Division of Obstetrics and Gynaecology, Tor Vergata University, Policlinico Casilino Hospital, Rome, Italy; Georg Macharey, MD, Helsinki University Central Hospital, Helsinki, Finland; Alexander Vietheer, MD, Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway; Ferenc Macsali, MD, Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway; Karel Marsal, MD, Department of Obstetrics and Gynecology, Lund University, Skåne University Hospital, Lund, Sweden; Pasquale Martinelli, MD, Department of Neurosciences, Reproductive and Dentistry Sciences, University of Naples Federico II, Naples, Italy; Edward Mullins, MD, Imperial College London, London, United Kingdom; Eva Ostermayer, MD, Department of Obstetrics and Gynecology, Klinikum Rechts Der Isar, Technical University of Munich, Munich, Germany; Aris Papageorghiou, MD, Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust and Molecular and Clinical Sciences Research Institute, St George's, University of London, London, United Kingdom; Rachel Peasley, MD, Fetal Medicine Unit, University College London Hospitals NHS Foundation Trust, London, United Kingdom; Angela Ramoni, MD, Department of Obstetrics and Gynecology, Medical University of Innsbruck, Innsbruck, Austria; Laura Sarno, MD, Department of Neurosciences, Reproductive and Dentistry Sciences, University of Naples Federico II, Naples, Italy; Laura Seikku, MD, Helsinki University Central Hospital, Helsinki, Finland; Serena Simeone, MD, Department of Health Sciences, University of Florence, Obstetrics and Gynecology, Careggi University Hospital, Florence, Italy; Baskaran Thilaganathan, MD, Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust and Molecular and Clinical Sciences Research Institute, St George's, University of London, London, United Kingdom; Grazia Tiralongo, MD, Department of Surgery, Division of Obstetrics and Gynaecology, Tor Vergata University, Policlinico Casilino Hospital, Rome, Italy; Andrea Valcamonico, MD, Department of Obstetrics and Gynecology, ASST Spedali Civili di Brescia and University of Brescia, Brescia, Italy; Caroline VanHolsbeke, MD, Department of Obstetrics and Gynaecology, Ziekenhuis Oost-Limburg, Genk, Belgium.

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Author and article information

From the Unit of Fetal Medicine and Prenatal Diagnosis, Institute for Maternal and Child Health, Istituto di Ricovero e Cura a Carattere Scientifico Burlo Garofolo, Trieste, Italy (Dr Stampalija); Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy (Dr Stampalija); Department of Obstetrics and Gynecology, Amsterdam University Medical Center (Location AMC), University of Amsterdam, Amsterdam, The Netherlands (Dr Wolf); Institute of Developmental and Reproductive Biology, Department of Metabolism, Digestion and Reproduction, Imperial College London, London, United Kingdom (Drs Mylrea-Foley, Shaw, and Lees); Department of Fetal Medicine, Queen Charlotte's and Chelsea Hospital, Imperial College National Health Service Trust, London, United Kingdom (Drs Mylrea-Foley, Stephens, Shaw, and Lees); and Institute for Womens Health, University College London, London, United Kingdom (Dr Marlow).

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Corresponding author: Christoph C. Lees, MD. christoph.lees@btinternet.com