Longitudinal Doppler Assessments in Late Preterm Fetal Growth Restriction

Longitudinale Doppler-Bewertungen bei später fetaler Wachstumsrestriktion

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ABSTRACT

Purpose To assess the longitudinal variation of the ratio of umbilical and cerebral artery pulsatility index (UCR) in late preterm fetal growth restriction (FGR).

Materials and Methods A prospective European multicenter observational study included women with a singleton pregnancy, 32^{+0}–36^{+6}, at risk of FGR (estimated fetal weight [EFW] or abdominal circumference [AC] < 10^{th} percentile, abnormal arterial Doppler or fall in AC from 20-week scan of > 40 percentile points). The primary outcome was a composite of abnormal condition at birth or major neonatal morbidity. UCR was categorized as normal (< 0.9) or abnormal (≥ 0.9). UCR was assessed by gestational age at measurement interval to delivery, and by individual linear regression coefficient in women with two or more measurements.

Results 856 women had 2770 measurements; 696 (81 %) had more than one measurement (median 3 (IQR 2–4). At inclusion, 63 (7 %) a UCR ≥ 0.9. These delivered earlier and had a lower birth weight and higher incidence of adverse outcome (30 % vs. 9 %, relative risk 3.2; 95 %CI 2.1–5.0) than women with a normal UCR at inclusion. Repeated measurements after an abnormal UCR at inclusion were abnormal again in 67 % (95 %CI 55–80), but after a normal UCR the chance of finding an abnormal UCR was 6 % (95 %CI 5–7 %). The risk of composite adverse outcome was similar using the first or subsequent UCR values.

Conclusion An abnormal UCR is likely to be abnormal again at a later measurement, while after a normal UCR the chance of an abnormal UCR is 5–7 % when repeated weekly. Repeated measurements do not predict outcome better than the first measurement, most likely due to the most compromised fetuses being delivered after an abnormal UCR.

ZUSAMMENFASSUNG

Ziel Beurteilung der longitudinalen Variation der umbilikozerebralen Ratio (UCR) der Pulsatilitätsindizes bei später fetaler Wachstumsrestriktion (FGR).

Material und Methoden Eine prospektive europäische multizentrische Beobachtungsstudie schloss Frauen mit Einlingsschwangerschaft (32^{+0}–36^{+6}) und Risiko für FGR ein (geschätztes fetales Gewicht (EFW) oder Abdomenumfang (AU) < 10. Perzentile, abnormaler arterieller Doppler oder Absinken der AU-Perzentile um > 40 Punkte im US in der 20. SSW). Der primäre Outcome war kombiniert aus auffälligen Geburtsparametern oder schwerer neonataler Morbidität. Die UCR wurde als normal (< 0,9) oder abnormal (≥ 0,9) eingestuft. Die UCR wurde im Messintervall bis zur Entbindung mittels SSW und mittels individuellen linearen Regressionskoeffizienten bei Frauen mit 2 oder mehr Messungen bewertet.

Ergebnisse 856 Frauen hatten 2770 Messungen; 696 (81 %) hatten mehr als eine Messung (Median 3, IQR 2–4). Bei Einschluss hatten 63 (7 %) eine UCR ≥ 0,9. Diese entbanden früher und hatten ein niedrigeres Geburtsgewicht und eine höhere Inzidenz für einen unerwünschten Outcome (30 % vs. 9 %, relatives Risiko 3,2; 95 %-KI 2,1–5,0) im Vergleich zu Frauen mit normaler UCR bei Einschluss. Wiederholte Messungen nach abnormaler UCR bei Einschluss waren in 67 % (95 %-KI 55–80) erneut abnormal, aber nach einer normalen UCR betrug die Wahrscheinlichkeit, eine abnormale UCR zu finden, 6 % (95 %-KI 5–7 %). Das Risiko für einen kombinierten unerwünschten Outcome war ähnlich, wenn man den ersten oder den nachfolgenden UCR-Wert verwendete.

Schlussfolgerung Eine abnormale UCR ist wahrscheinlich bei einer späteren Messung wieder abnormal, während nach einer normalen UCR die Wahrscheinlichkeit einer abnormalen UCR bei wöchentlicher Wiederholung 5–7 % beträgt. Wiederholte Messungen sagen das Ergebnis nicht besser voraus als die erste Messung, was höchstwahrscheinlich darauf zurückzuführen ist, dass die am stärksten gefährdeten Föten nach einer abnormalen UCR entbunden werden.

Introduction

Late preterm fetal growth restriction (FGR) is generally considered to have only moderate risk for perinatal complications. However, the condition is associated with lower scores in neurodevelopmental outcome and school achievement [1–3] and thus has impact on long-term development and health. Management remains centered on optimal timing of delivery, but which monitoring parameters should trigger this and at what thresholds remains to be elucidated. Serial ultrasound assessment with fetal biometry and Doppler velocimetry is the usual method of follow-up, with umbilical artery (UA) pulsatility index (PI) as the mainstay of FGR monitoring [4], together with cardiotocography. Other Doppler measurements, in particular cerebral Doppler indices, have garnered increased interest of late. However, there is only limited evidence from observational studies, which are generally hampered by intervention bias, and no evidence from randomized controlled trials (RCTs) to support the use of these for clinical decision making.

Various national and international recommendations for monitoring FGR after 32 weeks have proposed strategies based on expert opinion [5]. The recently published guidelines from the International Society of Ultrasound in Obstetrics and Gynecology advise twice weekly Doppler monitoring of late FGR but concede that "there is currently no evidence as to how cerebral Doppler should be utilized in the delivery timing of FGR" [4]. The Royal College of Obstetricians and Gynecologists recommends the use of the middle cerebral artery (MCA) in FGR with normal UA Doppler. However, for late preterm it is less clear, stating that the MCA "may be a more useful test" with no clear guidance on its use at this time [6]. There is insufficient knowledge to define an effective threshold for MCA to UA ratios, cerebro-placental ratio (CPR) or umbilical-cerebral ratio (UCR), and at which interval measurements should be repeated.

A limited number of studies presented longitudinal data [7–13]. However, all these studies pooled measurement data, and therefore the data analysis became similar to a cross-sectional study. Thus, differences in gestational age and growth restriction at entry and delivery in the population do not allow for information on the pattern of individual UCR values over time. The objectives of this secondary analysis of data from a prospective multicenter European observational feasibility study in women at risk for FGR at a gestational age of 32–36 weeks (TRUFFLE 2) are to determine:

1. How the UCR values vary between consecutive measurements during the observational period;
2. Whether the use of repeated longitudinal Doppler observations improves the association with adverse composite outcome in comparison to a single measurement.

Methods

Study population

Study data were collected during the TRUFFLE 2 feasibility study, 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 detailed methodology of this study was described previously [14]. In brief, women were eligible if they had a singleton pregnancy at 32^{+0} to 36^{+6} weeks of gestation with a fetus considered to be at risk for growth restriction, defined as estimated fetal weight (EFW) or abdominal circumference (AC) < 10^{th} percentile, an abnormal arterial Doppler, or a fall in AC growth velocity from the 20-week scan of more than 40 percentile points, and an expected date of delivery verified by ultrasound < 20 weeks. The references for EFW, AC, and Doppler parameters were based on local charts. Fetuses with absent end diastolic flow in the umbilical artery (UA), an abnormal cardiotocograph (CTG), an immediate indication for delivery, or structural abnormalities were not eligible. Preeclampsia was defined as hypertension and proteinuria, or hypertension and clinical signs of preeclampsia, at any time during pregnancy [15]. The study protocol advised the use of computerized CTG or absent/reversed UA flow to decide if delivery was needed. UCR was not specified as a criterion for delivery.

Study endpoint

The primary adverse outcome was a composite of abnormal condition at birth or major neonatal morbidity. Abnormal condition at birth was defined as at least one 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 one of the following: neurological abnormality (intracerebral hemorrhage grade 3 or 4, periventricular leukomalacia grade 2 or 3, encephalopathy, or seizures necessitating anti-epileptic drug treatment); cardiovascular abnormality (hypotensive treatment, ductus arteriosus treatment, or disseminated coagulopathy); respiratory morbidity (respiratory support for more than 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 greater], or meningitis).

Data analysis

The gestational age at measurement of UCR and EFW was categorized to complete gestational age week. If a woman had more than one measurement in a week, then only the last measurement was selected. A second classification was made for complete weeks 0 to 5 before delivery, allowing only one (last) measurement/week/woman. Box plots that show median, interquartile range (IQR), and the 5^{th} and 95^{th} percentile were made for UCR by gestational age week and by weeks before delivery to show a change over time. The box plots were further subdivided for women who delivered before 35 weeks, at 35–37 weeks, and at 38 weeks or later.

UCR was categorized as normal (< 0.9) or abnormal (≥ 0.9), corresponding to a CPR of 1.1, as reference charts of UCR or CPR show very little variation in the gestational age window of 32–37 weeks, and this threshold was most closely associated with adverse birth and neonatal outcome in a previous study of TRUFFLE2 data [16]. Birth weight Multiple of the Median (MoM) and EFW MoM were calculated using the Hadlock fetal growth chart [17].

A Cox regression analysis using gestational age at delivery as the time axis, composite outcome as status variable, a UCR < 0.9 and ≥ 0.9 as strata, and EFW MoM and gestational age at inclusion as covariates was made to assess if the timeline of gestational age from inclusion to delivery differed for women with an abnormal versus a normal UCR.

A flowchart was compiled to graphically describe the results of a maximum of 5 consecutive measurements with UCR at each step divided into ≥ 0.9 or < 0.9. For each measurement from the 1^{st} to the 5^{th}, in a logistic regression analysis, the odds ratio (OR) for an abnormal UCR ≥ 0.9 was calculated, using gestational age and EFW MoM at the specified measurement, and the number of previous measurements that were either normal or abnormal. Similarly, including also the UCR at the specified measurement, the OR for an adverse composite outcome was calculated by logistic regression analysis at each measurement node in the flowchart.

For each individual measurement series with two or more measurements, a linear regression line was calculated, using UCR as the dependent variable and gestational age at measurement in weeks as the independent variable. A possible difference in increase of UCR over time between adverse and normal composite outcome groups was assessed by comparison of the median of all regression coefficients.

Data were presented as number with percentage or median with interquartile range (IQR). Groups were compared by Kruskal Wallis test, Median test, or Chi Square test as appropriate. Statistical significance was calculated two-sided at $p < 0.05$. Logistic regression was performed by backward procedure with the probability for removal at 0.1. Calculations were made with IBM SPSS software (version 25; IBM Corp., New York, NY, USA).

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 six countries (19 centers) ethical approval was required and obtained, and participating women gave informed signed consent. In the remaining five countries, this was not required.

Results

Study population

Complete delivery and outcome data were recorded for 873 women. 17 women were excluded because of the presence of major congenital abnormalities, leaving 856 women and their fetuses for the final cohort analysis. Demographic, obstetric, and fetal Doppler velocimetry characteristics of the women included in the cohort are shown in ▶ **Table 1**. ▶ **Table 2** shows neonatal outcome. 2770 measurements of UCR and EFW were performed (median 3 [IQR 2–4]/woman). In 696 (81 %) women with more than one measurement of UCR, the median interval between measurements was 7 (IQR 5 to 10) days; 160 (19 %) women had only one measurement. At inclusion, 63 (7 %) of the women had a UCR ≥ 0.9. These women had fetus with a lower EFW at inclusion. While gestational age at study entry was similar, they delivered earlier, had neonates with a lower birth weight and with higher incidence of composite adverse outcome (30 % vs. 9 %, relative risk [RR] 3.2; 95 % confidence interval [CI] 2.1–5.0) than women with a normal UCR at inclusion (▶ **Table 3**, first row).

Analysis by week of gestation

The profile of all UCR measurements by gestational age was horizontal (linear regression coefficient 0.000; p = 0.22). At 32, 33, and 34 weeks, the UCR was higher in women with an adverse composite outcome compared to a normal outcome. In the remaining epochs, the UCR was similar (data not shown). However, when these data were further specified for gestational age at delivery < 35 weeks, 35–37 weeks and ≥ 38 weeks (▶ **Fig. 1**), it became clear that these overall differences were caused by significant differences between the three gestational ages in the delivery groups, with those delivered < 35 weeks having the highest UCR values. ▶ **Fig. 1** further shows that the distribution of UCR differs across categories of gestational age at measurement with a slight increase over time.

Analysis by week before delivery

The UCR in the last two periods (1 and 0 weeks) before delivery was higher than in the first two periods (5 and 4 weeks before delivery) (p < 0.00; data not shown). ▶ **Fig. 2** shows that this was due to a significantly higher UCR in women who delivered < 35 weeks. In women who delivered > 35 weeks, the distribution of UCR differed across categories of weeks before delivery with a slight increase.

Survival analysis

A Cox regression analysis using gestational age at delivery as the time axis, composite outcome as the status variable, a UCR < 0.9 and ≥ 0.9 at inclusion as the strata, and EFW MoM and gestational age at inclusion as covariates is shown in ▶ **Fig. 3**. EFW MoM (OR 0.07; 95 % CI 0.03–0.17/median) and gestational age at measurement (OR 0.96; 95 % CI 0.92–1.00/week) contributed significantly to the model. Delivery was approximately 2 weeks earlier after an abnormal UCR at inclusion.

Sequential measurements of UCR

▶ **Fig. 4** shows a flowchart of the first five consecutive fetal Doppler measurements for normal (< 0.9) and abnormal (≥ 0.9) UCR. The total number of women decreased at each following measurement due to censoring by delivery. Repeated measurements of UCR were fairly consistent. When previous measurements were normal, the median chance of an abnormal value was 6 % (IQR 5–7) at a next weekly measurement. In women with abnormal UCR at first or at any subsequent measurement, the median chance of a repeated abnormal UCR value was 67 % (IQR 55–80).

▶ **Table 3** shows further details of the repeated measurements. The table shows for each measurement order the gestational age at measurement, the abnormal UCR rate and the number of women who delivered after this measurement. From the 63 women (7 %) who had an abnormal UCR at inclusion, 24 (38 %) delivered before a next measurement was performed. These women had an adverse composite outcome rate of 33 %, while this was 10 % in the remaining 136 women (p < 0.05). At any measurement epoch, the median interval to delivery after an abnormal UCR was approximately a week or less, which was significantly shorter compared to women who had a normal UCR, and the birth weight MoM was significantly smaller, except in those who delivered after the first measurement.

▶ **Table 4** shows odds ratios for having an abnormal UCR at the 1st to the 5th measurement, calculated by logistic regression analysis, using gestational age at measurement, EFW MoM, and the number of previous abnormal UCR measurements as independent parameters. Gestational age and EFW MoM at measurement and the number of previous abnormal UCR measurements were the most relevant parameters on an alternating basis. However, the predictive efficacy of the model was similar for all measurement epochs, and repeated measurement data did not improve prediction.

▶ **Table 5** shows a similar analysis with composite endpoint as the dependent variable. The results are similar to the results in ▶ **Table 4** and no improvement of the prediction of adverse outcome by repeating measurements is observed.

Individual linear regression analysis

For 696 (81 %) women with more than one UCR measurement, a regression line could be calculated for each woman. ▶ **Table 6** specifies the regression coefficient for gestational age in the delivery groups (< 35w, 35–37w, and ≥ 38w), and for abnormal UCR at inclusion, at any time thereafter, or never abnormal. Only the group who delivered < 35 weeks and had an abnormal UCR at inclusion had a significantly higher weekly UCR increase (0.3; IQR 0.0–0.5) than the other groups. The lowest linear coefficient, not significantly different from zero, was observed in women who delivered ≥ 38 weeks and/or never had an abnormal UCR. The UCR regression coefficients were similar between adverse and normal outcome.

▶ **Table 1** Demographic and obstetric characteristics of the study population.

variable		women (n = 856)
maternal age		31 (28 to 35)
nulliparity		524 (61 %)
body mass index (kg/m²)		22.5 (20.3 to 26.0)
smoking		68 (8 %)
diabetes type 1, 2, or gestational		70 (8 %)
chronic hypertension		19 (2 %)
at inclusion		
gestational age (weeks)		34 (33 to 35)
inclusion indication*	EFW or AC < 10°pc	792 (93 %)
	AC growth velocity drop ≥ 40°pc	50 (6 %)
	Doppler abnormality	98 (11 %)
EFW (g)		1894 (1624 to 2145)
EFW MoM		0.79 (0.73–0.83)
umbilical artery PI		1.00 (0.86–1.14)
umbilical artery PI ≥ = p95		141 (17 %)
middle cerebral artery PI		1.75 (1.51–2.01)
middle cerebral artery PI < p5		91 (11 %)
UCR		0.56 (0.47–0.69)
CPR		1.79 (1.45–2.14)
UCR ≥ = 0.9		63 (7 %)
before delivery		
preeclampsia or HELLP		79 (9 %)
any hypertensive disorder of pregnancy		119 (14 %)
corticosteroids for fetal lung maturation (> 24 hrs. before delivery)		98 (11 %)
arterial Doppler measurements – number		2770
arterial Doppler measurements – per women		3 (2 to 4)
interval inclusion to delivery (days)		27 (14 to 38)
umbilical artery PI&		0.97 (0.82–1.15)
umbilical artery PI ≥ = p95&		137 (25 %)
middle cerebral artery PI&		1.42 (1.27–1.62)
middle cerebral artery PI < p5&		112 (20 %)
last UCR&		0.67 (0.55–0.84)
last CPR&		1.49 (1.19–1.81)
UCR ≥ = 0.9&		116 (21 %)
delivery		
planned CS	**indication**	219 (26 %)
	fetal condition (CTG or Doppler)	155 (71 %)
	fetal growth/EFW	25 (11 %)
	maternal condition	39 (18 %)

▶ **Table 1** (Continuation)

variable		women (n = 856)
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 %)
cesarean section after onset of labor		117 (18 %)

Data are presented as number (%) or median (interquartile range).
* Multiple indications possible.
& Measurement within one week before delivery, n = 551.

▶ **Table 2** Neonatal outcomes.

variable	infants (n = 856)
gestational age at delivery, weeks	38 (37 to 39)
birth weight, g	2478 (2140 to 2790)
birth weight MoM**	0.76 (0.70–0.82)
birth weight < 10°pc**	596 (70 %)
male sex	372 (44 %)
composite adverse outcome (abnormal condition at birth or major neonatal morbidity)	**93 (11 %)**
abnormal condition at birth*	27 (3 %)
▪ fetal death	2 (0 %)
▪ pH art < 7.0 or pH ven < 7.1 (17 % missing data)	7 (1 %)
▪ Apgar score at 5 minutes < 7	15 (2 %)
▪ resuscitation with intubation or medication	10 (1 %)
major neonatal morbidity*	77 (9 %)
▪ cerebral	7 (1 %)
▪ cardiovascular	7 (1 %)
▪ respiratory	53 (6 %)#
▪ infection	17 (2 %)
neonatal death	0

Data are presented as number (%) or median (interquartile range).
** Reference chart for calculation by Hadlock [17].
* Multiple conditions possible.
# 39/53 (74 %) had only some respiratory support of short duration in the 1st week.

Discussion

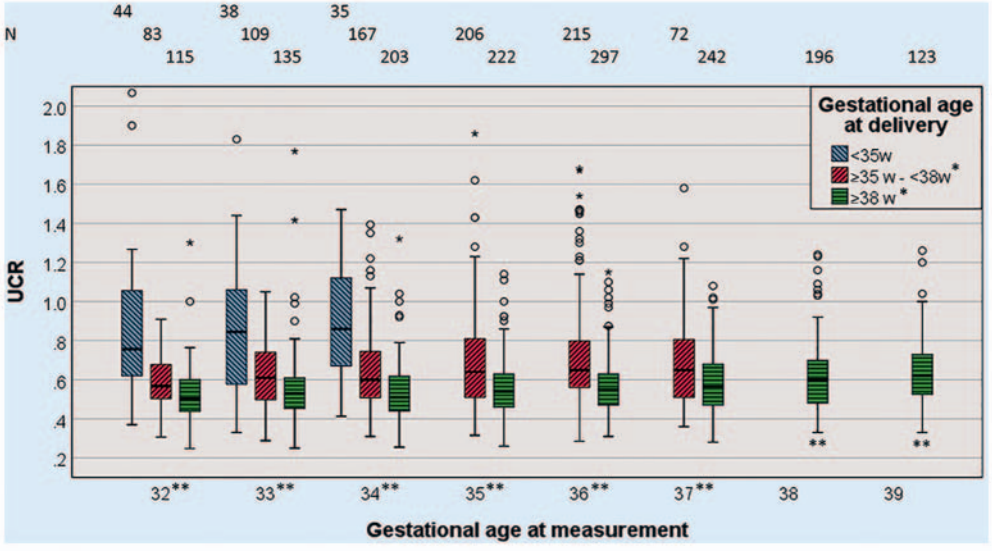
A first abnormal measurement of the UCR was significantly associated with adverse composite outcome, with or without adjustment for gestational age and EFW MoM at first measurement. If the initial measurement of UCR was abnormal, there was a 67 % chance that a subsequent measurement would also be abnormal, while this occurred in only 6 % (IQR 5–7 %) of the women after a normal UCR. This recurrence rate was similar at the first five consecutive measurements. Abnormal measurements are more likely to remain or return to being abnormal, whereas the likelihood of developing an abnormal UCR de novo is around 1 in 20 at each follow-up assessment. The most likely reason for the lack of change of UCR over time is that women with an abnormal UCR were delivered earlier than those with a normal UCR. Within the latter group, 6 % (IQR 5–7 %) of women had an abnormal UCR, replacing those with elevated UCR values that had been delivered. This occurred equally in women with or without adverse composite outcome. An abnormal UCR was associated with a shorter interval to delivery and lower birth weight MoM at all measurement epochs. However, UCR was associated with adverse outcome only in those delivered < 35 weeks. These associations were not affected by the number of previous abnormal or normal UCR measurements.

Analysis of longitudinal UCR data in subgroups with different gestational age at delivery showed that those who delivered earliest (< 34 weeks) had the highest UCR. Although we cannot exclude delivery being triggered by an abnormal UCR, it is more likely that the early delivery was a sign of the severity of the FGR in these pregnancies. In this respect, gestational age at delivery can be viewed as an independent indicator of perinatal risk (and not as a dependent factor as it is usually considered). In FGR the underlying pathology is insufficient oxygen and nutrient supply to maintain normal fetal growth. The severity of the condition is balanced by individual growth velocity and need for nutrition, versus the maximum amount that can be supplied. Fetal adaptation is first by reduced growth. However, if malnutrition increases or persists, fetal condition can deteriorate, ultimately resulting in fetal death. Therefore, those with the most severe FGR need the earliest delivery and in this way gestational age at delivery may indicate the severity of FGR. Though many other factors are also responsible, we have no methods to measure these. The parameters that we can measure are fetal Doppler and EFW. However,

▶ **Table 3** For each order of measurements, gestational age, abnormal UCR rate, and number of women for whom this was the last UCR measurement are shown. For those who had their last measurement at the indicated measurement order, the rate of composite adverse outcome, interval to delivery, and birth weight MoM are specified by UCR being abnormal or normal.

order of measurement	gestational age at doppler	abnormal UCR rate	delivered after this UCR (n)	composite adverse outcome rate		interval to delivery (days)		birth weight MoM	
				UCR ≥ 0.9	UCR < 0.9	UCR ≥ 0.9	UCR < 0.9	UCR ≥ 0.9	UCR < 0.9
first	34 (33–35)	63/856 = 7 %	160/856 (19 %)	**8/24 (33 %)**	13/136 (10 %)	**5 (2–11)**	17 (5–34)	0.77 (0.64–0.80)	0.77 (0.68–0.84)
second	35 (34–37)	35/696 = 5 %	179/696 (26 %)	6/26 (23 %)	22/153 (14 %)	**2 (1–6)**	8 (4–17)	**0.71 (0.60–0.81)**	0.78 (0.72–0.84)
third	36 (35–37)	25/517 = 5 %	214/517 (41 %)	1/28 (4 %)	21/186 = 11 %	**2 (1–5)**	5 (2–9)	**0.74 (0.69–0.79)**	0.78 (0.73–0.84)
fourth	37 (36–38)	20/303 = 7 %	115/290 (40 %)	3/15 (20 %)	6/100 (6 %)	**2 (1–6)**	4 (2–6)	**0.70 (0.66–0.73)**	0.77 (0.71–0.82)
fifth	37 (36–38)	10/188 = 6 %	92/188 (49 %)	1/14 (7 %)	8/78 (10 %)	**1.5 (0.6–2.4)**	5 (2–7)	**0.68 (0.63–0.77)**	0.76 (0.70–0.81)

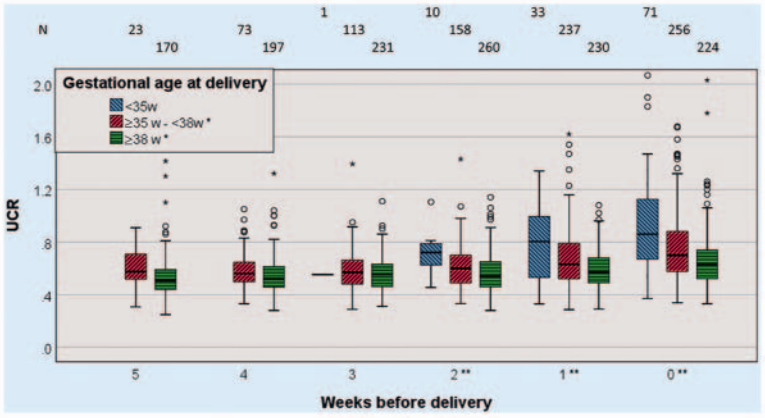
Specification of women delivered for abnormal UCR: No earlier abnormal UCR + abnormal UCR at earlier measurement. Total 14 + 18 – four deliveries indicated by abnormal UCR occurred after a later measurement order.
Bold = Chi-Square test or Kruskal-Wallis test $p < 0.05$, ≥ compared to the next column.



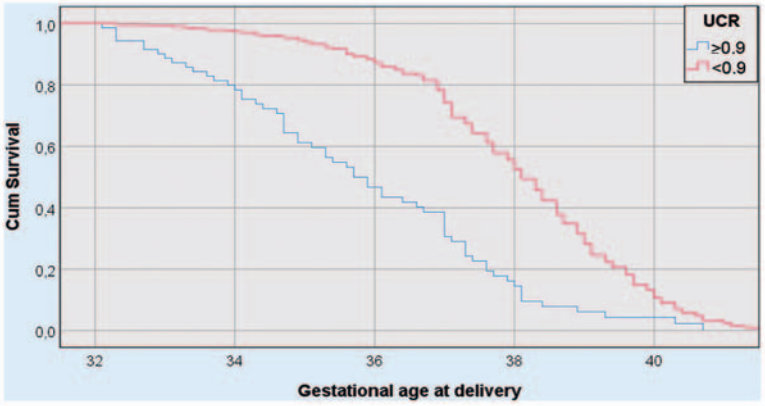
▶ **Fig. 1** Box plot of UCR and gestational age at measurement – one measurement/woman/gestational age period. 2502 measurements (268 double measurements in a week excluded), 856 women. * The distribution of UCR differs across categories of gestational age at measurement (Kruskal-Wallis). ** The medians of UCR differ across the categories of gestational age at delivery for each gestational age in the measurement group (Median test).

even though they are significantly related to perinatal adverse outcome, they are relatively poor predictors of it.

Several studies reported longitudinal changes of fetal Doppler in association with the severity of FGR and earlier delivery [7–13]. All collected data were from clinical databases, except Hecher et al., who performed measurements prospectively for research purposes in a selected predefined population. Studies that targeted early FGR < 32 weeks described a more predictable sequential pattern of deterioration of fetal monitoring parameters [7–10]. These findings differ from our results as the pattern of Doppler measurement values is different in women with early vs. late preterm FGR.



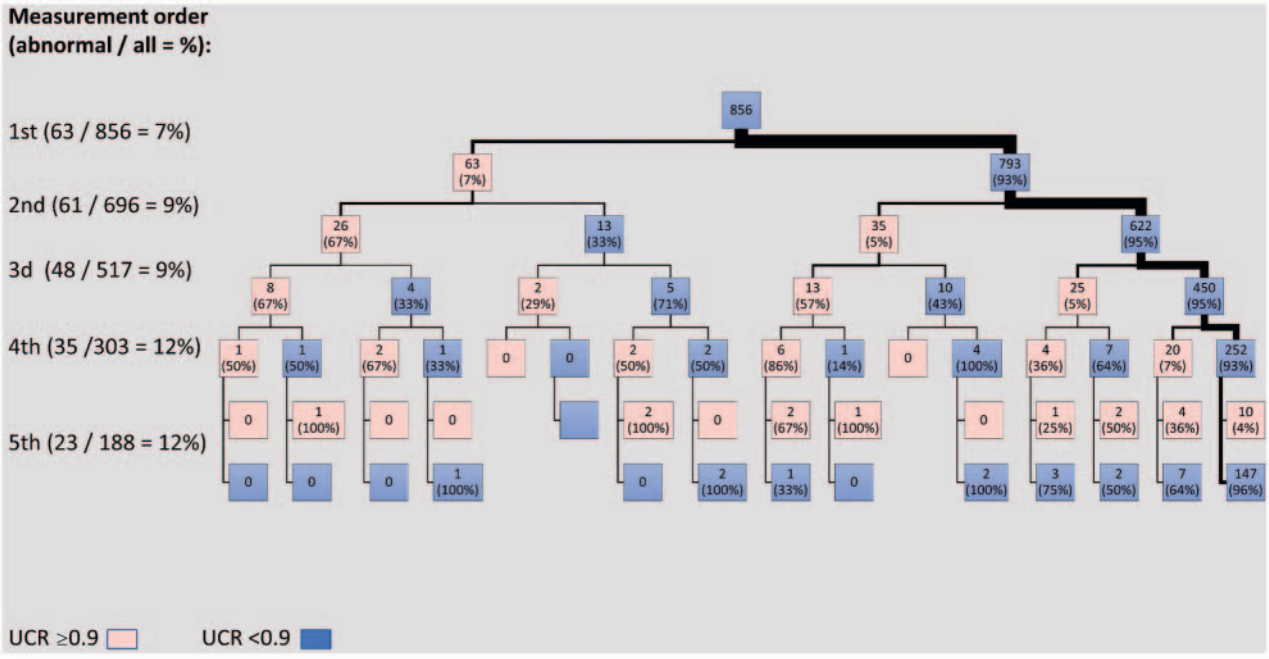
▶ **Fig. 2** Boxplot of UCR and weeks to delivery – one measurement/woman/week. N = 2287 measurements (209 excluded with an interval of more than 5 weeks and 274 excluded to prevent > 1 measurement/period/woman, 856 women, specified for gestational age at delivery and composite outcome. * The distribution of UCR differs across categories of weeks before delivery (Kruskal-Wallis). ** The medians of UCR differ across the categories of gestational age in the delivery groups within each interval to delivery group (Kruskal Wallis).



▶ **Fig. 3** Cox regression analysis for delivery after inclusion, specified for an abnormal UCR ≥ 0.9 or normal UCR < 0.9 at inclusion, adjusted by gestational age and EFW at inclusion.

Where fetal arterial Doppler was measured biweekly in women with FGR diagnosed at 30–36 weeks, a gradual, nearly linear decrease of CPR Z-score from 0 at 30 weeks to –1.3 at 40 week was reported [11]. 7 % of the women had an abnormal CPR at 37 weeks and 23 % at the last measurement before birth. In contrast, we observed less change with increasing gestational age in women with both normal and adverse composite outcome. 7 % had an abnormal UCR at inclusion and 15 % at last measurement, recognizing that we used absolute values and not Z-scores. However, when we adjusted for gestational age at delivery, this increase in UCR disappeared because those who delivered earlier had more abnormal values. A study that compared two CPR measurements after 30 weeks described only a small decrement in CPR Z-scores between measurements (–0.02/week) [13]. In 941 women with small for gestational age (SGA) in whom repeated Doppler measurements were performed from 20 weeks onwards [12], the prediction of stillbirth was best using the last measured CPR, while earlier longitudinal changes did not improve prediction. A plot of CPR against gestational age showed a fairly horizontal pattern after 32 weeks, in both normal women and those with an SGA fetus, although the values in the latter group were lower. Thus, longitudinal studies that have reported on late preterm FGR had conclusions comparable to our study.

There has been some debate in relation to the preference of CPR [18, 19] or UCR [20, 21] for describing the degree of cerebral blood flow redistribution. Our preference for UCR derives from the analysis of the early FGR TRUFFLE cohort [22], where UCR and MCA z-score but not CPR were related to long-term outcome. Moreover, most ratios used in medicine show a progressively greater separation in the abnormal (not normal) range as is the case for UCR but not CPR. This is true for sflt/PLGF ratio for risk assessment of preeclampsia, protein creatinine ratio in the diagnosis of preeclampsia, and V/Q ratio for ventilation: perfusion mismatch [16].



▶ **Fig. 4** Flowchart of 5 sequential UCR measurements, specified for abnormal (≥ 0.9) or normal (< 0.9) UCR. At first measurement, the total group of 856 women was measured. Thereafter, numbers decreased due to delivery. The median interval between measurements was 7 days (IQR 5 to 10).

▶ **Table 4** Odds ratios with 95 % confidence intervals for an abnormal UCR >= 0.9 at consecutive measurements (the first is at inclusion), calculated by logistic regression analysis. The area under the curve (AUC) of a receiver operating characteristic (ROC) curve is calculated using the probability for an abnormal UCR calculated by the regression analysis. The logistic regression was started with all parameters in the title row; absent results: —: the parameter was removed from the model because p >= 0.10.

order of measurement	N	gestational age/week	EFW MoM	count of earlier UCR ≥ 0.9	AUC ROC
first	856	—	0.57 (0.41–0.78)	—	0.68 (0.62–0.75)
second	696	—	0.59 (0.42–0.83	31.2 (14.4–68)	0.71 (0.64–0.78)
third	517	0.74 (0.59–0.93)	—	8.3 (4.43–15.52)	0.60 (0.51–0.69)
fourth	303	0.74 (0.56–0.96)	—	0.45 (2.51–0.96)	0.65 (0.53–0.77)
fifth	188	—	0.56 (0.33–0.97)	3.49 (1.91–6.36)	0.77 (0.64–0.89)

A characteristic of all observational studies, including this one, is that obstetric management is frequently based on Doppler observations. The association of an abnormal UCR and adverse perinatal outcome is clear, but whether perinatal outcome can be improved by using the UCR 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.

Conclusion

An abnormal UCR is likely to be abnormal again at a later measurement in 67 % (IQR 55–80), while after a normal UCR the chance of an abnormal value is 6 % (IQR 5–7). Repeated measurements do not predict outcome better than the first measurement, most likely due to the most compromised fetuses being delivered earlier. Adverse outcome is most strongly linked to an earlier gestational age at abnormal UCR measurement.

▶ **Table 5** Odds ratios with 95 % confidence intervals for an adverse composite outcome at consecutive measurements (the first is at inclusion), calculated by logistic regression analysis. The area under the curve (AUC) of a receiver operating characteristic (ROC) curve is calculated using the probability for adverse outcome calculated by the regression analysis. The logistic regression was started with all parameters in the title row; absent results: —: the parameter was removed from the model because p > = 0.10.

order of measurement	N	gestational age/week	EFW MoM	UCR > = 0.9	earlier UCR ≥ 0.9	AUC ROC
first	856	0.83 (0.71–0.98)	0.48 (0.36–0.63)	3.2 (1.8–6.20)	—	0.72 (0.66–0.78)
second	696	0.82 (0.68–0.99)	0.48 (0.35–0.66)	—	2.27 (0.99–5.20)	0.72 (0.66–0.79)
third	517	0.81 (0.66–1.01)	0.67 (0.45–0.99)	—	—	0.65 (0.57–0.74)
fourth	303	—	0.51 (0.30–0.88)	8.0 (1.10–58)	—	0.74 (0.63–0.84)
fifth	188	—	0.41 (0.23–0.75)	—	—	0.73 (0.58–0.88)

▶ **Table 6** Medians and interquartile range of the individual linear regression coefficients of UCR for women with > = 2 measurements (n = 696), specified for the first abnormal UCR > = 0.9 at inclusion, at a later measurement, or never abnormal, and gestational age at delivery.

gestational age at delivery	UCR > = 0.9 rate	UCR regression coefficient (= change/week)				
		1st UCR > = 0.9	later UCR > = 0.9	always UCR < 0.9	adverse endpoint	normal endpoint
< 35 w	21/45 (47 %)	**0.29 (0.00–0.50)**	0.12 (0.03–0.27)	0.04 (–0.10–0.23)	0.09 (–0.02–0.37)	0.06 (0.00–0.29)
> = 35 w – < 38 w	78/256 (30 %)	0.08 (–0.28–0.18)	0.10 (0.06–0.20)	**0.02 (–0.02–0.08**	0.04 (–0.06–0.09)	0.03 (–0.01–0.10)
> = 38 w	41/395 (10 %)	–0.07 (–0.12–0.00)	0.07 (0.03–0.12)	**0.02 (–0.01–0.04)**	0.01 (–0.01–0.03)	0.02 (–0.01–0.04)

Bold = median differs significantly from other categories (Median test).

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Conflict of Interest

The authors declare that they have no conflict of interest.

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