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MATERNAL-FETAL MEDICINE

Performance of computerized cardiotocography-based short-term variation in late-onset small-for-gestational-age fetuses and reference ranges for the late third trimester

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Abstract

Purpose Fetal Doppler changes are well characterized in early-onset small-for-gestational-age (SGA) and fetal growth restriction (FGR) but less well characterized where the condition is late-onset. The aim of the study was to evaluate the role of computerized CTG (cCTG)-based short-term variation (STV) in late-onset SGA and FGR as an additional monitoring modality and to establish STV reference ranges in late third trimester healthy pregnancies.

Methods Of 86 late-onset SGA fetuses diagnosed after 32 weeks, 66 were diagnosed with FGR. 138 healthy pregnancies acted as controls. All underwent umbilical artery pulsatility index (PI), middle cerebral artery PI, cerebroplacental ratio and mean uterine artery PI. cCTG recordings were analyzed by Sonicaid FetalCare software for STV calculation as described by Dawes/Redman.

Results Median interval between inclusion and delivery was 13 (interquantile range = 4–30) days in the FGR group, 22 (12–37) days in the SGA group and 25 (10–40) days in the control group. STV was not different between controls (11.2 ms, 9.7–13.1), late-onset SGA (11.2 ms, 8.1–12.6) and FGR (10.5 ms, 8.5–12.4) fetuses. A greater proportion of late-onset SGA fetuses had STV < 5th percentile (7/86) compared to controls (4/138) (8.1% vs. 2.9%, $p = 0.077$). In the control group a significant positive correlation was seen between STV, and 1-min ($\rho = 0.195$, $p = 0.026$), 5-min ($\rho = 0.247$, $p = 0.004$) and 10-min ($\rho = 0.211$, $p = 0.014$) Apgar values.

Conclusions We report no significant difference in STV median values between controls, SGA and FGR pregnancies. However, more SGA fetuses had a low STV compared to controls. Prospective longitudinal studies are needed to investigate if low STV is a useful surveillance method for late-onset FGR.

Keywords Fetal monitoring · CTG · Small-for-gestational-age · Fetal growth restriction · Doppler ultrasound · Short-term variation

Introduction

Newborns with a birth weight below the 10th percentile are commonly considered to be small-for-gestational-age (SGA). Of these, many will be healthy and small but some

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will have suffered a pathological restriction of their growth, most commonly due to uteroplacental insufficiency.

Clinical studies relating fetal size and associated outcome have defined fetal growth restriction (FGR), requiring both low weight and fetal Doppler abnormalities [1], most commonly of the umbilical artery (UA) [2, 3]. In a recent Delphi consensus for late-FGR (≥ 32 weeks), two solitary parameters (abdominal circumference (AC) or estimated fetal weight (EFW) < 3rd centile) and four contributory parameters (EFW or AC < 10th centile, AC or EFW crossing centiles by > two quartiles on growth charts and cerebroplacental ratio < 5th centile or UA pulsatility index > 95th centile) were defined [4]. However, the majority of late-onset SGA fetuses do not present pathological findings in the umbilical artery (UA) Doppler [5–7]. Some of these term SGA fetuses have poorer perinatal outcome: higher risk of subtle neurodevelopmental deficits and higher postnatal cardiovascular risk compared with appropriate for gestational age (AGA) neonates [5–10]. This observation has led to a realization that a significant proportion of SGA fetuses are in reality "late-onset" FGR where placental insufficiency is not represented by pathological UA Doppler. Hence, additional markers might predict poor perinatal outcome and identifying late-onset FGR among SGA fetuses.

Recent research on late-onset FGR has primarily been focused on cerebral Doppler ultrasound parameters or (anti) angiogenic factors [11]. Abnormal fetal heart rate (FHR) patterns measured by cardiotocography (CTG) have also been considered as markers of impaired perinatal outcome. These are commonly used for fetal surveillance, but interpretation of CTG shows a substantial inter- and intra-observer variability [12–14]. Thus, a computer-based CTG (cCTG) analysis developed by Dawes allows objective assessment of the fetal heart rate trace, the major component of which is short-term variation (STV) reflecting FHR variation [15, 16]. Low values for STV have been described as reflecting late fetal decompensation [17–21]. STV is more commonly used and now recommended in the surveillance of early-onset FGR fetuses [2]. The aim of the present study was to develop reference ranges for STV during the late third trimester and to evaluate how STV performs in late SGA fetuses and the subgroup of those that can be defined as FGR especially in the subgroup of late-onset FGR among SGA fetuses. A secondary objective was to correlate fetomaternal Dopper and short-term neonatal outcome data with STV.

Methods

A single center cohort analysis was performed from January 2014 until September 2016 at a single obstetric teaching hospital unit. According to recent consensus definition we defined early-onset SGA as the occurrence of SGA < 32 weeks and late-onset as the occurrence of SGA ≥ 32 weeks [4]. FGR was defined as an estimated fetal weight (EFW) < 3rd percentile or EFW < 10th percentile in combination with at least one of the following Doppler abnormalities: umbilical artery (UA) pulsatility index (PI) > 95th percentile, middle cerebral artery (MCA) PI < 5th percentile, cerebroplacental ratio (CPR) < 5th percentile and/or a mean uterine artery (mUtA) PI > 95th percentile We retrospectively included singleton pregnancies fulfilling the following criteria: pregnancies between 32 and 40 weeks complicated by SGA or FGR, respectively. These patients were routinely seen in a high-risk SGA outpatient clinic. Those SGA pregnancies, which underwent at least one cCTG using the original Dawes/Redman algorithm for STV calculation, were included. Gestational age was defined based on the first day of the last menstrual period and confirmed by crown–rump length measurement at the first-trimester ultrasound scan. The diagnosis SGA could be confirmed in all cases postnatal.

Inclusion criteria were maternal age between 18 and 50 years, and no evidence of malformation. Healthy singleton pregnancies at 32–40 weeks with estimated weight appropriate for gestational age were also included. The control group was recruited prospectively from September 2014 to April 2015 including 15–18 fetuses per gestational week from 32 weeks onwards. All control patients were recorded once performing cCTG of 40 min, ultrasound biometry and UA Doppler measurement (under publication) [22].

An ultrasound and Doppler evaluation was performed by abdominal ultrasound with 4–6 MHz probes (Voluson E 8 or Voluson 730 Expert GE Medical Systems, Munich, Germany). EFW was calculated by measuring biparietal diameter (BPD), head circumference (HC), abdominal circumference (AC) and femur length (FL). Doppler recordings were performed in the absence of fetal movements and voluntarily suspended maternal breathing. The examination at enrolment included: UA PI calculated from three or more consecutive waveforms obtained from a free-floating portion of the umbilical cord, at insonation angles < 30; UA PI was defined as normal when it was < 95th centile for gestational age [23]. MCA PI was measured in a similar fashion, distal to the junction with the internal carotid artery. Abnormal values were defined as MCA PI < 5th centile [23]. CPR was calculated as the ratio of MCA PI to UA PI, and considered abnormal when < 5th centile [24]. For UtA evaluation the probe was placed on the lower quadrant of the abdomen, angled medially, and color Doppler imaging was used to identify the UtA at the apparent crossover with the external iliac artery. Mean UtA PI was calculated as average PI of right and left arteries. Mean UtA PI was defined as abnormal when it was > 95th centile [25].

According to our clinical protocols, fetuses with late-onset FGR were delivered electively (induction of labor)

between 37 and 38 weeks. The rest of SGA pregnancies were allowed to continue until 40 weeks, when elective delivery was indicated, the women with healthy pregnancies (controls) were offered induction of labor at 40+ 7–10 days.

Prenatal cCTG recordings were collected using the Sonicaid System 8002 (Oxford Instruments Medical Ltd, Surrey, UK). We performed cCTG recordings for 40 min. The complete CTG signal was used for analysis. Data were analyzed by Sonicaid FetalCare software for STV as described in detail by Dawes/Redman [15, 16]. The result of the cCTG was revealed to clinicians caring for the participants in the study. First measurements of STV at the time of enrollment and perinatal outcome data (Apgar, pH, base excess, admission to neonatal intensive care unit, cesarean section rate, birth weight, and gestational age at delivery) were collected for all groups.

Statistical analysis

As most quantitative data followed a skewed distribution, medians and interquartile ranges were reported. For categorical data, we show the absolute and relative frequencies. For comparison between groups, Mann–Whitney *U* tests, and Pearson Chi-squared test were used. For correlation of STV and perinatal outcome data as well as fetomaternal Doppler findings we used Spearman's rank correlation. All statistical tests were conducted two-sided and a p value < 0.05 was considered statistically significant. Scatterplots for the STV against the gestational age at sampling were constructed, where the 5th, 50th and 95th centile were obtained after LMS quantile regression in R.

Statistical analysis was performed using IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, NY, USA) and R version 2.15.2 (The R Foundation for Statistical Computing).

Ethical approval

The local Institutional Ethics Board (Ethikkommission der Fakultät für Medizin der Technischen Universität München) approved the study (protocol number 117/17, date of approval: March 29, 2017). The study was not registered in a public trial registry.

Results

224 women between 32 and 41 weeks of gestation were included; 86 women with pregnancies complicated by SGA, 66 were subclassified as FGR and 138 controls. The median gestational age at inclusion was 36.4 (34–38.7) weeks of gestation in the control group, 37.1 (34.1–37.3) weeks of gestation in the SGA group and 35.3 (33.6–36.6) weeks of gestation in the FGR group. Median interval between inclusion and delivery was 13 (4–30) days in the FGR group, 22 (12–37) days in the SGA group, and 25 (10–40) days in the control group. Table 1 shows pregnancy outcome data of both groups (controls and SGA fetuses) and the Doppler findings in the FGR group. All umbilical artery Doppler measurements were normal in the control group. There were no findings of absent or reverse end diastolic flow in the umbilical artery Doppler in the FGR group.

Box plots of STV of the single FHR recordings are shown in Fig. 1. The median STV was 11.2 (9.7–13.1) ms in the control group, 11.2 (8.1–12.6) ms in the late-onset SGA and 10.5 (8.5–12.4) ms in the FGR group. There was no significant difference between the STV values (Fig. 1). In the control pregnancies, STV was not related to gestational age ($\rho = 0.045$ $p = 0.600$). There were more late-onset SGA fetuses with an STV < 5th percentile (7/86) compared to controls (4/138) (8.1% vs. 2.9%, $p = 0.077$), without reaching statistical significance.

There was a significant positive correlation of STV, and 1-min ($\rho = 0.195$, $p = 0.026$), 5-min ($\rho = 0.247$, $p = 0.004$) and 10-min ($\rho = 0.211$, $p = 0.014$) Apgar values in the control group. No further significant correlations between STV values and perinatal outcome data were found in the groups (Table 2). In the FGR group no significant correlation was found between STV and fetomaternal Doppler findings (UA PI: $\rho = -0.137$, $p = 0.271$; MCA PI: $\rho = 0.070$, $p = 0.579$; CPR: $\rho = 0.155$, $p = 0.213$; mUtA PI: $\rho = -0.018$, $p = 0.891$).

STV measurements in relation to gestation with adjusted 5th and 95th percentile including MCA PI, CPR, UA PI and mUtA PI FGR subgroups are displayed in Fig. 2. Reference values for the 5th percentile of STV during third trimester are shown in Table 3. An overview of short-term perinatal outcome data in each individual case of STV values < 5th percentile are provided in Table 4 (supplementary material).

Discussion

To our knowledge, this is the first study describing the performance of cCTG-based STV in late SGA using Dawes/Redman criteria. Lower values of STV have been shown in severe cases of FGR, which usually occur before 32 weeks gestation and are correlated with fetal acidemia and early neonatal death [1, 17–21]. The findings of our study indicate that median STV was not different in late-onset SGA, FGR and healthy fetuses. However, a higher proportion of late-onset SGA fetuses had an STV < 5th percentile compared to controls. This is consistent with the findings of Amorim Costa et al. who reported no differences in mean STV between normal and SGA fetuses between 24 and 40 weeks in SGA fetuses using the Omniview-SisPorto 3.6 system [26]. However, in contrast to Dawes/Redman they define

Table 1 Doppler findings in fetal growth restriction (FGR) fetuses and pregnancy outcome data in late-onset FGR/small for gestational age (SGA) fetuses and controls

Doppler characteristics	Late-onset FGR ($n=66$)	Late-onset SGA ($n=20$)	Controls ($n=138$)
UA-PI > 95th percentile	4 (6.1%)	0	0
MCA-PI < 5th percentile	27 (40.9%)	0	–
CPR < 5th percentile	22 (33.3%)	0	–
mUtA-PI > 95th percentile	21 (33.9%)	0	–
EFW < 3rd percentile	41 (62.1%)	0	–

Neonatal outcome	Late-onset FGR ($n=66$)	Late-onset SGA ($n=20$)	Controls ($n=138$)	p value
Median time to deliver (days)	13 (4–30)	22 (12–37)	25 (10–40)	$0.045^{\#}$*, 0.003^{+}*, 0.978°
Median GA at delivery (weeks)	37.7 (37.1–39.1)	39.8 (38.9–40.4)	40.1 (39–40.9)	$<0.001^{\#}$*, $<0.001^{+}$*, 0.158°
Cesarean delivery	36 (56.3%)	8 (40%)	50 (37%)	$0.204^{\#}$, 0.011^{+}*, 0.798°
Primary	23 (63.9%)	4 (50%)	25 (50%)	$0.466^{\#}$, 0.201^{+}, 1.0°
Secondary	13 (36.1%)	4 (50%)	25 (50%)	
Median birth weight (g)	2325 (2160–2550)	2780 (2655–2875)	3380 (3160–3650)	$<0.001^{\#}$*, $<0.001^{+}$*, <0.001°*
5-min APGAR ≤ 7	4 (6.2%)	1 (5%)	6 (4.4%)	$0.848^{\#}$, 0.603^{+}, 0.911°
pH (artery) ≤ 7.15	5 (7.6%)	5 (25%)	16 (11.9%)	$0.033^{\#}$*, 0.344^{+}, 0.112°
Median pH (artery)	7.30 (7.24–7.34)	7.24 (7.20-7.28)	7.27 (7.22–7.32)	$0.019^{\#}$*, 0.057^{+}, 0.110°
Median base excess (mmol/l)	−4.5 (−6.5 to 2.2)	−6.5 (−8.1 to 3.2)	−4.9 (−7.3 to 2.6)	$0.092^{\#}$, 0.416^{+}, 0.205°
Neonate intensive care unit (NICU)	37 (56.1%)	3 (15%)	4 (3.1%)	$0.001^{\#}$*, $<0.001^{+}$*, 0.018°*

Cesarean indication	Late-onset FGR	Late-onset SGA	Controls
Pathologic Doppler	4 (11.1%)	0	0
Decelerations (CTG)	11 (30.6%)	1 (12.5%)	7 (14.3%)
STV < 4 ms	0	0	–
Other	21 (58.3%)	7 (87.5%)	43 (85.7%)

Early-onset SGA was defined as the occurrence of SGA < 32 weeks and late-onset as the occurrence of SGA ≥ 32 weeks. FGR was defined as an estimated fetal weight (EFW) < 3rd percentile according to local standards *or* EFW < 10th percentile in combination with at least one of the following Doppler abnormalities: Umbilical artery (UA) pulsatility index (PI) > 95th percentile, middle cerebral artery (MCA) PI < 5th percentile, cerebroplacental ratio (CPR) < 5th percentile and/or a mean uterine artery (mUtA) PI > 95th percentile. Data are given as median or quantity. The corresponding interquartile range or percentage values are given in brackets. For comparison between groups, Mann–Whitney *U* test (quantitative data) and Pearson Chi squared test (categorical data) were used

*p values < 0.05 were considered statistically significant

$^{\#}$Comparison between late-onset FGR and late-onset SGA fetuses, $^{+}$Comparison between late-onset FGR and controls, $^{\circ}$Comparison between late-onset SGA and controls

STV as the average short-term variability calculated by the mean difference between adjacent FHR signals, which was a different algorithm to that of Dawes–Redman and must be taken into account in interpreting the data. This is in contrast to fetal distress in early-onset FGR fetuses where reported values for STV were significantly lower in FGR fetuses than in healthy controls [27, 28].

Furthermore, we found a relationship between low STV and low 1, 5 and 10 min Apgar score in control healthy fetuses. This is a novel finding with potential implications for fetal surveillance. The role of the Apgar score has been debated over recent years, however, in a recent study of over one million deliveries in Scotland, a low Apgar score at 5 min was strongly related to all cause neonatal and infant mortality [29]. Hence, the STV might be a more sensitive indicator of general fetal well-being in a normal population than previously assumed.

Less is known about the role of STV to detect fetal compromise in late-onset FGR and to differentiate between constitutional late-onset SGA and FGR. As reported from the TRUFFLE trial, STV is a "gold standard" for determining the timing delivery in early-onset FGR fetuses [30] as the combination of fetal Doppler and cCTG-STV leads to optimal survival and neurodevelopmental outcomes in the growth-restricted fetus with poor placental function [30, 31]. We report median STV values in late-onset FGR fetuses as being higher compared to other earlier studies, where fetal deterioration was described for values lower than 3 ms [15]. It is reported that values for STV increase during gestation notably prior to 30 weeks [32]. However, we saw no change

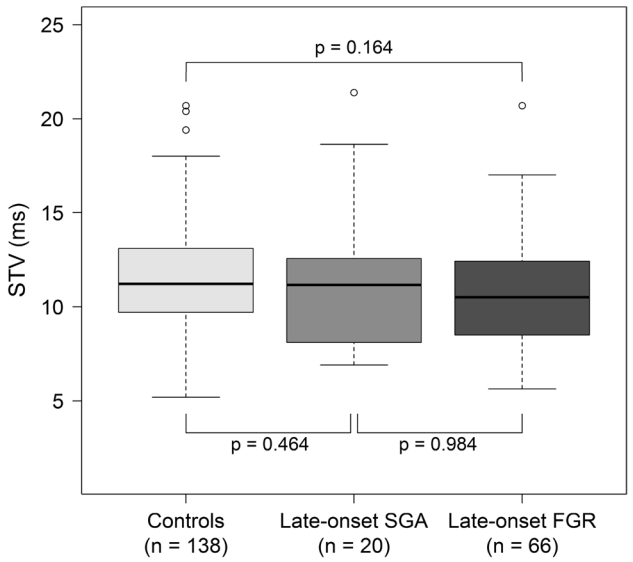

Fig. 1 Box plots of short-term variation (STV) of the single fetal heart rate recordings in the different subgroups. Late-onset fetal growth restriction (FGR): estimated fetal weight (EFW) < 3rd percentile or EFW < 10th percentile in combination with abnormal fetoplacental and uterine Doppler findings. Late-onset small-for-gestational-age (SGA): EFW < 10th percentile and normal Doppler findings

in STV with gestational weeks in the third trimester. The lower limit of the normal distribution, though, is hardly different throughout gestation and the overall increase in STV may not suffice as the sole explanation of higher STV values in late-onset FGR when compared to TRUFFLE results.

Several study groups searched for adequate identifying and monitoring tools for late-onset SGA fetuses. Cruz-Martinez et al. who evaluated 210 fetuses > 37 weeks of gestation suspected of having late-onset SGA found that an abnormal CPR is associated with a significantly higher rate of emergency cesarean delivery, acidosis or NICU admissions [33]. This is in line with Figueras et al. who evaluated 509 fetuses with late-onset SGA. They reported about 39% having an abnormal CPR at term [34]. Interestingly, we found no significant correlation between low STV values and both, abnormal CPR/MCA PI values.

The fetal response to hypoxia of cerebral redistribution seems to define those babies at particular risk. Hence, Doppler evaluation of the MCA is necessary for late-onset SGA fetuses having a relationship with abnormally low MCA impedance and perinatal adverse outcome [35], though how predictive this isolated parameter is remains open to debate. Therefore, the CPR is emerging as being associated with adverse pregnancy outcome and of potential utility as an assessment tool of well-being in fetuses diagnosed as SGA and even those AGA close to term [36, 37]. A significant association between SGA and an abnormal CPR as indicators for fetal distress in labor requiring emergent delivery and admission to the neonatal intensive care unit (NICU) was found [38, 39]. We observed in general a NICU admission rate of 56% in the subgroup of late-onset FGR; this is explained largely because in our unit newborns weighing < 2500 g were routinely admitted to NICU during the study period.

Our study has several limitations. SGA STV values were collected retrospectively, whereas the control STV group was included prospectively and the sample size of SGA with cCTG was low in comparison to the SGA cases that we see. The low number of available cases did not allow stratifying the STV results by Doppler severity. Despite the description of STV measurements in relation to gestation, data were analyzed cross-sectionally not taking into account the longitudinal evolution of each individual fetus. Furthermore, our STV values were recorded at quite an early stage: 13 days before delivery for FGR fetuses, 22 days for SGA fetuses and 25 days for controls. For a "subacute" situation which late-FGR in contrast to early-FGR represents this time interval might be too large. It would be interesting to investigate the longitudinal progression of STV in both subgroups.

Diagnosis of FGR by means of ultrasound is imperfect as estimated fetal weight calculation using four parameters

Table 2 Correlation of short term variation (STV) and perinatal outcome data in late-onset fetal growth restriction (FGR), small for gestational age (SGA) and controls

Outcome	1-min Apgar	5-min Apgar	10-min Apgar	pH value	Base excess	Birth weight
Late-onset FGR						
STV	0.086	−0.074	−0.085	0.010	−0.005	0.177
p value	0.494	0.556	0.499	0.936	0.967	0.154
Late-onset SGA						
STV	−0.278	−0.262	0.205	0.093	0.105	0.227
p value	0.235	0.265	0.386	0.695	0.659	0.335
Controls						
STV	0.195*	0.247*	0.211*	0.123	0.101	0.022
p value	0.026	0.004	0.014	0.158	0.254	0.804

Data are given as Spearman's rank correlation coefficient (ρ) for quantitative data

*p values < 0.05 were considered statistically significant

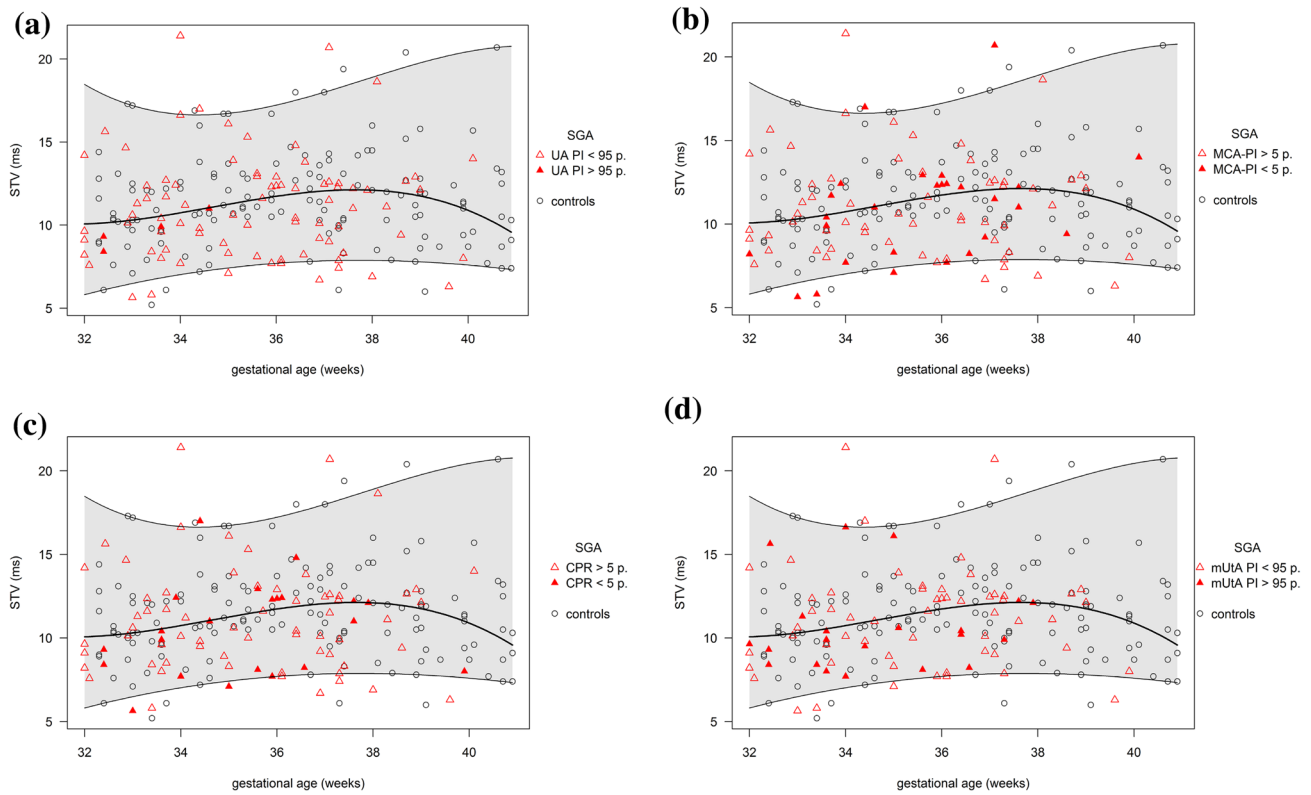

Fig. 2 **a**–**d** Short-term variation (STV) measurements in relation to gestation with adjusted 5th and 95th percentile for controls (circle) and all small-for-gestational-age (SGA) fetuses (red triangle), highlighted subgroup (fulfilled red triangle) with pathologic umbilical artery (UA) pulsatility index (PI), middle cerebral artery (MCA) PI, cerebroplacental ratio (CPR), mean uterine artery (mUtA) PI

Table 3 Estimated values of the 5th percentile for short term variation (STV) during the third trimester for healthy controls

Weeks of gestation (weeks)	5th percentile of STV (ms)	STV median value (ms)
32	6.1	10.3 (8.9–12.8)
33	6.8	10.1 (8.7–12.1)
34	7.2	11.2 (9.5–13.5)
35	7.6	11.7 (11.0–13.1)
36	7.8	12.8 (11.3–13.8)
37	7.9	11.7 (9.9–14.3)
38	7.8	11.9 (9.9–14.7)
39	7.7	11.3 (9.3–12.0)
40	7.5	10.0 (8.5–13.3)

Daily estimates were derived using quantile regression, estimates on a weekly basis were calculated as means of daily estimates for the corresponding week

(BPD, HC, AC, FL) means four potential sources of error. Furthermore, the possibility of documenting individual growth is not well described using common growth charts. This may have an influence in a small study population.

In summary, our results indicate that Apgar scores at 1, 5 and 10 min may be related to the STV in the antepartum cCTG even when recorded many days ahead of delivery. There is no significant difference in median STV values between controls, SGA and FGR pregnancies. However, we found that a higher proportion of late-onset SGA fetuses showed STV values < 5th percentile compared to controls. Larger prospective longitudinal studies are needed to examine the usefulness of STV analysis by cCTG as a surveillance method for late-onset growth-restricted fetuses especially regarding prediction of outcome and timing of delivery.

Author contributions OG project development, data collection, data analysis, data interpretation, manuscript writing. JUO data interpretation, critical revision of the manuscript. BH data analysis, critical revision of the manuscript. AW-G data collection, critical revision of the manuscript. RO data collection, critical revision of the manuscript. BK: Data interpretation, critical revision of the manuscript. JW data interpretation, critical revision of the manuscript. CL project development, data analysis, data interpretation, critical revision of the manuscript. SML project development, data collection, data analysis, data interpretation, critical revision of the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee, and with the 1964 Helsinki Declaration, and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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