Effects of antenatal betamethasone on fetal Doppler indices and short term fetal heart rate variation in early growth restricted fetuses

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Einfluss von antenatalem Betamethason auf fetale Doppler-Indizes und die Kurzzeitvariation der fetalen Herzfrequenz bei Föten mit früher Wachstumsrestriktion

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ABSTRACT

Purpose To investigate the effects of the antenatal administration of betamethasone on fetal Doppler and short term fetal heart rate variation (CTG-STV) in early growth restricted (FGR) fetuses.

Materials and Methods Post hoc analysis of data derived from the TRUFFLE study, a prospective, multicenter, randomized management trial of severe early onset FGR. Repeat Doppler and CTG-STV measurements between the last recording within 48 hours before the first dose of betamethasone (baseline value) and for 10 days after were evaluated. Multilevel analysis was performed to analyze the longitudinal course of the umbilico-cerebral ratio (UC ratio), the ductus venosus pulsatility index (DVPIV) and CTG-STV.

Results We included 115 fetuses. A significant increase from baseline in CTG-STV was found on day + 1 ($p = 0.019$) but no difference thereafter. The DVPIV was not significantly different from baseline in any of the 10 days following the first dose of betamethasone ($p = 0.167$). Multilevel analysis revealed that, over 10 days, the time elapsed from antenatal administration of betamethasone was significantly associated with a decrease in CTG-STV ($p = 0.045$) and an increase in the DVPIV ($p = 0.001$) and UC ratio ($p < 0.001$).

Conclusion Although steroid administration in early FGR has a minimal effect on increasing CTG-STV one day afterwards, the effects on Doppler parameters were extremely slight with regression coefficients of small magnitude suggesting no clinical significance, and were most likely related to the deterioration with time in FGR. Hence, arterial and venous Doppler assessment of fetal health remains informative following antenatal steroid administration to accelerate fetal lung maturation.

ZUSAMMENFASSUNG

Ziel Untersuchung des Effekts der antenatalen Gabe von Betamethason auf den fetalen Doppler und die Kurzzeitvariation der fetalen Herzfrequenz (CTG-STV) bei Föten mit früher Wachstumsrestriktion (FGR).

Material und Methoden Post-hoc-Analyse von Daten der TRUFFLE-Studie, einer prospektiven, multizentrischen, randomisierten Managementstudie bei schwerer, früh einsetzender FGR. Wiederholte Doppler- und CTG-STV-Messungen zwischen der letzten Aufnahme innerhalb von 48 Stunden vor der ersten Betamethason-Dosis (Ausgangswert) und über 10 Tage wurden bewertet. Eine mehrstufige Analyse erfolgte, um den longitudinalen Verlauf der umbilikal-zerebralen Ratio (UC-Ratio), des Pulsatilitätsindex des Ductus venosus (DVPIV) und der CTG-STV zu analysieren.

Ergebnisse Wir haben 115 Föten eingeschlossen. Ein signifikanter Anstieg der CTG-STV gegenüber dem Ausgangswert wurde am Tag + 1 ($p = 0{,}019$) ermittelt, danach gab es keinen Unterschied. Der DVPIV unterschied sich an keinem der 10 Tage nach erster Betamethason-Dosis signifikant vom Ausgangswert ($p = 0{,}167$). Eine mehrstufige Analyse ergab, dass die verstrichene Zeit nach der antenatalen Betamethason-Gabe über 10 Tage hinweg signifikant mit der Abnahme der CTG-STV ($p = 0{,}045$) und der Zunahme des DVPIV ($p = 0{,}001$) und der UC-Ratio ($p < 0{,}001$) assoziiert war.

Schlussfolgerung Obwohl die Steroidverabreichung bei früher FGR eine kleine Auswirkung auf den Anstieg der CTG-STV 1 Tag darauf hatte, waren die Effekte auf die Doppler-Parameter äußerst gering mit Regressionskoeffizienten von geringer Höhe, die nicht auf klinische Signifikanz schließen lassen. Sie stehen höchstwahrscheinlich in Zusammenhang mit der Verschlechterung bei FGR im Laufe der Zeit. Daher bleibt die Beurteilung der arteriellen und venösen Doppler bezüglich des Gesundheitszustandes des Fötus aussagekräftig, nachdem diesem zur Beschleunigung der fetalen Lungenreifung antenatal Steroide verabreicht wurden.

Introduction

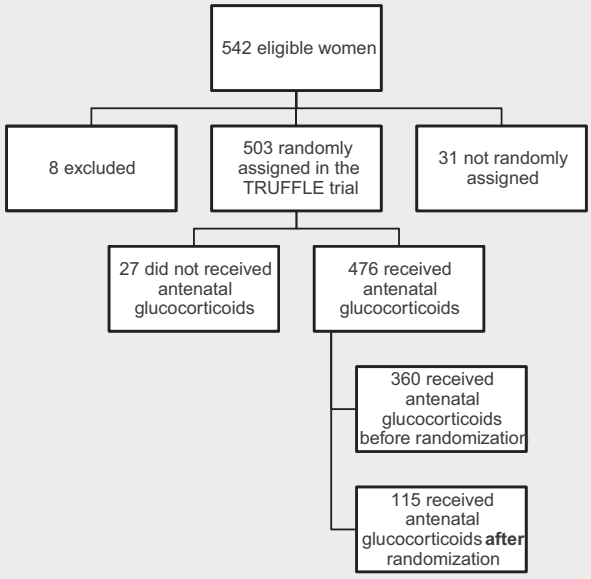
In human pregnancy, a single course of antenatal corticosteroids reduces the occurrence of respiratory distress syndrome and other complications following preterm birth [1]. However, antenatal betamethasone treatment has been reported to induce transient effects on fetal behavior, including a decrease in fetal heart rate and reduced short term fetal heart rate variation without decelerations, observed up to 4 days after administration [2]. Doppler studies in small cohorts of human pregnancies complicated by fetal growth restriction (FGR) have observed a temporary decrease in the pulsatility index (PI) of the umbilical artery (UA), the reappearance of end-diastolic flow in this vessel, and/or a decrease in the ductus venosus PI (DVPIV) [3–5]. Other studies have not observe such changes [6, 7]. Therefore, there is ongoing discussion as to whether such effects of betamethasone represent ominous clinical signs of worsening of the fetal condition or simply transient effects with no significant sequelae for the developing infant [2]. This discussion is further compounded by the current paucity of data derived from large human cohorts, particularly those involving pregnancies with FGR.

The recent Trial of Umbilical and Fetal Flow in Europe (TRUFFLE) multicenter study on the management of severe early onset FGR has reported a more favorable neurological outcome among fetuses who were delivered based on both Doppler assessment of the ductus venosus (DV) and cardiotocography (CTG) [8]. In this context, the possible effects of glucocorticoids on changes in DVPIV and fetal CTG short term variability (CTG-STV) might have played a significant role that would benefit from clarification.

The aim of this study was to investigate the effects of antenatal betamethasone administration on fetal CTG-STV, DV Doppler waveform and umbilico-cerebral ratio (UC ratio, calculated as the ratio between the pulsatility index of the umbilical artery and the pulsatility index of the middle cerebral artery) in the TRUFFLE cohort.

Methods

We conducted a post hoc analysis of data from the TRUFFLE study, a prospective, multicenter, randomized management trial that took place in 20 European tertiary care centers in 5 countries [8]. Eligible participants for the TRUFFLE trial were women over 18 years of age, with a singleton pregnancy at 26^{+0} to 31^{+6} weeks of gestation diagnosed with early isolated FGR, defined as fetal abdominal circumference below the 10th percentile and umbilical artery Doppler PI above the 95th percentile. Details about inclusion and exclusion criteria have been previously reported [8]. The intervention was delivery of the fetus according to the criteria of the randomization group, determined by CTG indices of reduced short-term variation (CTG-STV; CTG-STV < 3.5 ms at < 29 weeks of gestation or CTG-STV < 4 ms at ≥ 29 weeks of gestation), early abnormalities of the DV waveform (DVPIV ≥ 95th percentile) or late DV changes (absent or negative A-wave). In cases where corticosteroids had been given to accelerate fetal lung maturation, no decision regarding delivery was made on the grounds of reduced STV from 24 h to 72 h after the first intramuscular injection. Following 32^{+0} weeks, the timing of delivery was determined according to the local management protocol and the decision to deliver was based on local criteria as DV waveforms were no longer taken into consideration [8]. In all groups, delivery could be undertaken based on maternal indications, such as severe preeclampsia. The study protocol was approved by the institutional ethics committee, and patients provided written informed consent. For the current post hoc study we selected women who had been treated with corticosteroids for improving fetal maturity because it was expected that delivery was imminent due to deterioration of the fetal condition in association with FGR. The timing of maternal prophylactic steroid administration was determined according to local protocols. Two doses of intramuscular 12 mg betamethasone were given, the second 12–24 h after the first. Repeated doses of steroids were never administered. To qualify for this post hoc study, women needed to have a CTG-STV value recorded within 48 hours before the first corticosteroid administration and at least 2 CTG-STV values recorded in the following week. CTG-STV values were categorized as pre-corticosteroids and in 24-hour periods after corticosteroids for up to 10 days. Because it was expected in this group of women with a pregnancy complicated by severe FGR that fetal wellbeing would deteriorate at a certain time, necessitating delivery, and that at that moment the CTG-STV would be low and the DVPIV and UC ratio would be high as a result of fetal condition, we excluded from the current analysis CTG-STV and Doppler values recorded within 48 hours from delivery in order to avoid possible bias. The Oxford Sonicaid 8002 system or an equivalent Dawes-Redman software-based algorithm was used for STV calculation. The recordings took at least 45 minutes. CTG-STV measurements were not necessarily performed in the same time intervals following betamethasone



▶ **Fig. 1** Study design and population. The population of this post-hoc analysis consisted of 115 women who received antenatal glucocorticoids for respiratory distress syndrome prophylaxis after being randomized in the TRUFFLE trial.

▶ **Table 1** Characteristics of the TRUFFLE fetuses included in the post hoc analysis compared to those of TRUFFLE fetuses not included.

	TRUFFLE fetuses included in the post hoc analysis (n = 115)	TRUFFLE fetuses not included in the post hoc analysis (n = 388)	P
gestational age at randomization, weeks	28.9 (27.7 to 30.0)	29.3 (27.9 to 30.3)	0.09
gestational age at the 1st dose of glucocorticoids	29.0 (28.0 to 30.7)	28.6 (27.1 to 29.7)	0.00
gestational age at delivery, weeks	30.7 (29.1 to 32.6)	30.6 (29.1 to 32.0)	0.46
EFW at inclusion	825 (677 to 1017)	876 (708 to 1047)	0.20
EFW p50 ratio at inclusion	0.66 (0.59 to 0.72)	0.65 (0.58 to 0.71)	0.47
randomization to delivery interval, days	11 (4 to 18)	7 (3 to 17)	0.01
day of the 1st dose of glucocorticoids to delivery interval, days	7 (3 to 16)	12 (5 to 24)	0.00
UA PI at randomization	1.8 (1.6 to 2.2)	1.9 (1.7 to 2.2)	0.44
UA PI at the 1st dose of glucocorticoids	1.9 (1.7 to 2.2)	–	–
MCA PI at randomization	1.5 (1.3 to 1.7)	1.4 (1.2 to 1.7)	0.23
MCA PI at the 1st dose of glucocorticoids	1.5 (1.2 to 1.8)	–	–
DVPIV at randomization	0.60 (0.47 to 0.70)	0.58 (0.49 to 0.70)	0.88
DVPIV at the 1st dose of glucocorticoids	0.57 (0.46 to 0.70)	–	–
CTG-STV at randomization, ms	6.5 (5.0 to 8.4)	6.2 (5.0 to 7.6)	0.43
CTG-STV at the 1st dose of glucocorticoids, ms	6.3 (5.0 to 8.3)	–	–
fetuses with UA ARED at randomization	38 %	43 %	0.45
fetuses with UA ARED at the 1st dose of glucocorticoids	46 %	–	–
fetuses with UA ARED within 1 week before delivery	61 %	55 %	0.29
male fetuses	56 (49 %)	196 (50 %)	0.75
female fetuses	59 (51 %)	192 (50 %)	0.75
birth weight, g	970 (800 to 1170)	980 (792 to 1179)	0.98
birth weight p50 ratio	0.58 (0.53 to 0.64)	0.59 (0.52 to 0.66)	0.63

Median and in parenthesis interquartile range (IQR) are shown for continuous variables. P-values are calculated by Mann-Whitney or Fisher exact test. Abbreviations: CTG-STV: cardiotocography short-term variation; DVPIV: ductus venosus pulsatility index; EFW p50 ratio: ratio between the estimated fetal weight (EFW) and the 50th percentile of the estimated fetal weight at the corresponding gestational age; MCA PI: middle cerebral artery pulsatility index; UA PI: umbilical artery pulsatility index; UA ARED: umbilical artery absent or reverse end diastolic flow.

administration or at the same time during the day. For all included fetuses, repeated measurements between the first betamethasone dose (day + 1) and 10 days after (+ 10) were considered. According to the study protocol, the UA pulsatility index (PI), middle cerebral artery (MCA) PI, DVPIV and CTG-STV were assessed in each fetus before randomization. For each different measurement in each fetus between + 1 and + 10, we evaluated the relative change from the last recording within 48 hours before the first dose of betamethasone (basal value) for the CTG-STV (i. e., CTG-STV_n-CTG-STV_0/CTG-STV_0), DVPIV, and UC ratio. After randomization, the TRUFFLE protocol recommended measuring the UA PI, MCA PI, CTG-STV and DVPIV (if randomized to the DV-groups) to be performed at least once weekly, but assessment could be more frequent according to local policies. Median and interquartile ranges (IQR) were used for descriptive statistics. The Kruskal–Wallis test was used to test if a difference in the medians of the CTG-STV and Doppler indices was detectable for 10 days after steroid administration. Multiple comparisons were subsequently performed using Dunn's test with Bonferroni correction. Based on the literature, we expected a small increase in STV during the first day and a decrease on day 2 or 3 [9]. Multilevel analysis was performed to verify such a pattern and to evaluate the course of the CTG-STV, DVPIV, and UC ratio longitudinally. We assessed whether there was a significant time effect on the Doppler and CTG-STV values for 10 days from steroid administration and whether changes in these biophysical parameters were significantly affected by other clinical variables. Multilevel analysis allows for the dependency of measurements and can be used if there are missing data and/or when measurements have been made at different time points. Repeat Doppler and CTG assessment in the same fetus at different gestational ages belong to the first level and the different fetuses in the study belong to the second level [10]. For further analysis of the CTG-STV and Doppler indices, a mixed model based on clinical predictors was constructed, removing items from the initial model in a stepwise manner when the t-test p-value was > 0.15. The variables evaluated in the models were: the ratio between the estimated fetal weight (EFW) and the 50th percentile for EFW at that gestational age (EFW p50

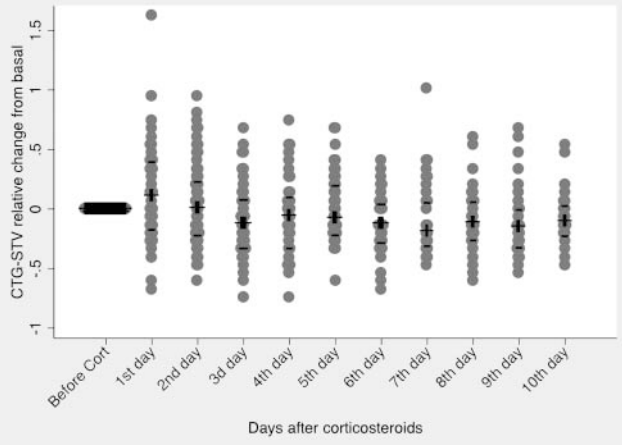
▶ **Table 2** Number of observations recorded and number of deliveries on each day of the study interval for CTG-STV.

days from the 1st dose of glucocorticoids	CTG-STV		number of pregnancies	
	observations (n)[1]	change from basal (%) (median [IQR])[1]	ongoing	delivered
before corticosteroids	102/115	0	113	2
+1	50/81	23 %[2] (–2 % to 42 %)	74	7
+2	55/89	8 % (–11 % to 29 %)	77	12
+3	56/86	–5 % (–23 % to 16 %)	74	12
+4	42/62	0 % (–19 % to 25 %)	53	9
+5	42/59	–13 % (–20 % to 16 %)	56	3
+6	41/60	–12 % (–28 % to 4 %)	50	10
+7	28/45	–11 % (–31 % to 12 %)	41	4
+8	32/45	–7 % (–19 % to 13 %)	38	7
+9	29/41	–15 % (–29 % to –3 %)	35	6
+10	31/37	–5 % (–17 % to 5 %)	34	3

Abbreviations: cardiotocography short-term variation (CTG-STV), interquartile range (IQR), number (n). The number of observations recorded and the number of fetuses delivered on each day of the study interval are shown for CTG-STV. Measurements were not necessarily taken on each day for all ongoing pregnancies. Moreover, measurements taken within 48 hours before delivery were excluded.

[1] Measurements taken within 48 hours before delivery were excluded.

[2] Values significantly different from before corticosteroids were marked with.



▶ **Fig. 2** Dot plot showing the relative changes in the cardiotocography short-term variation (CTG-STV) from the last recording within 48 hours before the first dose of betamethasone for the following 10 days expressed as a proportion of the basal value. The + symbol shows the median and the – symbols show the 25th and 75th percentiles of the dataset on every day.

ratio), fetal gender, presence of fetal heart rate decelerations at cardiotocography, CTG-STV, DVPIV, umbilical artery end diastolic flow (UAEDF, present versus absent or reverse), and days from delivery. The dependent variables were the individual Doppler indices and CTG-STV (the dependent variable was of course removed from the variables tested in the model). Since the main aim of the study was to evaluate the longitudinal course of fetal Doppler waveforms and CTG-STV after corticosteroid administration, we never removed from the model the time variable expressed as the number of days elapsed from the first dose of corticosteroids. Since the decision to administer steroids is usually made on the basis of worsening fetal or maternal condition in view of a decision to terminate the pregnancy, we performed an analysis forcing the steroid-to-delivery interval (expressed in days) into the model. The Wald test was used to assess the significance of parameter estimates. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed with Stata 13.1 (StataCorp. 2013. Stata: Release 13. Statistical Software. College Station, TX: StataCorp LP) [11].

Results

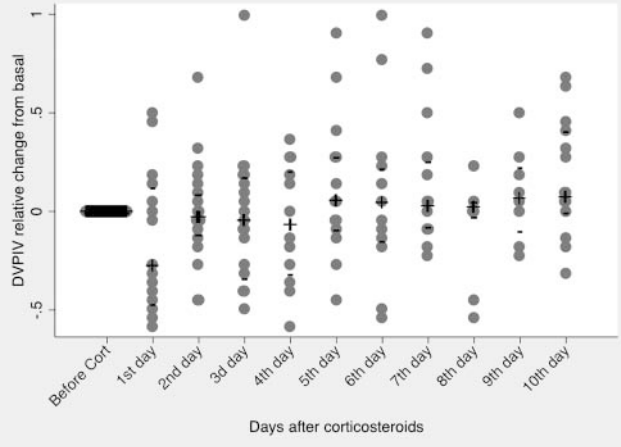
The TRUFFLE trial [8] included 503 women, 476 (95 %) of these received corticosteroids to improve fetal maturity. Most of these women (n = 361; 72 %) did not have a computerized CTG within 48 hours before the first corticosteroid administration recorded in the study database, because corticosteroids had been given before referral from a secondary care center, or before study inclusion was considered. A total of 115 women (23 %) qualified for this secondary analysis (▶ **Fig. 1**, ▶ **Table 1**). ▶ **Table 2** shows the number of observations and the change from baseline (median, IQR) recorded on each day of the study interval for CTG-STV and Doppler parameters. An increase in CTG-STV from basal value was found on day + 1 ($p = 0.019$), after the first dose of corticosteroids (▶ **Table 2**, ▶ **Fig. 2**). DVPIV was not significantly different from basal in any of the 10 days following the first dose of betamethasone ($p = 0.167$), although a slight, non-significant decrease could

▶ **Table 3** Number of observations recorded and number of deliveries on each day of the study interval for DV.

days from the 1st dose of glucocorticoids	DVPIV		number of pregnancies	
	observations (n[1])	change from basal (%) (median [IQR])[1]	ongoing	delivered
before corticosteroids	61/64	0	64	0
+1	15/24	−28 % (−46 % to 13 %)	24	0
+2	20/30	−3 % (−11 % to 9 %)	25	5
+3	19/33	−5 % (−33 % to 18 %)	30	3
+4	12/20	−7 % (−31 % to 21 %)	18	2
+5	15/24	−9 % (5 % to 28 %)	23	1
+6	13/19	4 % (−14 % to 22 %)	18	1
+7	13/22	3 % (−7 % to 25 %)	21	1
+8	9/16	2 % (−2 % to 5 %)	13	3
+9	8/13	7 % (−9 % to 23 %)	12	1
+10	14/20	7 % (0 % to 41 %)	18	2

Abbreviations: ductus venosus pulsatility index (DVPIV). The number of observations recorded and the number of fetuses delivered on each day of the study interval are shown for DVPIV. Measurements were not necessarily taken on each day for all ongoing pregnancies. Moreover, measurements taken within 48 hours before delivery were excluded.

[1] Measurements taken within 48 hours before delivery were excluded.



▶ **Fig. 3** Dot plot showing the relative changes in the ductus venosus pulsatility index (DVPIV) from the last recording within 48 hours before the first dose of betamethasone for the following 10 days expressed as a proportion of the basal value. The + symbol shows the median and the – symbols show the 25th and 75th percentiles of the dataset on every day.

be observed on day +1 (▶ **Table 3**, ▶ **Fig. 3**). During the 10-day period of observation, there were no significant changes from baseline in the UC ratio (▶ **Table 4**, ▶ **Fig. 4**).

Multilevel analysis applying the steroid-to-delivery interval into the model demonstrated that after stepwise removal of less significant predictors, the time elapsed from antenatal administration of betamethasone was associated with a decrease in the CTG-STV in the following 10 days ($p = 0.045$; ▶ **Fig. 2**, ▶ **Table S1**). In addition, the time elapsed from the first dose of steroids was associated with an increase in the DVPIV ($p = 0.001$, ▶ **Table S2**) and in the UC ratio ($p < 0.001$, ▶ **Table S3**). However, all the regression coefficients were of small magnitude (ranging from -0.01 to 0.02), suggesting no clinical significance [12].

Discussion

In a cohort of early FGR fetuses with abnormal umbilical artery Doppler, we showed that antenatal administration of betamethasone is associated with a clinically detectable increase in the CTG-STV the first day after the first dose of steroids followed by a small decrease in the CTG-STV afterwards. Multilevel analysis further revealed that although the time elapsed from steroid administration was statistically significantly associated with the relative changes in the CTG-STV, DVPIV and UC ratio, the magnitude of these associations was clinically irrelevant. The change we observed in the CTG-STV, a short increase after the first dose of betamethasone followed by a small decrease in the STV in the days afterwards, was similar to the effect described by Mulder et al. [13]. The current data show that the effect of betamethasone in FGR fetuses is similar to that seen in pregnancies with preterm premature rupture of the membranes or premature labor. This strongly suggests that the change in the CTG-STV is independent of placental function.

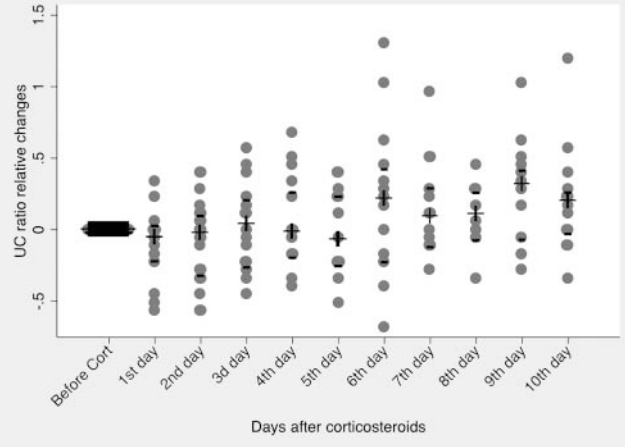
Previous research has described a possible effect of antenatal maternal administration of corticosteroids on fetal heart rate variables. A transient increase in fetal arterial blood pressure, induced by glucocorticoids [14], will increase the vagal drive to the fetal heart by recruiting baroreceptor afferent fiber discharge as part of a baroreflex [15]. The withdrawal of sympathetic outflow will lower the low frequency/high frequency ratio of the fetal heart

▶ **Table 4** Number of observations recorded and number of deliveries on each day of the study interval for UC ratio.

days from the 1st dose of glucocorticoids	UC ratio		number of pregnancies	
	observations (n[1])	change from basal (%) (median [IQR])[1]	ongoing	delivered
before corticosteroids	83/93	0	93	0
+1	19/34	−5 % (−20 % to 5 %)	34	0
+2	21/36	−2 % (−30 % to 11 %)	30	6
+3	22/30	4 % (−24 % to 23 %)	29	1
+4	16/25	−2 % (−17 % to 28 %)	22	3
+5	15/25	−7 % (−23 % to 25 %)	23	2
+6	14/20	22 % (−21 % to 44 %)	17	3
+7	13/21	9 % (−10 % to 31 %)	21	0
+8	10/20	11 % (−0.5 % to 28 %)	15	5
+9	13/17	32 % (0.5 % to 43 %)	16	1
+10	14/21	20 % (−0.1 % to 28 %)	19	2

Abbreviations: Umbilical cerebral pulsatility index ratio (UC). The number of observations recorded and the number of fetuses delivered on each day of the study interval are shown for the UC ratio. Measurements were not necessarily taken on each day for all ongoing pregnancies. Moreover, measurements taken within 48 hours before delivery were excluded.

[1] Measurements taken within 48 hours before delivery were excluded.



▶ **Fig. 4** Dot plot showing the relative changes in the umbilico-cerebral ratio (UC ratio) from the last recording within 48 hours before the first dose of betamethasone for the following 10 days expressed as a proportion of the basal value. The + symbol shows the median and the – symbols show the 25th and the 75th percentiles of the dataset on every day.

rate power spectrum, thereby in keeping with the transient depressive effects of glucocorticoids on fetal heart rate variation [9]. Clinical studies observing an effect of steroids on the CTG-STV, however, have never been performed on a large population of well-defined early severe FGR fetuses such as the TRUFFLE cohort [2]. In FGR, high placental vascular resistance leads to an increase in fetal cardiac afterload, myocardial dysfunction and ductus venosus dilatation, all possibly associated with the decrease in the CTG-STV and the increase in the DVPIV [16]. It is possible that the severe progressive chronic hypoxia characterizing TRUFFLE fetuses might limit further compensatory responses to steroids.

With regards to short-term changes in Doppler indices, our findings are in agreement with an earlier study in 57 early FGR fetuses [7] and with a recent prospective study reporting no change in DVPIV in the preterm FGR fetus following maternal treatment with betamethasone [17]. However, in the latter study this was observed in FGR fetuses with a mean gestational age of 34 weeks, significantly later than in our cohort. During the 10-day period of observation, the course of the CTG-STV, the DVPIV and the UC ratio are consistent with progressive deterioration of the fetal condition due to worsening chronic fetal hypoxemia [16] rather than the use of betamethasone. In agreement with some previous studies, both the UC ratio and DVPIV changes shortly after maternal betamethasone administration were not clinically significant [7, 18, 19]. Our observations did not confirm previous reports of a DVPIV reduction after betamethasone [5]. We highlight that a progressive deterioration of the fetal condition, due to chronic fetal hypoxia, is likely to be the main determinant of longitudinal CTG-STV and Doppler changes in early FGR fetuses [16] even after betamethasone exposure. Chronic fetal hypoxia leads to circulatory compromise that accounts for increased ductus venosus shunting [20], myocardial dysfunction and fetal acidosis [21, 22]. This can be documented as a progressive increase in the DVPIV, manifested initially as a deepening and, ultimately, reversal of the A-wave [23]. Compared with delivery based only on the CTG-STV, deferring delivery until absent or reverse flow during the A-wave, unless delivery is mandated earlier by the CTG safety net criteria, is a safe management strategy with regard to intact survival without impairment at 2 years of age corrected for prematurity [8, 24–27]. According to our data, any CTG-STV decrease [8, 28] within 72

hours from the first dose of steroids might be interpreted as a sign of fetal deterioration due to progressing chronic fetal hypoxia. At the same time, the occurrence of spontaneous FHR decelerations, included in the TRUFFLE study as a safety net criterion for delivery of the fetus, does not seem to be induced by corticosteroids [2] and therefore remains important for fetal surveillance after steroid administration, as does the assessment of the ductus venosus.

The main strength of our analysis is that the effects of antenatal steroids on Doppler indices and the CTG-STV were evaluated in a large population of early severe FGR fetuses followed up longitudinally until delivery. We analyzed the UC ratio rather than the cerebroplacental ratio (CPR), as we previously demonstrated that the former allows for better discrimination in the abnormal range [29]. A limitation is that the evaluation of the effects of betamethasone on fetal Doppler and the CTG-STV was not the aim of the TRUFFLE study [8]. Therefore, the number of Doppler and CTG-STV measurements per day is relatively small. Moreover, Doppler and CTG-STV measurements were not necessarily performed in the same time intervals following betamethasone administration nor at the same time during the day. However, we can assume that such intervals varied randomly. Transient reductions in the STV and fetal movement following betamethasone are not found in the morning, most likely since betamethasone abolishes diurnal rhythms, i. e., increases these variables that normally occur during the course of the day [30].

In conclusion, we demonstrate that betamethasone administration in early FGR fetuses is not associated with a decrease in the CTG-STV after adjusting for confounders. The data available at the inception of the TRUFFLE trial [8], although not specific for an early FGR population, suggested a short term effect of steroids on the CTG-STV [2]. Therefore, according to the original study protocol, no decision regarding delivery was to be made on the grounds of reduced CTG-STV from 24 h to 72 h after the first dose of corticosteroids. The current study suggests that, given the lack of clinically significant effect of betamethasone on the CTG-STV in early FGR, CTG-STV assessment remains valid even following steroid administration. Therefore, delivery for fetal indication should be considered if the CTG-STV falls below the safety net criteria of the TRUFFLE protocol, spontaneous repeated persistent and unprovoked FHR decelerations occur or if the DVPIV becomes significantly abnormal.

Conflict of Interest

The authors declare that they have no conflict of interest.

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