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## Full Length Article

## Reduced short-term variation following antenatal administration of betamethasone: Is reduced fetal size a predisposing factor?

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## ABSTRACT

**Objective:** To assess the association between fetal size and the incidence of reduced short-term variability (STV) following betamethasone administration for fetal lung maturity.**Study design:** This was a retrospective, multicenter, cohort study conducted in two Tertiary University Units. Only uncomplicated singleton pregnancies admitted for threatened preterm labor between 26 and 34 weeks and submitted to betamethasone for fetal lung maturity were included. Delivery occurring within 72 h from betamethasone administration represented criteria for exclusion. Computerized cardiotocography was carried out on a daily basis. Cases were identified by persistently reduced STV, defined as <5th percentile for gestational age and lasting for at least 72 h after the first dose of betamethasone. The primary outcome was estimated fetal weight (EFW) at ultrasound in fetuses with normal and in those with persistently reduced STV. Pregnancy outcomes were also evaluated.**Results:** Persistently reduced STV occurred in 33/405 of the included patients (8.1%). Compared to women with normal STV, those with persistently reduced STV had significantly lower EFW ( $1472 \pm 435$  vs  $1812 \pm 532$  g,  $p = 0.04$ ), lower birthweight ( $2353 \pm 635$  vs  $2857 \pm 796$  g,  $p < 0.01$ ) and earlier gestational age at delivery ( $35.1 \pm 4.2$  vs  $37.3 \pm 2.4$  weeks,  $p < 0.01$ ), whereas all the other variables including gestational age on admission were comparable.**Conclusions:** Reduced STV following maternal betamethasone administration among appropriately grown fetuses seems to correlate with lower fetal size. Furthermore, fetuses with such abnormal response to steroids seem to carry a higher risk of perinatal complications, including lower birthweight and earlier gestational age at delivery.

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## Introduction

A course of antenatal steroids between 24 weeks and 34 weeks + 6 days is universally recommended in pregnant women at risk for impending delivery as it has been consistently demonstrated to decrease the occurrence of perinatal mortality and morbidity in preterm infants [1,2].

Betamethasone (BMT) has shown to produce some transient effects including a reduction in body and breathing movements and a decrease in the short-term variability (STV) observed with computerized cardiotocography (cCTG) [3–7]. In a small proportion of cases such profound depressive effects on the fetal heart

rate variability may persist up to 3 days after its administration [4], leading to inappropriate clinical decisions if they are misinterpreted as a sign of brain hypoxia.

It is still unclear why only some fetuses exhibit a reduced heart rate variability following steroids administration [6].

The aim of this study was two-fold: to assess the incidence of reduced STV following BMT administration for fetal lung maturity in a group of fetuses at risk of preterm delivery and identify which factors may predispose to this abnormal response.

## Methods

## Study design and study population

This was a retrospective, multicenter, cohort study. Clinical records of all consecutive women admitted for threatened preterm labor (PTL) to the Department of Obstetrics of the University

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Hospital of Bologna (Bologna, Italy) and to the Department of Reproductive Science, University of Naples Federico II (Naples, Italy) from January 2009 to December 2014 were collected in a dedicated merged database.

All charts recorded in the database were reviewed. All variables reported were collected for all the subjects included in the study.

All patients were aged 18 or above and submitted to BMT administration for fetal lung maturity between 26 and 34 weeks of gestation. In this group, two doses of BMT 12 mg were administered intramuscularly 24 hours apart as recommended [1]. Threatened PTL was defined by the presence of regular uterine contractions (2–3 every 10 min) associated with early cervical changes at clinical examination (effacement and/or dilatation >1 cm). As per internal protocol of the Centres involved, tocolysis was administered in all women submitted to RDS prophylaxis for threatened PTL. Cervical length measurement at transvaginal ultrasound or result of the fibronectin test were not considered for the purpose of this study.

Exclusion criteria were multiple pregnancy, congenital anomalies, intrauterine growth restriction (IUGR), defined by abdominal circumference (AC) or ultrasound estimated fetal weight (EFW) <10th centile with or without umbilical artery Doppler pulsatility index >95th percentile, any preexisting medical condition including hypertensive disorders, chronic drug consumption and diabetes mellitus or gestational diabetes, abnormal CTG and/or cCTG on admission and delivery within 72 h from steroids administration. Women with premature rupture of membranes (PROM) and antepartum haemorrhage (APH) were also excluded.

### Management

All women included in the study received daily cCTG assessing fetal heart rate and STV starting from admission. Algorithm for cCTG were based on Dawes/Redman antepartum CTG analysis by using Sonicaid (Sonicaid Obstetric Solutions, Huntleigh) [8,9]. The recordings were at least 45 min in duration. STV values were recorded for each assessment. cCTGs were performed on a daily basis in the morning. We considered “day 1 cCTG” only those performed at least 12 h after BMT administration.

The study cohort was divided in two groups according to the STV findings: group A (cases) showed persistently reduced STV defined by values below the 5th percentile for gestational age [10] following BMT administration and lasting up to 72 h after the 1st dose; group B (controls) STV >5th percentile after the administration of BMT or <5th percentile for less than 72 h after first dose.

Ultrasound assessment of fetal weight was performed in all cases within 3 days from admission and accordingly to the local reference charts [11].

### Outcomes

A comparison of demographics, clinical characteristics and pregnancy outcomes was performed between cases with persistently reduced vs those with normal STV following BMT administration. Due to its retrospective design, the study did not affect the clinical management of the patients, which was based upon the judgement of the attending physician. As this was a retrospective analysis of routinely collected anonymized clinical data, no ethical committee approval was necessary according to national regulations.

The primary outcome was mean EFW at ultrasound. Secondary outcomes were mean birthweight in grams, prevalence of small for gestational age (SGA) at birth, gestational age at delivery, mode of delivery. SGA neonates were defined as those whose birthweight was below the 10th centile according to the national neonatal

charts [12]. Neonatal outcomes, including Apgar score at 5 min, umbilical artery pH and base excess at delivery were also recorded.

### Statistical analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v. 19.0 (IBM Inc., Armonk, NY, USA). Data were shown as mean  $\pm$  standard deviation or as number (percentage). Categorical variables were compared using the Chi-square or Fisher exact test. Between-group comparison of continuous variables was undertaken using T-test for parametric analysis. Standardized scores were created to assess Z-score for birth weight and ultrasound EFW.

Two sided p-values were calculated and p values <0.05 were considered as statistically significant. The study was performed following the STROBE guidelines [13].

### Results

Over the study period, 4120 women were admitted between 26 and 34 weeks for PTL and received prophylactic BMT. Of them, 405 (9.8%) met the inclusion criteria and were included in the study (Fig. 1).

Mean gestational age at admission and at delivery was  $31.5 \pm 2.4$  weeks and  $36.2 \pm 3.1$  weeks, respectively. Overall, 33 fetuses (8.1%) showed STV below the 5th centile following BMT administration and lasting up to 72 h whereas 372 had normal or temporarily reduced STV <5th percentile lasting <72 h. No significant differences were noted in terms of maternal demographics between the two groups (Table 1).

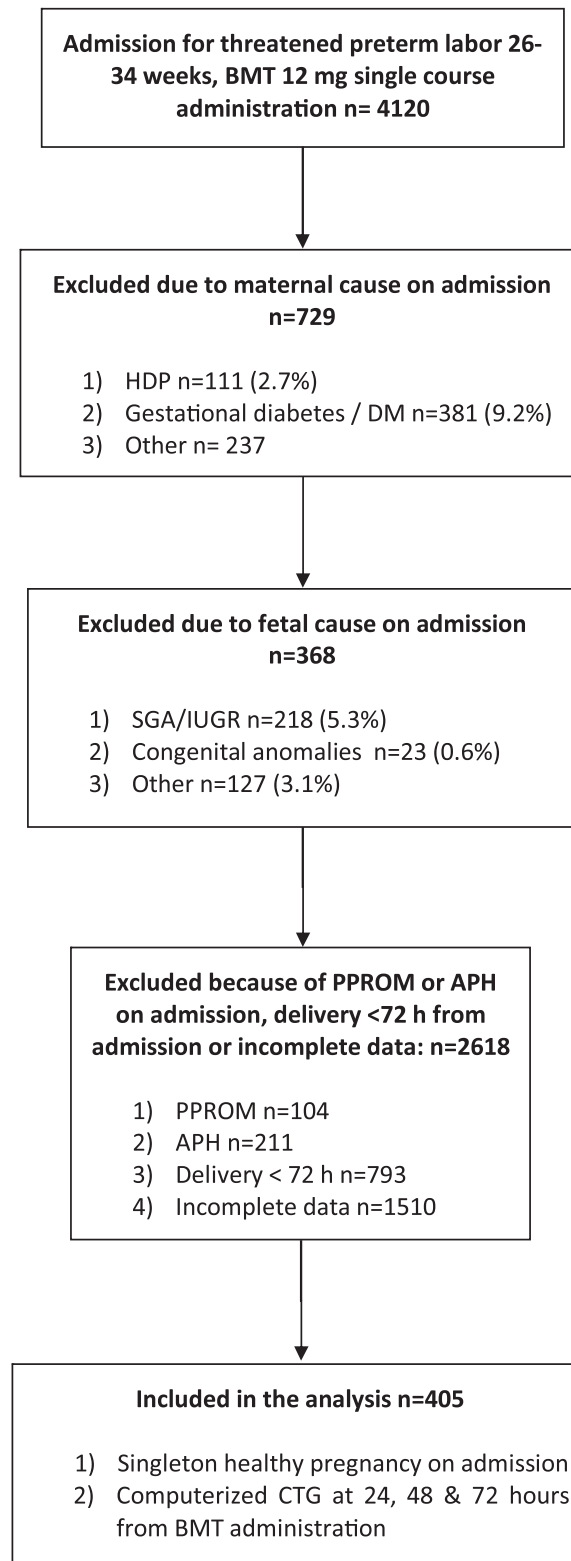
Women with persistently reduced STV following BMT administration had significantly lower EFW and EFW Z-score on admission ( $1472 \pm 435$  vs  $1812 \pm 532$  g,  $p = 0.04$  and  $0.002 \pm 0.411$  vs  $0.401 \pm 0.612$ ,  $p = 0.04$ , respectively) and lower birthweight and birthweight Z-score ( $2353 \pm 635$  vs  $2857 \pm 796$  g,  $p < 0.01$  and  $-0.463 \pm 0.470$  vs  $-0.103 \pm 0.315$ ,  $p = 0.03$ , respectively) compared with those with normal STV showed. The incidence of SGA at birth was significantly higher (18.2% vs 7.8%,  $p = 0.04$ ) and the gestational age at delivery was lower ( $35.1 \pm 4.2$  vs  $37.3 \pm 2.4$ ,  $p < 0.01$ ) among fetuses who showed persistently reduced STV following steroids administration (Table 2).

### Discussion

Our study confirmed that a reduced STV is observed at cCTG in a small proportion of fetuses (8.1%) following antenatal BMT administration for fetal lung maturity. Interestingly, despite all fetuses of this series were of appropriate size for gestational age at inclusion, those who presented the reduced STV following steroids appeared significantly smaller than those with normal STV. In addition, pregnancy outcome appeared to be different in those with reduced STV after steroids compared to controls, as they were delivered a couple of weeks earlier and had a smaller birthweight and a higher incidence of SGA neonates.

The transient depressive effect of antenatal betamethasone on fetal heart rate variability has been largely documented [3–7]. Available data have shown that a decrease in the STV within 72 h from the first dose is not related to acid–base changes [14] but might be due to a direct effect of betamethasone on glucocorticoid receptors. Such receptors are believed to be present in the brainstem and other areas of the human brain involved in the control of the fetal heart activity [4,5,15,16].

The STV reduction due to BMT administration seems to be inversely related to the gestational age at steroids administration [14,17]. In our group of fetuses with reduced STV the gestational age at BMT exposure was not different compared with those with



**Fig. 1.** Flow chart (according to STROBE guidelines) for inclusion of cases. BMT, Bethametasone; HDP, hypertensive disorder of the pregnancy; DM, diabetes mellitus; SGA, small for gestational age; IUGR, intrauterine growth restriction; PPROM, premature preterm rupture of the membranes; APH, antepartum haemorrhage; CTG, cardiotocography.

normal CTG response and the only significant difference was the smaller weight noted in the former group.

This observation leads us to speculate that the depressive effect of BMT on fetal brain may be favored in cases of slightly reduced placental reserve. As recently proposed, early stage placental insufficiency does not lead to fetal smallness but may induce

relevant haemodynamic changes. More in details, fetal biometry at ultrasound may remain within the normal range but the weight percentile is smaller compared to previous measurements and blood flow redistribution may be noted [18]. Recently, a reduced cerebroplacental ratio has been described during the third trimester in normal sized fetuses with subtle placental

**Table 1**

Characteristics of the included women (n = 405).

	STV <5th percentile N = 33	Normal STV N = 372	p-value
Age	32.8 ± 4.9	33.6 ± 5.3	0.22
BMI	24.3 ± 2.6	24.9 ± 3.1	0.37
Ethnicity			
Caucasian	25 (75.8%)	301 (80.9%)	0.13
Non-Caucasian	8 (24.2%)	71 (19.1%)	
Nulliparous	13 (39.4%)	143 (38.4%)	0.74
GA at admission	31.8 ± 4.2	31.2 ± 3.4	0.81
STV			
Before steroids	11.2 ± 1.1	11.4 ± 3.2	<b>0.61</b>
24 h	6.3 ± 2.2	9.8 ± 3.1	<b>&lt;0.01</b>
48 h	4.4 ± 1.4	8.8 ± 2.7	<b>&lt;0.01</b>
72 h	6.1 ± 3.1	8.7 ± 3.3	<b>0.03</b>

Data are presented as number (percentage) or as mean ± standard deviation. Boldface data, statistically significant.

GA, gestational age; STV, short-term variability; BMI, body mass index.

**Table 2**

Primary and secondary outcomes.

	STV < 5th percentile <sup>a</sup> N = 33	Normal STV N = 372	p-value
EFW	1472 ± 435	1812 ± 532	0.04
EFW Z-score	0.002 ± 0.411	0.401 ± 0.612	0.04
Birthweight	2353 ± 635	2857 ± 796	< 0.01
Birthweight Z-score	-0.463 ± 0.470	-0.103 ± 0.315	0.03
GA at delivery	35.1 ± 4.2	37.3 ± 2.4	< 0.01
Mode of delivery			
SVD	18 (54.5%)	222 (59.7%)	0.74
OVD	1 (3.1%)	6 (1.6%)	
CD	14 (42.4%)	144 (38.7%)	
Vaginal delivery	n = 19	n = 228	0.53
Spontaneous onset	16 (84.2%)	178 (78.1%)	
Induction of labor	3 (15.8%)	50 (21.9%)	
CD	n = 14	n = 144	0.29
Planned	11 (78.6%)	93 (65.6%)	
Emergency	3 (21.4%)	51 (34.4%)	
SGA	6 (18.2%)	29 (7.8%)	0.04
APGAR at 5 min	9.0 ± 0.4	9.0 ± 0.6	0.95
Umbilical artery pH	7.23 ± 0.04	7.28 ± 0.08	0.06
Base excess	-5.8 ± 1.2	-5.5 ± 2.0	0.21

Data presented as number (percentage) or as mean ± standard deviation. Boldface data, statistically significant.

GA, gestational age; EFW, ultrasound estimated fetal weight; SVD, spontaneous vaginal delivery; OVD, operative vaginal delivery; CD, cesarean delivery; SGA, small for gestational age.

Primary and secondary outcomes in cases with reduced short-term variability (STV) after bethametasone administration and controls with normal STV.

<sup>a</sup> According to Snijders et al., Fetal Diagn Ther 1990 [10].

insufficiency whose risk of perinatal complications seems to be significantly higher [19,20]. Some Authors previously described a higher frequency of reduced STV after BMT in fetuses with cerebral vasodilatation at Doppler ultrasound [21]. Unfortunately, in our study group the fetal cerebral flow was not assessed and we are unable to confirm if Doppler findings witnessed blood flow redistribution and reduced placental reserve in those fetuses with reduced STV, whose weight percentile was in the lower range of normality.

On the other hand, in the same group of fetuses with transiently depressed STV after steroids, a significantly lower birthweight and a higher incidence of SGA neonates was noted. This may lead us to envisage that the abnormal CNS response at steroids could be looked not as an incidental finding but as an early sign of reduced placental reserve in apparently normal sized fetuses and, at the same time, as a useful predictor of late onset placental dysfunction and lower birthweight requiring a modified obstetric management.

On this basis, we suggest that whenever an apparently appropriately grown fetus exposed to BMT exhibits a transiently reduced STV a comprehensive maternal and fetal Doppler ultrasound should be performed in order to spot early signs of placental dysfunction. Furthermore, we propose that if spontaneous preterm delivery does not occur, these fetuses should be incorporated in a program of intensive antepartum surveillance since their risk of late onset placental insufficiency may be increased.

Some limitations need to be acknowledged in this study, including the small number of cases with reduced STV and its retrospective design. Furthermore, having excluded those patients with a true threatened PTL who delivered within 72 h from admission, we could only assess the depressive effects on the fetal heart rate variability in those fetuses who remained undelivered and could not generalize our results to all cases exposed to antenatal steroids. In this study, as widely reported [22], only a small proportion of patients admitted with PTL actually delivered shortly following BMT administration. Most women with threatened PTL have minimal cervical dilation on manual exam, and over 60% do not deliver preterm [23]. Finally, the selection of only normally grown fetuses at inclusion may introduce a bias by the insufficiency of methods to perform this selection and discriminate between IUGR and non IUGR fetuses. On the other hand, inclusion of pregnancies complicated by IUGR would introduce a confounder which may impact on the aim and the results of the study, as chronic hypoxia per se may be cause of fetal behavioral changes including a reduced STV at cCTG.

Despite these limitations, we have observed that among apparently normal sized fetuses a depressive effect of antenatal steroids is more likely if the weight percentile is in the lower range and this effect may herald an increased risk for late onset placental insufficiency and lower birthweight. This original finding is worthy to be reported and confirmed prospectively in a larger study where a comprehensive Doppler assessment following antenatal administration is included.

## Disclosure of interests

The authors report no conflict of interest.

## Contribution to authorship

- Tullio Ghi, Nicola Rizzo: study design
- Tullio Ghi, Andrea Dall'Asta: manuscript writing and editing
- Gabriele Saccone, Federica Bellussi: data collection
- Tiziana Frusca, Pasquale Martinelli, Ganluigi Pilu, Nicola Rizzo: comments and final review of the manuscript

## Ethical approval

This is a retrospective analysis of routinely collected and fully anonymized clinical data and no ethical committee approval was required according to national regulations.

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