Full-term-pregnancy effects of antenatal betamethasone administration on short-term variation as assessed by computerized cardiotocography

Juan Piazze[1],
Kathleen Comalli Dillon[2],
Cerekja Albana[3]

[1] Ospedale di Ceprano/Osp. SS Trinità, Sora, (FR) Italy
[2] ComalliWrites Consulting, LLC, Petaluma, CA, USA
[3] Ultrasound Service, Radiology Department, ASL Roma B, Italy

Corresponding author:
Juan Piazze
Ospedale di Ceprano/Osp. SS Trinità, Sora, (FR) Italy
Mobile: 00 39 3397843942
E-mail: jjpiazze2000@hotmail.com

Summary

Objective: to verify whether there are other than transitory effects of antenatal betamethasone (administered for fetal lung maturity [FLM] enhancement) on fetal heart rate (FHR) variability detected by computerized cardiotocography (cCTG) in cases where formerly steroid-treated fetuses reached term.
Materials and methods: cCTG of one hundred sixty-four women (study group) exposed to antenatal betamethasone for risk of preterm delivery in third trimester period were compared to controls (pregnancies who presented risk of preterm labour in the same period of cases, although with no steroids administration). cCTG was performed weekly as of standard schedule when pregnancies reach term from 37-40 weeks' gestation for cases and controls.
Results: regarding data concerning cCTG at term for cases and controls, no significant difference was found for FHR, Acc (accelerations) 10 min, and FM (fetal movements) between groups. LV (low variation)/min and LV/msec were absent in cCTG parameters of fetuses in the study group.
Instead, for all weeks studied (37 to 40), cCTG parameters were higher for HV (high variation)/msec, STV(short term variation)/msec, and Acc 15 in cases with respect to controls.
Conclusion: interestingly, maternal corticosteroid administration may be related to higher fetal reactivity when fetuses exposed to steroid therapy reach term. Our observation may help in the interpretation of a "more reactive" CTG trace in babies whose mothers previously received steroid therapy for FLM enhancement.

Key words: computerized cardiotocography, betamethasone, intrauterine long-term effects.

Introduction

Maximal efficacy of maternal steroid administration is observed within the first week after administration. Glucocorticoid receptors are present not only on type II pneumocytes but also in many other organs and tissues (1). In fact, steroids reduce timydine kinase activity (2) with negative effects on DNA and RNA synthesis and therefore on cellular division as shown in significant physiological growth restriction of numerous organs and structures other than bone growth, with global reduction of birth weight in animals and, according to some authors (3,4), in humans as well. Regarding the negative effect of corticosteroids on organ growth, in particular on the fetal brain, some animal experiments have shown that corticosteroids, especially in case of repeated courses, reduce oligodendrocyte proliferation with consequently delayed myelination; reduce brain growth, particularly of regions such as the brainstem and cerebellum; and mediate inadequate constitution of regular synaptic connections (5). In particular, functional glucocorticoid receptors in the brainstem and other brain areas determine transitory reduction of respiratory and body movements and alter fetal heart rate (FHR) variability (6-8). cCTG, first developed to overcome problems inherent in inter- and intra-observer variation in CTG trace interpretation, has proven over time to be a method of extreme clinical utility for its reliability in the assessment of fetal well-being.

The observation of several traces at term revealing high reactivity in fetuses whose mothers received betamethasone for fetal lung maturity (FLM) enhancement prompted a study to evaluate the effects of betamethasone on cCTG parameters in pregnancies at risk of preterm delivery as compared with controls, i.e. similar pregnancies but not those requiring steroid therapy for FLM improvement.

Materials and methods

This study comprises data registered prospectively at the Institute of Gynecology, Perinatology, and Child Health, University "La Sapienza", Rome, Italy, between September 1997 and September 2008.
Preterm labor was defined as the presence of uterine con-

tractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix prior to term gestation (between 20 and 37 wk).

One hundred sixty four pregnant women previously given steroids indicated for risk of preterm delivery (a single betamethasone cycle, 12 mg IM 24 hrs apart for two consecutive days) were registered as cases. From the study group we excluded preterm deliveries, other complications of pregnancy, patients who smoked, and patients who received more than one cycle of betamethasone. After these rigid exclusion criteria, study group gestational age [GA] range at steroid administration was from 30 to 33 weeks.

A group of pregnancies at risk of preterm labour, in whom no steroid for FLM enhancement was administered, were considered as control group (risk of preterm delivery within 30 to 33 wks' gestation as for the study group) and selected based on similar age and parity, nonsmokers, and those without pregnancy complications.

Both pregnancy groups delivered at term and exclusively ≥ 40 wks' gestation.

The cCTG was performed by an automated system using Oxford 8002 software (Manor Way, Old Woking Surrey, England). The cCTG was interpreted as described elsewhere (7).

From 37 to 40 wks' gestation, cCTG from both cases and controls was collected (1768 cCTG traces from 442 pregnant women considered as controls, and following statistical clustering, see statistics section).

In all 164 study cases (656 traces), cCTG was performed once a week from 37 to 40 weeks following the same standard plan scheduled for controls; all cCTG parameters were compared by GA in weeks in order to have a single value to compare each week examined (i.e., cCTG parameters for cases against controls, hence cases versus controls parameter points for each week from 37 to 40 wks' gestation).

cCTG was always performed between 1600h and 1800h in cases and controls (9). Cases and controls delivered at term. All newborns in the study group and the controls were developmentally appropriate for GA and did not develop any neonatal complications.

cCTG parameters compared between study group and controls were FHR in beats per minute (bpm); number of accelerations, defined as the changes of the heart rate >10 (Acc 10) and 15 (Acc 15) bpm, above the baseline for at least 15 sec; number of decelerations, defined as changes of the heart rate > 20 bpm under the baseline for at least 15 sec; episodes of high and low variation measured in minutes and milliseconds and short-term variation (STV) measured in milliseconds and defined as variation of FHR in 1/16 min (3.75 sec) intervals; peaks of contractions (per hour); and fetal movements (FM) assessed by maternal perception (per hour). In all pregnant women, a researcher obtained informed consent for the study at the third trimester traces.

All patients in cases and control groups were treated with tocolytic agent (ritodrine), I.M. or under venous infusion as suggested by the initial uterine contractions and passed to oral therapy until uterine activity ceased.

Ethics committee approval for this research was obtained from the Hospital committee on human research.

Statistical analysis

The differences among groups have been evaluated by means of a t-test.

Statistical analysis was performed by means of Sigma Stat 2.03 (Jandel Scientific, Ekrath, Germany).

For testing differences in cCTG analysis, we used FHR traces performed in the absence of consistent uterine activity for both cases and controls. The statistical advisor suggested and performed cCTG data clustering (since more than one cCTG strip from each patient was considered for mean parameters comparison).

To achieve a 80% power to detect a significant difference in variables considered of about 85% (p minor of 0.05, two sided), we calculated that we would need 150 women in each group.

Results

Comparing parameters between the study group (n = 164) and controls (n = 442), GA at recording of 38 weeks (37+4 to 40+0 days) versus 38+1 weeks (37+5 days to 40+5 days), respectively, were observed; mean GA at delivery was 40 weeks for cases and 39.8 weeks for controls.

Weekly cCTG parameters were obtained from controls to compare them with weekly cCTG parameters from cases. Regarding cCTG data at term for cases and controls, no significant difference was found for FHR, Acc (accelerations) 10 min, and FM (fetal movements) between groups. Interestingly, LV (low variation)/min and LV/msec were absent in cCTG parameters of fetuses in the study group. Instead, for all weeks studied (37 to 40), cCTG parameters were higher for HV/msec, STV/msec and Acc 15 in cases with respect to controls (Tab. 1).

Discussion

Maternal corticosteroid administration for induction of fetal lung maturity (FLM), other than creating transitory immediate effects on motor and respiratory activity and on FHR variability, may feature long-term effects on FHR parameters such as Acc 15, HV/msec and STV/msec. The fact that minutes of LV were absent shows that most likely fetuses of the study group spent less time in quiet (non-REM) sleep (1F) in comparison to controls. The significantly higher number of Acc 15, HV/msec, and STV/msec shows that fetuses instead spent more time in a state of active sleep (2F and 4F) (8). Theoretically this can be explained by a different hypothesis: steroids exert direct effects on a variety of cerebral regions. In particular, besides their action on centers involved in the regulation of the body and respiratory movements, steroids exert a specific action on the raphe nuclei and the locus coeruleus, parts of the presumptive sleep centers. Sloboda et al. (10) specify that deleterious effect on brain development and myelination are associated with alterations of the hypothalamic-pituitary-adrenal axis (HPA axis). Other literature suggests that cortisol mechanism does not supply complete answers regarding ma-

Table 1. cCTG parameters in cases and controls for gestational age considered (37-40 weeks).

cCTG	37 weeks			38 weeks			39 weeks			40 weeks		
parameter												
	Cases (n:164)	*Controls (n:442)**	*P*	*Cases (n:164)*	*Controls (n:442)**	*P*	*Cases (n:164)*	*Controls (n:442)**	*P*	*Cases (n:164)*	*Controls (n: 442)**	*p*
Acc 15	9	4	**<0.01**	9	4	**<0.01**	10	5	**<0.02**	9	5	**<0.01**
HV min	22.3 (24.1-21.7)	18.6 (22.6-18.4)	**<0.01**	22.8 (25.7-21.8)	16.3 (20.7-18.1)	**<0.01**	21.7 (22.9-20.0)	17.9 (20.2-16.5)	**<0.02**	21.6 (22.4-20.9)	16.1 (17.0-16.4)	**<0.02**
STV msec	12.2 (15.3-12.0)	7.2 (8.0-7.2)	**<0.001**	12.0 (14.8-11.0)	7.0 (7.1-6.5)	**<0.001**	12.0 (13.1-11.8)	7.0 (7.1-6.3)	**<0.01**	11.5 (12.4-11.1)	6.2 (6.5-7.1)	**<0.02**

HV min and STV msec in mean + 2 S.D.
a) No significant difference was found for FHR, Acc (accelerations) 10 min, and FM (fetal movements) between groups. b) LV (low variation) min and LV msec were absent in cCTG parameters of fetuses in the study group, c) cCTG traces in the study group were repeated weekly as for controls until delivery.
*from 878 cCTG examinations.

ternal laboratory stress mediation of fetal neurobehavior (11).
Betamethasone is related to profound but transient effects on FHR parameters which can mimic fetal distress; this effect is clinically recognized by visual FHR analysis (8,11). Effect of other drugs on FHR tracings, i.e. clonidine used for hypertension in pregnancy, have been observed to have no significant influence on STV of the FHR (12). Corticosteroids may create effects not evident immediately after exposure observed in neonatal growth parameters, but which become evident at term pregnancy with reduction of time spent by the fetus in the 1F phase, probably because of increased fetal HPA axis responsiveness as demonstrated in our research by higher values, particularly of short-term variation and long acceleration activity at term pregnancy, assessed by computerized CTG trace analysis.
On the basis of these results, of inability to provide a pathophysiologic explanation and a clinical value, and in agreement with other authors, we conclude that despite over 30 years of experience, there still exist many unexplored questions regarding use of corticosteroid therapy in induction of fetal lung maturity, questions all requiring further investigation. It may only be interpreted as more "awake" fetuses when a CTG strip is evaluated in mother who previously underwent steroid therapy for risk of third trimester preterm labour with no development of any neonatal complication.

Conclusions

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Conflict of interest: the authors disclose any potential conflicts of interest, whether of a financial or other nature.

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