Effects of betamethasone on fetal heart rate

G. LO DICO, G. MINNECI, A. CATANESE, R. DE GREGORIO, A. SPATA

Summary: Effects of betamethasone on fetal heart rate.

Objective. To evaluate the modifications provoked by betamethasone, used in prophylaxis for RDS, on fetal heart rate and variability.

Materials and methods. Retrospective study including 58 pregnant women treated with corticosteroids for risk of preterm birth. Fetal heart rate and long term variability have been reviewed and evaluated with cardiotocographic examinations performed for each patient at time 0 (before betamethasone administration), within the first 12 hours after administration, between 12 and 24 hours, between 24 and 36 hours and after 36 hours.

Results. Long term variability of fetal heart rate is altered above all in the period between 24 and 36 hours after the first administration of betamethasone (in the 48% of cases). This modification consists in the increase of variability in the 68% of cases. The baseline of heart rate shows a modification inversely proportional to the variability’s one.

Conclusion. The influence of corticosteroids on the fetal nervous centers involved in the regulation of the sleep-wake rhythm and in the sympathetic-vagal balance implies the possible transitory alteration of the fetal heart rate baseline and variability.

Key words: Betamethasone - Cardiotocography - Fetal heart rate - Variability.

Introduction

It was established that, in case of risk of preterm delivery, the administration of corticosteroids reduces the index of fetal mortality and morbidity of 50%. In fact, many randomized studies show a reduction of 50% in the incidence of respiratory distress syndrome, necrotizing enterocolitis and intraventricular hemorrhage (1, 2).

The protocol involves the intramuscular administration of 12 mg of betamethasone, repeated after 24 hours. Rarely, if the intramuscular administration is not possible (for example for a great risk of bleeding) the intravenous dose is preferred (3).

Corticosteroids reach the full effect 48 hours after the first dose (4).

The administration of betamethasone is indicated in all conditions of risk of preterm spontaneous or induced...
delivery, between 24 and 34 weeks gestational age (wGA).

Recent not randomized studies suggest that the use of corticosteroids could reduce the index of mortality also before than 24 wGa (5). Vice versa, a real efficacy of corticosteroids in reducing morbidity after 34 wGa has not been demonstrated yet (6). However, a study by Stutchfield et al. on 1000 patients suggests that also in late preterm fetuses the administration could be useful in order to reduce pulmonary complications (7). In this conditions, risks and benefits could be evaluated on a case-by-case basis.

The administration is contraindicated when the immediate delivery is required (for example in case of pathological CTG, abruption placenta) (8). In case of subclinical chorioamnionitis, the use of corticosteroids is safe and efficient, while the employment in case of clinically manifest chorioamnionitis is still under study (9).

Many Authors do not approve the use of corticosteroids for more than one cycle (10-12), because there is not a demonstrated benefit in the repetition. Moreover, some adverse effects seem to be related to repeated administrations (13, 14), such as low birth weight, small size of the brain, neuronal damage (15, 16). However, a study of 2009 by Garite et al. on 500 patients, justifies a second cycle 4-6 weeks after the first, if the first administration was very early during the gestation (for example at 24 wGA) (17).

In addition to the desired effects of betamethasone, we know a series of collateral effects on some indices of fetal well-being. Betamethasone is associated to a reduction in fetal movements, perceived by mother and sonographically observable, and in respiratory movements. Dexamethasone has not the same effects on fetal movements, but this difference has not been explained yet (18).

Many Authors suppose that corticosteroids short-term influence on fetal heart indices is mediated by the bond of betamethasone to receptors of glucocorticoids, sited in the brainstem or in other areas of the encephalo (19, 20). However, these receptors have not been identified in the human fetal brain, yet.

Moreover the variations depend on the gestational age and the level of fetal activity (21-23).

The aim of this study is the evaluation of the modifications which are induced by betamethasone on the FHR, in particular long-term variability (defined as the global trend of frequency in one minute) and heart frequency. These two parameters have been revealed by not-computerized CTG.

**Materials and methods**

The study is retrospective. It involves a group of pregnant women who were hospitalized in the O.U. of Gynecology and Obstetrics of the A.O.U.P. “P. Giaccone” in Palermo, from January 2011 to December 2013. All patients were treated with corticosteroids for risk of preterm delivery.

12 mg of betamethasone were administered intramuscularly and repeated after 24 hours.

The modifications of FHR and long-term variability have been evaluated according to the following method:

1) CTG carried out at time 0 (before betamethasone administration);
2) CTG carried out within 12 hours since the first administration of betamethasone;
3) CTG carried out between 12 and 24 hours;
4) CTG carried out between 24 and 36 hours;
5) CTG carried out after 36 hours since the first administration of betamethasone.

About each patient, we reported maternal age, weeks of gestation and cause of the risk of preterm delivery.

We did not include in the study twin pregnancies, patients who had not completed the standard cycle of double administration of betamethasone, patients with an incomplete series of CTG and patients with altered CTG before the administration of betamethasone (that is to say with variability <6 beats per minute or >25 bpm). We excluded also the cases with gestational age <29 wGA, on the assumption that before this age betamethasone does not modify the heart rhythm.

Our date have been analyzed with the comparison between proportions.

**Results**

The study involves 58 pregnant women aged 16-41 years. The gestational age at the moment of the access in the hospital is between 29 and 35 wGA (mean 32±1 wGA and median 32+2 wGA).

The causes of risk of preterm delivery we identified are:

- idiopathic in 36 cases (62%)
- preterm premature rupture of membranes (pPROM) in 8 cases (13,7%)
- intrauterine growth restriction (IUGR) in 4 cases (6,8%)
- metrorrhagia for marginal placenta previa in 2 cases (3,4%)
Effects of betamethasone on fetal heart rate

- uterine hyperkinesia in 2 cases (3.4%)
- polyhydramnios in 2 cases (3.4%)
- gastroschisis in 2 cases (3.4%)
- decompensated diabetes mellitus in 2 cases (3.4%).

We define long-term variability as:
- normal, if $\geq 6$ bpm and $\leq 25$ bpm
- altered:
  - reduced, if $< 6$ bpm
  - increased, if $> 25$ bpm.

At time 0 the whole group presents normal long-term variability.

Right after the use of corticosteroids, that is to say within the first 12 hours (Figure 1 A), long-term variability results normal in 38 cases (65%) and altered in 20 patients (35%), in particular it is reduced in 4 cases (20% of CTG with altered variability) and increased in 16 cases (80%) (Tables 1, 2).

Between 12 and 24 hours (Figure 1 B) variability is normal in 42 cases (73%) and altered in 16 cases (27%), in particular it is reduced in 6 cases (37%) and increased in 10 (63%) (Tables 1, 2).

After the second administration of betamethasone (between 24 and 36 hours from the first) (Figure 1 C), variability appears normal in 30 cases (52%) and altered in 28 (48%), in particular reduced in 10 cases (36%) and increased in 18 (64%) (Tables 1, 2).

After 36 hours since the beginning of the procedure (Figure 1 D), variability appears normal in 44 cases (76%) and altered in 14 patients (24%) and in particular it is reduced in 8 cases (57%) and increased in 6 cases (43%) (Tables 1, 2).

The cases with an increase of long-term variability are totally 50, those with a reduction of variability are as a whole 28.

The baseline of FHR is normal (>110 bpm and <160 bpm) in all the periods we examined. We related it to CTG with altered long-term variability.

Regardless of the time, CTG with increased variability (in total 50) present baseline of FHR:
- lower than at time 0 in 30 cases (60%);
- greater in 15 cases (30%);
- similar in 5 cases (10%).

Regardless of the time, in CTG with reduced variability (in total 28) we observe baseline of FHR:
- lower than at time 0 in 9 cases (32%);
- greater in 16 cases (57%);
- similar in 3 cases (11%) (Figure 2).

**Discussion**

Our data confirm partially the data of literature. They evidence the modification of FHT and its long-term variability after the administration of glucocorticoids following the procedure that is described above. This action occurs in a range between hours and days, according to the involvement of transcellular transcription factors by corticosteroids and according to the slow penetration of glucocorticoids into the brain. In our experience, in fact, the greater number of alterations occurs after 24 hours from the administration. In various studies (24-26) the biggest modification of variability consists of its global reduction. Instead, in our experience the modifications do not consist just of the reduction of

<table>
<thead>
<tr>
<th>TABLE 1 - RELATION BETWEEN NORMAL AND ALTERED VARIABILITY OF FHR IN FOUR PERIODS FOLLOWING CORTICOSTEROIDS ADMINISTRATION.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Normal variability</td>
</tr>
<tr>
<td>Altered variability</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE 2 - RELATION BETWEEN THE ALTERATIONS OF FHR VARIABILITY IN FOUR PERIODS FOLLOWING CORTICOSTEROIDS ADMINISTRATION.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Reduced variability (totally 28)</td>
</tr>
<tr>
<td>Increased variability (totally 50)</td>
</tr>
</tbody>
</table>

© CIC Edizioni Internazionali
Figure 1 - Modifications of variability within 12 hours from the administration of betamethasone (A), between 12 and 24 hours (B), between 24 and 36 hours (C) and after 36 hours (D). In light grey: unchanged variability. In middle grey: reduced variability. In dark grey: increased variability.

Figure 2 - Modifications of FHR baseline in relation to modifications of variability.
Effects of betamethasone on fetal heart rate

variability, but also and above all of its increase (Table 2).

To explain this event, we mention Piazza et al.‘s study of 2012 (27). According to the Authors, steroids have an effect on the nerve centers that are involved in the regulation of corporal and respiratory movements. They also have a specific action on raphe nuclei and locus ceruleus, which are involved in the regulation of sleep-wake cycle. The observation of ‘more active’ fetuses after corticosteroids administration (CTG showing greater number of accelerations and variability increase) could be explained like the passage to a phase of active sleep.

About FHr baseline modifications, in agreement with Literature (28), in our study frequency and variability show an inverse relationship (Figure 2).

Betamethasone has transient effects on FHr and can simulate a state of fetal suffering. This influence is clinically recognized by the analysis of FHr on CTG. It can be explained with the effect of those molecules on the sympathetic-vagal balance. The reduction of frequency with the increasing of variability suggests the presence of a functional baroreceptor reflex: studies on animals show that betamethasone causes an increase of peripheral vascular resistances and systolic blood pressure, because of the increasing of vascular tone (29). Pressure increase stimulates the baroreceptors activity, provoking a reflex of inhibition of the sympathetic nervous system and a reflex of activation of the parasympathetic system. For this way there is the reduction of heart frequency.

We excluded from our study two fetuses with gestational age <29 wGA on the assumption that before this age betamethasone does not modify the heart rhythm. Many studies evidenced that modifications of cardiac parameters are influenced by gestational age (30). In particular, those changes occur just after 28–29 wGA and not before this age. This finding strengthens the hypothesis of the existence of cerebral glucocorticoids receptors, which can be easily reached in older gestational age, when the permeability of hematoencephalic barrier is bigger (31).

The fewer effect of betamethasone in earlier age could be related to the immaturity of glucocorticoids receptors and to an incomplete cardiovascular and neuroendocrine development.

About our two cases at 27+4 wGA (pPROM) and 27+6 wGA (idiopathic risk of preterm delivery), actually before and after the administration of betamethasone, HRT variability do not modify. Instead, the cardiac frequency usually decreases.

Conclusions

The protocol of administration of glucocorticoids is extremely important to drastically reduce the pathological consequences of preterm delivery. It shows an action on FHr, its variability, fetal respiratory movements and quiescence in uterus, because of the “stressful” action of these molecules on the fetus.

The influence of glucocorticoids on the mechanism regulating FHr and variability and its respiratory and body movements, mimics a state of fetal distress. It depends on the entrance of the pharmacologic molecules into specific brain structures, above all into the brainstem. Here there are specific receptors which activation alters those functions. The entrance of betamethasone in the brain is consequent to the permeability of fetal hematoencephalic barrier. This property is acquired as the pregnancy develops, since 29 wGA.

Our data and those of Literature agree in observing alterations and variations of fetal cardiac frequency, reduction of respiratory movements and increase of fetal quiescence, after the administration of two intramuscular doses of 12 mg of betamethasone since 29 wGA. These modifications occur above all in the period between 24 and 36 hours from the beginning of treatment.

When CTG is executed in the hours and days following corticosteroids administration, its examination cannot be conceived without considering the transit effects which these molecules exercise on fetal nervous system.

References

8. NIH. Effect of corticosteroids for fetal maturation on perinatal