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Low dose of Betamethasone throughout the whole course of pregnancy and fetal growth: a clinical study

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Abstract. – AIM: To assess the eventual influence of low dose betamethasone throughout pregnancy on fetal growth.

PATIENTS AND METHODS: 320 patients – admitted to the Section of Obstetrics and Gynecology of Ferrara University from January 2005 to December 2010 – were subdivided in two groups: 160 patients affected by recurrent spontaneous abortion (Group A), treated by low dose of betamethasone (0.5 mg/daily) throughout pregnancy for preventive purposes, 160 patients with physiological pregnancy as control group (Group B). Primary measured outcomes were neonatal biometric parameters such as birth weight, head circumference and neonatal length. Unpaired *t*-test was used to compare the neonatal biometric parameters.

RESULTS: Birth weight, length and circumference head resulted significantly lower in groups treated by GCs. However, excluding bias as pregnancy complicated by diseases, which could affect fetal growth, biometric neonatal parameters were not different between two groups. Furthermore, analyzing the distribution of the value of birth weight we observed that in the group A there were 44 newborns with a weight even higher than fiftieth percentile.

CONCLUSIONS: Betamethasone seems not to influence fetal growth. Our analysis demonstrates that fetal growth is influenced by several factors, therefore, homogeneous study population is essential to have convincing results.

Key Words:

Homocysteine (Hcy), Atherosclerosis (AS), Oxidative stress, Lutein.

Introduction

Glucocorticoids (GCs) produced by the maternal-fetal unit, as well as those administrated for therapeutic purpose, regulate the utero-placental vascular adaptation in order to ensure adequate perfusion of gestational tissues, thus, favoring embryo-fetal morphogenesis and growth[1]. Such effects are accomplished throughout the modulation of the inflammatory response. Indeed, inflammation represents a general pathway leading to pregnancy complications, such as abortions, premature delivery and perinatal death, up to neonatal damage of high degree[2]. Despite their protective actions, GCs are not routinely utilized in obstetrical practice, due to deep concern about their possible adverse effects, among which their supposed negative influences on fetal growth. Such a concern was raised by experimental studies on animals showing that high doses of GCs given throughout pregnancy lead to fetal weight restriction[3-4]. However, studies on human pregnancy lead to conflicting results. Indeed, while some Authors reported increased prevalence of miscarriage, preterm delivery and fetal growth restriction[5-6], such complications were denied by others[7-9]. As it often happens in clinical-statistical studies, various confounders limit the real significance of these results. For instance, the effect on birth weight of GCs administered to prevent respiratory distress syndrome in cases of premature delivery was driven from the study of a population characterized by heterogeneous conditions, some of which leading themselves to fetal growth restriction. As a consequence, in spite of the short time between drug assumption and birth, birth weight reduction was ascribed to a side effect of the hormone, rather than to the underlying disease. Based on the considerations above, we decided to assess the effect of low dose betamethasone on fetal growth, focusing on the discrimination of the effects of the hormone from those of the clinical complications for which they were administrated. To this aim, we first analyzed the study population as a whole and subsequently we divided it into homogeneous classes by grouping patients according to their clinical features.

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Patients and Methods

We have conducted a prospective cohort study including patients admitted to the Section of Obstetrics and Gynecology of Ferrara University from January 2005 to December 2010. The inclusion criteria were: singleton pregnancy, "preventive" use of low dose betamethasone (0.5 mg/daily) throughout pregnancy for previous history of recurrent pregnancy loss (2 or more abortions), early start of treatment (about 6th week of gestation). The exclusion criteria were: fatal outcome of pregnancy (abortion prior to 24th week of gestation), use of betamethasone at doses higher than 0.5 mg/daily, caesarean section (CS) in previous pregnancy. Patients with physiological pregnancy at term and without risk factors were evaluated as a control group. Local Ethics Committee approved the study. The patients gave a written informed consent.

A total of 320 patients were included in the study and were subdivided in two groups:

1. 160 patients treated by low dose (0.5 mg/daily) of betamethasone (one tablet orally) throughout pregnancy for preventive purposes (history of recurrent miscarriage) from the 6th week of gestation until the end of pregnancy (Group A);
2. 160 patients with physiological pregnancy (Group B).

Primary outcomes measured were neonatal biometric parameters such as birth weight, head circumference and neonatal length.

Statistical Analysis

Unpaired *t*-test was used to compare the continuous variables (maternal age, week of gestation, neonatal biometric parameters). Contingency analysis with Chi-square test was performed for the categorical variables (mode of delivery, previous spontaneous deliveries, neonatal gender). Differences with $p < 0.05$ were considered statistically significant (SS).

Results

The two groups showed significant difference as regards to age ($p < 0.0005$; Table I). Given the influence of maternal age on fetal growth, it is important to register the following distribution of women aged between 38 and 45 years in the two groups: (1) Group A: 60 (37%); (2) Group B: 18 (11.8%).

Average length of pregnancy was 38.2 weeks (median 39 w; min 29 w, max 42 w) in the group A, 39.3 w (median 39 w, min 37 w, max 41 w) in the group B. Statistical analysis showed a significant difference between the two groups ($p < 0.0005$; Table I). There were not significant differences between the groups regarding neonatal gender and the number of patients with previous spontaneous delivery. Nonetheless, statistically significant differences ($p < 0.0005$) were detected about mode of delivery (Table I); the rate of CS was 62.5% in the group A compared to 20.6% in the group B.

Table I. Evaluation of the total study population.

	Group A (n= 160)	Group B (n=160)	CI 95%	*p* value
Age (y)	35.2 (± 4.6)	31.8 (± 5)	2.2-4.4	0.0005
Week of gestation	38.2 (± 2.5)	39.3 (± 1)	–1.5 (–0.6)	0.0005
Mode of delivery				0.0005
Spontaneous	60	127		
Caesarean section	100	33		
% CS	62.5%	20.6%		
N. previous spontaneous deliveries				n.s.
1	46	42		
2	6	10		
3	0	2		
Neonatal gender				n.s.
Male	94	80		
Female	66	80		
Neonatal biometric				
Birth weight (g)	2843.4 (± 674.4)	3251.8 (± 346)	–526.2 (–290.4)	0.0005
Length (cm)	48.3 (3.9)	49.9 (1.4)	–2.2 (–0.9)	0.0005
Head circumference (cm)	33.6 (1.8)	34 (1.1)	–0.8 (–0.1)	0.007

In the group A, the mean birth weight was 2843.4 g, that compared to the mean length of pregnancy was equivalent to fetal growth at 20th percentile (median 2965 g; minimum value 810 g at 32th week of gestation; maximum value 4100 g at 40th week of gestation). In the group B, the mean birth weight was 3251.8 g equivalent to fetal growth at 55th percentile for week of gestation (median 3230 g, minimum value 2680 g at 38th week of gestation, maximum 4400 g at 40th week of gestation). Statistical analysis, taking into account different percentiles, showed a significantly lower birth weight in the group A ($p < 0.0005$; Table I).

The mean length of the newborns was distributed as follows: 48.3 cm (minimum 30 cm, maximum 54 cm) in the group A, 49,9 cm (minimum 46 cm, maximum 53 cm) in group B with a SS difference ($p < 0.0005$) between the groups (Table I). Also the mean head circumference at birth was SS ($p = 0.007$), distributed as follows: 33.6 cm (minimum 26 cm, maximum 37 cm) in the group A and 34 cm (minimum 30, maximum 36.5 cm) in group B.

In evaluating biometric parameters of newborns, the pathological conditions, that may lead to fetal growth restriction occurred during pregnancy, must be considered. Among these, 24 cases of premature delivery[10] were present in our study. Further maternal diseases that may affect fetal growth are represented by gestational diabetes and hypothyroidism[11,12]. 17 such patients were found in the treated group, presenting hypothyroidism in 8 cases and gestational diabetes in 9 cases. Therefore, a total of 41 patients were excluded from the group A. So doing, we obtained two more homogeneous groups as regards to baseline characteristics of patients. Indeed, no significant difference was found between the two groups as regards to gestational age, a basic criterion for comparison of neonatal biometric parameters. By contrast, the mean age of the patients and CS rate remained within significance, thus, confirming the increased obstetric risk for group A while no significant difference was found for neonatal gender as well as for the number of patients with previous spontaneous deliveries (Table II). However, the most important result was represented by loss of significant differences in evaluating the neonatal biometric parameters (Table II; Figure 1). Furthermore, analyzing the distribution of the value of birth weight we observed that in the group A there were 44 newborns with a weight even higher than fiftieth percentile.

Discussion

The use of GCs during pregnancy is indicated in several pathological maternal conditions such as Addison's syndrome, autoimmune diseases, recurrent miscarriage[13-15], as well as for preventing fetal respiratory distress syndrome[16] and other life threatening complications of preterm birth. Therefore, knowing the possible negative effects of these hormones on the fetus is extremely important. A fundamental aspect to study is the claimed

Table II. Reassessment of the study population based on obstetrical disease.

	Group A (n= 111)	Group B (n=160)	CI 95%	*p* value
Age	35.4 (±4.8)	31.8 (±5)	2.3-4.7	0.0005
Week of gestation	39.3 (±1.1)	39.33 (±1)	–0.2-0.3	n.s.
N. previous deliveries				0.3
1	31	42		
2	4	10		
3	0	2		
Mode of delivery				0.0005
Spontaneous	51	127		
Caesarean section	60	33		
% CS	54%	20.6%		
Neonatal gender				n.s.
Male	68	80		
Female	43	80		
Neonatal biometric				
Birth weight (g)	3189 (±345.6)	3251.8 (±346)	–146.9-21.3	n.s.
Length (cm)	49.9 (±1.5)	49.9 (±1.4)	–0.3-0.3	n.s.
Head circumference (cm)	34.3 (±1.1)	34 (±1.1)	0.02-0.5	n.s.

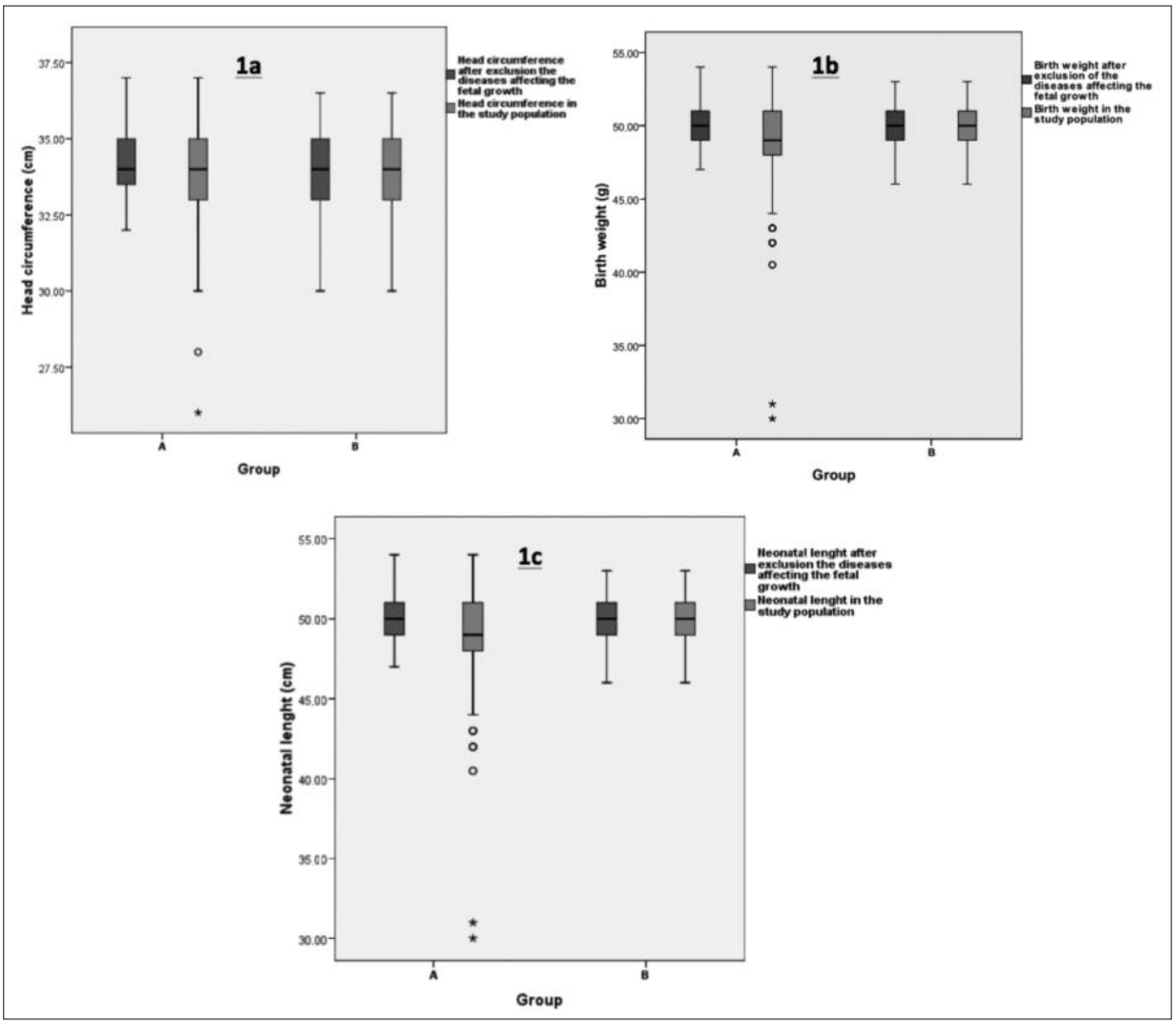

Figure 1. Head circumference ***(1a)***, birth weight ***(1b)*** and neonatal length ***(1c)*** between the two groups in the total study population and after exclusion of the diseases affecting the fetal growth.

influence of GCs on fetal growth[5-9]. In analyzing such influence from a physiopathological standpoint, two aspects must be considered: (1) effect of GCs on other hormones and growth factors involved in the fetal development; (2) effect of GCs on 11-β-hydroxysteroid dehydrogenase, the enzyme that regulates the trans-placental passage of the hormone. For instance, it has been reported that cortisol is a physiological stimulator of IGF-I receptor, and that an exposure to excess of GCs can lead to suppression of fetal growth via an alteration of the Insulin-like growth factor axis[17]. On the other hand, growth may be influenced via a stimulatory effect on the Growth Hormone receptor, known to be exerted by cortisol[18]. The claimed negative influence of GCs appears to be mediated by the placenta. Indeed, direct administration of betamethasone to ovine fetuses does not result in growth restriction[19]. Therefore, the effect of GCs on 11-β-hydroxysteroid dehydrogenase must be taken into account. Because GCs exert a stimulatory action on this enzyme[20], they should reduce their own supposed negative placental mediated effects. It has been reported that maternal administration of dexamethasone to pregnant rats in the second half of gestation decreases by 23% fetal and by 51% placental weight[21]. A systematic review of animal studies examining the association of GCs on birth outcome reported a reduction in fetal growth[4]. However, it should be considered that animal experiments demonstrating negative effects on fetal development and growth em-

ployed doses equivalent to 20-100 times a "replacement" dose of steroids for a human patient. Nevertheless, based on this and other type of results[22], studies in humans were addressed to assess both the effect of early exposure protracted for a long time and that of late administration for preventing the complications of premature delivery. Interestingly, although a study suggests that fetal growth becomes sensitive to GCs when the treatment starts early and is prolonged for a long time[23], dexamethasone given from the 10th week throughout pregnancy in the presence of female fetuses affected by 21-hydroxylase deficiency did not influence weight, length and head circumference of the newborns[24]. As for advanced pregnancy, randomized controlled studies have shown that treatment for preventing respiratory distress syndrome of the neonate leads to birth weight reduction only after four or more courses, and that these parameters normalized by the time of hospital discharge[5]. A further work reported instead that even a single course of prenatal GCs does reduce the birth size of term newborns[6]. Finally, a meta-analysis of five trials in which 2028 pregnant women were treated with GCs in late pregnancy found no significant effect on birth weight[7]. Two main exceptions can be raised towards such studies: first, the time elapsing between administration of the drug and delivery appears to be too short to influence fetal growth; second, obstetrical diseases affecting fetal growth are necessarily included in the study sample. In order to avoid such bias the ideal study population should be represented by physiological pregnancies, a sample that cannot be chosen for ethical reasons. Alternatively, an attempt to exclude the cases where a pathologic condition possibly affecting fetal growth can be recognized must be made. The present paper is unique in evaluating fetal growth in patients treated with low dose steroid therapy throughout the course of pregnancy.

Analysis of the initial sample of 320 patients revealed data that may seem crushing: neonatal biometric parameters were significantly lower in groups treated with GCs (Figure 1). However, some considerations need to be made: in the group A patients whose pregnancy had a sincerely pathological course leading to preterm delivery complicated by fetal growth restriction were observed. Therefore, it isn't plausible to consider GCs as responsible for the genesis of diseases such as preeclampsia since it goes against the principles of obstetric pathophysiology. Thus, in an attempt to reconstitute the ideal study groups, it was necessary to trim the sample by removing any confounders, i.e. patients suffering from diseases which could affect fetal growth. The revaluation of the data is extremely interesting given that some significant differences remain, such as the age of patients and CS rate. These differences highlight the increased obstetrical risk in treated patients. Indeed, the mean age of patients is higher than the control group (35.4 versus 31.8). This is a key parameter since the vascular resistance is age-dependent[25]. Therefore, altered vascular resistance can lead to utero-placental hypoperfusion and, thus, cause a slowdown in fetal growth. The CS rate (54% in group A versus 20.6% in group B) should also be considered. This data confirms the presence of high-risk pregnancies in treated group. However, the most important result is the loss of significant differences in term of neonatal biometric parameters (Figure 1).

A further aspect to be emphasized is the presence in the group A of 44 fetuses (39% of the sample) with birth weight over 50th percentile. If betamethasone had such a negative influence on fetal growth, we should not expect a birth weight even higher than average in almost a third of the sample. Therefore it is reasonable to think that there are other factors that influenced fetal growth in the remaining 67 fetuses. Our attempt to homogenize the sample of patients has a great clinical significance. It shows how the results in the literature on the role of GCs on the fetal weight can be misguided. In high-risk pregnancy builds up a series of pathophysiological mechanisms and, therefore, to consider the impact of GCs in these patients is conceptually wrong.

Conclusions

The opinion that use of GCs by itself possibly influences human fetal growth when therapeutic doses are administered since the beginning of pregnancy appears to be unjustified. Furthermore, it is neither known in what measure the type of GCs, and the duration of administration are related with growth, nor it is possible to comparatively discriminate any influence from that of the disease requiring the therapy. As for short treatment during advanced gestation, there is no persuasive evidence for any adverse effect on fetal growth. In this perspective our study has great clinical relevance. If further studies will demonstrate this trend, we could finally dispel the taboo of GCs as a drug not safe in pregnancy.

Conflict of Interest

The Authors have no conflict of interest to declare.

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