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Effect of Antenatal Dexamethasone on Serum Umbilical Cord C-peptide and Glucose Levels in Term Neonates Delivered by elective Cesarean Section

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ABSTRACT

Background: Antenatal steroid therapy recently has been considered for term and late preterm neonates delivered by Cesarean section (CS), with the aim of preventing adverse respiratory morbidity. The main aim of this study was to investigate the metabolic effects of antenatal dexamethasone on blood glucose (BG), homeostasis, and serum C-peptide level when administered to term fetuses.

Methods: Umbilical cord blood C-peptide and BG were measured in singleton newborns of 37 weeks gestational age or older with planned CS; furthermore, the history of dexamethasone receiving was taken from mothers. Other parameters, such as, Apgar score, neonatal birth weight, BG follow-ups, and admission to the neonatal nursery were collected.

Results: Totally, 117 mothers met the inclusion criteria, of whom 60 had received antenatal dexamethasone. This study demonstrated that babies treated with antenatal dexamethasone had a decrease in umbilical cord BG (P=0.001) and BG follow-up three hours after birth (P=0.001) compared to untreated group. However, there was no statistically significant difference in the BG measurements within both groups in the first 24 h post birth (P=0.14). Furthermore, no statistically significant difference was observed within the two groups regarding umbilical cord C-peptide measurements (P=0.08), birth weight (P=0.17), and the numbers of neonates that needed admission to the nursery (P=0.36).

Conclusion: Although antenatal dexamethasone causes immediate mild BG homeostasis alterations in term newborns delivered by elective CS, its use is not associated with a statistically significant effect on serum umbilical cord C-peptide measurements, neonatal birth weight, and the rate of neonatal nursery admission.

Keywords: Antenatal dexamethasone, Blood glucose, Cesarean section, Cord blood C-peptide, Full-term infant

Introduction

Five decades ago, Liggins indicated an inflation in the lungs of lambs born prematurely after antenatal steroid injections (1). Liggins and Howie published the first randomized controlled trial in humans in 1972 investigating the possible role of antenatal corticosteroids for accelerating fetal lung maturation in women at risk for preterm birth (2). A recent meta-analysis reviewed 21 published trials in preterm neonates and concluded that antenatal corticosteroids did not increase a mother's risk of death, chorioamnionitis, and puerperal sepsis. Treatment was associated statistically significant with decreases in neonatal morbidity and mortality, with reduction in neonatal death, respiratory distress syndrome (RDS), cerebroventricular hemorrhage, and necrotizing enterocolitis (NEC) as 31%, 34%, 46%, and 54%, respectively (3).

In regard to late preterm and full-term neonates, there was an increased risk of transient tachypnea of the newborn (TTN), RDS, and persistent pulmonary hypertension (PPHN) for neonates delivered by elective Cesarean section (CS) compared to newborns delivered by vaginal delivery (4, 5). Some research and meta-analyses suggest that these neonates may benefit from

treatment with antenatal corticosteroids prior to delivery by CS (6-10).

Stutchfield et al. (8) examined the effect of antenatal betamethasone given to women who planned to deliver by elective CS at 37 weeks of gestation or greater. A reduction in respiratory distress-related neonatal unit admission was observed with betamethasone administration, with incidence decreasing from 0.051% in the control group to 0.024% in the treatment group (P=0.02). However, despite the recommendations for antenatal administration of corticosteroids to near-term and term neonates, there is no great evidence for its safety and efficacy in this group (11, 12).

Considering antenatal corticosteroid safety, Sifianou et al. (13) investigated possible immediate alterations of the endocrine and metabolic status of term and near-term babies treated with antenatal betamethasone. They found that prophylactic betamethasone therapy caused immediate hormonal alterations after birth, which might interfere with the metabolic adaptation of the newborn later in life.

In the present study, the possible immediate effects of antenatal dexamethasone were investigated on glucose homeostasis in neonates. Umbilical C-peptide, blood glucose (BG), and other neonatal short-term outcomes were evaluated in full-term delivered by elective CS. Mothers with or without antenatal dexamethasone receiving assigned to the case and control group, respectively.

Methods

Study design

The current clinical study was performed at the neonatal intensive care unit (NICU) in the Pediatrics Department, in cooperation with the Department of Obstetrics and Gynecology and Clinical Pathology, at Sohag University, Egypt from October 2017 to April 2018. Local ethical approval for the study and written informed consent were obtained from the Research Committee of the Faculty of Medicine at Sohag University (No. 64, 2017) and all parents of the children .

Subjects selection

All singleton neonates with gestational age (GA) of 37 weeks or greater delivered by elective CS were included in the study. Exclusion criteria were mothers who suffered from gestational diabetes or diabetes mellitus type 1 or type 2, delivered twins, received multiple courses of antenatal corticosteroids, did not complete the course of steroids, delivered preterm, had premature rupture of membrane (PROM), had pre-eclampsia/eclampsia, and received dextrose solutions intraoperatively.

Subjects data

A total of 117 singleton newborns delivered by elective CS that were more than 37 weeks GA were met the inclusion criteria and enrolled in the study. Of the total cases, it was found from history taking that 60 neonates' mothers had received prophylactic antenatal dexamethasone , included 4 intramuscular doses of 6 mg dexamethasone delivered to the mother every twelve hours with the last dose at least twenty-four hours prior to birth.

On the other hand, 57 neonates of comparable GA whose mother had no history of receiving antenatal dexamethasone were assigned as control group. Both the treated cases and the controls were drawn from the same population characteristics.

Maternal data such as GA, maternal age and body mass index, history of previous vaginal delivery, CS, and maternal diseases and PROM were collected. Neonatal data such as gender, weight, Apgar score at 1 and at 5 minutes, umbilical cord pH, causes of admission to NICU if indicated, duration of admission to NICU, discharge from NICU, and hypoglycemia symptoms were recorded if presented. If the neonate's BG indicated hypoglycemia, follow-up BG evaluations were performed until BG was normalized.

Laboratory methods

Approximately 5 mL of umbilical cord blood was drawn immediately after delivery from all newborns who met the inclusion criteria.

Drawn blood was chilled to 4ºC, centrifuged as soon as possible, and stored at −84ºC. For complete blood counts (Cell Dyn 3700, automated cell counter, Abbott Diagnostics, USA), 2 mL blood was put into K3 ethylenediaminetetraacetic acid (EDTA) Vacutainer tubes. The remaining blood was delivered into plain tubes for other investigations. Umbilical BG and its follow-up were determined by the Roche HITACHI Cobas C-311 Auto-Analyzer System. Umbilical cord serum C-peptide was measured using a third-generation enzyme-linked immunosorbent assay (ELISA) (Modular Analytics E170, Roche Diagnostics, Singapore), employing the sandwich ELISA method. The ELISA microplate provided in the kit was pre-coated with an antibody specific to C-peptide.

C-peptide was chosen over insulin. Contrary to insulin, which is easily degraded, C-peptide is unaffected by several blood processing conditions, such as hemolysis (14, 15). The procedure for C-peptide measurement was as follows:

1. 100 μL standard or sample was added to each well and incubated 90 minutes at 37°C.
2. The liquid was removed and 100 μL biotinylated detection antibody was added and incubated 1 hour at 37 °C.
3. The solution was aspirated and washed three times.
4. 100 μL horseradish peroxidase (HRP) conjugate was added and incubated 30 minutes at 37 °C.
5. The solution was aspirated and washed five times.
6. 90 μL substrate reagent was added and incubated 15 minutes at 37 °C.
7. 50 μL stop solution was added, the plate was read at 450 nm immediately, and then results were calculated.

Statistical analysis

The sample size was determined using the formula $n = 2 * Cp/d^2$, where n is the number of subjects required in each group, d is the standardized difference, and Cp is power (a constant defined by values chosen for the P value and power required; for P value 0.05 and power 90% the constant is 10.5) . With regard to BG level, our targeted difference and standard deviation were 10 mg/dL and 16, respectively

(16). The standardized difference was obtained as (d) = target difference/standard deviation = 10/16 = 0.62. So, n = 2 x 10.5/(0.62)^2 = 54.63.

Therefore, the sample size in each group must be at least 55 cases.

Data were analyzed using Stata/IC (version 14.2). In addition, the unpaired t-test was applied to compare the means of two groups .Quantitative data were represented either as mean, standard deviation, median and range. Moreover, the Mann-Whitney test was used when the data was not normally distributed. Qualitative data was presented as number and percentage and compared using either the Chi square test or Fisher exact test. P value less than 0.05 was considered statistically significant.

Results

Study population

The results showed that 117 mothers who met the inclusion criteria were enrolled in the study. The case and control groups included 60 and 57 mothers with and without antenatal dexamethasone receiving, respectively.

As shown in Table 1, there were no discrepancies with regard to maternal and gestational age, body mass index, PROM, and numbers of previous deliveries within the case and control groups.

Table 2 presents the neonatal weight mild reduction in the case group (2995±329 g) compared to the control group (3089±416 g);

Table 1. Maternal characteristics either treated or not treated with antenatal dexamethasone

	Mothers treated with dexamethasone (60 mothers)	Mothers not treated with dexamethasone (57 mothers)	P value
Age (years)	27.06±5.67	27.89±5.83	0.44
Gestational age (weeks)	38.77±0.24	38.81±0.20	0.53
Numbers of primagrvida (n) %	40 (66.66%)	39 (68.4%)	0.48
Maternal weight (kg)	75.86±9.48	73.78±9.11	0.22
Maternal body mass index	28.8±4.57	27.9±3.84	0.24

Table 2. Neonatal outcomes in dexamethasone treated group or not treated

	Dexamethasone group (60 neonates)	No dexamethasone group (57 neonates)	P value
Birth weight (g)	2995±329	3089±416	0.17
Apgar score at 1 minute	8 (6-9)	8(6-9)	0.86
Apgar score at 5 minute	10 (8-10)	10 (8-10)	0.87
Umbilical cord PH	7.37±0.12	7.35±0.24	0.67
Cord C peptide (ng/dL)	3.13±0.96	2.84±0.81	0.08
Cord blood glucose (mg/dL).	59.35±11.72	75.05±15.08	0.001
Blood glucose after 3 hours (mg/dL)	67.90±14.65	86.79±12.07	0.001
Blood glucose at 24 hours post birth (mg/dL)	88.44±30.25	96.23±25.45	0.14
Hemoglobin level (g/dL)	14.23±3.45	13.73±3.72	0.09
Numbers of admission to neonatal nursery	2 (3.3%)	4 (7%)	0.36

however, this difference is still not statically significant (P=0.17). Furthermore, there were no statically significant differences regarding the Apgar score at 1 minute (P=0.86), at 5 minutes (P = 0.87), umbilical cord hemoglobin (P=0.09), and the umbilical cord pH (P = 0.67) within the two groups.

Umbilical cord C-peptide measurements

Serum umbilical cord C-peptide in neonates that received antenatal dexamethasone was increased (3.13±0.96 ng/dL) compared to cord C-peptide in neonates that did not receive dexamethasone (2.74±0.81 ng/dL); however, this increase was not statically significant (P=0.08).

Blood glucose homeostasis

There was a statistically significant difference in immediate umbilical cord BG within the case and control groups (59.35 ± 11.72 mg/dL; 75.05 ± 15.08 mg/dL, respectively; P=0.001). This pattern was repeated in BG follow-up three hours after birth, which showed a statistically significant decrease in the case group (67.90±14.65mg/dL) versus the control group (86.79±12.07mg/dL, P=0.001). However, no statistically significant difference in BG measurements in the first 24 h was observed within the case and control groups. (88.4±30.3mg/dL vs. 96.2±25.5mg/dL, respectively; P=0.14). Furthermore, neither group had BGs that reached hypoglycemic levels (≤47mg/dL) nor developed hypoglycemic symptoms.

Neonatal admission to the NICU

Incidence of neonatal admission to the NICU was increased in neonates who did not receive antenatal dexamethasone (4 total, 3 with TTN, and 1 with PPHN) compared to neonates that received antenatal dexamethasone (2 total, 1 with TTN, and 1with early neonatal sepsis). However, these differences were not statistically significant (P=0.36). All neonates were discharged from the NICU with an average 4–5 admission days with no recorded deaths.

Discussion

This study demonstrated that antenatal dexamethasone had a statistically significant immediate effect on infant glucose homeostasis in the form of a mild decrease in umbilical cord BG and its follow-up after three hours. However, the use of antenatal dexamethasone did not result in a statistically significant differences between case and control groups in serum umbilical cord C-

peptide measurements, neonatal birth weight, infant admission to the neonatal nursery, and serum BG at follow-up at 24 h post birth.

The use of antenatal steroids was analyzed in a recent meta-analysis by Saccone and Berghella (9) consisting of 6 trials, most of which are from high income countries and comprising 5698 singleton pregnancies. Of the total trials, 3 studies included 3200 women at 34–37 weeks gestation and at risk of imminent premature delivery at the time of hospital admission. The other three trials included 2498 women undergoing planned CS delivery at ≥ 37 weeks. The results showed that antenatal steroids administered at 34 or more weeks gestation reduced neonatal respiratory morbidity (e.g., RDS, TTN, reduced use of surfactant, decreased duration of mechanical ventilation, and significantly lowered time receiving oxygen). Furthermore, they a shorter NICU stay in was observed.

However, Althabe et al. (17) in a meta-analysis, compared the effect of antenatal corticosteroids to that of standard practices for reducing neonatal mortality in pregnant women at risk for preterm birth in low-income and middle-income countries. The findings indicated that the antenatal corticosteroids were ineffective at reducing neonatal mortality in preterm neonates. Furthermore, the strategy seemed to increase the risk of maternal infectious morbidity. These results are not in line with the present study findings. The current results showed that the neonatal mortality rate was not increased in dexamethasone group; moreover, there was a non-statistically significant reduction in admissions to the neonatal nursery. Furthermore, it was found that there were no neonatal deaths, and the duration of admission to the neonatal nursery was the same in both groups. The obtained results are consistent with the study conducted by Kirshenbaum et al. (12). They found that antenatal corticosteroids prior to elective CS at 34–37 weeks of gestation did not result in a significant reduction in neonatal respiratory morbidity.

The intrauterine environment plays a key role in regulating fetal growth and development; data predominantly taken from rodent studies (18, 19) suggests that it can also program health throughout life. Corticosteroids are key mediators in this process, and excess exposure to antenatal corticosteroids is associated with adverse pregnancy outcomes, including reduced birth weight, and a host of persistent changes in the hypothalamic–pituitary–adrenal axis programming. These changes, consequently are manifested as

elevated stress responses and glucose metabolism alterations (18, 19).

The current study demonstrated the effect of a single course of dexamethasone on neonatal glucose homeostasis. The results showed no statistically significant change in serum umbilical C-peptide in the dexamethasone group compared to the control, which in not consistent with the study conducted by Sifianou et al. (13). They indicated that C-peptide levels were significantly higher in the treated group than the non-treated group (2.85 mcg/L vs. 1.19 mcg/L in, P<0.0001).

Furthermore, umbilical cord BG and its follow-up at three hours were statistically decreased in the dexamethasone-treated group. This may be explained by dexamethasone stimulating maternal gluconeogenesis and producing maternal hyperglycemia, which was transmitted to the fetus. This can induce neonatal hyperinsulinemia which is demonstrated by an increase C-peptide levels (20). After umbilical cord clamping, interruption of the maternal glucose supply can lead to hypoglycemia (21). This is similar to the increase in C-peptide levels reported in neonates of diabetic mothers (20). The present study results are not in line with the study carried out by Sifianou et al. (13). In the aforementioned study it was found that umbilical cord BG increased in the steroid and non-treated group up to 62.5 mg/dL and 56.0 mg/dL, respectively.

Nevertheless, the study conducted by Kamath-Rayne et al. (22) showed that the corticosteroid-exposed neonates had approximately twice the rate of hypoglycemia and need for intravenous fluids for hypoglycemia compared to neonates not receiving corticosteroids. Bannerman et al. (23) reported similar results that neonatal hypoglycemia was more common in the betamethasone group than in the placebo group (24.0% vs. 15.0%; relative risk, 1.60; 95% CI, 1.37 to 1.87; P<0.001).

However, preterm and late preterm deliveries accounted for the majority of these previous studies (22, 23). Furthermore, the original trial of antenatal glucocorticoids in preterm neonates showed no significant between-group difference in the rates of neonatal hypoglycemia (2). In the current study, late preterm neonates were excluded from the study and term newborns were only enrolled. It was found that neither group had BG levels that reached hypoglycemic levels (≤47 mg/dL) nor developed hypoglycemic symptoms. Furthermore, at 24 hours post birth there were no statistically significant differences in the serum BG measurements in both groups.

The Royal College of Obstetrics and Gynecology (11) recommends antenatal corticosteroids to all women at risk for preterm birth and all women for whom an elective CS is planned. The most extensively studied regimens to prevent RDS are betamethasone (two doses of 12 mg each 24 hours apart) and dexamethasone (four doses of 6 mg each 12 hours apart), both given intramuscularly. In this study, the dexamethasone regimen was used.

These recommendations have been published recently; therefore, antenatal steroids have been used extensively especially in late and full-term newborns. In this study, a short-term side effect of dexamethasone on glucose homeostasis was found.

In regards to the long term effects of antenatal steroids, Davis et al. (24) showed an exaggerated response to the painful stress of the heel-stick procedure among full-term newborns treated with a single course of betamethasone.

Moreover, Alexander et al. (25) observed significantly increased cortisol reactivity to acute psychosocial stress in children 6–11 years old who had been exposed to antenatal synthetic corticosteroid therapy, independent of the type of synthetic steroid.

This effect was found to be more pronounced in females. Stutchfield et al. (26) followed school-age children exposed to steroids before elective CS at term and found that these children were twice as likely to be in the bottom quartile of academic ability than children who did not receive steroids in both antenatal betamethasone and the control group (17.7% [33/217] vs. 8.5% [14/190], respectively , P=0.03).

Recently, there has been avoidance of repeated courses of antenatal steroids in preterm and full-term neonates due to a small increase in benefits weighed against increased side effects (3, 11, 27, 28). Data from animal models have highlighted that repeated doses have beneficial effects on lung function but can have adverse effects on brain function and fetal growth (29). Randomized trials have highlighted similar effects in newborns with reductions in weight and head circumference (27).

In the present study, pregnant mothers who received multiple courses of antenatal steroids were excluded. The current findings indicated that a single course of dexamethasone in full-term neonates did not affect neonatal weight (2995±329 vs. 3089±416 g in the case and control group, respectively; P=0.17). These results are in line with Sifianou et al. (13) findings. It appears that the growth restricting effects of a single

course of antenatal steroids are more pronounced in preterm newborns (30). Moreover, repeated courses of antenatal steroids, especially in preterm infants, not only had growth restricting effects but also had poor neurological outcomes (3, 11, 27, 28).

No statistically significant difference was also observed in Apgar score at 1 or 5 minutes and umbilical cord pH between the case and control groups. This is consistent with the results of study conducted by Eriksson et al. (31). They found that the use of antenatal steroids in term newborns was beneficial with regard to respiratory morbidity; however, it was associated with a low Apgar score. Nevertheless, in the study carried out by Stutchfield et al. (8) and a meta-analysis by Saccone and Berghella (9), it was found that neonates whose mothers had received corticosteroids had significantly better Apgar scores at 1 and 5 minutes, with less necessity for interventions in the delivery room.

Conclusion

This study demonstrated that neonates whose mothers received antenatal dexamethasone had a statistically significant reduction in umbilical cord BG measurements and its follow-up after three hours.

Whether these effects have implications beyond the neonatal period remains to be determined in further studies. However, the use of antenatal dexamethasone compared to the control group in this study was not associated with statistically significant differences in serum umbilical cord C-peptide measurements, neonatal birth weight, rate of infant admission to the neonatal nursery, and serum BG follow-up at 24 h post birth.

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Authors' contributions

RAM, Planning, data collection, and helped to perform the statistical analysis and writing of the article.MAM, Planning, data collection, and helped to perform the statistical analysis and revision of draft manuscript.SPA,Planning, responsible for interpretation of laboratory data of subjects, and revision of the manuscript.All authors read and approved the final manuscript.

Conflicts of interests

Authors state no conflict of interest.

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