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MATERNAL-FETAL MEDICINE

Neonatal outcomes in term pregnancies treated with antenatal corticosteroids for suspected pre-term labor

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Abstract

Objective To evaluate the association between antenatal corticosteroid treatment and neonatal outcome when delivery occurs at term.

Study design A retrospective cohort study of all women with singleton gestations who delivered at term (37 + 0 to 41 + 6 weeks) in a tertiary medical center (2012–2015). Women with diabetes, suspected fetal growth restriction, antepartum fetal death, and fetal structural or chromosomal anomalies were excluded. The cohort was divided according to prior preterm (24 + 0 to 33 + 6 weeks) antenatal corticosteroids treatment due to threatened preterm labor (study group), vs. no such treatment (control group). Primary outcome was birthweight at delivery. Secondary outcomes were composites neonatal adverse outcomes. Logistic regression analysis was utilized to adjust results for potential confounders.

Results Of 25,872 women who were included in the study, 722 (3%) were treated with antenatal corticosteroids. Women in the treatment group had higher rates of nulliparity compared to controls (43% vs. 38%, $p = 0.002$). Birth weight was significantly lower in the corticosteroid treatment group (3077 g vs. 3264 g, $p = 0.001$), with higher rates of small for gestational age (11% vs. 6%, $p = 0.001$). Multivariate analysis adjusting for parity and gestational age demonstrated that corticosteroid treatment was associated with lower birth weight ($B = -93$ g, 95% CI −123 to −66, $p = 0.001$). Treatment was not found to be associated with adverse neonatal outcomes composites.

Conclusion Antenatal corticosteroid treatment is associated with lower birth weight and higher rates of small for gestational age neonates among women who eventually deliver at term. However, it is not associated with short-term adverse neonatal outcomes.

Keywords Antenatal corticosteroids · Small for gestational age · Birth weight · Term

Abbreviations

ACS	Antenatal corticosteroid
RDS	Respiratory distress syndrome
TTN	Transient tachypnea of the newborn
NICU	Neonatal intensive care unit
BMI	Body mass index
MAS	Meconium aspiration syndrome
HIE	Hypoxic ischemic encephalopathy
IVH	Intraventricular hemorrhage
NEC	Necrotizing enterocolitis

Introduction

Antenatal corticosteroid (ACS) treatment prior to anticipated preterm delivery is one of the most important interventions to improve neonatal outcome [1]. Neonates delivered preterm, whose mothers were treated with ACS, have significantly lower frequency and severity of respiratory distress syndrome, intracranial hemorrhage, necrotizing enterocolitis and death compared to preterm neonates, whose mothers did not receive ACS [2, 3]. A single ACS course which may be repeated once is recommended when preterm birth may occur between 24 + 0 and 33 + 6 gestational weeks [1]. ACS may be considered as early as 23 + 0 gestational weeks

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when preterm delivery is imminent within 7 days [2, 4, 5]. Furthermore, a recent study extended recommendations for ACS treatment for up to 36 + 6 gestational weeks [6], and a large randomized control study [7] demonstrated reduction in frequencies of admission to special care baby units with respiratory distress after elective caesarean delivery at term.

Although the benefits of ACS treatment are widely accepted, paucity of information exists regarding adverse outcome of this intervention, specifically when delivery occurs at term. Animal models and human studies of multiple ACS courses suggest that this treatment may adversely affect neurodevelopmental outcome [8], and are associated with a reduction in birthweight and an increased risk of small for gestational age neonate (especially after four courses of ACS) [8, 9]. Conversely, other studies have shown no evidence of long-term harm, specifically mortality and adverse neurodevelopmental outcome after administering a single course of corticosteroids before 34 + 0 weeks [3, 10].

Some women suspected of being at high risk for preterm delivery, and, therefore, treated with ACS, ultimately deliver at term. This population, from a retrospective point of view, received unnecessary treatment and might have been exposed to adverse outcome yet to be established. The purpose of this study was to investigate the association between ACS administration prior to 34 + 0 gestational weeks, for suspected imminent preterm delivery, and perinatal outcome when delivery eventually occurred at term.

Materials and methods

Study population

This is a retrospective cohort study of all women carrying a singleton, term (37–42 weeks of gestation), living fetus, who delivered at a single university-affiliated tertiary medical center, between 01 July 2012 and 31 December 2015. The cohort was divided according to prior treatment with ACS before 33 + 6 weeks of gestation. Women who were treated were allocated to the study group and compared to controls who received no such treatment. Neonatal outcome was investigated in both groups.

The study was approved by our local institutional review board (0232-16-RMC). Informed consent was waived due to the retrospective design of the study.

According to our local protocols, ACS therapy is recommended in cases of anticipated preterm birth (24 + 0 to 33 + 6 weeks of gestation) to improve neonatal outcomes [1]. Among women who delivered at term, we identified those treated with ACS due to an increased risk for preterm birth between 24 + 0 and 33 + 6 gestational weeks. Indication for treatment was threatened preterm labor, defined as cervical dynamics diagnosed by either trans-vaginal ultrasound cervical length shorter than 25 mm, or digital vaginal examination demonstrating a cervical dilation of more than 1.5 cm and 60% effacement. Premature contractions were not an obligatory finding for treatment. The treatment of choice was two 12-mg doses of betamethasone given intramuscularly 24 h apart, during hospitalization.

Exclusion criteria included: pre-term premature rupture of membranes, suspected fetal growth restriction, major fetal anomalies and fetal chromosomal abnormalities. Since maternal diabetes mellitus may influence both birthweight and neonatal adverse outcome, we excluded these cases. This population was investigated it in a different study [11]. According to our department protocol suspected fetal growth restriction is defined when ultrasound biometry measurements demonstrate either estimated fetal weight or abdominal circumference below 10th percentile for gestational age [12].

Data collection

Data were retrieved from our delivery ward's comprehensive computerized perinatal database. We traced patients treated with corticosteroids according to computerized medication-order history search. Data from the neonatal nursery and the neonatal intensive care unit (NICU) were integrated into the delivery-ward database using the unique admission numbers assigned to each woman and her offspring.

The following demographic and obstetrical variables were recorded: maternal age, gravidity, parity, body mass index (BMI), hypertensive disorders, gestational age at delivery, and mode of delivery. Recorded neonatal outcomes included: birthweight, neonatal gender, 5-min Apgar score, umbilical arterial pH, hypoglycemia, transient tachypnea of the newborn (TTN), respiratory distress syndrome (RDS), the need for mechanical ventilation, meconium aspiration syndrome (MAS), neonatal sepsis, hypoxic ischemic encephalopathy (HIE), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and admission to the NICU.

Missing data were completed by manual chart review performed by the study personnel.

Definitions

Birthweight percentile was calculated using gender-specific local population-based birthweight curves [13]. Large-for-gestational-age babies were defined as newborns with birthweight above the 90th percentile for gestational age. Small-for-gestational-age babies were defined as newborns with birthweight below 10th percentile for gestational age.

Primary outcome was defined as birthweight. Secondary outcomes were defined as neonatal respiratory composite outcome, including any one of the following: TTN, RDS, mechanical ventilation and meconium aspiration syndrome;

and neonatal adverse composite outcome including any one of: Apgar at 5 min < 7, Umbilical arterial pH < 7.1, NICU admission, TTN, RDS, mechanical ventilation, MAS, hypoglycemia, sepsis, HIE, IVH, and NEC.

Statistical analysis

Data analysis was performed with the SPSS v21.0 package (Chicago, IL, USA). Continuous variables were compared using Mann–Whitney *U* test. The Chi-square and Fisher's exact tests were used for categorical variables, as appropriate. Differences were considered significant when *p* value was less than 0.05. Following the bivariate analysis, logistic regression analysis was utilized to adjust outcomes for potential confounders. Variables with clinical impact or variables which were found to be different between the groups ($p < 0.05$) in the bivariate analysis entered the regression model: birthweight, gestational age at delivery, gravidity, parity, hypertensive disorders, BMI and antenatal corticosteroid treatment.

Results

During the study period, there were 28,998 term deliveries at our institution, and 25,872 women met inclusion criteria and comprised our cohort. Of them, 722 (3%) were treated with ACS due to threatened preterm labor prior to 34 + 0 gestational weeks, and delivered at term (Fig. 1).

Baseline characteristics of women in both study groups are presented in Table 1. Groups did not differ regarding maternal age, pre-pregnancy BMI and rates of hypertensive disorders. More women in the treatment group were nulliparous (42% vs. 38%, $p = 0.008$). In bivariate analysis, mode of delivery did not differ between groups, and overall cesarean delivery rates were comparable (16% in the treatment group vs. 15% in the non-treatment group $p = 0.48$). However, using a multivariate analysis regression model adjusting for parity and gestational age at delivery, ACS treatment was found to be associated with a higher rate of cesarean delivery (aOR = 1.65, 95% CI 1.1–2.0, $p = 0.001$).

Table 1 Baseline characteristics of the study groups

	Antenatal corticosteroid treatment $N = 722$	Not treated $N = 25{,}150$	*p* value
Maternal age (years)	30 (19–41)	31 (19–51)	0.143
Maternal age over 35 (years)	144 (20)	6539 (26)	0.07
Gravidity	2 (1–16)	2 (1–10)	0.001
Parity	0 (0–7)	1 (0–13)	0.002
Nulliparity	303 (42)	9557 (38)	0.008
Body mass index (kg/m^2)	21.5 (16–41)	22.5 (12–63)	0.07
Hypertensive disorders[a]	29 (4)	754 (3)	0.14
Cesarean delivery	115 (16)	3629 (15)	0.48

Values are presented as median (range) for continuous variables, and as *n* (%) for categorical variables

[a]Hypertensive disorders—any of the following: chronic hypertension (HTN), gestational HTN, preeclampsia or eclampsia

Birth and neonatal outcomes are presented in Table 2. The median neonatal birthweight in the treatment group was approximately 200 g less than in the control group (3077 g vs. 3264 g, $p = 0.001$). Gestational age at delivery differed statistically between groups, although was clinically insignificant, considering a median of 38 + 6 gestational weeks in the treatment group and 39 + 4 gestational weeks in controls ($p < 0.001$). Analysis of birthweight percentile as described in "Materials and methods", revealed a median birthweight percentile of 46 in the treatment group compared to 56 in controls ($p = 0.020$). Lower rates of large for gestational age neonates (LGA) were diagnosed in the treatment group (5 vs. 10% in controls, $p = 0.017$). Furthermore, higher rates of small for gestational age neonates (SGA) were diagnosed in the treatment group (11% vs. 6% in controls, $p = 0.001$)

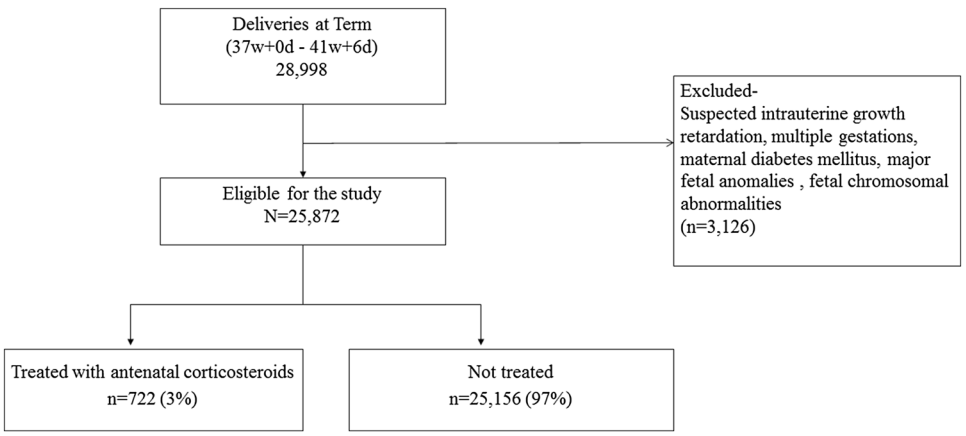

Fig. 1 Selection of the study cohort

Table 2 Neonatal outcomes

	Antenatal corticosteroid treatment $N=722$	Not treated $N=25,150$	p value
Gestational age at delivery (weeks + days)	38 + 6 (37 + 0 to 41 + 5)	39 + 4 (37 + 0 to 41 + 6)	< 0.001
Birthweight (g)	3077 (1979–4952)	3264 (1875–5421)	0.001
Birthweight percentile[a]	46 (1–99)	56 (1–99)	0.02
Male neonate	367 (51)	12,323 (49)	0.62
Large for gestational age	36 (5)	2574 (10)	0.017
Small for gestational age	78 (11)	1509 (6)	0.001
TTN	0 (0)	166 (1)	0.028
RDS	2 (0)	26 (0)	0.38
Hypoglycemia	4 (1)	73 (0)	0.351
Respiratory composite outcome[b]	8 (1)	444 (2)	0.09
Neonatal adverse composite outcome[c]	47 (6)	1565 (6)	0.82

Values are presented as median (range) for continuous variables, and as n (%) for categorical variables

[a]Birthweight percentile by local reference values as defined in "Materials and methods"

[b]Respiratory composite outcome—one of the following: TTN, RDS, mechanical ventilation, meconium aspiration syndrome

[c]Neonatal adverse composite outcome—one of the following: Apgar at 5 min < 7, umbilical arterial pH < 7.1, NICU admission, TTN, RDS, mechanical ventilation, MAS, hypoglycemia, sepsis, HIE, IVH, and NEC

(Table 2). Following adjustment for potential confounders as defined in the methods section, ACS treatment remained associated with lower birthweight ($B=-93$ g, 95% CI −123 to 66, $p=0.001$).

Bivariate analysis of individual and composite neonatal outcomes is presented in Table 2. Respiratory complications, composite respiratory outcome, neonatal composite outcome and individual outcomes did not differ between groups. Multivariate analysis following adjustment for potential confounders demonstrated that ACS treatment was not associated with adverse composite neonatal outcome (aOR = 1.01, 95% CI 0.75–1.37, $p=0.927$) or with composite respiratory outcome (aOR = 1.63, 95% CI 0.81–3.3, $p=0.169$).

Discussion

The aim of our study was to investigate birth outcomes in a specific population of women treated with ACS for suspected imminent preterm birth, who eventually delivered at term. Our key findings were: (1) three percent of women who delivered at term were suspected during pregnancy to be at risk for immediate preterm birth, and were accordingly treated with corticosteroids; (2) among women treated with corticosteroids and delivering at term, there was a higher rate of nulliparity; (3) there is a higher risk for cesarean delivery in the group treated with ACS; (4) neonatal birthweight was lower in pregnancies treated with ACS, with significantly higher rates of SGA.

The benefits of corticosteroid treatment for women at risk for imminent preterm delivery are well established, [4, 14–23] making the treatment 'standard of care' whenever preterm birth is anticipated. Pursuing antenatal corticosteroid treatment whenever imminent preterm birth is suspected is associated with a significant quantity of unnecessary treatment—for ongoing term pregnancies. Braun et al. [24] examined the effects of ACS on fetal growth and neonatal outcomes. In their study, one-third of women treated with ACS for indications including: preterm labor, cervical insufficiency, preterm premature rupture of membranes or vaginal bleeding, eventually delivered at term. In our cohort, we found that up to 3% of all pregnancies delivering at term received ACS due to preterm cervical dynamics. This finding amplifies the importance of understanding adverse outcomes related to ACS treatment. Medical centers should strive to limit the use of ACS to cases of true imminent preterm labor. Approximately, 30% of preterm labor spontaneously resolves and 50% of patients hospitalized for preterm labor actually give birth at term [25]. Consideration should be given to withhold treatment in cases of preterm contractions without progressive cervical change or cervical change with no significant contractions or a history of preterm birth. An alternative of close conservative management in such cases might prevent generating an unnecessary pathology.

In an attempt to characterize women who received unnecessary ACS treatment, we found them to have higher rates of nulliparity. This may be explained by the lack of history-based information regarding previous pregnancy outcomes and gestational ages at birth, which could alter decision-making regarding steroid use at initial presentation. Specifically, one may refrain from treatment in face of a history of previous term deliveries, and administer it in the face of a

lack of prior pregnancy history, even if estimated risk of preterm delivery is low.

We also demonstrated that ACS treatment was associated with higher cesarean delivery rates at term. A possible explanation for this finding is the higher rate of SGA babies delivered in the treatment group. These fetuses presumably have smaller intrinsic reserves and are less equipped to handle the stress of labor, possibly predisposing them to non-reassuring fetal heart rate, [26] eventually leading to increased risk for cesarean delivery. Of note, this is only a theoretical hypothesis, as we did not have exact information regarding the indications for cesarean deliveries in each subgroup. Another possible explanation for this finding is a premature bias of physicians when faced with women treated with ACS, assuming them to have a more "complicated" pregnancy, thus leaning them to opt for a cesarean delivery more easily than they might have for an apparent otherwise "uneventful" pregnancy.

Previous studies on multiple courses of ACS suggest that they may have the potential to adversely affect neurodevelopmental outcome [8], and may cause reduction in birthweight [23] and an increase SGA rate [9]. The Antenatal Late Preterm Steroids study [6] that leads the precedence of extending ACS treatment to 36 + 6 gestational weeks has not obtained long-term outcome data. In addition, long-term follow-up of children to mothers treated with ACS prior to elective term cesarean delivery demonstrated a difference in subjective teacher evaluation of a child's quartile of ability, with more children assessed at less than 25% for performance in the treatment group [27]. This did not lead international guidelines to recommend against corticosteroid use; however, continued surveillance was supported by such [1], implying lack of confidence in advocating ACS treatment close to term. Battin et al. [28] investigated the effect of repeated ACS on postnatal outcome, and similarly found a decrease in z-scores for weight and length in the first 2 weeks after birth. We chose neonatal birthweight as the primary outcome both because the aforementioned studies suggested an association between corticosteroid treatment and lower birthweight, and since this parameter is well documented and fits the retrospective design. In our study, birthweight was found to be lower in pregnancies exposed to ACS treatment, with significantly higher rates of SGA in these women. By excluding pregnancies complicated with fetal growth restriction, we eliminated possible bias, since this might be an indication for corticosteroid treatment. An alternative explanation for this finding could be found in a study by Espinoza et al. [29] who demonstrated that patients with an episode of increased uterine contractility that subsided and who delivered at term are at risk for delivering an SGA neonate. They proposed that such an episode of uterine contractions may represent an insult not severe enough to trigger preterm labor, but which may put the fetus at increased risk for additional pregnancy complications, including growth restriction. Preterm uterine contractions were not, admittedly, an obligatory finding for inclusion in our study population, but one cannot rule out the possibility that many of those women with cervical dynamics had some degree of preterm uterine activity, even if undocumented by cardiotocography. Be that as it may, the precise etiology of SGA demonstrated both in the aforementioned study [29] and in our results is not fully understood. Further studies are necessary to investigate whether treatment with corticosteroids do impact fetal growth.

Other composite outcomes chosen in our study are associated with known benefits of corticosteroid treatment for preterm infants, including respiratory benefits that were not found to be statistically significant in term infants. This is most probably due to the small percentage of respiratory abnormalities in grossly intact fetuses at term. The other outcomes encompassing the neonatal adverse composite outcome, including IVH, NEC, sepsis and NICU admission represent severe neonatal outcomes that need to be addressed with regard to safety of corticosteroid treatment. As shown, they were not found to be different between the study and control groups.

The limitations of our study are mainly due to its retrospective nature, lack of control for the exact time-period elapsed between corticosteroid treatment and delivery and the frequency of a second rescue dose. Neonatal complications at term are generally rare, and hence comparison requires a larger cohort, representing another disadvantage of the chosen study design. Additionally, maternal complications and long-term neonatal outcomes were lacking from our database, thus inhibiting a full appreciation of the possible repercussions of antenatal steroid treatment for women delivering at term. However, the strength of our study lies in its relatively large sample size at a single tertiary center with a strict management protocol for ACS treatment.

Conclusion

Our findings imply that antenatal corticosteroid treatment for suspected imminent preterm delivery might be associated with higher rates of SGA when pregnancy occurs at term. However, we found no evidence of associated short term neonatal morbidity. Thus, ACS treatment should not be withheld whenever preterm delivery is suspected taking into consideration its proven maturation benefits in preterm infants. Further studies are needed to fully delineate possible adverse ramifications of corticosteroid use in term-delivered infants to assess its risk and benefit profile.

Author contributions EK and EH contributed to all process of submission from the preliminary hypothesis, data collection, data analysis

and manuscript writing. AB and LS contributed to data collection and analysis. AH, RC and AW took part in the project development and manuscript writing and drafts editing.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required. This article does not contain any studies with animals performed by any of the authors. The Rabin Medical Center institutional review board approved the study (0232-16-RMC), with waiver of informed consent due to the retrospective, observational design of the study.

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