Small for Gestational Age in Late Preterm Deliveries - The Impact of Antenatal Corticosteroids on Perinatal Outcome

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Research Article

Keywords: Antenatal corticosteroids, small for gestational age, late preterm, perinatal outcome

Posted Date: February 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-163777/v1

Abstract

Purpose

The aim of this study is to evaluate the impact of antenatal corticosteroids (ACS) on late preterm small for gestational age neonates.

Methods

A retrospective cohort study of all women, carrying a singleton gestation, who had late preterm delivery (34 + 0–36 + 6, gestational weeks) of small for gestational age neonates, in a single, tertiary, university-affiliated medical center (July 2012- December 2017). Exclusion criteria included: birth weight above the 10th percentile, termination of pregnancy and intrauterine fetal death. Outcomes were compared between those who were treated with ACS prior to delivery and those who did not receive ACS. The primary outcome was neonatal composite outcome which included: neonatal intensive care unit admission, respiratory distress syndrome, mechanical ventilation and transient tachypnea of the newborn.

Results

Overall, 228 women met inclusion criteria.102 (44.7%) received ACS and 126 did not (55.3%). Birth weight among non-ACS group was significantly higher (1880.38 ± 171.54 vs 1774.84 ± 229.15 grams $p < 0.001$). Rates of NICU and Jaundice requiring phototherapy were higher among the ACS group (53.92% vs 31.74%, $p = 0.01$ and 12.74% vs 5.55%, $p = 0.05$, respectively). Composite neonatal outcome was significantly higher among the ACS group (53.92% vs 32.53%, OR 2.42, CI 1.41–4.15, $p = 0.01$). After adjustment for potential confounders, using multivariate regression analysis this association remained significant (OR 2.38, 95% CI 1.39–4.10, $p = 0.002$).

Conclusion

Our findings suggest that ACS delivered during pregnancy did not improve respiratory adverse outcome for SGA neonates born in late preterm. ACS in this specific cohort might be associated with worse outcome than those not treated with ACS.

Introduction

Antenatal corticosteroid (ACS) therapy for preterm infants has been shown to improve neonatal outcome. Back in 1972, Liggins et al. demonstrated that ACS therapy reduces respiratory distress syndrome (RDS) in preterm deliveries [1]. The latest Cochrane review which included the results of 30 trials, concluded that a single course of a corticosteroids, given to the parturient in preterm labor, reduces the rates and severity of serious adverse outcomes related to prematurity, including: RDS, intraventricular hemorrhage (IVH),

necrotizing enterocolitis (NEC), need for respiratory support and neonatal intensive care unit (NICU) admission [2]. In addition, ACS treatment was found to significantly reduce the risk of perinatal and neonatal death. The impact of ACS on late preterm neonates was assessed in a recent randomized trial and found that antenatal administration of betamethasone to women at risk for late preterm delivery (34 weeks 0 days to 36 weeks 6 days of gestation) decreased the need for substantial respiratory support during the first 72 hours after birth [3].

Notwithstanding the above, ACS are associated with several adverse effects especially when repeated courses are given. Murphy et al. demonstrated that multiple courses of ACS, every 14 days, do not improve preterm-birth outcomes and are associated with a decreased birth weight, length and head circumference at birth [4]. In a another study that evaluated long term outcomes after repeated doses of ACS, where children were followed up to 2–3 years of age, found higher rate of cerebral palsy among children who had been exposed to repeated doses of corticosteroids [5].

Although ACS are widely used, there are several unanswered questions regarding this treatment, one of which is the impact of this treatment on growth restricted fetuses [6]. It is well established that SGA contributes to neonatal morbidity in preterm and term neonates as it contributes to higher risk for premature complications including RDS, IVH and NEC, and also for long term adverse outcomes such as cerebral palsy, major psychiatric sequelae in later years and adult cardiovascular diseases [7]. In one study, neonatal outcome was compared between growth restricted fetuses that received ACS and those who did not receive ACS, they concluded that administration of corticosteroid to growth restricted preterm fetuses does not appear to be beneficial with respect to short term neonatal outcome [8]. However, this study included only early preterm (up to 34 weeks of gestation) growth restricted fetuses. To the best of our knowledge, little is known on the impact of ACS on SGA neonates born in late preterm. Hence, our research aimed to assess whether exposure to ACS during pregnancy improves adverse neonatal outcome in late preterm SGA.

Material And Methods

Study population

A retrospective cohort study of all women, carrying a singleton gestation, who had a preterm delivery in a single, tertiary, university affiliated medical center between July 2012 and December 2017.

We only included late preterm deliveries (34+0-36+6 gestational weeks) who had small for gestational age newborns defined as birth weight (BW) below the 10th percentile, according to the Israeli national birthweight curves [9].

Exclusion criteria included: termination of pregnancy (TOP), intrauterine fetal death (IUFD) and birth weight at or above the 10^{th} percentile.

Ethical approval

The study was approved by the institutional review board of Rabin Medical Center (RMC-19-0557). Informed consent was waived due to the retrospective design of the study.

Data collection

Data were retrieved from the comprehensive computerized perinatal database of our center. Data from the neonatal unit and the neonatal intensive care unit (NICU) were integrated into the delivery room database using the unique admission number assigned to each woman and her offspring. Collected data included demographic and obstetric parameters, labor and short-term maternal and neonatal outcome (up to discharge).

Outcome measures

The study population comprised two groups, those who were treated with ACS prior to delivery and those who did not receive ACS prior to delivery. Maternal and neonatal outcomes were compared between groups.

The primary outcome was composite neonatal outcome which included: NICU admission, RDS, mechanical ventilation and transient tachypnea of the newborn (TTN).

Secondary outcome was adverse neonatal outcome, adverse maternal and labor outcome. Neonatal adverse outcome included: birth weight, gender, umbilical arterial PH, RDS, TTN, IVH, mechanical ventilation, NEC, retinopathy, sepsis, antibiotic treatment, NICU, jaundice requiring phototherapy, neonate major anomaly, blood products transfusion and hypoglycemia. Adverse maternal and labor outcome included: postpartum hemorrhage (PPH), blood product transfusion, mode of delivery and onset of labor (elective, spontaneous or induction).

ACS was delivered in cases with suspected preterm delivery. By departmental protocol, the treatment course includes two 12-mg doses of betamethasone given intramuscularly 24 hours apart. In few cases, where pregnancy was continued and there was an imminent threat of preterm delivery, additional rescue course was given in the same manner.

Delivery methods of induction were prostaglandin E2 -PGE2, extra-amniotic balloon, and oxytocin infusion, which were chosen according to the physician’s discretion and local institutional practice.

Statistical analysis

Continuous variables were compared using Mann–Whitney test. Correlations between continuous variables were evaluated using the Spearman correlation coefficient. The Chi squared test was employed to compare categorical variables. Logistic regression analysis was used to determine which factors were significantly and independently associated with ACS treatment.

Odds ratios (OR) with 95% confidence interval (CI) were reported. All statistical tests were 2-tailed, and $p < 0.05$ was considered as statistically significant. All calculations were performed using IBM SPSS (Ver. 26.0).

Results

Overall, 228 patients met inclusion criteria. Of them, 102 (44.7%) received ACS and 126 did not (55.3%). Among the group that received ACS, 27 (26.47%) received a second (rescue) course of ACS. Maternal characteristics are summarized in Table 1.

There were no differences between groups regarding maternal age, body mass index, gravidity and parity. There were significantly higher rates of gestational diabetes and lower rates of preeclampsia among women who received ACS (9.8% vs. 2.38%, p = 0.01 and 9.8% vs 19.9%, p=0.03, respectively). Regarding obstetric outcomes, the group that received ACS delivered earlier (35.5 vs. 36.1 gestational weeks, P = 0.00).

Aa for onset of labor, in the non-ACS group, there was a higher prevalence of spontaneous delivery versus elective delivery and induction of labor (Table 2).

Regarding neonatal outcome, there was a significantly higher mean birthweight among non-ACS group (1891.20±173.75 vs 1773.76±224.68 grams p<0.001).

Rates of NICU admission and Jaundice were significantly higher among the ACS group, (53.92% vs 31.74%, p= 0.01 and 12.74% vs 5.55%, p =0.05, respectively), (Table 3).

In addition, rates of composite neonatal outcome were significantly higher among the ACS group (53.92% vs 32.53%, OR 2.42, CI 1.41-4.15, p=0.001). After adjustment for nulliparity, using regression analysis, this association remained significant (OR 2.38, 95% CI 1.39-4.10, p=0.002).

A sub-analysis was performed for the group that received ACS. There was a higher rate of NICU admission among the group that received a rescue course of ACS (70.37% vs 47.14%, p=0.04). In addition, composite neonatal outcome was significantly higher among women that received a rescue course of ACS (70.37% vs 47.14%, OR 2.66, CI 1.03-6.88, p=0.04). Following regression analysis this association remained significant (OR 2.65, CI 1.01-6.91, p=0.04).

Discussion

In this study we found that administration of ACS during pregnancy does not appear to be beneficial on short term outcome and can even result in higher rates of adverse outcome in SGA neonates born in the late preterm. Our study showed that the rate of NICU admission was significantly higher among the ACS group along with higher rates of composite neonatal outcome. This association remained significant among fetuses that received a rescue course of ACS in sub-analysis for the ACS group only.

ACS therapy for decreasing neonatal morbidity and mortality is recommended by guidelines around the world and is widely used. Its benefits among intrauterine growth restriction (IUGR) fetuses remains largely unknown, and controversy exists on the benefit of ACS for IUGR/SGA fetuses to improve preterm birth outcome. There is insufficient evidence to withhold routine ACS therapy in cases of suspected IUGR with a high risk of preterm birth.

The benefit of ACS in specific obstetric population such as SGA neonates, is yet to be determined. A previous study by Gyamfi-Bannerman et al., investigated the effects of ACS for women at risk for late preterm delivery. In this randomized trial, women with a singleton pregnancy who were at high risk for delivery during the late preterm period were recruited. In this study ACS significantly reduced rates of neonatal respiratory complications. It should be noted though that the frequency of IUGR among the ACS group was 3.2% and among the control group was 3.4%, and the impact on ACS on this sub group was not analyzed [3]. Another study by Haviv et al., investigated the role of ACS on late preterm in special populations. They concluded that there is insufficient evidence regarding the benefits or harms of ACS therapy in pregnancies with IUGR, especially in the late preterm period. They recommended an individualized approach when administering corticosteroids at later gestations in specific obstetric populations such as IUGR [10].

Several studies reported no effect of ACS on neonatal morbidity or mortality among IUGR fetuses in the early preterm (up to 34 weeks of gestational age) [8, 11,12,13,14]. Van Stralen et al. demonstrated that administration of ACS to IUGR fetuses does not appear to be beneficial with respect to short term neonatal outcome in preterm deliveries[8]. Another recent study showed the same results where ACS did not improve neonatal morbidities, in SGA neonates delivered between 29 and 34 gestational weeks. Rather, ACS seemed to increase the risk of RDS. They concluded that ACS therapy for women who are at risk for preterm delivery with IUGR fetus, need to be further evaluated, especially after 32 weeks of gestation [13]. A recent meta-analysis, examined 16 observational cohort and case-control studies published from 1995 to 2018, they concluded that ACS reduces neonatal mortality in SGA infants delivered preterm, with no apparent effect on neonatal morbidity (RDS, NEC, IVH and periventricular leukomalacia, bronchopulmonary dysplasia or chronic lung disease of prematurity, or neonatal sepsis). The study concludes that future studies are required on the effect of ACS administration to SGA infants in the late preterm period, because data on this issue is limited [14]

One assumption for our results is that poor intrauterine growth, by itself, actually enhances lung maturation. This assumption has been demonstrated in several studies. The physiological adaptations that growth restricted fetus experience in response to nutrient and oxygen restriction alter the ability to

regulate endogenous glucocorticoid availability. As a result, these fetuses may be exposed to higher ACS concentrations, which may result in an exacerbation of the potentially negative side effects of antenatal glucocorticoid treatment, especially in cardiovascular development. Possibly without the full capacity to benefit from the lung maturational effects [15]. Conversely, a previously published study demonstrated that IUGR fetuses accelerate lung maturation is not supported in comparisons of SGA and appropriate for gestational age (AGA) infants of the same gestational age, sex and race [16].

Secondly, it has been suggested that elimination of ACS via the placenta or the blood–brain barrier is impaired with IUGR, and hence, the fetus is exposed to excessive corticosteroids in the lung, brain, and heart tissues [15].

Nevertheless, some studies showed lower risk of adverse outcomes [16,17,18,19,20]. Bernstein et al. demonstrated the association of IUGR fetuses with increased morbidity and mortality. Furthermore, it showed that the benefits of ACS therapy were similar among infants with IUGR and normally grown infants for neonates from 25 to 30 weeks of gestation [19]. A population-based study on singleton infants of 24–31 weeks of gestation, concluded that ACS therapy was associated with significantly reduced mortality and major neonatal morbidities among preterm SGA neonates which was generally similar to the effect in the AGA preterm infants [17]. A previous review (2018) concluded that based on the current clinical evidence, it is reasonable to give a single course of glucocorticoids to pregnant women with IUGR fetuses who are at risk of preterm birth, however there is insufficient evidence to conclude whether repeated or rescue ACS administration is beneficial for IUGR infants [18].

We also found that birth weights were significantly higher among non-ACS group. Our results are aligned with previous studies which have shown that ACS is associated with reduction in birth size for infants born preterm, near term, or at term [21]. These studies even showed reduction in head circumference among preterm newborns [21,22]. However, it is unclear whether this difference in birth weight is a result of the ACS treatment or was it the reason for administering the ACS.

The novelty of the present study is that we examined ACS therapy for SGA fetuses eventually born at late preterm. To the best of our knowledge, all existing studies examined ACS therapy for SGA fetuses in the early preterm. Moreover, most studies refer to IUGR fetuses (defined as an estimated fetal weight <10th percentile) and not SGA fetuses.

Nevertheless, it is not free of limitations. The main limitation of this current study is its retrospective design, which could lead to an unknown selection bias such as the reason for administering or withholding ACS. In addition, the timing of administering ACS was missing. Another limitation is that we only studied short-term neonatal outcomes in this specific population, and the long-term impact of ACS is yet to be determined.

In conclusion, our study demonstrated that ACS did not decrease neonatal morbidity, in SGA neonates at the late preterm. It might be even associated with adverse neonatal outcome. This should be further evaluated in large prospective studies.

Declarations

Funding: Not Applicable

Conflicts of interest/Competing interests: K Zloto, L Salman, A Shmueli, E Krispin, E Hadar declare that they have no conflict of interest.

Availability of data and material: Data were retrieved from the comprehensive computerized perinatal database of Rabin Medical Center (RMC-19-0557).

Code availability: Not Applicable

Ethics approval: The study was approved by the institutional review board of Rabin Medical Center (RMC-19-0557).

Consent to participate: Informed consent to participate was waived due to the retrospective design of the study.

Consent for publication: Informed consent for publication was waived due to the retrospective design of the study.

AUTHOR CONTRIBUTIONS

K Zloto, L Salman: Study conception and design; Acquisition of data: Analysis and interpretation of data: Drafting of manuscript; Final approval of the manuscript to be published

A Shmueli, E Krispin: Study conception and design; Acquisition of data; Critical revision of the article; Final approval of the manuscript to be published.

E Hadar: Study conception and design; Acquisition of data: Analysis and interpretation of data: Critical revision of the article; Final approval of the manuscript to be published.

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Tables

Table 1
Demographic characteristics of the study population

Chareristics	ACS	Non-ACS	p-value
Maternal age (years)	31.27(± 5.3(	32.17) ± 5.57)	0.272
Pregestational BMI (kg/m^2)	23.22(± 3.85)	24.12(± 4.86)	0.516
Gravidity	2.17(± 1.43)	2.52(± 1.879)	0.207
Parity	0.71(± 0.95)	1.04(± 1.461)	0.177
Gestational age at delivery (Weeks)	35.41(± 0.85)	35.87(± 0.63)	< 0.001
BMI – Body Mass Index;			
Continuous variables are presented as mean ± standard deviation and categorical variables are presented as n (%)			

Table 2
Obstetric outcomes of the study population

Variables		ACS	Non-ACS	P-value
Gestational diabetes		10(9.8)	3(2.38)	0.01
Oligohydramnios		8 (7.84)	5(3.96)	0.21
Polyhydramnios		0 (0)	2(1.5)	0.20
Episiotomy		3 (2.94)	8(6.34)	0.23
Postpartum hemorrhage		1 (0.98)	3(2.38)	0.42
Transfusion		1 (0.98)	2(1.5)	0.68
Abruption		2 (1.96)	1(0.75)	0.44
Hypertensive disease of pregnancy	Pregnancy-induced hypertension	0(0)	2(1.58)	0.20
	Chronic hypertension	1(0.98)	1(0.75)	0.88
	Pre-eclampsia	10 (9.8)	25(19.84)	0.03
Mode of delivery	Vaginal delivery	29 (28.43)	47(37.3)	
	Caesarean	67(65.67)	71(56.34)	
Mode of starting delivery	Elective	48 (47.05)	47 (37.3)	
	Spontaneous	11(10.78)	30(23.8)	0.03
	Induction	27(26.47)	35(27.77)	

Continuous variables are presented as mean ± standard deviation and categorical variables are presented as n (%)

Table 3
Neonatal outcomes

Characteristic	ACS	Non-ACS	p-value
Birth weight (g)	1773.76 ± 244.68	1891.2 ± 173.75	< 0.001
5-min Apgar score < 7	1(0.75)	1(0.75)	0.88
Umbilical artery PH	7.32(± 0.07)	7.23(± 0.7)	0.02
composite neonatal outcome	55(53.92)	41(32.53)	< 0.001
Respiratory distress syndrome	4(3.92)	2(1.5)	0.27
Transient tachypnea of the newborn	5(4.9)	4 (3.17)	0.50
Intraventricular hemorrhage	2(1.96)	1(0.75)	0.44
Mechanical ventilation	1 (0.98)	4 (3.17)	0.26
Necrotizing enterocolitis	0 (0)	1(0.75)	0.55
Neonatal intensive care unit admission	55 (53.92)	40 (31.74)	0.01
Jaundice requiring phototherapy	13(12.74)	7 (5.55)	0.05
NeonateMajorAnomaly	8(7.84)	8(6.34)	0.66
Transfusion	3(2.94)	5(3.96)	0.67
Hypoglycemia	6(5.88)	9 (7.14)	0.70
Continuous variables are presented as mean ± standard deviation and categorical variables are presented as n (%)			