Association between antenatal corticosteroid administration and neonatal hypoglycaemia in infants born at term: an observational cohort study

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Abstract

OBJECTIVE Assess whether antenatal corticosteroids for fetal lung maturation are associated with hypoglycaemia in neonates born at term. DESIGN Cohort study of term singleton deliveries over a 3-year period. SETTING Tertiary UK hospital. POPULATION The cohort includes neonates not exposed to corticosteroids; those exposed before 34 weeks because of suspected preterm birth but delivered at term (group 1); those exposed after 34 weeks because of anticipated late preterm birth (group 2); and - included in the latter - a subgroup of neonates exposed within 7 days of their actual delivery (group 2a). METHODS Retrospective analysis of the association between exposure and neonatal outcomes using multivariate regression to adjust for confounders. MAIN OUTCOME MEASURES Severe neonatal hypoglycaemia requiring admission to NNU; and need for ventilatory support. RESULTS Amongst 20102 eligible pregnancies, 143 women received corticosteroids before 34 weeks; and 187 after 34 weeks, of which 106 were within 7 days of delivery. Severe hypoglycaemia occurred in 227 neonates. Univariate predictors of hypoglycaemia were maternal BMI, nulliparity, hypertension, diabetes, gestation at birth, birthweight<10 centile and corticosteroid exposure. Following adjustment for covariates, corticosteroid exposure was independently associated with hypoglycaemia in all exposed groups: group 1 adjusted odds ratio (aOR) 3.26 (1.38-7.73); group 2 aOR 4.56 (2.47-8.42); and group 2a aOR 5.70 (2.49-13.03). Ventilatory support was not significantly different in any of the exposed groups. CONCLUSION There is increased risk of hypoglycaemia in neonates exposed to antenatal corticosteroids who are born at term. The risk of hypoglycaemia is higher with decreasing corticosteroid-to-birth interval.

INTRODUCTION

The antenatal administration of high dose corticosteroids for neonates born before 34 weeks is a key priority in maternity and neonatal practice [1-4]. Clear benefits in perinatal death and serious morbidity are reported [2].

Most exposed neonates, however, are born after 34 weeks; many at term[5], as the prediction of preterm labour is so imprecise[6]. Further, the upper gestation at which antenatal corticosteroids (ACS) are commonly given has increased. Several guidelines [1-4] and trials recommend ACS after 34 weeks[7-9], and even prior to caesarean section at early term gestation [10-12] due to the latter's association with neonatal respiratory complications [13].

These policies are controversial and not universal [4]. As birth at later gestation is more common and the consequences of prematurity less severe, any capacity for corticosteroid-related harm is correspondingly greater. ACS appear to increase the risk of neonatal hypoglycaemia [8, 14]. Where severe, this is a common cause of term neonatal unit admission [15] and has been associated with long term neurological deficit [16]. As most

corticosteroid trials focus on participant outcomes before term[8] or have not assessed hypoglycaemia[10, 11], good data in term neonates is lacking.

The aim of this study was to assess the association between antenatal corticosteroid administration and severe hypoglycaemia in neonates born at term. The analysis addresses two groups: 1) those exposed before 34 weeks because of a perceived risk of severe preterm birth but subsequently deliver at term; and 2) those exposed after 34 weeks because of anticipated late preterm or early term birth.

METHODS

This is an observational cohort study of singleton term ([?] 37 weeks) neonates born in a single tertiary centre between October 2016 and September 2019. STROBE guidelines were followed. Exclusion criteria were diagnosis of neonatal sepsis [17], multiple pregnancies, those with uncertain dates, and those complicated by major structural fetal abnormalities, aneuploidy, or genetic syndromes.

Outcome measures were 1) severe neonatal hypoglycaemia, defined as capillary blood glucose $<$ 2.0 mmol/l in the first 24 hours of life and requiring admission to NNU and 2) the need for mechanical ventilation or CPAP, (selected due to inconsistency in diagnosis of respiratory distress syndrome (RDS)). Where measured, the lowest blood glucose in the first 24 hours was also recorded.

Blood glucose level was measured in neonates considered at risk (BAPM) using an Abbott 'i-STAT handheld' glucometer 2-4 hours after birth, (usually before the second feed) and immediately if there were clinical signs suggestive of hypoglycaemia (lethargy, abnormal feeding behaviour, high pitched cry, altered level of consciousness, hypotonia, seizures, hypothermia (<36.5°C), apnoea). Criteria for admission to the Neonatal Unit (NNU) due to neonatal hypoglycaemia were single glucose measurement $<$ 1 mmol/l; two or more consecutive measurements between 1.0-1.9 mmol/l despite ongoing feeding support; or clinical signs consistent with hypoglycaemia.

One complete corticosteroid course of two doses Betamethasone 12 mg 24 hours apart was administered where the risk of preterm birth ($< 34^{+0}$ weeks) in the following 7 days was perceived to be high. Betamethasone was also used at the discretion of the clinician from 34^{+0} weeks, prior to planned elective late preterm or early term birth. If a course of betamethasone was previously administered for any indication, a second course was not given. Breastfeeding was supported within the first hour and for those declining, formula feed 10-15ml/kg was offered, with 3-hrly subsequent feeds.

Pregnancies were dated using crown-rump length (CRL) between 9^{+0} and 13^{+6} weeks. Birthweight (BW) was converted into centiles according to Intergrowth-21st standards[18]: small for gestational age (SGA) was defined as $< 10^{\text{th}}$ centile. Gestational diabetes and hypertensive disorders were defined according to NICE criteria[19, 20].

Prospectively collected data were merged from electronic maternity record (Cerner Millennium) and neonatal records (Badgernet, Clevermed, Edinburgh, UK). Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) v26.0 (IBM Inc., Chicago, IL, USA).

The study cohort was divided into three groups according to corticosteroid exposure: the non-exposed (comparison) group; the exposed group 1 where ACS were given before 34^{+0} weeks; and the exposed group 2 where ACS were given at or after 34^{+0} weeks. A subset of the latter group, where ACS were administered within 7 days before planned caesarean birth was further analysed (exposed group 2a).

As neonates born from diabetic mothers represent the group with the highest risk of developing neonatal hypoglycaemia, a secondary subgroup analysis was carried out to assess relationship between ACS exposure and neonatal outcomes in pregnancies affected by pre-existing or gestational diabetes.

Continuous variables were presented as median and interquartile range (IQR), while categorical variables were presented as absolute numbers and percentages. Demographic and pregnancy variables were calculated for each group of neonates. Demographic characteristics, pregnancy characteristics and corticosteroid exposure, including timing, were then compared between hypoglycaemic and normoglycaemic neonates. Group

comparisons of variables were performed with Mann–Whitney U test, χ^2 test or Fisher's exact tests where appropriate. Differences were considered significant when p value was <0.05.

The association between ACS exposure and neonatal outcomes was assessed for each group. Demographic and pregnancy characteristics significantly associated with neonatal outcomes on univariate analysis were then included into a multivariate backward-stepwise regression model to adjust for potential confounders. Adjusted odds ratios (aOR) and 95% confidential intervals (CI) were calculated.

Finally, among neonates exposed to ACS who had a glucose measured within 24 hours of birth, the correlation between time interval between corticosteroid exposure and birth, and minimum neonatal glucose value, was assessed using scatter plots. Pearson's correlation was performed to assess the relationship between variables.

NHS Health Research Authority ethical approval for this analysis was granted on 27/07/2017 (IRAS project ID 222260; REC reference 17/SC/0374).

RESULTS

Of 22,678 singleton births between 1st October 2016 and 1st September 2019, 2,576 pregnancies were excluded: 674 (2.97 %) for suspected congenital abnormalities and 1,902 (8.38 %) because of birth before 37^{+0} weeks (Fig 1). Of 20,102 eligible pregnancies, (Fig 1) 330 women (1.6%) received antenatal corticosteroids: 143 (47.6%) before 34^{+0}weeks; 187 (56.6%) at or after 34^{+0} weeks, of which 106 (56.7%) were within 7 days of planned caesarean delivery; 19,772 (98.4%) women received no antenatal corticosteroids.

The characteristics of the study population according to groups are shown in Table 1. Severe hypoglycaemia occurred in 227 (1.13%) neonates, with a median glucose value of 1.4 mmol/l (IQR: 0.50 mmol/l). Factors associated with severe hypoglycaemia (Table 2) on univariate analysis were higher mean BMI, nulliparity, hypertension, pre-existing and gestational diabetes, earlier gestation at birth, ACS exposure and birthweight below the 10^{th} centile.

The association between ACS exposure and severe hypoglycaemia in term neonates is shown in Table 3 for all groups. After adjustment for covariates, ACS exposure was associated a higher incidence of severe hypoglycaemia in all exposed groups; whereas the respiratory outcomes (ventilation or CPAP) were not significantly different. The adjusted odds ratios for severe neonatal hypoglycaemia were highest when ACS were administered in later gestation and nearest to delivery.

In pregnancies affected by pre-existing or gestational diabetes, the risk of severe hypoglycaemia was significantly increased in neonates exposed to ACS at or after 34 weeks (Table 4). No conclusion can be drawn for the 13 neonates of diabetic pregnancies exposed to ACS before 34 weeks as none were severely hypoglycaemic.

There was a significant positive correlation between the corticosteroid-to-birth interval and neonatal glucose in the first 24 hours of life ($r = 0.592$, $p < 0.001$) (Fig 2). Lower glucose values were recorded in neonates exposed to ACS closer to birth.

DISCUSSION

Main Findings

This analysis demonstrates the increased risk of hypoglycaemia in neonates exposed to antenatal corticosteroids but born at term. This applies in those exposed remote from birth because of a perceived risk of preterm birth; it also applies in those exposed prior to planned early term caesarean section. The risk is particularly high in pregnancies affected by diabetes. We also suggest an increasing risk of hypoglycaemia with decreasing corticosteroid-to-birth interval. After adjustment for covariates, no association with the use of ventilation or CPAP was found.

Interpretation

Neonatal hypoglycaemia, though common, has been independently associated with severe and long term adverse outcomes [16, 21]. Recent data has linked ACS exposure to an increased risk of 'any mental and

behavioural disorder' (Hazard ratio 1.47; 95%CI, 1.36-1.69) in term born neonates [5]. Despite this, hypoglycaemia has not even been assessed in some RCTs investigating the use of ACS[10, 11]. A common mechanism is plausible.

Corticosteroid exposure remote from term

In neonates exposed to ACS before 34 weeks, remote from birth, our findings build on a recent cohort study of pregnancies 'diagnosed as having threatened preterm labour at some point' who nevertheless delivered from 37^{+0} weeks [22]. In this, the 27.4% of pregnancies that received ACS were compared to those who did not. The mean gestational age at ACS administration was 32.2 weeks (SD 3.3). The incidence of treated hypoglycaemia was more than twice as high in exposed neonates, although this relationship was not examined using adjustment for covariates. Our adjustment suggests this is causal.

Similarly, Raikkonen et al [5] demonstrated that exposure to maternal ACS was significantly associated with mental and behavioural disorders in children, especially when born at term (HR 1.47 (95% CI 1.36 – 1.69)). In this cohort the vast majority of term pregnancies received ACS before 34^{+0} weeks.

The overall benefit of ACS in preterm neonates is unequivocal[2] but is greatest in the most preterm neonates[23]. Whilst developmental delay is reduced in those born under 34 weeks [24], no overall effect on neurodevelopment delay has been detected in RCTs of antenatal corticosteroids in pregnancies at risk of (as opposed to having a) preterm birth [2].

Given their effect on mortality, any potential disadvantage of ACS will be outweighed by the benefits where very preterm birth occurs. Therefore public health initiatives appropriately encourage corticosteroid administration. However if more neonates are exposed to corticosteroids, the proportion that go to term will increase, and any adverse effects will then become more common. The challenge is both better sensitivity and better specificity in predicting preterm birth: identification of those at most risk is improved using point of care tests, but even these have a low specificity [25].

Corticosteroid exposure after 34 weeks and prior to planned caesarean birth

Our findings concur with a large RCT of pregnancies from 34^{+0} weeks at risk of late preterm birth[8]. The relative risk of any hypoglycaemia in the corticosteroids (2 doses of 12mg of betamethasone) arm was 1.60 (95% 1.37–1.87). With a 15% incidence in the placebo arm, the definition included much less severe hypoglycaemia than in our analysis. Importantly, 84% of neonates were born before 37^{+0}weeks, so the findings are less relevant than for our term cohort. Further, in the trials assessing corticosteroids specifically prior to planned early term caesarean birth [10-12], hypoglycaemia has not been recorded. Our data importantly addresses this specific group and highlights the risk of severe hypoglycaemia in these term neonates. A particular issue is pregnancies complicated by diabetes, on which existing literature is limited[26-29]. In the UK, recommendations state diabetes should not be a 'contraindication to antenatal corticosteroids for fetal lung maturation' [3]. Our numbers preclude the assessment of effects of ACS administration before 34 weeks in infants born at term. However, we demonstrated that infants exposed to ACS at or after 34 weeks had a higher incidence of severe hypoglycaemia compared to those not exposed (31% vs 3.8%, aOR: 5.76, 95% CI 2.28-14.52). Whilst respiratory benefits are likely to remain, this risk should be considered alongside that of poorer maternal glucose control.

The relationship between SGA and ACS needs to be addressed. McKinzie et al [22] found a higher risk of SGA among term pregnancies who had received ACS before 34^{+0} weeks; we did not (Table 1). We postulate that ACS may, and this may vary in different units, be given more in pregnancies where SGA is suspected and so the relationship is not causal. This is supported by our finding of increased SGA in pregnancies exposed after 34 weeks.

The positive correlation between corticosteroid-to-birth interval and neonatal glucose level, albeit as a univariate analysis, pictorially demonstrates the increased risk in those who benefit least. It may also shed light on the mechanism. Temporary maternal hyperglycaemia frequently follows corticosteroid administration and

this could cause fetal hyperinsulinemia, but this mechanism has not been proven[30]. That hypoglycaemia is more common even many weeks later suggests that longer term metabolic changes are induced.

Strengths and Limitations

Neonatal hypoglycaemia is variously defined, is variably tolerated by neonates and universal screening is unusual [31-34]. In our cohort neonatal glucose measurement was not universal but neonatal testing was performed according to BAPM Guidelines; maternal corticosteroids administration was not a criterion [34]. For this reason we also chose the stricter outcome of 'severe hypoglycaemia' and defined it to include a requirement for NNU admission. This is reflected in our 1.3% overall incidence of severe hypoglycaemia compared to the 4.1% incidence of 'treated hypoglycaemia' in a recent analysis [22]. It is also possible that the administration of ACS, particularly after 34 weeks, could reflect other risk factors for hypoglycaemia. This is addressed in the multivariate logistic regression, but residual confounding cannot be ruled out. Indeed, this could account for our finding of no reduction in severe respiratory morbidity. We were unable to adjust for confounders when assessing the relationship between time and interval and neonatal glucose level. A further limitation is the largely white ethnicity. Despite the large numbers, the number of term births exposed to ACS was relatively small.

CONCLUSION

Antenatal corticosteroids exposure is associated with an increased risk of severe hypoglycaemia in term neonates, particularly where ACS are given prior to planned caesarean birth. An association also remains in neonates exposed much earlier in the pregnancy, but hypoglycaemia becomes less common with increasing time interval to birth. Better identification of pregnancies where preterm birth will occur within 7 days is required. Nearer term, neonatal hypoglycaemia might cause more long term harm than the respiratory morbidity that corticosteroids reduce and better long term data is required before ACS usage after 34 weeks is universally offered.

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- Cavallaro A: conception, planning, data collection, data analysis and writing up of the article

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Table 1 Pregnancy characteristics according to antenatal corticosteroid exposure

	No ACS exposure	**Group 1: ACS < 3**
	n = 19772	**n = 143**
Maternal age	31.09 (5.38)	30.54 (5.68)
Body mass index	25.61 (5.57)	25.17 (5.77)
Nulliparity	8818 (44.60)	47 (32.90)
Previous preterm delivery	740 (3.74)	13 (9.10)
Smoking	1918 (9.70)	21 (14.68)

	No ACS exposure	**Group 1: ACS < 3**
Ethnicity Caucasian Afro-Caribbean Asian Mixed	17889 (91.27) 308 (1.56) 1136 (5.75) 280 (1.42)	131 (92.26) 3 (2.11) 6
Hypertensive disorders of pregnancy	527 (2.70)	4 (2.80)
Essential hypertension	574 (2.90)	7 (4.90)
Diabetes type 1 or type 2	77 (0.40)	1 (0.70)
Gestational diabetes	1146 (5.80)	13 (9.10)
Gestational age at corticosteroid exposure (days)	-	212.54 (19.53)
Corticosteroid-to-birth interval (days)	-	59.52 (22.21)
Gestational age at delivery (days)	280.36 (8.37)	272.06 (9.76)
Birthweight centile	62.30 (27.83)	54.16 (26.54)
Birthweight $<10^{th}$ centile	847 (4.28)	9 (6.29)
Planned caesarean delivery	1865 (9.43)	27 (18.88)

ACS = antenatal corticosteroid exposure; continuous variables are expressed as median (interquartile range) and categorical variables are expressed as n (%).

Table 2 Pregnancy characteristics in neonates with or without severe hypoglycaemia

	Severe hypoglycaemia n = 227	**No severe hypoglycaemia n = 19875**	**p-value**
Maternal age	31.54 (5.38)	31.10 (5.39)	0.22
Body mass index	29.49 (7.10)	25.58 (5.55)	<0.001
Nulliparity	126 (55.5)	8786 (44.2)	<0.001
Previous preterm delivery	9 (4.0)	770 (3.9)	0.94
Smoking	18 (7.9)	1770 (8.9)	0.60
Ethnicity Caucasian Others	205 (90.30) 22 (9.70)	18,004 (90.58) 1,868 (9.42)	0.99
Hypertensive disorders of pregnancy	21 (9.3)	532 (2.7)	<0.001
Essential hypertension	13 (5.7)	581 (2.9)	0.01
Diabetes type 1 or type 2	21 (9.3)	72 (0.4)	<0.001
Gestational diabetes	39 (17.2)	1146 (5.8)	<0.001
ACS exposure	23 (10.1)	307 (1.82)	<0.001
Gestational age at ACS administration (days)	243.74 (24.07)	237.09 (26.33)	<0.001
Corticosteroid-to-birth interval (days)	20.35 (27.52)	31.30 (30.63)	<0.001
Gestational age at delivery (days)	276.30 (11.25)	280.21 (8.48)	<0.001
Birthweight centile	63.15 (34.79)	62.14 (27.81)	0.59
Birthweight $<10^{th}$ centile	28 (12.33)	858 (4.32)	<0.001
Planned caesarean delivery	30 (13.2)	1989 (10.0)	0.11

ACS = antenatal corticosteroid exposure; continuous variables are expressed as median (interquartile range)

and categorical variables are expressed as n (%).

Table 3 Relationship between antenatal corticosteroid exposure and neonatal outcomes following adjustment for confounders

No ACS exposure

Group 1:

ACS < 34 weeks

Group 1:

ACS < 34 weeks

Group 1:

ACS < 34 weeks

Group 2:

ACS [?] 34 weeks

Group 2:

ACS [?] 34 weeks

Group 2:

ACS [?] 34 weeks

Group 2a: ACS within 7 days of planned delivery

Group 2a: ACS within 7 days of planned delivery

Group 2a: ACS within 7 days of planned delivery

No ACS exposure n = 19772

ACS before 34 weeks n = 143

Odds Ratio (95% CI)

Adjusted Odds Ratio* (95% CI)

ACS after 34 weeks n = 187

Odds Ratio (95% CI)

Adjusted Odds Ratio* (95% CI)

ACS [?] 7 days before delivery n = 106

Odds Ratio (95% CI)

Adjusted Odds Ratio* (95% CI)

Ventilation or CPAP

499 (2.52)

8 (5.59)

2.29 (1.12-4.70)

2.02 (0.97-4.21)

12 (6.40)

2.65 (1.47-4.78)

1.52 (0.81-2.85)

7 (6.60)

2.69 (1.24-5.82)

1.58 (0.70-3.61)

Hypoglycaemia

204 (1.03)

6 (4.20)

4.20 (1.83-9.62)

3.26 (1.38-7.73)

17 (9.10)

9.59 (5.72-16.09)

4.56 (2.47-8.42)

10 (9.43)

9.49 (4.88-18.45)

5.70 (2.49-13.03)

*ACS = antenatal corticosteroid exposure; CPAP = continuous positive airway pressure; * BMI, nulliparity, hypertensive disorders in pregnancy, pre-existing diabetes, gestational diabetes, gestational age at delivery and birthweight centile were adjusted for as confounders; planned caesarean delivery was a confounder for groups 1 and 2 only.*

Table 4 Relationship between antenatal corticosteroid exposure and neonatal outcomes in pregnancies affected by diabetes following adjustment for confounders

No ACS exposure n = 1223

Group 1:

ACS < 34 weeks

Group 2:

ACS [?] 34 weeks

Group 2:

ACS [?] 34 weeks

Group 2:

ACS [?] 34 weeks

ACS before 34 weeks n = 13

ACS after 34 weeks n = 42

Odds Ratio (95% CI)

Adjusted Odds Ratio* (95% CI)

Ventilation or CPAP

58 (4.7%)

0

6 (14.3%)

3.35 (1.36 – 8.26)

0.70 (0.24 – 2.00)

Hypoglycaemia

47 (3.8%)

0

13 (31%)

11.22 (5.48 – 22.96)

5.76 (2.28 – 14.52)

*ACS = antenatal corticosteroid exposure; CPAP = continuous positive airway pressure; * BMI, nulliparity, hypertensive disorders in pregnancy, pre-existing diabetes, gestational diabetes, gestational age at delivery, birthweight centile and planned caesarean delivery were adjusted for as confounders.*

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