A retrospective cohort study on effects of antenatal steroids on respiratory morbidity for term elective caesarean sections in South Asian women [version 1; peer review: awaiting peer review]

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**Abstract**

**Background**

Respiratory distress (RD) is higher among newborns born by caesarean section (CS) compared to vaginal delivery. Royal College of Obstetricians and Gynaecologists recommend steroid administration for CS prior to 39 weeks. Effectiveness of steroids for neonatal RD at term is inconclusive. The racial differences are yet to be studied.

**Methods**

A single center retrospective cohort study was conducted in Colombo, Sri Lanka from December 2016 to February 2019. All mothers delivered by CS between 37+0 and 38+6 weeks were included. Mothers with severe maternal hypertension, fetal rhesus sensitization, intrauterine infection, multiple pregnancies and who received steroids at a prior gestation were excluded. Cohort was subdivided according to administration of intramuscular dexamethasone prior to CS. Primary outcomes measured were RD, admissions to neonatal intensive care unit (NICU) and special care baby unit (SCBU). Neonatal infections and maternal duration of hospital stay were recorded as secondary outcome measures.

**Results**

560 patients were included. 23.2\% of patients received antenatal corticosteroids. Incidence of RD, NICU admissions and SCBU admissions in the study cohort was 10\%, 0.9\%, and 2.7\% respectively. Relative risk for developing RD in the steroid group compared to non-steroid group was 2.67 (95CI 1.64-4.35). 4.6\% of the steroid group and 3.3\% of the non-steroid group needed to be admitted to the NICU/SCBU (p=0.464). A significantly higher number of babies in the steroid group needed IV antibiotics. The average number of days the
mothers were admitted to the hospital was 2.45 days (SD+/- 1.424) for steroid group and 1.4 days (SD+/- 0.856) for the non-steroid group (p < 0.001).

**Conclusions**
There is a significant increase in the respiratory morbidity in the dexamethasone administered south Asian mothers at term prior to CS. However, this effect has no clinical significance since the admissions to NICU and SCBU were not significantly different.

**Keywords**
Dexamethasone, term, elective caesarean, respiratory distress, RDS
Introduction
Gestational age is the most important risk factor for respiratory distress (RD) in the newborn. As gestation increases, neonatal respiratory morbidity decreases. The incidence of respiratory distress (RD) exponentially decreases from 12.9/1000 to 1.1/1000 for vaginal deliveries prior to 39 weeks compared to vaginal deliveries from 39+0 weeks onwards (Zanardo et al. 2004). It has also been shown that caesarean section (CS) is an independent risk factor for respiratory morbidity with an odds ratio (OR) of 2.3 (95% confidence interval (CI) 2.1–2.6) compared to vaginal delivery (Gersten et al. 2005). Therefore, American College of Obstetricians and Gynecologists (Guidelines for Perinatal Care, 5th edition, p 148) and National Institute for Health and Care Excellence recommends avoiding all planned CS, if possible, before 39 weeks of gestation. However, this is not practical in many instances. 30-80% of planned CS are carried out prior to 39 weeks of gestation due to various reasons such as maternal medical problems, fetal indications and convenience, across the world (Tita et al. 2011).

RD is defined as signs of breathing difficulties in the neonate. In term RD is reported in up to 7% of newborns (Edwards, Kotecha, and Kotecha 2013). RD leads to admission to a special care baby unit (SCBU) and neonatal intensive care unit (NICU), separation from the mother, and in turn secondary problems with ICU care as well as long term complications like asthma with a very high cost of overall management (Jain and Dudell 2006). Transient tachypnoea of the newborn (TTN), respiratory distress syndrome (RDS), congenital pneumonia and meconium aspirations syndrome (MAS) are some of the common causes that can lead to respiratory distress at term.

RDS is primarily a condition that occurs due to surfactant deficiency in the preterm. Antenatal steroids had been a revolutionary treatment for preterm birth (before 34+0 weeks) as this reduces respiratory problems, intraventricular haemorrhage (IVH) and necrotizing enterocolitis (NEC) and improves the overall neonatal health and decreases mortality rates (McGoldrick et al. 2020).

In the term infant respiratory distress appears to have different pathophysiology based on retention of physiological fluids in the lungs (Hopkins 2015). Traditionally it was thought that vaginal delivery squeezes fluid out of the lungs during delivery. Current evidence suggests that lung epithelial sodium channels (ENaC) play a crucial role in the alveolar fluid drainage (Jain and Dudell 2006). Catecholamine increases the activity of ENaCs, which may explain the reduction in respiratory complications in labour (Brown et al. 1983). ENaCs are also directly regulated by glucocorticoids (Venkatesh and Katzberg 1997). After exposure of 4 to 24 hours glucocorticoids increase the number of ENaCs and their function through genomic effects. Additionally, glucocorticoids increase the responsiveness of ENaCs to catecholamines and thyroid hormones.

Since the Antenatal Steroids for Term Caesarean Section (ASTECS) trial demonstrating the protective effect of betamethasone on respiratory morbidity in term newborns (P. Stutchfield, Whitaker, and Russell 2005), Royal College of Obstetricians and Gynaecologist (RCOG) recommend corticosteroids be administered for all planned caesareans before 38+6 weeks of gestation.

Steroid administration is a relatively safe procedure. However, steroids can lead to transient suppression of the maternal-fetal production of Adrenocorticotropic hormone (ACTH), Dehydroepiandrosterone sulfate (DHEA-S) and circulating estradiol (Ogueh et al., 1999). Fetal problems such as impaired growth, transient hypoglycemia, childhood poor school performance, increased vulnerability to stress related diseases and metabolic illness in later life have been reported in some studies (Haviv, Said, and Mol 2019). Maternal hyperglycemia, pain associated with intramuscular injections and additional hospital visits or increased stay duration are some of the other recognized complications (Kalra, Kalra and Gupta, 2014).

Administering steroids is a common procedure where clinicians are challenged frequently. Sotiriadis et al. concludes that more quality studies are needed due to a bias of the current studies on steroid for term CS. Also, the Cochrane review questioned the clinical significance of steroid administration given the low event rates of significant respiratory morbidity (Sotiriadis et al. 2018). There is conflicting evidence for using steroids at term for preventing respiratory morbidity. Haviv et al. in their review do not recommend steroid administration for early term deliveries given the potential risk weighing against the benefits (Haviv, Said, and Mol 2019), and the American, Canadian, Australian and New Zealand societies do not recommend steroids at term. There can be racial differences in effect of steroids on neonatal respiratory complications at term with Asians having relatively less RD compared to Caucasians (Nada et al., 2016). These effects in south Asian pregnancies are yet to be studied.

Methods
A retrospective cohort study was conducted to look for the effects of corticosteroid administration for respiratory morbidity in Sri Lankan neonates delivered by elective caesarean section (ELCS) between 37 and 38+6 weeks.
All the CS prior to February 2019, in University Obstetrics and Gynaecology Unit, Colombo South Teaching Hospital (Prof-unit CSTH) were assessed for eligibility. Prof-unit CSTH was chosen for the study for several reasons. This is a teaching unit which practices RCOG guidance. There are five practicing consultants with differing opinions on term steroid administration and therefore it was easier to recruit groups with and without corticosteroid administration. The neonatal care is provided by a single unit and therefore diagnosis and admission criteria were similar for all the neonates.

Mothers undergoing ELCS between 37 and 38+6 weeks of gestation were included for the study. Pregnancies complicated with severe maternal hypertension, severe fetal rhesus sensitization, and evidence of intrauterine infection (maternal temperature, cardiotocographic finding of tachycardia or fetal distress, meconium-stained liquor at delivery), those who received steroids due to other indications up to 36 weeks of gestation and multiple pregnancies and any intrapartum CS were excluded. On average Prof-unit CSTH has about 200 deliveries a month. The CS rate of the unit is about 30% with nearly half being ELCS. This accounts for about 30 ELCS a month. Due to strict inclusion and exclusion criteria, we could recruit about 20 patients a month for the study. The neonatal policies of the unit were changed in late 2016. Therefore, recruiting was done only up to December 2016.

The data from bed head tickets, which were traced from the archives in the record room, were extracted by a research assistant on to a data collection sheet. Data collection was carried out from April to September 2019. One research assistant who was not involved with the research protocol development or the management of the patients was used to eliminate observer bias. Maternal demographic data were collected including age, parity and previous and current medical problems, gestational age at CS, surgical details, and postoperative complications. Maternal corticosteroid administration was recorded. All neonatal information including birth weight, gender, and Apgar scores were recorded. Primary outcomes measured were RD and admissions to NICU and SCBU. The data key for the variables is shown in Table 1.

Neonatal records were used to arrive at the diagnosis of RD. RD in the newborn was diagnosed in the presence of at least one of the following criteria: respiratory rate of 60/min or more, increased respiratory effort (subcostal recessions, xiphoid retraction, suprasternal in-drawing), nasal flaring, expiratory grunting and cyanosis (Flidel-Rimon and Shinwell, 2005). Neonatal infections, medical interventions, and duration of hospital stay were recorded as secondary outcome measures.

The cohort was analyzed in two groups. Group 1 consisted of mothers who received IM dexamethasone 12mg, two doses 12 hours apart within a week from delivery up to 24 hours prior to the delivery. Group 2 consisted of mothers who did not receive corticosteroids in the antenatal period. Analysis was done using IBM SPSS version 25 in February 2021. Relative risks for developing complications were analyzed and Pearson’s chi-square test was used to compare the independent and dependent categorical variables. A sensitivity analysis using binary logistic regression model was used to look for the confounders. There were no missing data for exposure or the outcomes since the records were obtained from bead head tickets.

**Ethics and consent**

Ethical approval was granted by the University of Sri Jayewardenepura ethical review committee on 30/05/2017 (application number 35/17). The ethical review committee concluded that since the data extracted are retrospective without any patient identification details it was not necessary to obtain written consent from the patients.

**Table 1. Data key.**

<table>
<thead>
<tr>
<th>Data item(s)</th>
<th>Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1. Sinhalese; 2. Tamil; 3. Muslim; 4. Other</td>
</tr>
<tr>
<td>7 – 10, 12</td>
<td>1. Yes; 2. No</td>
</tr>
<tr>
<td>20 – 21</td>
<td>0. No; 1. Yes</td>
</tr>
<tr>
<td>23 – 26</td>
<td>0. No; 1. Yes</td>
</tr>
</tbody>
</table>
Results
560 patients were included in the study (Piyadigama, 2022). Amongst the study cohort 130 (23.2%) patients received antenatal corticosteroids.

Average gestation age of delivery was 38 weeks for both the groups. Average birth weights of steroid and non-steroid groups were 2.951kg and 2.924kg respectively. There was no significant difference in parity, pregnancy complications and birth weights within the groups. However, there was a significant difference in the gestation age at delivery between the two groups with a slightly advanced gestation in the non-steroid group. 46.2% women in the steroid group and 40.3% of women in the non-steroid group included in the sample had delivered between 37 to 37+6 weeks. 53.8% of women of steroid group and 59.7 % of women of non-steroid group had delivered at 38-38+6 weeks (p=0.238) (Table 2).

Incidence of RD, NICU admissions and SCBU admissions in the study cohort was 10% (56), 0.9% (5), 2.7% (15) respectively. There was a significantly higher incidence of RD of 19.2% in the steroid group compared to 7.2% in non-steroid group (p<0.001). NICU and SCBU admissions were needed by 4.6% (6) in steroid group and 3.3% (14) in non-steroid group without a significant difference (p=0.464). There was a 2.67 times higher risk of respiratory morbidity in the steroid administered group compared to non-steroid group (Table 3).

A significantly higher number of babies in the steroid group needed intravenous antibiotics. On average the number of days these mothers remained in the hospital was 2.45 days (SD 1.424) for steroid group and 1.4 days (SD 0.856) for the non-steroid group. The hospital stay was significantly higher in the steroid group (p < 0.001) (Table 3).

Amongst the neonates who developed primary outcomes (respiratory complications), the mean birth weight was 3.104kg (SD ±0.463) in the steroid group and 2.833kg (SD ±0.574) in the non-steroid group. The gestational age at delivery was 265.2 (SD ±4.523) days and 264.5 (SD ±3.741) days respectively (Table 4). There was no significant difference in the birth weights and gestational age at delivery amongst the neonates with respiratory complications (Table 5).

A logistic regression was performed to ascertain the effects of steroid administration and gestational age at the delivery. The model explained 6.7% (Nagelkerke $R^2$) of the variance in respiratory distress and correctly classified 90.0% of cases. Neonates exposed to steroids were 3.03 times more likely to exhibit RD than neonates who were not exposed to steroids. Increasing gestational age at delivery was associated with a 0.93 times reduction in respiratory distress.

### Table 2. Characteristics of the two groups.

<table>
<thead>
<tr>
<th>Characteristic of the study sample</th>
<th>Steroid group</th>
<th>Non steroid group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>32.26 (SD ±4.437)</td>
<td>32.28 (SD ±4.528)</td>
<td>0.989</td>
</tr>
<tr>
<td>Parity</td>
<td>1.97 (SD ±0.896)</td>
<td>1.99 (SD ±0.976)</td>
<td>0.121</td>
</tr>
<tr>
<td>Mean gestational age at delivery (days)</td>
<td>265.72 (SD ±4.141)</td>
<td>265.87 (SD ±3.529)</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean birth weight (kg)</td>
<td>2.951 (SD ±0.463)</td>
<td>2.924 (SD ±0.415)</td>
<td>0.055</td>
</tr>
<tr>
<td>GDM mothers (number)</td>
<td>16 (12.4%)</td>
<td>77 (16.9%)</td>
<td>0.138</td>
</tr>
<tr>
<td>PIH mothers (number)</td>
<td>9 (7%)</td>
<td>47 (11%)</td>
<td>0.187</td>
</tr>
<tr>
<td>FGR pregnancies (number)</td>
<td>2 (1.5%)</td>
<td>22 (5.1%)</td>
<td>0.077</td>
</tr>
</tbody>
</table>

SD – Standard deviation, GDM – Gestational diabetes mellitus, PIH – Pregnancy induced hypertension, FGR – Fetal growth restriction.

### Table 3. Respiratory morbidity according to groups (Number, proportion, p value and RR).

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Steroid</th>
<th>Non-steroid</th>
<th>P value</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>RD</td>
<td>25 (19.2%)</td>
<td>31 (7.2%)</td>
<td>&lt;0.001</td>
<td>2.67 (1.64-4.35)</td>
</tr>
<tr>
<td>NICU admissions</td>
<td>2 (1.6%)</td>
<td>3 (0.7%)</td>
<td>0.372</td>
<td>2.21 (0.37-13.05)</td>
</tr>
<tr>
<td>SCBU admission</td>
<td>4 (3.1%)</td>
<td>11 (2.6%)</td>
<td>0.748</td>
<td>1.20 (0.39-3.71)</td>
</tr>
<tr>
<td>Administration of IV antibiotics</td>
<td>94 (72.3%)</td>
<td>67 (15.6%)</td>
<td>&lt;0.001</td>
<td>4.64 (3.64-5.93)</td>
</tr>
</tbody>
</table>

When considering the indications for admission to NICU and SCBU the RDS and TTN were recorded as the primary indications for admission in 2 (33.3%) neonates in the steroid group and 10 (71.4%) neonates in the non-steroid group. There was no significant difference in respiratory complications being the primary indication for admission amongst the two groups (p=0.112) (Table 5).

**Discussion**

Our findings conclude that there is no protective benefit of maternal dexamethasone administration at term prior to CS. Some studies have demonstrated protective effects of steroids at term. The Antenatal Steroids for Term Caesarean Section (ASTECS) trial was one of the first studies to show beneficial effects of steroids. The relative risk of admission to special care baby unit with respiratory distress was 0.46 (95%CI 0.23-0.93) in favor of the steroid administration (P. Stutchfield, Whitaker, and Russell 2005). The Cochrane review in 2018, looking at four large randomized controlled trials was also able to demonstrate the beneficial effects of corticosteroids at term by reducing respiratory distress syndrome. However, it was concluded that the evidence of these studies are of low quality (Sotiriadis et al. 2018).

Several studies have failed to demonstrate protective effects of steroids on respiratory morbidity of newborns delivered by CS at term (de la Huerga López et al. 2019; Nooh et al. 2018). An observational study done in Oman looking at RDS in neonates delivered at term by ELCS which included 650 patients showed 2.5% RDS prevalence in the overall study sample. There was no significant difference in the respiratory morbidity with and without dexamethasone administration in this study (3.7% vs. 2.1%; p = 0.340) (Al Riyami et al. 2020).

The use of steroid at term and the effect on different ethnicities is not yet sufficiently studied. The ASTECS study identifies race as a contributory factor for steroid effects. However, the study was not powered enough to analyze these effects (P. Stutchfield, Whitaker, and Russell 2005). Although western studies have shown a beneficial effect of term steroid administration, studies with Arabic and Egyptian pregnant women have failed to demonstrate this (Al Riyami et al. 2020; Nooh et al. 2018). Our study, looking at South Asians, also could not show beneficial effects of steroids.

A recent Sri Lankan study in a tertiary care hospital reported the RD prevalence as 8.2% for all newborns delivered at term (Gamhewage et al. 2020). International literature also reports similar incidences (Edwards, Kotecha, and Kotecha 2013). In our study the prevalence of overall respiratory morbidity was 10%, in keeping with these findings.

Our study showed a significantly higher rate of respiratory morbidity in the steroid administered group which has not been reported in any other studies. Although the reported respiratory morbidity was higher in the steroid group, there was no significant difference in admission to SCBU or NICU. Asian mothers are more prone for glycemic problems in...
pregnancy (Chen et al. 2019). Dexamethasone can lead to transient changes in blood sugar levels. In turn this can affect the newborn which may not have enough time for equilibrate its blood sugar levels since delivery occurs within 24 to 48 hours of steroids. Neonatal hypoglycemia is a known complication associated with steroids (Thevathasan and Said 2020). This may explain the transient increase in RD in the steroid group without needing further interventions. In fact, the ASTECS study showed higher rates of admissions to special care unit without respiratory complications in the betamethasone administered group. However, the reasons for these admissions and neonatal glycemic levels were not reported.

Gamhewage et al. looked at different causes of RD in a Sri Lankan tertiary care hospital and found out TTN, congenital pneumonia, MAS and neonatal sepsis without pneumonia were the major contributors in descending order (Gamhewage et al. 2020). Therefore, neonatal infections seem to play a larger role than RDS for RD at term in the Sri Lankan setup. A significant proportion of neonates in the steroid administered group in our study receiving IV antibiotics may reflect this phenomenon. Increasing the hospital stay can have various adverse effects on surgical patients, especially increasing their risk of acquired hospital infections. The steroid administered group had a longer hospital stay needing at least 24 to 48 hours prior to the planned surgery. The mechanism of congenital pneumonia and early neonatal infections without ruptured membranes is difficult to explain. Neonatal antibiotics administration was a secondary finding of the study and we have not collected sufficient data to test if neonatal infections were the cause for higher RD in the steroid administered group.

We used IM dexamethasone 12mg, 2 doses with a 12-hour gap. Some of the studies have used IM betamethasone 12mg two doses with a 24 hour gap (P. R. Stutchfield et al. 2013) while most of the others have used IM dexamethasone 24mg with two or three divided doses within a 24 hour period (Ahmed, Sayed Ahmed, and Mohammed 2015; Nooh et al. 2018; Nada et al. 2016). Both these steroids are structurally similar fluorinated compounds. However, there are differences in structure of these and therefore effects in vitro. Because of the acetate included, betamethasone has longer half-life compared to dexamethasone (Thevathasan and Said 2020). Dexamethasone has demonstrated stronger non-genomic effects. When comparing the effects of the two medications on preterm infants betamethasone seems to have better respiratory outcomes with a larger reduction of RDS (Feldman et al. 2007) whereas dexamethasone administered had more effect on reducing IVH (Nooh et al. 2018). The effect of different formulations of steroids on term respiratory morbidity had not yet been assessed but should be considered in future research.

Our study was a retrospective analysis which helped to get a larger sample within a limited time. However due to the design there was loss of information. Observer bias also was unavoidable. There were multiple confounders leading to outcomes which we have not separately analyzed. The primary outcomes were dependent on diagnosis already made by clinicians at the time of delivery rather than looking at different clinical or radiological features individually. Therefore, different causes for RD could not be analyzed.

We recommend further evaluation of the effect of dexamethasone administration in term pregnancies of south Asian mothers prior to CS. Prospective studies or randomized control trials of high quality are needed. Also, it may be beneficial to compare the effects of dexamethasone versus betamethasone in term respiratory morbidity prevention. Looking at neonatal infections and hypoglycemia may give further insight to the subject.

Conclusions
There is a significant increase in the respiratory morbidity in the dexamethasone administered group with a RR of 2.67 (1.64-4.35). However, this is not clinically significant since the NICU and SCBU admissions are not significantly different with or without steroid administration [RR-1.42 (0.56-3.62)].

Data availability
Underlying data
Dryad: A Retrospective Cohort Study on Effects of Antenatal Steroids on Respiratory Morbidity for Term Elective Caesarean Sections in South Asian Women https://doi.org/10.5061/dryad.g79cnp5qs (Piyadigama, 2022).

This project contains the following files:

- Dexamethasone_final_data_set.sav (raw data file)

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).
Author contributions
IP, MJ, UC contributed to the concept, data collection, analysis and writing up of the manuscript.

Acknowledgments
We thank all the health staff involved in the care for the study cohort.

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Edwards MO, Kotecha SJ, Kotecha S: Newborn Infant. Gerten KA, Coonrod DV, Curtis Bay R, 2020; Term Newborns: Can We Predict the Outcome? Publisher Full Text
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