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Immediate outcomes of late preterm neonates in NICU in a group with antenatal corticosteroids exposure versus non-exposed group: A retrospective observational study

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Abstract
Objective: To evaluate the short-term outcome of neonates born late preterm and admitted to NICU receiving antenatal corticosteroids in contrast to no intervention.
Study design: This was a Retrospective observational study of neonates born between $34^{0/7}$ to $36^{6/7}$ admitted to Neonatal intensive care for prematurity. Short term neonatal outcomes of corticosteroid group were compared with the non-exposed neonates.
Results: During this 18-month study period, 174 subjects admitted to the NICU were enrolled. Among this, 72 were exposed to antenatal corticosteroids and 102 were the non-exposed group. The demographic data among the exposed and non-exposed antenatal corticosteroid groups were identical. The respiratory support was statistically significant in the exposed group for 30 subjects (41.67%) compared to non-exposed group 62 subjects (60.78%) with significant P value. The duration of the stay in NICU among the exposed group had a mean of 80.88 hours compared to non-exposed group with a mean of 114.96 hours. The statistical significance with P value was <0.05. There was no statistical significance among exposed and non-exposed groups with regards to surfactant therapy, neonatal hyperbilirubinemia and hypoglycemia. However, among the gestational age analysis with regards to respiratory support, 34 weeks LPN had significant P value in the exposed group compared to non-exposed group.
Conclusion: Short term outcomes of antenatal corticosteroid exposed group appear to reduce respiratory morbidity, less duration of stay. There is no difference with regards to Hyperbilirubinemia, Hypoglycemia and sepsis.

Keywords: NICU, antenatal corticosteroids exposure, non-exposed group

Introduction

Late Preterm Neonates (LPNs) make up approximately 70% of all preterm births, which in turn represent about 10% of total births [1]. When compared to term-born neonates (those born between 37 and 40 weeks of gestation), LPNs face a higher risk of various complications, including the necessity for resuscitation at birth, respiratory distress, Neonatal Hyperbilirubinemia (NNH), and hypoglycaemia. Given their significant numbers, LPNs place a substantial strain on the healthcare system [2]. Respiratory Distress Syndrome (RDS) and Transient Tachypnoea of Newborn (TTN) are common respiratory symptoms noticed in LPN. RDS is inversely correlated with gestational age, affecting 100% of infants born before 28 weeks' gestation, around 30% of those born between 28 and 34 weeks, and 1% to 14% of infants born after 34 weeks' gestation. The other common diagnosis for respiratory distress in LPN is Transient Tachypnoea of Newborn (TTN) [4]. TTN is a form of transitional delay due to fluid retention in lungs which normally resolves over 2 to 12 hours and sometimes may accept up to 72 hours like RDS [5]. Admission to NICU for these complications results in separation of baby from mother further leading to anxiety and feeding issues. This will lead to increased duration of stay in the NICU and rise in the care costs [6].
Antenatal Corticosteroids (ACS) has received strong endorsement for pregnancies at risk of early preterm delivery (before 34 weeks of gestation) to promote foetal lung maturation [6].

The benefits include a decrease in neonatal morbidity, such as respiratory distress syndrome, intraventricular haemorrhage, admissions to the neonatal intensive care unit (NICU), and mortality [8]. The Antenatal Late Preterm Steroids (ALPS) trial, published in 2016, showed that administering betamethasone in singleton pregnancies considered late preterm (34-36 weeks gestation) and at high risk for preterm delivery significantly lowered the incidence of neonatal respiratory complications, although it also resulted in a higher rate of neonatal hypoglycemia [9]. In 2016, the American College of Obstetricians and Gynaecologists (ACOG) and the Society for Maternal-Fetal Medicine recommended the use of Antenatal Corticosteroids (ACS) for women with a singleton pregnancy between 34 0/7 and 36 6/7 weeks who are at imminent risk of preterm birth within the next 7 days [10].

However use of ACS in LPN, indicate that children born late preterm and full term, particularly those in the full-term group who made up approximately half of the exposed population, faced significantly higher risks of adverse neurocognitive and psychological outcomes when they were exposed to a likely single course of antenatal corticosteroids, in contrast to their unexposed counterparts.[11]The objective of our study was to examine the LPN admitted to NICU with short term outcomes of the ACS exposed group to the non-exposed.

Methodology

This was a Retrospective observational cohort study conducted over a period of 18 months between May 2022 to October 2023, in a NICU set up of mother and childcare hospital in southern region of India. LPN born between $34^{0/7}$ to $36^{6/7}$ weeks and admitted to NICU for preterm care were included in the study. Pregnant women who were at risk of preterm delivery receiving ACS and those who did not for distinct reasons requiring NICU care were included.

Inclusion criteria

- Only singleton pregnancies.
- Gestational Age between $34^{0/7}$ to $36^{6/7}$ weeks requiring NICU care.
- Either Betamethasone or Dexamethasone drug used and completed the course before 14 days of delivery.

Exclusion criteria

- Major congenital or chromosomal abnormalities.
- Incomplete/ partial ACS with extended duration beyond 14 days.
- More than 1 course of ACS.
- Twins or higher multiple gestation.
- Those LPN who did not have complete demographic data.

INSTITUTIONAL Ethics Committee approved the study. Informed consent from the parents of the subjects was not taken applying the HIPAA privacy rule. Demographic data compiled for this study included the parity, maternal age, mode of conception and delivery, maternal risk factors, neonatal weight, gender, and indication for delivery. Indications for NICU admission were weight less than <1800 grams, respiratory morbidity requiring invasive or non-invasive ventilation support, suspected sepsis, persistent hypoglycemia, poor feeding, and neonates requiring observational care post resuscitation. Short term outcomes such as RDS, TTN, Hypoglycemia, Neonatal Jaundice, Sepsis, duration of stay and other adverse neonatal morbidity of the participants were collected between the ACS intervention and no intervention group and compared. Feeding concerns and APGAR scores of the participants were not compared.

The primary outcome of the study were respiratory complications before 72 hours of delivery requiring CPAP, HFNC, invasive ventilation, Surfactant therapy and duration of stay. Secondary outcomes included hypoglycemia defined as glucose levels <45mg/dl on 2 separate occasions in first 72 hours from birth. Neonatal jaundice is defined as the cut off value ≥ to American Academy of Pediatrics guidelines for phototherapy as per gestational age, risk factors and hours of life.

Statistical analysis

In both the groups, data were expressed as number of cases in percentage or mean ± standard deviation. The continuous variables of the subjects were calculated using the parametric test and for discrete variables and odds ratio, non-parametric test like chi square test was used. Sample size of the subjects was calculated considering power of 80% with β of 0.2 and α 0.05 with expected incidence in Respiratory distress in ACS of 25% and non-ACS group as 45% as per existing data and studies. The sample required was 172 using Rosner *et al* calculations. A 'P' value' of < 0.05 of the subjects was considered significant. Statistical Package for the social sciences (SPSS) version 25 was used to execute statistical analysis. Based on this, data for 18 months duration was collected for completion of the study.

Results

The hospital-based study period of 18 months was conducted between May 2022 to October 2023. A total of 458 LPN deliveries took place in our institution as shown in flow diagram 1. Of those 261 cases were shifted to NICU and remaining 197 cases were shifted to mother side. 84 cases were excluded from the study for distinct reasons not fitting into the Inclusion criteria. A total of 174 cases were considered, satisfying the inclusion criteria. Amongst the 174 cases the subjects were divided into two groups. ACS group (n=72) that received intervention and non-ACS group (n=102) that did not receive the intervention.

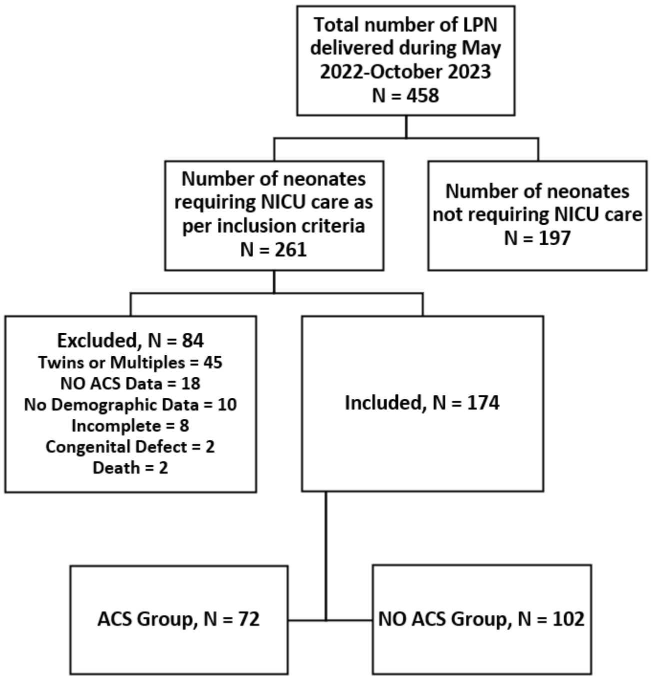

Fig 1: Diagram of subject selection.

Table 1: Demographic Characteristics

	No ACS (n=102)	ACS (N=72)	P value
Mean Maternal Age (y)	29.20±2.94	30.36±3.38	0.874
Gestational Age (weeks)	35.41±0.73	34.71±0.79	0.561
Primi Parity, n (%)	79 (77.45)	53 (73.61)	0.559
LSCS Delivery, n (%)	92 (90.20)	64 (88.89)	0.78
PIH, n (%)	10 (9.80)	7 (9.72)	0.985
GDM, n (%)	18 (17.65)	7 (9.72)	0.142
PPROM, n (%)	7 (6.86)	8 (11.11)	0.325
Mean Birth Weight (g)	2285.09±260.4	2184.1±254	0.732
Male Gender, n (%)	52 (50.98)	30 (41.66)	0.461

Data presented as numbers (percentage) or mean± standard deviation.

The basic and clinical demographic characteristics of the two groups are shown in Table 1. Both the groups were matched in terms of maternal age, parity, sex, mode of delivery and gestational age. Similarly, the clinical characteristics mean birth weight, Gestational Diabetes Mellitus, Hypertension and Preterm Premature Rupture of Membranes were compared and none of the parameters had any significant P value. Among the two groups, most significant antenatal risk factors were Gestational Diabetes Mellitus and Pregnancy induced Hypertension contributing 25% and 17% respectively. Mean gestational age among the ACS group was 35.41 weeks and non-ACS group was 34.71 weeks. Primi parity was highest among both groups. Average birth weight among the two groups were comparable.

Table 2: Neonatal outcomes following ACS administration VS. NO ACS administration

Outcome	NON-ACS (n=102)	ACS (n=72)	p Value
Respiratory Support	62(60.78%)	30 (41.66%)	**0.012***
Sepsis	7(6.86%)	5(6.94%)	0.983
NNH	45 (44.11%)	39(61.51%)	0.172
Hypoglycemia	14 (13.72%)	4 (5.52%)	0.813
Surfactant Use	9 (08.82%)	6 (08.33)	0.909
Mean NICU Stay (avg hours)	114.96	80.88	**0.017***

*Indicates p value is significant

Table 2 summarises the primary and secondary outcome of the study. The primary outcome variable, Respiratory support among the ACS group and non-ACS group had a significant p value. In the ACS group, 30/72 (41.66%) subjects required Respiratory support as compared to 62/102 (60.78%) in non-ACS group and this was statistically significant with P value being 0.012. With regards to the need for Surfactant administration, both groups did not have any statistical significance. In comparison with duration of stay in the NICU, the ACS group had mean duration of 80.88 hours and the non-ACS group had 114.96 hours with a significant P value of 0.017. In the secondary outcomes of this study, Neonatal Hyperbilirubinemia, Hypoglycaemia and Sepsis were comparable to both groups and did not have any statistical significance.

Table 3: Neonatal outcomes following exposure to ACS VS. no ACS exposure according to gestational age

Outcome		34 Weeks	35 Weeks	36 Weeks
Respiratory support	NO ACS	19/26	15/25	27/41
	ACS	16/36	9/22	4/14
	p Value	0.0248*	0.8846	0.0089*
Sepsis	NO ACS	3/26	1/25	3/41
	ACS	2/36	2/22	1/14
	p Value	0.3932	0.3048	0.9827
NNH	NO ACS	14/26	15/25	15/41
	ACS	24/36	9/22	6/14
	p Value	0.3064	0.6766	0.6766
Hypoglycaemia	NO ACS	7/26	3/25	4/41
	ACS	1/36	1/22	2/14
	p Value	0.051	0.5346	0.6387

*Indicates p value is significant

The neonatal outcomes following exposure to ACS and non-ACS with respect to the gestational age of LPN were compared. In respiratory support among the individual gestational ages, 34 weeks and 36 weeks ACS group had statistical significance with P value for both less than 0.05. Rest of the short-term parameters NNH, Sepsis and Hypoglycemia did not show any statistical significance between the ACS and non- ACS groups with regards to the gestational age. However, Hypoglycemia was slightly higher in the 34 weeks gestation of the non-ACS group compared to ACS group but did not have a significant P value.

Discussion

Our Retrospective Observational Cohort study including the LPN admitted to NICU among the ACS group and non-ACS group showed significant decrease in the respiratory support in the ACS group. In the non- ACS group 62 subjects (60.78%) required respiratory support as compared to thirty subjects (41.66%) in ACS group with significant P value of 0.012. Our findings were consistent with Cynthia Gyamfi-Bannerman *et al.* who conducted a multicentric randomized control trial where there was a greater need for respiratory support within 72 h of birth in the placebo group (14.4%) as compared to the steroid group (11.6%) ($p = 0.02$, relative risk = 0.8). The steroid group had lower rates of TTN, severe respiratory complications and bronchopulmonary dysplasia [9] Another study published in BMC pregnancy and child birth by Vieira *et al* also had the similar results with decreased respiratory support among the ACS group with reduced odds of respiratory complications (OR = 0.53, 95% CI:[0.31-0.85], $p<0.01$) [12]. The basis for ACS in LPN came from the ASTECS trial carried out in Term Elective Caesarean Sections who received steroids before the delivery. The trial decreased risk of TTN (0.040 vs 0.021; relative risk (RR) 0.54, 95% CI 0.26 to 1.12) and RDS (0.011 vs 0.002; RR 0.21, 95% CI 0.03 to 1.32). respiratory distress at 37 weeks was 11.4% in the control group and 5.2% in the treatment group, at 38 weeks 6.2% and 2.8%, and at 39 weeks 1.5% and 0.6%, respectively, confirming a 50% reduction in respiratory morbidity up to 39 weeks gestation [13]. In relation to respiratory outcomes to specific gestational age, $34^{0/7}$ to $34^{6/7}$ and $36^{0/7}$ to $36^{0/7}$ gestation babies had significant P value for ACS group in comparison to Non ACS group.

Duration of NICU stay among the LPN in our study demonstrated that ACS group has lesser mean duration of stay as compared to the non-ACS group (80.88 vs 114.96) with P value of 0.017. This indicating the health costs among the LPN who received antenatal ACS were much lesser compared to non-ACS group, thereby reducing the financial burden. Cynthia Gyamfi-Bannerman *et al.*, in secondary analysis of a RCT on cost effectiveness had a similar results with the risk for late preterm birth was associated with a total mean (SD) cost of $4681 ($5798) in the steroid group, which was significantly less than the $5379 ($8422) cost for pairs who were randomized to placebo (difference, $698; 95% CI, $186-$1257; P = .02) [14].

Late Preterm Neonates in our study did not have any difference in relation to Hypoglycemia among the ACS group versus non- ACS group. In contrast to Ramadan *et al.*, study which concluded that the incidence of hypoglycemia among the ACS group was 15/74 (20.3%) compared to 24/221 (10.9%) in non-ACS group with significant P value of 0.039 with odds ratio of 2.087 [15]. However, the non-ACS group had slightly higher incidence of Hypoglycemia compared to ACS group. The difference in this could be due to the case selection where Ramadan *et al* included all cases of late preterm neonates with or without ACS. In our study, the case selection was those neonates getting admitted to NICU. Small for gestational age, Intrauterine growth restriction and other neonates admitted to NICU were enrolled.

Early Onset Sepsis in the study population did not have any significance among the ACS and non-ACS group. These results were consistent with Rekha Upadya *et al.*, study where sepsis among the steroid group vs no steroid group was not significant with P value 0.3. similarly neonatal Hyperbilirubinemia results were consistent with no significance, in correlation to Cynthia Gyamfi-Bannerman *et al.*, study which had similar results among the ACS and non- ACS group (Betamethasone 167 (11.7%) vs Placebo 140 (10.0%) with odds Ratio 1.17 (0.95-1.40) and P value of 0.15 [9].

Conclusions

In conclusion, our study was first of its kind to analyse those LPN admitted to NICU with ACS intervention versus without ACS intervention and comparing their immediate outcome for respiratory support and other clinical outcomes. This study further enhances that ACS in late preterm neonates' benefit reducing the need for respiratory support and decreased duration of stay in NICU thereby reducing the cost burden on the family. However, long term outcomes in these neonates were not evaluated. Further larger RCT trials over a period will yield better results on long term adverse events on ACS intervention.

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