TITLE OF STUDY: IMPACT OF ANTENATAL CORTICOSTEROIDS ON NEONTAL HYPOGLYCEMIA AND HYPERBILIRUBINEMIA IN PRETERMS - A PROSPECTIVE COHORT STUDY

By

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ABSTRACT

Background:

Antenatal corticosteroids (ACS) are routinely administered to pregnant women at risk of preterm delivery to promote fetal lung maturation and reduce neonatal morbidity and mortality. However, emerging evidence suggests that ACS may influence neonatal metabolic outcomes such as hypoglycemia and hyperbilirubinemia, with inconsistent findings across studies.

Objectives:

To evaluate the incidence of neonatal hypoglycemia and hyperbilirubinemia in preterm neonates and determine their association with antenatal corticosteroid exposure.

Methods:

This prospective cohort study was conducted for 1.5 years at R.L. Jalappa Hospital. A total of 120 preterm neonates (<37 weeks gestation) were enrolled—60 with maternal ACS exposure and 60 without. Neonates with maternal diabetes, sepsis, hypoxic ischemic encephalopathy, or Rh incompatibility were excluded. Blood glucose was monitored every 6 hours for 72 hours post-birth. Hyperbilirubinemia was assessed via transcutaneous or serum bilirubin every 12 hours. Data were analysed using SPSS ve 21.0, with $p<0.05$ considered statisticall significant.

Results:

Hypoglycemia was significantly more common in the ACS group (55%) compared to the non-ACS group (5%) ($p < 0.001$), with odds ratio of 23.22). The highest hypoglycemia incidence was seen in neonates receiving two doses of ACS. In contrast, hyperbilirubinemia incidence was comparable between groups (41.7%

in ACS vs. 53.3% in non-ACS, p = 0.20), and no significant associations were found with the type, timing, or dose of corticosteroids.

Conclusion:

Antenatal corticosteroid exposure in preterm neonates is significantly associated with increased risk of neonatal hypoglycemia but not hyperbilirubinemia. These findings highlight importance of vigilant glucose monitoring in ACS-exposed premature infants, during first 72 hours of life.

INTRODUCTION

Preterm birth is a major global health concern, with approximately 14.8 million infants born premature each year.[1] It is a leading cause of perinatal mortality, accounting for nearly 35% neonatal deaths. To enhance outcomes in preterm neonates, mothers at risk of delivering early are administered antenatal corticosteroids (ACS). Multiple studies have demonstrated that antenatal corticosteroids (ACS) contribute to a substantial decline in the rates of neonatal mortality, intraventricular haemorrhage (IVH), necrotizing enterocolitis (NEC), and the need for NICU admission. [2,3]

Despite these well-established benefits, ACS administration is not without potential adverse effects on foetus.[4] One such concern is maternal hyperglycemia, a known consequence of corticosteroid therapy. The primary mechanisms involve enhanced glucose production by the liver (hepatic gluconeogenesis), elevated circulating glucagon concentrations, and reduced glucose uptake in peripheral tissues—attributable to changes in glucose transport mechanisms and receptor function.[5] Maternal hyperglycemia can, in turn, lead to fetal hyperinsulinemia, predisposing the neonate to postnatal hypoglycemia.

In addition to hypoglycemia, ACS have also been implicated in neonatal hyperbilirubinemia. Some evidence suggests that ACS may increase the risk by decreasing hepatic uptake of unconjugated bilirubin and competitively inhibiting its binding.[6] Conversely, other studies suggest a potential protective effect, as ACS accelerate hepatic enzyme maturation, particularly Uridine Diphosphate glucuronosyltransferase(UDP-GT)—thereby enhancing bilirubin conjugation and excretion.[7,8]

Both neonatal hypoglycemia and hyperbilirubinemia are clinically significant metabolic complications. Hypoglycemia can lead to acute neurological dysfunction and long-term neurodevelopmental impairment, while severe hyperbilirubinemia may result in bilirubin-induced neurological dysfunction (BIND) and increased morbidity. However, due to the potentially serious consequences of hyperbilirubinemia and the conflicting evidence surrounding its association with ACS, this study emphasises evaluating the potential risks rather than the benefits. [7,8]

A limited number of studies have explored the possible relationship between antenatal corticosteroid exposure and these metabolic complications in preterm neonates.[4] To address this gap in current research, the present-study was designed to determine impact of antenatal corticosteroids on neonatal hypoglycemia and hyperbilirubinemia in infants.

OBJECTIVES OF STUDY

- To determine hypoglycemia and hyperbilirubinemia in preterm neonates.
- To determine the association between maternal antenatal corticosteroids(ACS) and neonatal hypoglycemia and hyperbilirubinemia.

REVIEW OF LITERATURE

Preterm Birth:

Preterm birthis defined as Worlds Health Organization (WHO), refers to birth occurring before the completed 37 weeks of getation. Worldwide, approximately 14.8 to 15. million babies were born each year, contributing to over one million neonatal deaths and making it the foremost cause of death among children below five years of age. [1,9] In addition to immediate health concerns, preterm birth is a major contributor to persistent complications such as respiratory disorders, neurodevelopmental delays, and metabolic disturbances. These challenges are more pronounced in low- and middle-income countries (LMICs), where perinatal healthcare services are often inadequate. [1,9]

Aetiology and Risk Factors:

The causs of preterm birth are diverse, encompassing maternal, fetal, and placental factors. Key biological mechanisms implicated in its onset include inflammation of the decidua, bleeding, excessive uterine stretching, and maternal-fetal physiological stress.[9,10] These underlying processes frequently interact and may result in either spontaneous preterm labor or necessitate medical intervention.

Established risk factors include:

- Placental complications (e.g., abruption, previa) [11,12]
- Preterm premature rupture of membranes (PPROM)
- Uteroplacental insufficiency (seen in hypertensive disorders, diabetes mellitus, autoimmune diseases) [12]
- Fetal growth restriction, abnormal Doppler flow.[12]
- Short cervical length. [13]
- Infections (intrauterine, urinary, or vaginal)

- Polyhydramnios or oligohydramnios[14]
- Multiple gestation, especially from assisted reproductive technologies (ART) [15–17]
- Extremes of maternal age (<17 or >40 years)
- Low body mass index (BMI), malnutrition, inadequate antenatal care, and substance use [9,12]

Pathophysiology:

The exact mechanisms initiating preterm labor remain incompletely understood. However, several key pathways have been proposed:

- Infection and inflammation, with elevated cytokines stimulating prostaglandin production and uterine contractility
- Hormonal changes, particularly involving corticotropin-releasing hormone (CRH)
- Mechanical factors like uterine overdistension or cervical incompetence.[10,12]

Additionally, placental insufficiency may result in fetal stress, further increasing the likelihood of spontaneous preterm birth.[11]

Over past two decdes, the increased use of ART for high-icome countries has contributed to rising rates of multiple-gestations, which are associated with a higher risk spontaneous preterm labor, PROM, and complications like preeclampsia or fetal anomalies. [15–17]

A phenotypic classification has been proposed to better categorize the various presentations of preterm birth, acknowledging it as a syndrme with multiple underlying etiologies. [14]

Disparities and Diagnostic Challenges:

Preterm birth rates vary substantially by region, ethnicity, and income level. Studies show that socioeconomic disparities, maternal comorbidities, and limited access to skilled obstetric care significantly influence outcomes, especially in LMICs.[1,9] In high-income countries, immigrant and minority populations often experience disproportionately high rates of preterm birth.[18]

Despite its prevalence, the diagnosis and classification of preterm birth remain inconsistent across countries due to differences in gestational age assessment [e.g., Last menstrual period (LMP) vs. ultrasound dating] and variable health system reporting practices. [9,12]

Diagnostic tools such as transvaginal cervica length measurement and fetal testing may help predict risk, but are not widely utilized in all settings. [13]

Interventions: ACS

The use of ACS in women at risk of preterm delivery has become standard practice and significantly improves neonatal outcomes. ACS are proven to reduce the incidence of RDS, intraventricular haemorrhage, NEC, and neonatal mortality.[2–4] However, ACS also carry potential metabolic side effects in the neonate, such as hypoglycemia and hyperbilirubinemia, which are critical to evaluate in further research.[4–6]

ANTENATAL CORTICOSTEROIDS:

Antenatal corticosteroids (ACS) are widely regarded as essential in managing pregnancies, risk for preterm delivery. They enhance fetal-lung development and significantly to decrease the likelihood of serious neonatal-complications. According to current evidence, infants who receive ACS have a lower risk of developing conditions such as RDS, IVH, NEC, and neonatal mortality, with relative risk estimates supporting their effectiveness. [3,19]

Corticosteroid Agents and Regimens

Two corticosteroids—**betamethasone** and **dexamethaone**—are commonly used due to their ability to cross the placenta in active form.

- **Beta-methasone**: Two intramuscular doses of twelve mg, twenty four hours apart. It has a longer half-life due to reduced clearance and greater volume of distribution.
- **Dexamethasone**: Four intramuscular doss of 6 mg, every 12 hours. [19,20]

Both lack mineralocorticoid activity and exert minimal immunosuppression during short-term treatment.

Clinical Uses and Indications

ACS use has been associated with a significnt reduction, in mortality and severe morbidities in preterm infants:

- Benefits extend to infants born as early as 23–25 weeks' gestation, with reductions in mortality, IVH, and NEC. [21,22]
- In **PPROM**, ACS remains beneficial without increasing neonatal infection rates.[23]
- In **twin pregnancies**, ACS administered 1–7 days before delivery improves neonatal respiratory and neurological outcomes, like singletons. [24]

Potential Adverse Effects:

While beneficial, ACS are not without risks:

- **Neonatal hypoglycemia** is more frequently observed after ACS exposure, particularly in late preterm gestations.[2]
- Multiple courses of ACS have been associated with lower birth weight, a higher occurrence of SGA newborns, and in certain studies, a reduction in head circumference**.**[25]
- Long-term safety data, especially after multiple or late courses, raise questions. One follow-up study found no significant neurocognitive deficits at school age but noted a **higher proportion of children rated in the lower performance quartile** by teachers.[26]

Implications for the Current Study

Given their substantial benefits, antenatal corticosteroids remain vital intervention for anticipated preterm delivery. However, their potential metabolic side effects—particularly **neonatal hypoglycemia and hyperbilirubinemia**—warrant further investigation. These outcomes are especially pertinent in **late preterm deliveries** and **multiple gestations**, underscoring the need for judicious use of ACS with careful attention to timing, dosage, and gestational age.[24–26] The current study aims to assess the effect of ACS on these specific outcomes, contributing to safer and more effective perinatal care.

Neonatal Hypoglycemia:

Definition and Thresholds

Neonatal hypoglycemia is commonly defined as a blood glucose concentration below 45 mg/dL. This operational threshold is widely accepted in clinical practice and supported by expert consensus for identifying at-risk neonates and guiding intervention strategies. [27]

Aetiology and Risk Factors

Neonatal hypoglycemia can result from several factors including prematurity, intrauterine growth restriction, maternal diabetes, perinatal stress, and administration of ACS. Preterm infants have immature metabolic pathways and limited glycogen and fat stores, making them susceptible to hypoglycemia. [28,29] The administration of ACS, while beneficial for lung maturation, has been associated with altered glucose homeostasis in neonates, leading to transient hypoglycemia due to increased insulin sensitivity. [30]

Pathophysiology

The pathophysiology of neonatal hypoglycemia involves an imbalance between glucose supply and utilization. In preterm and low birth weight infants, inadequate glycogen stores and immature gluconeogenic pathways contribute to poor glucose regulation. Insulin dysregulation and delayed adaptation to extrauterine life further exacerbate this condition.[29,31]

Clinical Presentation

Symptoms can range from asymptomatic to severe, including jitteriness, lethargy, apnea, seizures, and poor feeding. However, many cases may be clinically silent, making routine monitoring essential in at-risk neonates. [27]

Screening and Monitoring

Routine screening is recommended for neonates at risk, especially during the first 24–48 hours of life. Bedside glucose testing should be performed frequently in the immediate postnatal period. Continuous glucose monitoring has shown promise in identifying episodes of asymptomatic hypoglycemia and may guide more effective interventions. [32]

Management

Initial management involves early feeding, preferably breastfeeding. If oral feeds are inadequate, intravenous glucose should be administered. Maintaining plasma glucose levels above 45 mg/dL is the target in most clinical guidelines.[27,33]

Neurodevelopmental Outcomes

Prolonged or recurrent neonatal hypoglycemia has been linked to adverse neurodevelopmental outcomes, including cognitive impairment, motor dysfunction, and executive function deficits.[34] Imaging and long-term follow-up studies confirm the potential for structural brain changes and persistent deficits.

Impact of ACS

Research indicates that exposure to antenatal corticosteroids (ACS) can temporarily raise the risk of neonatal hypoglycemia. This is primarily due to corticosteroid-induced maternal hyperglycemia, which prompts fetal hyperinsulinemia and heightened insulin sensitivity—factors that may contribute to reduced postnatal glucose levels, especially in late preterm and term infants.(30) However, this risk must be balanced against the substantial benefits of corticosteroids in reducing respiratory morbidity and other complications of prematurity. Recent research has emphasized that while corticosteroid-associated hypoglycemia is generally transient and manageable, careful postnatal monitoring remains essential to mitigate any potential risks. [35–37]

Neonatal Hyperbilirubinemia:

Neonatal hyperbilirubinemia, characterized by elevated serum bilirubin levels, is a common condition in preterm infants, with distinct etiological factors, pathophysiological mechanisms, and management strategies compared to term neonates.[38]

Epidemiology and Clinical Relevance in Preterm

Hyperbilirubinemia affects more than sixty percent of termand eighty of preterm infants in the 1st week of life. In preterm neonates, the condition often more pronounced,prolonged due to hepatic immaturity, lower albumin levels, and increased bilirubin production resulting from higher red cell turnover. Early recognition and management are critical, as preterm infants are more susceptible to BIND because of immature blood-brain barrier and reduced serum albumin-binding capacity.[38–40]

Miscellaneous Causes in Preterm Infants

- **Sepsis**: Inflammatory cytokines impair bilirubin conjugation.
- **Perinatal asphyxia**: Hepatic ischemia exacerbates conjugation defects.
- **Intrauterine growth restriction (IUGR)**: Associated with immature liver function.
- **Breastfeeding-related jaundice**: Delayed feeding in preterm increases enterohepatic circulation.[41,42]

Pathophysiology

In preterm infants, several factors contribute to increased bilirubin levels:

- **Immature hepatic conjugation:** Reduced activity of the enzyme UDP-GT leads to impaired bilirubin conjugation.
- **Increased enterohepatic circulation:** Decreased intestinal motility and reduced bacterial colonization enhance reabsorption of unconjugated bilirubin.
- **Enhanced haemolysis:** Shorter red blood cell lifespan and increased erythropoiesis in preterm contribute to elevated bilirubin production.[43,44]

Histopathology and Neurological Risk

High bilirubin levels can cross the blood-brains barriers in preterm, depositing in basal ganglia,brainstem nuclei, causing kernicterus. Histologically,bilirubin-encephalopahy reveals yellow discolouration and neuronal necrosis in these areas, which correlates with long-term neurodevelopmental deficits like cerebral palsy and auditory dysfunction.[45,46]

Diagnostic Workup

Diagnosis of neonatal hyperbilirubinemia in preterm involves:

- **Total serum bilirubin (TSB) levels** using age and gestation-specific nomograms.
- **Transcutaneous bilirubinometry** as a non-invasive screening tool.
- **Coombs test, blood group typing, and peripheral smear** to identify haemolytic causes.
- **Albumin levels** to evaluate bilirubin-binding capacity. [47–49]

Clinical Evaluation

Clinical jaundice may not be visibly prominent in preterm. Hence, routine monitoring of bilirubin levels is essential. Neurological assessment is necessary to detect early signs of BIND. Risk stratification involves gestational age, weight, sepsis, and acidosis, all of which increase susceptibility.[50]

Role of ACS:

The impact of ACS on neonatal hyperbilirubinemia remains a subject of ongoing research, with studies showing conflicting results. Some studies suggest that ACS reduces the possibility of hyperbilirubinemia-promoting liver enzyme maturation, improving bilirubin-conjugation and clearance. A 2019 study reported a significantly lower incidence of hyperbilirubinemia infants exposed to ACS - beforeor at34 weeks of gestation, indicating a potential protective effect.[51] In contrast, other studies have associated antenatal betamethasone exposure with an increased incidence of neonatal hyperbilirubinemia, suggesting possible adverse modulation of bilirubin metabolism.[4,52] These divergent findings underscore the complex interplay between ACS exposure and bilirubin metabolism, particularly in preterm neonates who more susceptible to bilirubin neurotoxicity due to hepatic immaturity. This highlights the need for further focused research in this vulnerable population.

Treatment Strategies

Phototherapy

1. First-line therapy, converting bilirubin into water-soluble isomers.
2. Initiation thresholds vary for preterm infants and depend on gestational age and TSB levels.
3. Blue light (460–490 nm) is most effective, with irradiance and surface exposure being key parameters.

4. Side effects include fluid losstemperature instabilityand interference with maternal-infant bonding.[53,54]

Exchange Transfusion

- Indicated in severe cases or when phototherapy fails.
- Removes bilirubin and sensitized RBCs while replenishing albumin and coagulation factors.
- Higher risk in preterm due to vascular access challenges and hemodynamic instability.[55]

Long-term Outcomes and Neurodevelopmental Concerns

A 2023 systematic review highlighted that elevated bilirubin levels might trigger neurodevelopmental disorders in full-term,infants during the first year of life. While more data are needed for preterm neonates, the evidence e of aggressive monitoring and management to prevent long-term sequelae such as cognitive impairment, attention deficits, and sensorineural hearing loss.[56]

Guidelines and Recommendations

The **Indian Academy of Paediatrics (IAP)** 2023 guidelines provide gestation-specific recommendations for early screening, phototherapy initiation, and individualized follow-up in preterm neonates. Similarly, the **NICE guidelines (UK)** offer comprehensive bilirubin thresholds in phototherapy in neonates as per postnatal age and gestation age, emphasizing safer intervention practices in preterm infants.[57,58]

Literature from previous studies:

In a prospective observational study on the association of ACS use with the incidence of hypoglycemia and hyperbilirubinemia in preterm neonates, **Mandal K et al.,** observed that out of 99 preterm neonates, 71.7% of mothers received ACS , 4% of cases had hypglycemia at birth with no caes of hypoglycemia at 12 hour and 24 hours after birth. They conclued that ACS was not associated with neonatal hypoglycemia but there was significant association with neonatal hyperbilirubinemia.[52]

In a prospective -observational study, **Janssen et al.** evaluated the ACS eexposure effect on the respiratory and glycaemic outcomes for late preterm neonate. Late preterm were further divided in to immature (34– 35 6/7 weeks) and mature (36 - 36 6/7 weeks) group. They observed that in the immature group, exposure to ACS within seven days prior to deliveryreduced the incidence inrespiratory distress .In contrast, no significant respiratory benefit was observed in the mature group. Interestingly, the mature group was statistically significant decrease in the blood glucose following ACS exposure, suggesting altered glycaemic control. The findings emphasize that the benefits and risks of ACS may vary by gestational age, with respiratory improvement more prominent in late preterm infants, and glycaemic disturbances more evident in those closer to term.[59]

In a study investigating the effect between antenatal corticosteroid exposure withe risk of neonatal-hyperbilirubinemia, **El-Hawary MA et al.** observed that birth weight was comparable between the groups, and there was a slight male predominance (57%) among the neonates. Among the jaundiced neonates, 68.5% had been exposed to ACS, while 31.5% had not. Most cases of jaundice were noted around the third day of life. They concluded that antenatal corticosteroid administration did not significantly increase the incidence of neonatal hyperbilirubinemia. [60]

In a prospective cohort study, **Nuran Ustun et al.** compared neonatal outcomes between mothers who received antenatal corticosteroids and those who did not. Among 595 participants, 234 were exposed to ACS. It was observed that while the use of ACS has reduced incidence of respiratory problems, increased hypoglycemia in ACS- grop. They concluded that administration of antenatal corticosteroids was with increased risk of neonatal hypoglycemia. [61]

In a retrospective multicentre cohort study evaluating determinant of hypoglycemia following antenatal corticosteroid exposure for maturation of lung, **Pasquo E et al.** observed that hypoglycemia occurred in 38.4% of newborns who had received ACS. They found that the occurrence of hypoglycemia was independent of both the type of exposure and the interval between ACS administration and delivery. Birth weight emerged as the important for the development of hypoglycemia after ACS administration.[62],[63]

In a retrospective analysis, **Zhou C et al.** investigated the impact of antenatal corticosteroid (ACS) administration on glucose variability in late-preterm infants. Of the neonates studied, 56.8% (n=134) had received a full course of ACS, 23.7% (n=56) had partial exposure, and 19.5% (n=46) had no exposure. The frequency of hypoglycemia was highest in those who received the complete course (16.4%), followed by the no exposure (6.5%) and partial course groups (3.6%). The authors reported that ACS administration, especially when complete, was associated with a greater decline in neonatal blood glucose levels, most notably during the first 12 hours post-birth. Additionally, male neonates appeared more susceptible to these glycemic changes. However, beyond 24 hours of life, blood glucose levels showed no significant variability across the groups. [64]

MATERIAL AND METHODS

SOURCE OF DATA: All Neonates with gestational age < 37 weeks admitted in R.L JALAPPA Hospital.

STUDY DESIGN: PROSPECTIVE COHORT STUDY

STUDY PERIOD: 1 1/2 years.

METHOD OF COLLECTION OF DATA:

- This study was initiated after obtaining ethical clearance from the, institutionalethics committee ,and consent from the parents.

INCLUSION CRITERIA:

- All preterm neonates born to mothers who received antenatal corticosteroids, and who did not receive antenatal corticosteroids.

EXCLUSION CRITERIA:

- Maternal diabetes mellitus
- Evidence of chorioamniotis
- Hypoxic-ischaemic encephalopathy
- Neonatal sepsis
- Major congenital anomalies
- Rh incompatibility

SAMPLE SIZE:

Samples were estimated based on difference in incidence of hypoglycemia between corticosteroid exposed group and nonexposed control group as reported in study by Nuran Ustun et al.[61] with an observed difference of 7.6%.

(n) = desired size of sample

$Z\alpha$ = 1.496 (ninety five percent of confidence level)

$Z\beta$ = 0.745

P1+= proportion of outcome in ACS exposed group

P2+= proportion of outcome in ACS unexposed group

Considering the power of 80% with 95% confidence to detect a difference of at least 15% in incidence of hypoglycemia between groups, the required sample size was 53 per group. Expecting a dropout rate of 10% during the study, final sample size was estimated as 53+6=59, rounded off to 60 per group.

METHODOLOGY:

This study was conducted in R.L JALAPPA hospital affiliated toSRI DEVRAJ URS MEDICAL COLLEGE, Data from women with gestational age < 37 weeks at risk of imminent delivery was collected.

Details of maternal ACS was collected, and recorded in pretested proforma. All preterm neonates delivered were recruited in two groups: one with maternal ACS exposure and the other without maternal ACS exposure.

Maternal data, including age, parity, mode of delivery, administration of ACS along with dose, time interval, and name of ACS, were collected. Primary outcomes of interest were hypoglycemia and hyperbilirubinemia.

Hypoglycemia is defined as a glucose-level less than 45 mg/dl.[27] Blood glucose concentration was measured taken by heel-prick,lance and analysed in glucometer using a Sinocare Safe AQ glucometer. Blood glucose was checked one hour after birth and every 6 hours till 72 hours of life according to institutional protocol, regardless of initiation of feeds or fluids. If found to be hypoglycaemic, that neonate was considered a case and was managed immediately according to institutional protocol.

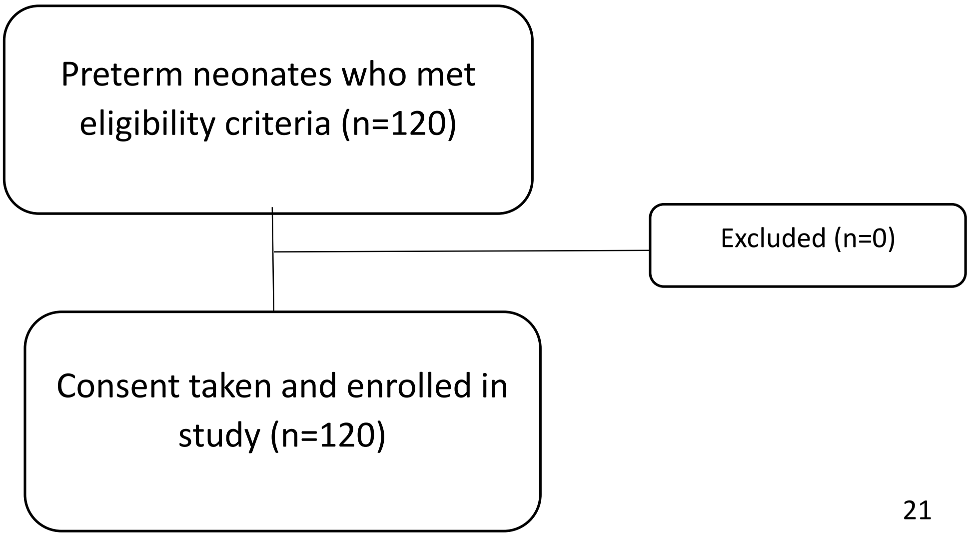
Hyperbilirubinemia is an elevation of the serum bilirubin to a level requiring treatment. Neonatal hyperbilirubinemia was assessed using either transcutaneous bilirubin (TCB) or serum bilirubin measurements every 12 hours until 72 hours of life. TCB or serum bilirubin level within the phototherapy range was diagnosed as hyperbilirubinemia. Once diagnosed it was considered as a case[66,67] and was treated as per NICE guidelines.[58]

STATISTICAL ANALYSIS:

Data were compiled in Microsoft Excel and subsequently analyzed using SPSS software version 21. Comparisons between the two study groups for the continous data were performed using Student's t-test, while categorical data were analyzed using Fisher's exact test. To adjust for potential confounding variables, multivariate logistic regression analysis was applied.

RESULTS

Figure 1: Flow diagram for collection and analysis of data



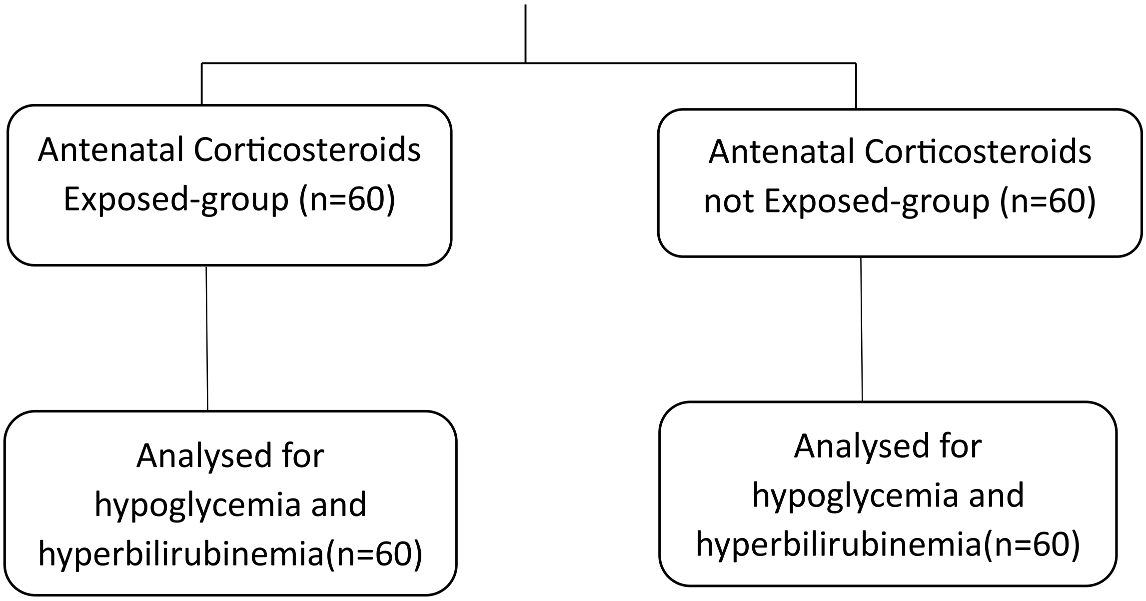


Table 1: Distribution of study subjects as per gestational age

Gestational age	With *ACS	%	Without *ACS	%
Extreme preterm	0	0.0	5	8.3
Very preterm	21	35.0	13	21.7
Moderate-late preterm	39	65	42	70
Total	60	100.0	60	100.0

*ACS- Antenatal corticosteroids

Figure 2: Distribution of study subjects as per gestational age

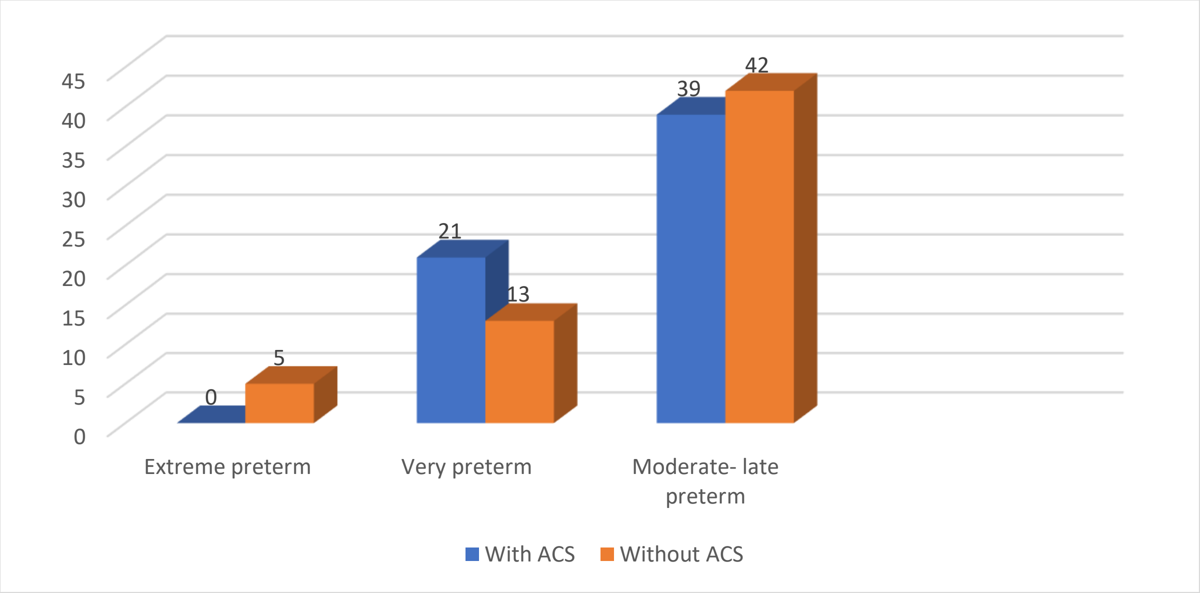


Table 1 & Figure 2 depict the distribution of subjects as per gestational age. It was observed that in the ACS group, majority (65%) of neonates were moderate to late preterm, followed by very preterm (35.0%). There were no neonates with extreme preterm. In the group that did not receive ACS, majority (70%) were moderate to late preterm, 21.7% were very preterm, and 8.3% were extreme preterm neonates.

Table2: Distribution ofneonates as per birth weight.

Birth weight	Mean	SD
With *ACS	1.63	0.42
Without *ACS	1.67	0.53

ACS- Antenatal corticosteroids

Figure 3: Distribution of neonates as per birth weight.

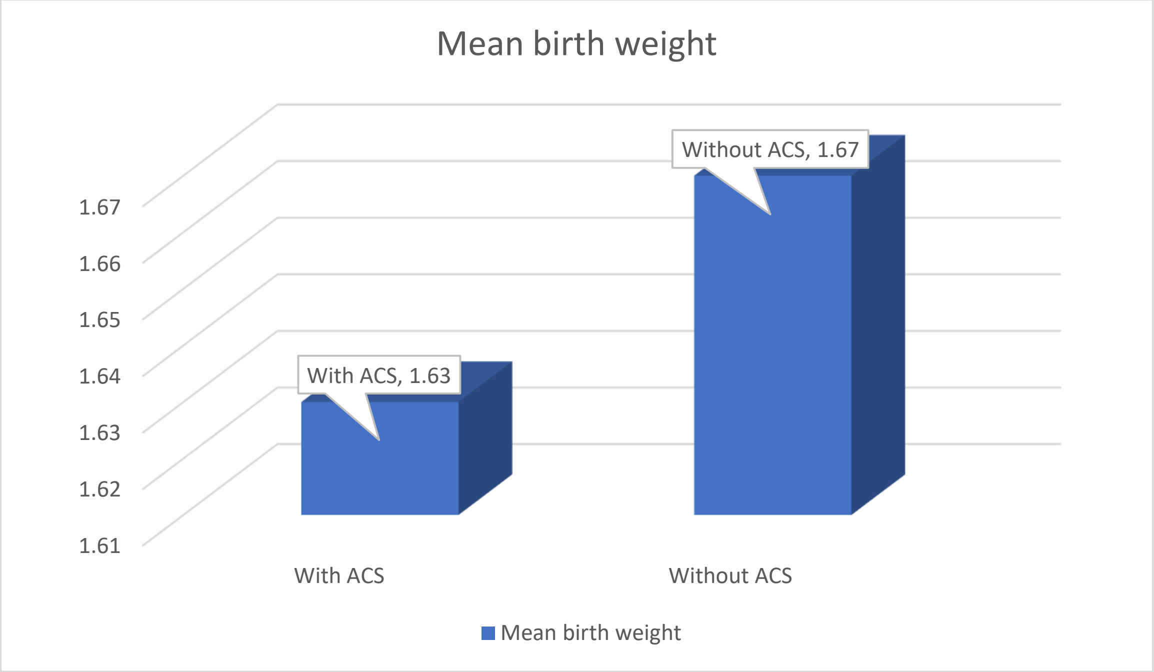


Table 2 & Figure 3 depict the mean birthweight of neonates. In the ACS group, mean birth weight was 1.63 ± 0.42 k_g, while mean birth weight in the group without ACS was 1.67 ± 0.53 kg.

Table 3: Distribution of neonates as per to weight for gestational age.

Weight for gestational age	With ACS	%	Without ACS	%
*AGA	40	66.7	40	66.7
^LGA	1	1.7	2	3.3
#SGA	19	31.7	18	30.0
Total	60	100.0	60	100.0

Figure 4: Distribution of neonates as per weight for gestational age.

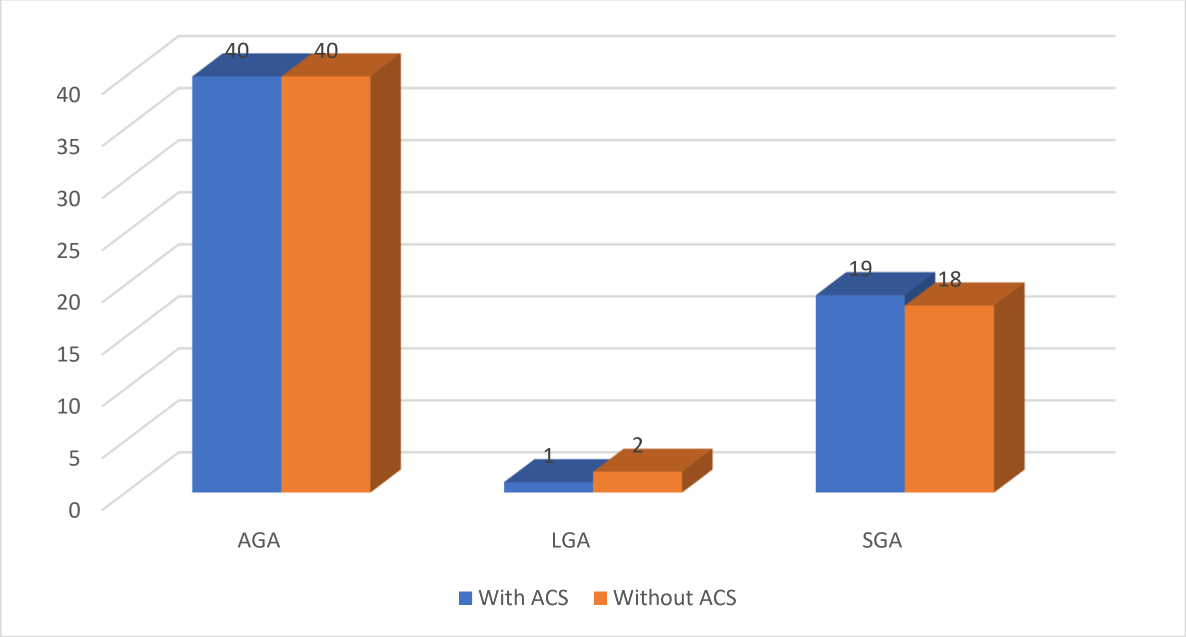


Table 3 & Figure 4 depict the distribution of neonates according to weight for gestational age. It was observed that in the ACS group, majority (66.7%) of neonates were AGA, while 31.7% were SGA and 1.7% were LGA. In the group without ACS, majority (66.7%) were AGA, 30% were SGA, and 3.3% were LGA.

Table4: Distribution of neonates based on mode of delivery

MOD	With *ACS	%	WITHOUT ACS	%
^LSCS	46	76.6	32	53.3
Vaginal	14	23.4	28	46.7
Total	60	100.0	60	100.0

*ACS- Antenatal corticosteroids ^LSCS-Lower segment caesaran section

Figure 5: Distribution of neonates based on mode of delivery.

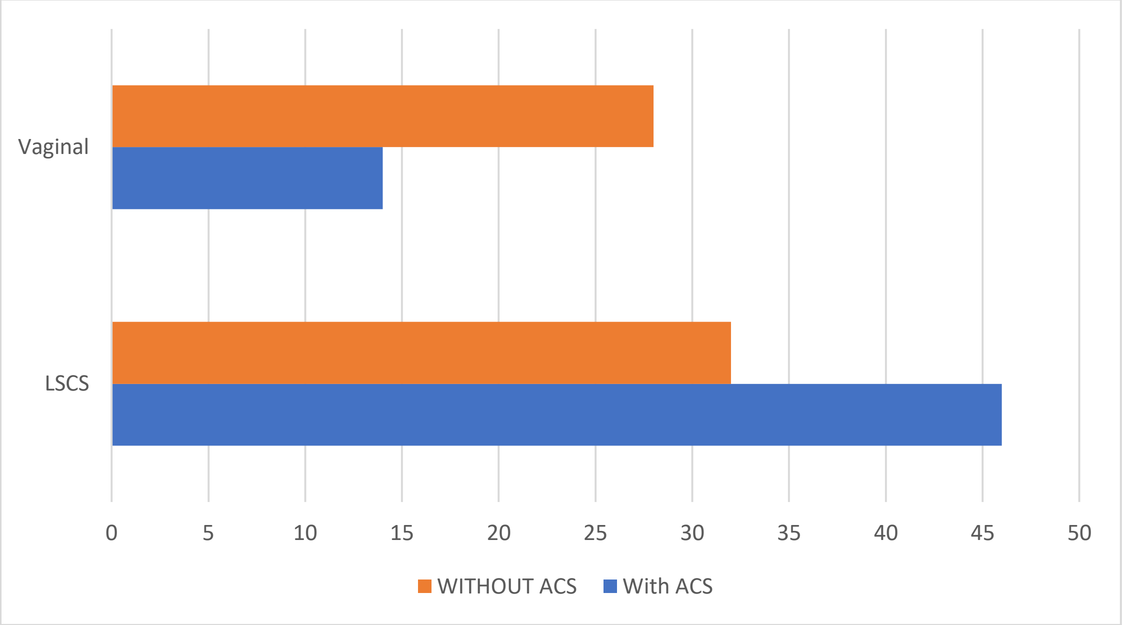


Table 4 and Figure 5 depict the distribution of neonates according to mode of delivery. It was observed that in the ACS group, majority(76.6%) of neonates were delivered through LSCS and remaining (23.4%) through vaginal delivery. In the group without ACS, 53.3% were delivered through LSCS and 46.7% were through vaginal delivery.

Table 5: Distribution of neonates based on hypoglycemia in both groups

	With *ACS	%	Without *ACS	%
Hypoglycemia	33	55	3	5
Without Hypoglycemia	27	45	57	95
Total	60	100	60	100

*ACS- Antenatal corticosteroids

Figure 6: Distribution of neonates based on hypoglycemia in both groups

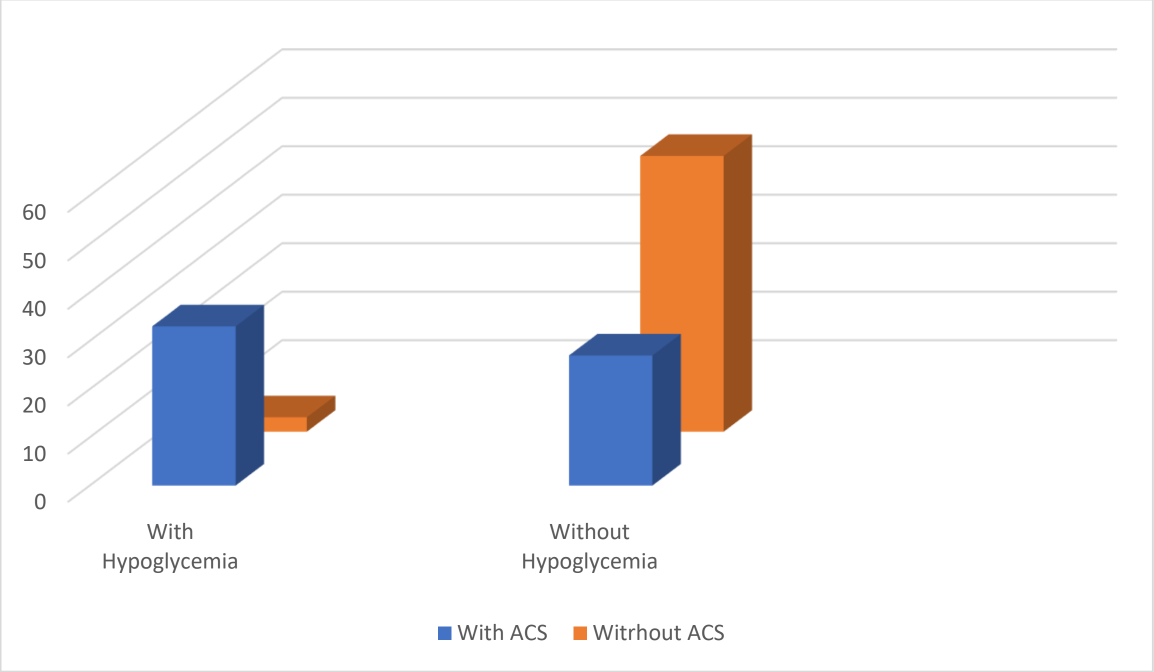


Table 5 and Figure 6 depict the distribution of neonates based on hypoglycemia in both groups. It was observed that hypoglycemia was present in almost half(55%) of neonates in ACS group, while it was only 5% in the non-ACS group.

Table 6: Distribution of neonates based on hyperbilirubinemia in both groups

	With *ACS	%	Without *ACS	%
Hyperbilirubinemia	25	41.7	32	58.3
Without Hyperbilirubinemia	35	58.3	28	46.7
Total	60	100	60	100

*ACS- Antenatal corticosteroids

Figure 7: Distribution of neonates based on hyperbilirubinemia in both groups

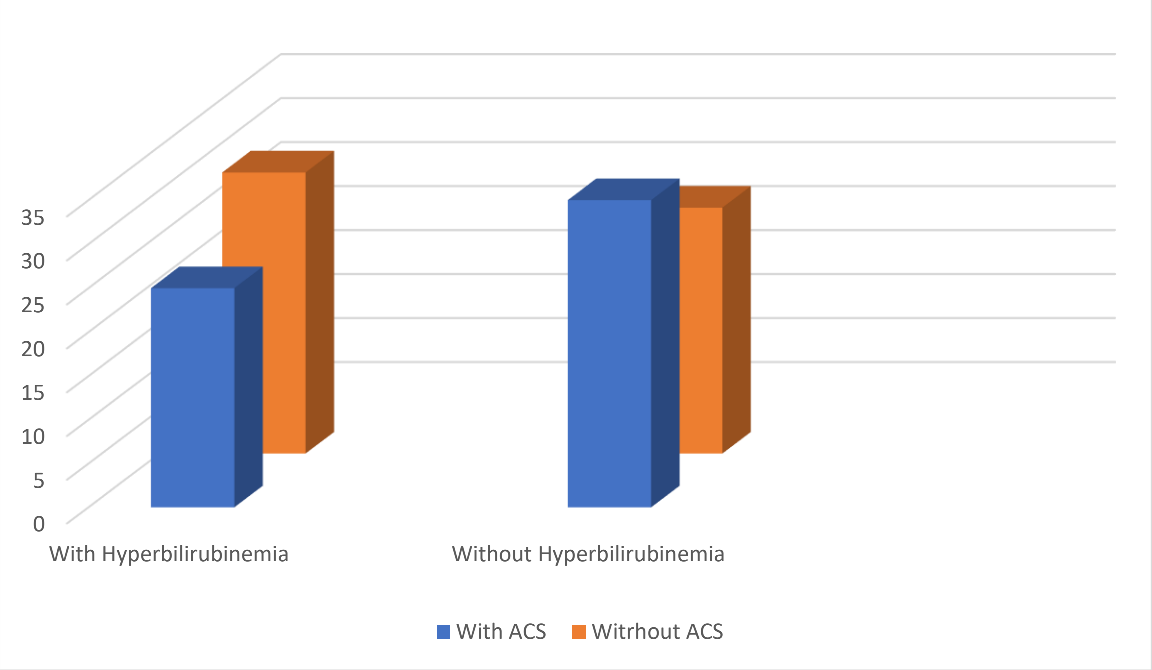


Table 6 and Figure 7 depict the distribution of neonates based on hyperbilirubinemia in both groups. It was observed that hyperbilirubinemia was present in 58.3% of non-ACS group and 41.7% of the ACS group.

Table7: Association between ACS and hypoglycaemia

	Hypoglycaemia		Total	P value	Odds ratio
	Present	Absent			
With ^ACS	33 (55.0)	27 (45.0)	60 (100.0)	<0.001*	23.22 (6.53 – 82.48)
Without ^ACS	3 (5.0)	57 (95.0)	60 (100.0)		

Total	36 (30.0)	84 (70.0)	120 (100.0)		

^ACS- Antenatal corticosteroids

Figure 8: Association between ACS and hypoglycaemia

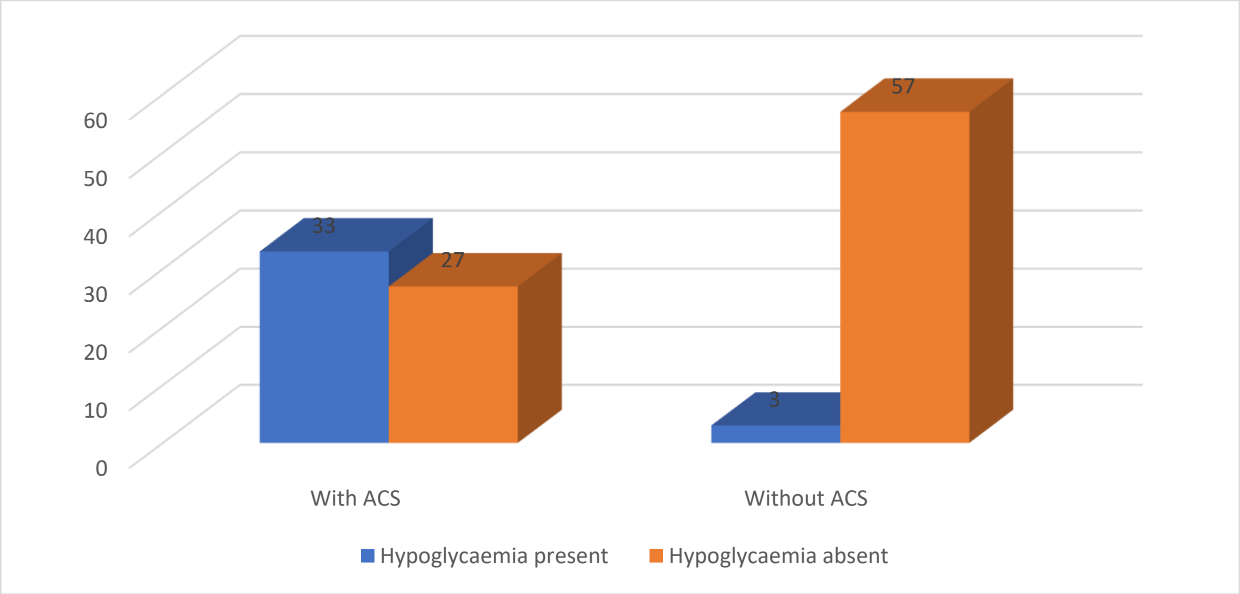


Table 7 & Figure 8 depict the association between ACS and hypoglycaemia. It was observed that 55% of neonates in the ACS group had hypoglycaemia against 5% in the non-ACS group. Neonates in the ACS group had almost 23.22 times(95% CI: 6.53-82.48) odds.

Table 8: Association between ACS and hyperbilirubinemia

	Hyperbilirubinemia		Total	P value	Odds ratio
	Present	Absent			
With *ACS	25 (41.7)	35 (58.3)	60 (100.0)	.201	
Without *ACS	32 (53.3)	28 (46.7)	60 (100.0)		

Total	57 (47.5)	63 (52.5)	120 (100.0)		0.625 (0.304 – 1.286)

*ACS- Antenatal corticosteroids

Figure 9: Association between ACS and hyperbilirubinemia

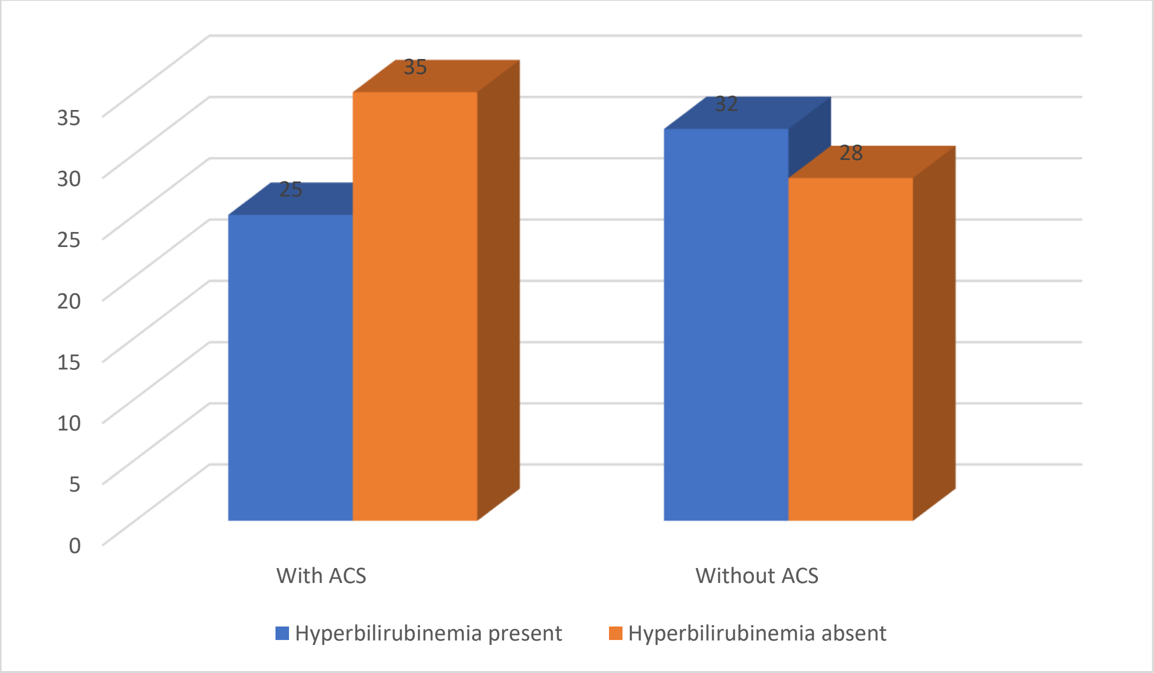


Table 8 & Figure 9 depict the association between ACS and hyperbilirubinemia. It was observed that hyperbilirubinemia was present in 41.7% and 53.3% of the ACS and non-ACS groups, respectively, which was not s significant (p=.201).

Table 9: Neonatal hypoglycemia and characteristics in the ACS exposed group (n=60).

Variable	Category	Hypoglycemia present(n=33)	Hypoglycemia absent(n=27)	P value

Time interval between *ACS administration and delivery	<24 hours	1 (3)	1 (3.7)	0.715
	24 – 48 hours	16 (48.5)	16 (59.3)	
	>48 hours	16 (48.5)	10 (37.0)	
Type of ACS	Betamethasone	25 (75.8)	20 (74.1)	0.881
	Dexamethasone	8 (24.2)	7 (25.9)	
Doses of ACS	1	4 (12.1)	13 (48.1)	0.010#
	2	23 (69.7)	11 (40.7)	
	3	2 (6.1)	0(0)	
	4	4 (12.1)	3 (11.1)	

*ACS-Antenatal corticosteroids ; #p value <0.05; Hence statistically significant

Table9 depicts various characteristics among ACS exposed neonates with and without hypoglycemia. Among neonates with hypoglycemia in the ACS exposed group, time interval between ACS administration and delivery was <24 hours in 3% while it was 48.5% each in 24-48 hours and more than 48 hours respectively which was statistically not significant (p=0.715). Among neonates with hypoglycemia in ACS group, betamethasone was administered in 75.8% and dexamethasone in 24.2%.

Table 10: Neonatal hyperbilirubinemia and characteristics in the ACS exposed group (n=60).

Variable	Category	Hyperbilirubinemia present	Hyperbilirubinemia absent	P value
Time interval between ACS administration and delivery	<24 hours	1 (4.0)	1 (2.9)	0.472
	24 – 48 hours	11 (44.0)	21 (60)	
	>48 hours	13 (52.0)	13 (37.1)	
Type of ACS	Betamethasone	18 (72)	27 (77.1)	0.650
	Dexamethasone	7 (28)	8 (22.9)	
Doses of ACS	1	4 (16)	13 (37.1)	0.131
	2	15 (60)	19 (54.3)	
	3	1 (4)	1 (2.9)	
	4	5 (20)	2 (5.7)	

*ACS-Antenatal corticosteroids

Table 10 depicts various characteristics among ACS exposed neonates with and without hyperbilirubinemia. Among neonates with hyperbilirubinemia in the ACS exposed,. Likewise, there was no statistically noted between type of ACS (p=0.650) and doses of ACS (p=0.131) in ACS exposed neonates with hyperbilirubinemia.

DISCUSSION

This prospective cohort study was conducted among 120 preterm neonates to look for the impact of antenatal corticosteroid (ACS) administration on the neonatal hypoglycemia and hyperbilirubinemia. Sixty neonates born for mothers who received ACS were compared with Sixty neonates whose mothers did not receive corticosteroids. The objective was for assessing the occurrence of hypo and hyperbilirubinemia in preterm neonate and to determine their association with maternal ACS exposure.

Gestational age and study cohort:

In the present study, the gestational age distribution among the study cohort revealed that in the antenatal corticosteroid (ACS) group, most neonates (65%) were moderate to late preterm (32–36 weeks), followed by 35% who were between 28–31 weeks, and none were <28weeks. In contrast, the non-ACS group had 70% moderate to late preterm, 21.7% very preterm, and 8.3% extreme preterm. These findings align partially with the longitudinal study by Mandal K et al., where very preterm infants constituted a substantial proportion of the cohort exposed to ACS (approximately 33%). However, the inclusion of extreme preterm neonates in their cohort, absent in ours, may reflect differences in population characteristics or institutional practices regarding steroid administration.(52)

Likewise, the study by Janssen et al., which categorised neonates into immature (34–35 6/7 weeks) and mature (36–36 6/7 weeks) late preterm, also focused on the gestational window most represented in our study. Their exclusion of extreme and very preterm infants mirrors our institutional trend, possibly indicating a shared caution in offering steroids at very early gestational ages due to either clinical limitations or survival considerations.(59)

Birth Weight Characteristics and study cohort:

In this study, no clinically significance in difference of mean birth weight in ACS-exposed (1.63 ± 0.42 kg) and unexposed (1.67 ± 0.53 kg) groups. Classification by weight for gestational age showed similar proportions of AGA neonates (66.7% in both groups), with comparable distributions of SGA (31.7% vs. 30.0%) and LGA (1.7% vs. 3.3%). These findings are consistent with Mandal et al., who reported 68.4% AGA and 29.3% SGA in their ACS group(52) and with Gyamfi-Bannerman et al., who observed minimal SGA differences between steroid-exposed and unexposed neonates.(63) The observed intergroup weight difference (0.04 kg) falls within expected biological variability and aligns with Zhou et al.'s report of 1.65 kg vs. 1.69 kg in ACS-exposed versus unexposed late preterm infants.(64)

Mode of delivery and study cohort:

In this study, LSCS was significantly more common in the ACS group (76.6) compared, to non-ACS group (53.3%), likely reflecting higher-risk pregnancies requiring intervention. This finding aligns with Mandal et al., who reported a 71% LSCS rate in ACS-exposed preterm.(52) Despite the difference in delivery mode, rates of hypoglycemia and hyperbilirubinemia were comparable between LSCS and vaginal deliveries, supporting findings by Zhou et al. that ACS-related metabolic outcomes are independent of delivery route.(64)

Study cohort and outcomes:

This study revealed a significantly higher rate of hypoglycemia in the ACS-exposed group (55%) compared to the non-ACS group (5%), aligning with findings by Mandal et al. (58% vs. 7%)(52) and supporting Zhou et al.'s evidence of corticosteroid-associated glucose fluctuations in late preterm.(64) In contrast, hyperbilirubinemia rates were comparable between groups (41.7% vs. 53.3%, p=0.20), consistent with Madendag and Sahin's findings that ACS does not significantly influence bilirubin metabolism in preterm.(51), though differing from El-Hawary et al., who reported higher rates in term infants exposed to ACS.(60)

Association between ACS and hypoglycemia:

This study demonstrated a strong and statistically significant association between antenatal corticosteroid (ACS) exposure and neonatal hypoglycemia, with ACS-exposed neonates exhibiting 23.22 times higher odds of developing hypoglycemia compared to unexposed neonates (95% CI: 6.53–82.48, p<0.001). This effect size notably exceeds those reported in several earlier studies.

Pettit et al. found that for confounders.(4) Similarly, Üstün et al. reported a statistically significant association with an odds ratio of 1.73, supporting the increased metabolic vulnerability in ACS-exposed neonates.(61) Janssen et al. observed a dose-dependent decline in the lowest glucose levels post-ACS, particularly in the mature preterm subgroup (mean: 38.6 ± 12.8 mg/dL).(59)

Mandal et al., while noting a high incidence overall (58% in the ACS group), observed most hypoglycaemic episodes occurring after 24 hours of life.(52) Di Pasquo et al. reported a 38.4% incidence of neonatal hypoglycemia, with earlier gestational ages showing increased risk.(62)

Collectively, these findings reinforce the biological plausibility of steroid-induced glucose dysregulation via fetal hyperinsulinemia and support the implementation of routine glucose monitoring for all ACS-exposed neonates, especially within the first 24–48 hours, when the risk is highest.

Association between ACS and hyperbilirubinemia:

In this study, no statistically significant association was observed between antenatal corticosteroid (ACS) exposure and neonatal hyperbilirubinemia (41.7% in ACS group vs. 53.3% in non-ACS group, p = 0.20). These findings are consistent with those of El-Hawary et al., who reported no significant differences in bilirubin levels or timing of jaundice onset between ACS-exposed and unexposed neonates.(61) Üstün et al. similarly found no difference in the of jaundice requiring phototherapy between groups (p = 0.32), reinforcing the notion that ACS does not significantly alter bilirubin metabolism in preterm infants.(61)

Although Pettit et al. reported hyperbilirubinemia in neonates exposed betamethasone, with a nearly threefold increased risk, their study focused on late preterm infants (32–36 weeks) and excluded earlier gestations, possibly limiting generalizability to our study population.(4) Mandal et al. observed similar hyperbilirubinemia rates among neonates who received one or two doses of ACS (46.3% each), suggesting that dosing frequency did not significantly impact bilirubin outcomes.(52)

Overall, these findings support the conclusion that ACS exposure does not confer a consistent or independent risk for neonatal hyperbilirubinemia in preterm populations. Hence, routine jaundice surveillance protocols remain appropriate, without the need for additional bilirubin-specific monitoring based solely on ACS exposure.

Neonatal hypoglycemia and ACS characteristics:

This study revealed a significat association between the number of antenatal corticosteroid (ACS) doses and neonatal hypoglycemia. Among the ACS-exposed neonates, 69.7% of hypoglycemia cases occurred in those who received two doses, compared to only 12.1% among those who received a single dose (p = 0.010), suggesting a possible dose-response relationship. This finding aligns with di

Pasquo et al., who reported a higher risk of hypoglycemia neonates exposed to a complete course of corticosteroids, emphasizing the importance of considering cumulative exposure when assessing metabolic risk.(62)

Although not statistically significant (p = 0.715), our study also noted a higher proportion of hypoglycemia in neonates born >48 hours after ACS administration (48.5%), compared to 24–48 hours (48.5%) and <24 hours (3.0%). This is similar to findings by Zhou et al., who demonstrated a significant between hypoglycemia and timing of ACS exposure, with the peak risk observed in neonates delivered 24–48 hours post-administration.(64) This pattern suggests that corticosteroid-induced glucose dysregulation may extend beyond the expected pharmacologic window, warranting further investigation into optimal timing strategies. Additionally,there was no differentiation in hypoglycemia incidence between neonates who was given betamethasone (75.8%) and those receiving dexamethasone (24.2%) (p = 0.881), which aligns with Üstün et al., who found no statstically significant in hypoglycemia incidence between steroid types.(61) These results underscore the importance of individualised glucose monitoring in neonates exposed to ACS, particularly those receiving multiple doses or born after prolonged latency.

Neonatal hyperbilirubinemia and ACS characteristics:

In this study, although no specific ACS-related variables showed a statistically significant association with neonatal hyperbilirubinemia, several clinically relevant patterns were noted. The incidence of hyperbilirubinemia was highest in neonates born more than 48 hours after ACS administration (52.0%), compared to 44.0% in the 24–48-hour group and only 4.0% in the <24-hour group (p = 0.472). This trend may suggest that prolonged latency after ACS exposure could influence bilirubin metabolism, although the lack of statistical significance limits definitive conclusions. Regarding dosage, a majority (60.0%) of hyperbilirubinemia cases occurred in neonates who received two doses of corticosteroids, with a notable 20.0% incidence even among those receiving four doses, highlighting the absence of a consistent dose-dependent pattern. These findings are in partial agreement with Mandal et al., who reported nearly identical hyperbilirubinemia rates in neonates receiving either one or two doses of ACS (46.3% for both), suggesting that bilirubin elevation may not be strongly influenced by the number of doses administered.(52)

Moreover, the type of corticosteroid used—betamethasone (72.0%) versus dexamethasone (28.0%)—did not significantly affect hyperbilirubinemia incidence ($p = 0.650$).(61)

CONCLUSION

This prospective cohort study demonstrated a statistically significant association with ACS exposure and increased frequency of neonatal hypoglycemia, emphasising the importance of routine and timely glucose monitoring in all preterm neonates following ACS administration. Conversely, no significant association was found between ACS exposure and neonatal hyperbilirubinemia, supporting the continuation of standard bilirubin surveillance protocols in this population. These findings highlight the need for close metabolic monitoring, particularly for glycaemic instability, in the postnatal period after ACS exposure in preterm infants.

LIMITATIONS

- Single-centre design with small sample size.

- Long term follow up not included.

SUMMARY

- A prospectve cohort study was conducted on 120 preterm neonates (<37 weeks gestation) to look for effects of ACS exposure on neonatal hypoglycemia and hyperbilirubinemia.
- The study population was divided into two equal groups: 60 neonates born to mothers who received ACS and 60 neonates born to mothers who did not receive ACS.
- Gestational age distribution showed the majority of neonates were moerate to latepreterm in both groups. No extreme pretem neonates were observed in ACS group, which may reflect clinical practice differences or survival limitations.
- There was no statistically significant difference in birth weight between ACS-exposed and unexposed neonates. Both groups had an equal proportion of appropriate for gestational age (AGA) neonates, with comparable rates of small and large for gestational age infants.
- Caesarean deliveries were more frequent in the ACS group (76.6% vs 53.3%), likely reflecting higher-risk pregnancies compared to vaginal deliveries.
- A significantly higher rate of neonatal hypoglycemia was observed in the ACS group (55%) compared to the non-ACS group (5%), with an odds ratio of 23.22 (95% CI: 6.53–82.48, $p < 0.001$), supporting the association of ACS with impaired neonatal glucose regulation.
- Neonatal hyperbilirubinemia occurred in 41.7% of ACS-exposed neonates and 53.3% of non-ACS neonates; this diference has no statistical significance, suggesting nlink between ACS exposure and hyperbilirubinemia.

- The risk of hypoglycemia increased significantly with two doses of ACS, while the timing of administration and steroid type (betamethasone or dexamethasone) did nostatistically significant differences.
- For hyperbilirubinemia, no specific ACS-related factors (dose, timing, or steroid type) were significantly associatewith increased risk of hyperbilirubinemia.
- The findings reinforce the established benefit of ACS in preterm management, but also highlight the need for vigilant glucose monitoring during the 72 hours of life in ACS-exposed neonates.
- Routine hyperbilirubinemia monitoring protocols remain adequate, as ACS was not associated in with an increase in risk of hyperbilirubinemia in the study.

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