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Effect of Timing of Administration of Corticosteroids on Preterm Delivery and Neonatal Outcome

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ABSTRACT

Background: Preterm birth is a leading cause of neonatal morbidity and mortality, and while antenatal corticosteroids (ACS) are widely used to enhance fetal lung maturity, the optimal timing of their administration remains uncertain in low-resource settings. **Objective:** To assess the impact of corticosteroid-to-delivery intervals on neonatal outcomes—specifically respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and neonatal mortality—among women at risk of preterm birth. **Methods:** This descriptive case series was conducted at CMH Gujranwala from 1 January to 2 April 2025, involving 100 high-risk pregnant women aged 18–40 years, at 27+0 to 36+0 weeks gestation. Corticosteroid timing was grouped into ≤ 2 , 2–7, 7–14, and >14 days before delivery. Outcomes were clinically assessed using standardized diagnostic protocols. Ethical approval was obtained, and informed consent secured. Data were analyzed in SPSS v25 using chi-square tests and logistic regression. **Results:** Although RDS occurred in all neonates (100%), the incidence of NEC was highest in the 7–14 day group (73.7%), followed by 2–7 days (60.0%), >14 days (45.5%), and ≤ 2 days (35.0%). Logistic regression showed a significantly higher risk of NEC in the 7–14 day group (adjusted OR = 5.60; 95% CI: 1.49–21.09; $p = 0.010$) compared to ≤ 2 days. BPD was more prevalent in the >14 day group (45.5%). No statistically significant associations were observed for IVH ($p = 0.612$) or neonatal mortality ($p = 0.994$). **Conclusion:** While corticosteroid administration remains crucial in preterm birth management, timing beyond 7 days may increase the risk of complications like NEC. Improved prediction of preterm labor and individualized timing strategies may enhance neonatal outcomes in resource-limited settings.

Keywords: Preterm birth, antenatal corticosteroids, necrotizing enterocolitis, neonatal outcomes, respiratory distress syndrome, intraventricular hemorrhage, maternal risk factors.

INTRODUCTION

Preterm birth remains a significant global health concern and is associated with both immediate and long-term adverse outcomes in neonates. It is recognized as the leading cause of neonatal mortality and a major contributor to under-five child mortality worldwide (1). A large-scale World Health Organization (WHO) study involving nearly 300,000 births across 29 countries demonstrated that different subtypes of preterm birth significantly influence perinatal outcomes, including stillbirth and early neonatal death (2). Preterm birth accounts for approximately 75% of infant morbidity and 70% of neonatal deaths, and is also linked with an increased risk of ocular anomalies, chronic pulmonary disease, and long-term neurodevelopmental impairments (3).

Advancements in neonatal care over recent decades have substantially improved the survival rates of extremely preterm infants. These gains are largely attributable to timely interventions such as exogenous surfactant administration and antenatal corticosteroid (ACS) therapy, rather than the prevention of preterm delivery itself (3,4). Among the most effective prenatal interventions, ACS remains central in the management of pregnancies at risk of preterm birth (5). ACS accelerates fetal lung maturation and has been associated with reductions in perinatal mortality, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and long-term neurological impairments, despite some ongoing debate regarding its optimal timing (6).

The timing of corticosteroid administration plays a critical role in determining neonatal outcomes. Evidence suggests that administering ACS 24 hours to 7 days prior to delivery is associated with significantly better survival rates compared to administration outside this window (7). In one study, the distribution of ACS administration relative to delivery was as follows: 27.5% received ACS less than 2 days before delivery, 36.3% between 2 to 7 days, 17.8% between 7 to 14 days, and 18.4% more than 14 days prior. Corresponding rates of neonatal complications such as necrotizing enterocolitis (NEC), bronchopulmonary dysplasia (BPD), IVH, and RDS varied notably across these groups (8). Another study reported that 50.3% of women received corticosteroids more than seven days prior to delivery, while 49.7% delivered within seven days. Infants born within the 7-day window required less respiratory support and had lower rates of NEC and IVH (9).

Despite global research on this subject, there is a lack of region-specific data from local populations in Pakistan. No prior studies have explored the relationship between the timing of corticosteroid administration and neonatal outcomes in this setting. Therefore, the objective of this study is to evaluate the frequency of corticosteroid administration across different prenatal intervals and to assess associated neonatal outcomes in women at risk of preterm birth. By generating local evidence, this study aims to enhance clinical decision-making regarding ACS timing and improve neonatal care strategies for high-risk pregnancies in our population.

MATERIALS AND METHODS

This was a descriptive case series conducted over a period of three months, from January 1st to April 2nd, 2025, at the Department of Obstetrics and Gynecology, Combined Military Hospital (CMH) Gujranwala. A total of 100 pregnant women were enrolled using non-probability consecutive sampling. Eligible participants included women aged 18–40 years, with parity less than five, presenting with a high risk of preterm delivery between 27+0 and 36+0 weeks of gestation. High-risk status was defined as the presence of one or more of the following conditions: a previous history of preterm delivery, abnormal body mass index (BMI <18.5 or >30 kg/m²), gestational diabetes (oral glucose tolerance test >186 mg/dL), gestational hypertension (blood pressure ≥140/90 mmHg), or premature rupture of membranes (PROM) confirmed through clinical examination. Written informed consent was obtained from all participants. The study adhered to the principles of the Declaration of Helsinki.

Exclusion criteria included multiple pregnancies, evidence of congenital anomalies on ultrasound, prior administration of more than one course of corticosteroids, medically indicated preterm induction or intrauterine fetal demise, and underlying chronic medical conditions such as diabetes mellitus (random blood sugar >200 mg/dL), chronic hypertension (BP ≥160/100 mmHg), and abnormal placental conditions including placenta accreta, increta, previa, or abruption.

All patients received antenatal corticosteroids during antenatal visits, administered by an obstetrician. The timing of corticosteroid administration was determined from antenatal records and categorized into four groups: less than 2 days, 2–7

days, 7–14 days, and more than 14 days prior to delivery. To assess neonatal outcomes, five complications were recorded: respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia (BPD), necrotizing enterocolitis (NEC), and neonatal mortality. RDS was defined as oxygen saturation below 90% at the time of delivery measured via pulse oximetry and requiring immediate respiratory support. However, we acknowledge that relying solely on this parameter may overestimate incidence, and that more comprehensive clinical and radiological confirmation (e.g., chest radiograph, arterial blood gas) would be preferable in future studies. IVH was confirmed through cranial CT imaging during hospitalization, while BPD was diagnosed based on the need for supplemental oxygen beyond 28 days of life. NEC was confirmed by the presence of pneumatosis intestinalis or free air on a horizontal-beam abdominal radiograph. Neonatal death was recorded if the infant expired during the initial hospital stay.

While efforts were made to apply standardized diagnostic definitions, variations in resource availability limited the adoption of globally validated scoring systems such as Bell's criteria for NEC or the NIH definition for BPD. This limitation is acknowledged and should be considered when interpreting results. Data were entered and analyzed using SPSS version 25. Continuous variables such as age, gestational age, BMI, and corticosteroid-to-delivery interval were assessed for normality using the Shapiro-Wilk test and presented as means with standard deviations or medians with interquartile ranges. Categorical variables such as maternal risk factors, corticosteroid timing groups, and neonatal outcomes were reported as frequencies and percentages. Chi-square tests were used to evaluate associations between corticosteroid timing and neonatal outcomes, with a p-value ≤0.05 considered statistically significant. Data were stratified for potential confounders including maternal age, gestational age, parity, BMI, and risk factors. Post-stratification analyses were conducted within each stratum to detect any subgroup-specific associations.

Given the relatively small sample size and the multiplicity of outcomes evaluated, we acknowledge the risk of Type II error, which may account for the lack of statistical significance in some observed associations. Multivariate logistic regression was not performed due to the sample size constraint, which limits the ability to adjust for confounders in a more robust manner. Nonetheless, descriptive trends—such as higher NEC incidence in the 7–14 days group—have been highlighted and warrant further exploration in larger studies. This study contributes preliminary local evidence on corticosteroid timing and neonatal outcomes and provides direction for future prospective multicenter investigations with extended follow-up and improved diagnostic rigor.

RESULTS

The study analyzed data from 100 women at high risk of preterm birth. The mean maternal age was 32.91 ± 4.09 years, with most participants (64.0%) between 31–40 years. The mean gestational age at delivery was 32.83 ± 2.69 weeks. Nearly half (49.0%) of the participants were obese (BMI >30), while 13.0% were very lean (BMI <18.5). Multiparity (<3 prior deliveries) was present in 70.0% of women. Risk factors included a history of previous preterm

birth (42.0%), gestational diabetes (56.0%), gestational hypertension (51.0%), and premature rupture of membranes (48.0%). Mode of delivery was nearly equally distributed, with 52.0% undergoing cesarean section and 48.0% delivering vaginally.

Corticosteroids were administered at varying intervals prior to delivery. The average interval between administration and delivery was 6.06 ± 21.88 days (median 5.0, IQR 6). Half of the participants (50.0%) delivered within 2–7 days of receiving corticosteroids, 20.0% within ≤ 2 days, 19.0% between 7–14 days, and 11.0% after >14 days.

Table 1: Descriptive statistics of age, gestational age, BMI and duration between corticosteroids and delivery

Variable	Mean \pm SD	Median (IQR)
Age (years)	32.91 \pm 4.09	33.00 (7)
Gestational age at delivery (weeks)	32.83 \pm 2.69	34.00 (3.7)
Body Mass Index (BMI)	27.07 \pm 2.55	27.00 (3)
Corticosteroid-to-delivery interval (days)	6.06 \pm 21.88	5.00 (6)

Respiratory distress syndrome (RDS) was observed in all neonates (100.0%) based on oxygen saturation criteria. Intraventricular hemorrhage (IVH) was reported in 34.0%, bronchopulmonary dysplasia (BPD) in 33.0%, and necrotizing

enterocolitis (NEC) in 56.0%. Neonatal mortality occurred in 45.0% of the cases. These complications occurred across all corticosteroid timing groups.

Table 2: Neonatal outcomes and corticosteroid-to-delivery timing distribution

Variable	Frequency	Percentage (%)
≤ 2 days before delivery	20	20.0
2–7 days	50	50.0
7–14 days	19	19.0
>14 days	11	11.0
Mode of delivery – Cesarean section	52	52.0
Mode of delivery – Vaginal	48	48.0
Respiratory distress syndrome (RDS)	100	100.0
Intraventricular hemorrhage (IVH) – Yes	34	34.0
Bronchopulmonary dysplasia (BPD) – Yes	33	33.0
Necrotizing enterocolitis (NEC) – Yes	56	56.0
Neonatal death – Yes	45	45.0

No statistically significant differences were found in maternal age, gestational age, parity, previous preterm birth, BMI category, gestational diabetes, gestational hypertension, or PROM across the corticosteroid timing groups (all $p > 0.05$). Similarly, there were no statistically significant associations between corticosteroid timing and neonatal outcomes including IVH ($p=0.612$), BPD ($p=0.232$), NEC ($p=0.078$), or neonatal death ($p=0.994$). However, a trend of higher NEC (73.7%) was observed

in the 7–14 day group, and BPD was most frequent in the >14 day group (45.5%). To account for potential confounding factors, a logistic regression analysis was conducted with NEC as the outcome variable. Compared to the ≤ 2 days reference group, neonates whose mothers received corticosteroids 7–14 days before delivery had significantly higher odds of developing NEC (OR = 5.60; 95% CI: 1.49–21.09; $p = 0.010$). The 2–7 day group also showed elevated but non-significant odds (OR = 2.90; $p = 0.062$).

Table 3: Comparison of corticosteroid timing with maternal and neonatal variables

Variable	p-value
Age group (25–30 vs 31–40)	0.598
Gestational age group	0.332
Parity	0.056
Previous preterm birth	0.157
Very lean	0.271
Obesity	0.654
Gestational diabetes	0.874
Gestational hypertension	0.138
PROM	0.499
Mode of delivery	0.824
Intraventricular hemorrhage	0.612
Bronchopulmonary dysplasia	0.232
Necrotizing enterocolitis	0.078
Neonatal death	0.994

Corticosteroid administration more than 14 days before delivery did not significantly influence NEC risk. Other variables including gestational age, gestational diabetes, PIH, and PROM were not significant predictors.

Table 4: Logistic Regression Analysis – Predictors of Necrotizing Enterocolitis (NEC)

Variable	Odds Ratio (OR)	95% Confidence Interval	p-value
Timing: 2–7 days	2.90	0.95 – 8.87	0.062
Timing: 7–14 days	5.60	1.49 – 21.09	0.010
Timing: >14 days	1.78	0.41 – 7.69	0.438
Gestational Age (per week)	0.85	0.67 – 1.08	0.186
Gestational Diabetes	1.42	0.58 – 3.45	0.438
Pregnancy-Induced Hypertension	1.28	0.52 – 3.14	0.593
PROM	1.76	0.73 – 4.26	0.211

Although no statistically significant differences were found in unadjusted group comparisons, adjusted logistic regression revealed a significant association between corticosteroid administration 7–14 days before delivery and increased NEC risk. These findings suggest that while timing may not appear influential in univariate analyses, potential effects may emerge after adjusting for clinical confounders. Such trends warrant further validation in larger, multicenter studies.

DISCUSSION

Prematurity continues to be the leading cause of death in children under five years of age, accounting for nearly one-third of all neonatal deaths within the first 28 days of life (10). In response, antenatal corticosteroid (ACS) therapy has emerged as one of the most effective interventions for improving neonatal outcomes when preterm delivery is imminent. The optimal timing of administration is widely considered critical, with greatest benefit observed when corticosteroids are administered between 24 hours and 7 days prior to delivery (11). This timing window has been associated with enhanced fetal lung maturation and reduced rates of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), and neonatal mortality (14,16).

In our study, the maternal population was characterized by high rates of known risk factors for preterm delivery—obesity (49.0%), gestational diabetes (56.0%), gestational hypertension (51.0%), and PROM (48.0%)—consistent with global data identifying these conditions as key contributors to prematurity (12). Despite the predominance of corticosteroid administration within the optimal 2–7 day window (50.0%), neonatal complications remained alarmingly frequent: 100.0% of neonates developed RDS, 34.0% experienced IVH, 33.0% developed BPD, and 56.0% were diagnosed with NEC. Neonatal mortality was recorded in nearly half (45.0%) of the cohort.

The universal incidence of RDS is particularly striking and raises concern about potential misclassification or the limitations of the diagnostic criteria used. In our setting, RDS was defined as oxygen saturation below 90% at birth without standardized duration thresholds or confirmatory imaging. This likely overestimates true RDS prevalence, especially in cases of transient desaturation or where supportive diagnostics were unavailable. In contrast, Lau *et al.* reported a significantly lower incidence of RDS (17.6%) in neonates delivered within 7 days of corticosteroid administration (13), suggesting that stringent

criteria and imaging confirmation may yield more accurate estimates. Future studies should incorporate standardized tools, including chest radiographs, arterial blood gas analysis, and NIH RDS criteria, to ensure comparability.

Similarly, our outcome definitions for NEC and BPD relied on radiographic signs and oxygen dependence, respectively, rather than international gold standards such as Bell's staging for NEC and NIH consensus criteria for BPD. These methodological deviations, though necessitated by resource constraints, limit the generalizability and internal validity of our findings. That said, our adjusted logistic regression model revealed a significantly increased risk of NEC when corticosteroids were administered 7–14 days before delivery (OR = 5.60; $p = 0.010$), even after controlling for gestational age, PROM, PIH, and gestational diabetes. This aligns with evidence from Battarbee *et al.*, who also observed an increased risk of adverse outcomes when the steroid-to-birth interval exceeded 7 days (8,16). The underlying mechanism may involve waning corticosteroid efficacy over time, as pharmacologic studies suggest that the beneficial pulmonary effects of betamethasone and dexamethasone begin to diminish beyond one week (11). Repeat dosing was not practiced in our study, which could have compounded the decline in protection for the >7-day group.

Although our unadjusted analysis showed no statistically significant associations between corticosteroid timing and neonatal outcomes such as IVH ($p = 0.612$), BPD ($p = 0.232$), or neonatal death ($p = 0.994$), several clinically relevant trends were observed. For instance, NEC incidence peaked in the 7–14 day group (73.7%), and BPD was most frequent among neonates whose mothers delivered >14 days after steroid administration (45.5%). These trends support the hypothesis that the benefit of ACS diminishes with time and emphasize the importance of timely delivery relative to dosing. The lack of statistical significance is likely due to limited power, as the sample size of 100 subjects restricts the ability to detect modest but meaningful differences. Importantly, while previous multicenter studies in high-income countries report improved outcomes with optimal ACS timing (7,16), such results may not be directly transferrable to low-resource settings like Pakistan. Variability in access to NICUs, availability of neonatal ventilation support, and inconsistency in steroid administration protocols may contribute to the high burden of neonatal morbidity observed in our cohort. For example, even when ACS was administered within the recommended window, the absence of advanced

neonatal care infrastructure may have attenuated the potential benefits. Furthermore, maternal comorbidities may exert additive effects, and their complex interactions were not fully accounted for in this analysis due to sample size limitations.

This study does, however, offer several strengths. It is among the first in Pakistan to explore the timing of ACS administration in a defined high-risk population using a structured observational design. Additionally, the stratification of outcomes across four distinct timing windows provides nuanced insights that challenge the assumption that any ACS exposure is uniformly protective. Nonetheless, our findings should be interpreted cautiously. The sample size was modest, limiting the robustness of multivariate analyses and increasing the likelihood of Type II error. Simplified outcome definitions, absence of repeat steroid dosing, and reliance on non-randomized data further restrict causal inference.

Future research should focus on large-scale, multicenter studies with standardized diagnostic criteria, longer follow-up periods, and consideration of repeat steroid dosing protocols. These studies should also incorporate cost-benefit analyses and explore the role of maternal biomarkers in predicting delivery timing, which could enable better synchronization of corticosteroid administration with the onset of labor. Such data will be critical in informing updated national guidelines and tailoring interventions to the specific realities of healthcare delivery in resource-constrained environments.

In conclusion, our study reinforces the importance of corticosteroid timing in mitigating preterm neonatal complications, especially NEC. While unadjusted analyses did not yield statistically significant differences, multivariate modeling highlighted a critical risk period beyond 7 days post-steroid administration. These findings underscore the need for vigilant monitoring, improved prediction of preterm birth, and timely obstetric intervention to maximize the benefits of ACS therapy.

CONCLUSION

It is concluded that the majority of women received corticosteroids within 2–7 days before delivery, followed by those who received them within ≤ 2 days, 7–14 days, and more than 14 days before birth. The findings suggest that while corticosteroid administration remains essential in the management of preterm births, the timing of administration did not show a statistically significant difference in neonatal outcomes. Key complications—including respiratory distress syndrome, intraventricular hemorrhage, bronchopulmonary dysplasia, necrotizing enterocolitis, and neonatal mortality—were observed across all timing groups. Furthermore, maternal characteristics such as age, gestational age, parity, history of preterm birth, obesity, gestational diabetes, and mode of delivery did not differ significantly with respect to corticosteroid timing.

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