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**Original Research Article**

# Comparison of single versus multiple doses of antenatal corticosteroid administration on neonatal mortality and morbidity: a prospective observational study

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## ABSTRACT

**Background:** Antenatal corticosteroids (ACS) reduce respiratory and other complications of prematurity, but the comparative benefit of a single versus a complete multiple-dose course in real-world, resource-limited settings is not well defined. Objectives were to compare the effect of single versus multiple doses of antenatal dexamethasone on neonatal mortality and morbidity among preterm neonates delivered between 24 and 34 weeks of gestation.
**Methods:** This prospective observational study was conducted over 18 months in the neonatal intensive care unit (NICU), Department of Paediatrics, Government Medical College and Hospital, Cuddalore. Two hundred preterm neonates (24-34 weeks) were enrolled by convenience sampling and stratified into five groups by antenatal dexamethasone exposure: no dose, one, two, three, or four doses. Maternal and neonatal variables were recorded on a structured proforma. Categorical data were analysed with the chi-square test and continuous data with one-way ANOVA/Student's t-test; multivariate logistic regression identified independent predictors of mortality. $P<0.05$ was considered significant.
**Results:** Groups were comparable for maternal age, comorbidities, gestational age, sex and mode of delivery (all $p>0.05$). Mean birth weight rose from 1385±310 g (no dose) to 1722±238 g (four doses, $p<0.001$), and 1- and 5-minute APGAR scores improved progressively ($p<0.001$). Respiratory distress syndrome (RDS) fell from 60.0% to 13.5% ($p<0.001$), intraventricular haemorrhage (IVH) from 20.0% to 3.8% ($p=0.042$), necrotising enterocolitis (NEC) from 16.7% to 1.9% ($p=0.038$), and overall neonatal sepsis from 33.3% to 7.7% ($p=0.019$). Requirement for CPAP, mechanical ventilation and surfactant, NICU admission and length of NICU stay all declined significantly with increasing dose ($p<0.05$). Neonatal mortality fell from 20.0% to 3.8% ($p=0.043$). Hypoglycaemia was more frequent with increasing exposure (16.7% to 25.0%, $p=0.042$). On multivariate analysis, gestational age <30 weeks (OR 3.24), birth weight <1500 g (OR 2.89), incomplete steroid exposure ≤2 doses (OR 2.52), RDS (OR 2.31), neonatal sepsis (OR 3.76) and IVH (OR 2.14) independently predicted mortality.
**Conclusions:** Completion of the recommended four-dose antenatal dexamethasone course was associated with a graded, significant reduction in neonatal mortality and major morbidity compared with partial or no exposure. Ensuring timely completion of the full ACS course in women at risk of preterm birth should be prioritised in clinical practice.

**Keywords:** Antenatal corticosteroids, Dexamethasone, Preterm birth, Neonatal mortality, Respiratory distress syndrome, Multiple doses

## INTRODUCTION

Preterm birth is the leading cause of neonatal death and the single largest contributor to under-5 mortality worldwide. Globally, an estimated 15 million babies are born preterm every year, representing more than 10% of all live births, and this proportion continues to rise in many low- and middle-income countries.[1,2] South and South-East Asia, including India, together account for the largest absolute share of preterm births globally, and national data confirm that prematurity-related complications remain a dominant driver of neonatal mortality in India.[3]

The risk of complications rises sharply as gestational age falls. Preterm neonates are vulnerable across virtually every organ system because of physiological immaturity, and this immaturity underlies the major morbidities of prematurity such as RDS, IVH, NEC and neonatal sepsis, that together account for the bulk of neonatal deaths and long-term disability among survivors.[4,5] Beyond the immediate neonatal period, survivors of extreme prematurity carry a disproportionate long-term burden of chronic lung disease, cerebral palsy, and neurodevelopmental and sensory impairment, imposing a substantial cost on families and health systems.[6]

At the level of individual organ systems, the pathophysiological basis of these morbidities is well characterised. Deficient surfactant production by immature type II pneumocytes leads to alveolar collapse and RDS; fragility of the periventricular germinal matrix vasculature predisposes to IVH; gut immaturity and impaired mesenteric perfusion predispose to NEC; and an immature innate and adaptive immune system leaves preterm neonates highly susceptible to early-and late-onset sepsis.[7-10] Interventions that accelerate maturation of these systems before birth therefore have the potential to meaningfully alter neonatal outcomes.

ACS remain the single most effective antenatal intervention available for this purpose. Since the landmark randomised trial by Liggins and Howie in 1972 first demonstrated that antepartum glucocorticoids reduced the incidence of RDS in preterm infants, a large body of subsequent trial and Cochrane-level evidence has confirmed that a single course of ACS given to women at risk of preterm birth between 24 and 34 weeks of gestation reduces neonatal mortality, RDS, IVH and NEC without major short-term maternal or fetal harm.[11-13] On this basis, the World Health Organization, the American College of Obstetricians and Gynecologists and comparable bodies uniformly recommend a single course of ACS for women at imminent risk of preterm delivery in this gestational window.[14] Two regimens are in common use-intramuscular betamethasone (two doses of 12 mg, 24 hours apart) or intramuscular dexamethasone (four doses of 6 mg, 12 hours apart)-with broadly comparable efficacy for fetal lung maturation.[15,16]

The clinical benefit of ACS is greatest when delivery occurs within seven days of treatment, and diminishes if birth is substantially delayed.[17] In practice, however, the precise timing of preterm delivery is difficult to predict, and a considerable proportion of women who begin a corticosteroid course do not deliver within this optimal window. This uncertainty has generated sustained clinical interest in whether administering additional-or "rescue"/multiple-doses beyond the first course can extend or enhance protection.[18] Large trials such as the multiple courses of antenatal corticosteroids for preterm birth (MACS) study and the antenatal late preterm steroids (ALPS) trial, together with individual participant data meta-analyses of repeat-dose regimens, have shown that additional corticosteroid exposure can further reduce respiratory morbidity, but the evidence is not uniform, and repeated or excessive exposure has been linked to concerns including fetal growth restriction, altered birth weight, hypothalamic-pituitary-adrenal axis suppression and possible long-term cardiometabolic and neurodevelopmental effects.[19-23] Consequently, the ideal number of antenatal corticosteroid doses-and the relative benefit of a partial versus a completed course-continues to be debated, and "rescue" courses are recommended cautiously and only in selected circumstances by current guidelines.[24]

This question carries particular weight in resource-constrained settings such as district and tertiary government hospitals in India, where referral delays, uncertain estimation of gestational age and variability in obstetric practice frequently result in women receiving an incomplete rather than a deliberately "multiple-dose" course of antenatal dexamethasone. Whether neonatal outcomes differ meaningfully across the full spectrum-from no exposure, through partial exposure, to a completed four-dose course-is therefore directly relevant to clinical decision-making and resource allocation in such settings, yet dedicated prospective data from this context are limited.

We therefore undertook this prospective observational study to compare neonatal mortality and major morbidity-RDS, IVH, NEC, neonatal sepsis, and a range of secondary respiratory and metabolic outcomes-across preterm neonates stratified by the number of antenatal dexamethasone doses received (none, one, two, three or four), with the aim of generating context-specific evidence to guide the appropriate and timely administration of antenatal corticosteroids in women at risk of preterm birth.

## METHODS

### *Study design and setting*

This was a prospective observational study conducted in the NICU, Department of Paediatrics, Government Medical College and Hospital, Cuddalore, Tamil Nadu, India. Antenatal corticosteroids were administered in the

Department of Obstetrics and Gynaecology of the same institution, and neonatal outcomes were subsequently followed and recorded in the NICU.

***Study duration and population***

The study was conducted over a period of 18 months, from (Augst 2024 to January 2026). The study population comprised preterm neonates born between 24 and 34 weeks of gestation who were delivered at, or referred to, the study institution during the study period.

***Sample size and sampling method***

A total of 200 preterm neonates fulfilling the eligibility criteria were enrolled. The sample size was estimated from previously published literature at a 95% confidence level and 5% level of significance. Participants were recruited by a convenience sampling method.

***Inclusion criteria***

Preterm neonates born between 24 and 34 completed weeks of gestation, neonates delivered at or referred to the study institution; and neonates whose mothers had either received antenatal dexamethasone or had no antenatal corticosteroid exposure were included in the study.

***Exclusion criteria***

Neonates with major congenital anomalies, chromosomal abnormalities, or incomplete medical records, and neonates born to mothers who received corticosteroids for maternal medical indications unrelated to fetal lung maturation were excluded.

***Ethical considerations***

Study was approved by institutional ethics committee, and written informed consent was obtained from parents or guardians of all enrolled neonates prior to inclusion.

***Study groups***

Enrolled neonates were stratified into five groups according to documented antenatal dexamethasone exposure of the mother: Group I-no antenatal corticosteroid exposure; Group II-one dose (6 mg intramuscularly); Group III-two doses, 12 hours apart; Group IV-three doses; and Group V-four doses, completing the standard antenatal corticosteroid protocol. All neonates were followed prospectively from birth until discharge or death.

***Data collection***

Maternal and neonatal data were recorded on a structured proforma from maternal case records, labour-room records, NICU records and neonatal case sheets. Maternal variables included age, gestational age at delivery, premature labour, premature/prelabour rupture of membranes, gestational hypertension/pre-eclampsia, gestational diabetes, multiple gestation, anaemia, oligohydramnios, antepartum haemorrhage, mode of delivery, and the number of antenatal corticosteroid doses received. Neonatal variables included sex, birth weight, 1-and 5-minute APGAR scores, small-for-gestational-age (SGA) status, NICU admission, requirement for CPAP/mechanical ventilation/surfactant, RDS, IVH, NEC, early-and late-onset sepsis, hypoglycaemia, hyperbilirubinaemia, duration of NICU stay, and neonatal mortality.

***Definitions and assessments***

Gestational age was assessed from the last menstrual period and confirmed by first-trimester ultrasonography, or by Ballard scoring where these were unavailable. Birth weight was recorded on a calibrated digital neonatal weighing scale. APGAR scores were assigned by the attending paediatrician at 1 and 5 minutes. RDS was diagnosed on clinical grounds (tachypnoea, chest retractions, grunting) supported by chest radiography. Neonatal sepsis was diagnosed using clinical features, sepsis screening parameters and blood culture where available.

Hypoglycaemia was confirmed by glucometer and laboratory testing per standard neonatal criteria. IVH was assessed by cranial ultrasonography on day 3 and day 7 of life (or earlier if clinically indicated).[25] NEC was diagnosed using modified Bell's staging criteria.[26] Hyperbilirubinaemia was assessed from serum bilirubin levels and clinical evaluation.

***Outcome measures***

Primary outcome measures were neonatal mortality, RDS, IVH, NEC and neonatal sepsis. Secondary outcome measures were birth weight, APGAR scores, NICU admission, requirement for CPAP/mechanical ventilation/ surfactant, hypoglycaemia, hyperbilirubinaemia, duration of NICU stay and SGA.

***Statistical analysis***

Data were entered in Microsoft excel and analysed using SPSS version 27.0. Categorical variables were summarised as frequencies and percentages and compared using the chi-square test. Continuous variables were expressed as mean±standard deviation and compared using one-way analysis of variance (ANOVA) or Student's t test, as appropriate.

Multivariate logistic regression was performed to identify independent predictors of neonatal mortality, with results expressed as adjusted odds ratios (OR) with 95% confidence intervals (CI). A two-tailed $p<0.05$ was considered statistically significant.

## RESULTS

A total of 200 preterm neonates born between 24 and 34 weeks of gestation were included in the study. Of these, 30 (15.0%) received no antenatal corticosteroid exposure, while 34 (17.0%), 40 (20.0%), 44 (22.0%), and 52 (26.0%) received 1-4 doses of antenatal dexamethasone, respectively.

### *Baseline maternal and neonatal characteristics*

Table 1 presents the baseline maternal and neonatal characteristics according to antenatal corticosteroid exposure. Maternal age distribution was comparable across all exposure groups, with the majority of mothers aged 20-25 years (35.0%) or 26-30 years (33.5%). The prevalence of maternal comorbidities, including pregnancy-induced hypertension/pre-eclampsia (19.0%), gestational diabetes mellitus (12.0%), PROM/PPROM (22.5%), and other comorbidities (10.5%), showed no significant differences between exposure groups. Similarly, gestational age at delivery, neonatal sex, and mode of delivery were evenly distributed across the five groups, indicating comparable baseline characteristics.

### *Birth characteristics and neonatal outcomes*

A progressive improvement in neonatal birth characteristics was observed with increasing antenatal corticosteroid exposure (Table 2). Mean birth weight increased significantly from 1385±310 g in the no-dose group to 1722±238 g among neonates receiving four doses ($p<0.001$). Likewise, mean APGAR scores at both 1 minute and 5 minutes increased steadily with greater corticosteroid exposure, rising from 5.7±1.4 and 6.5±1.3, respectively, in the no-dose group to 7.5±0.8 and 8.3±0.8 in the four-dose group (both $p<0.001$).

The requirement for intensive neonatal care decreased significantly as the number of corticosteroid doses increased. NICU admission declined from 100.0% in neonates without corticosteroid exposure to 80.8% among those receiving four doses ($p=0.018$). Similarly, the need for continuous positive airway pressure (CPAP), mechanical ventilation, and surfactant therapy showed significant reductions with increasing corticosteroid exposure (all $p<0.01$). In contrast, the proportion of small-for-gestational-age neonates remained similar across groups ($p=0.312$).

Respiratory and infective morbidities also demonstrated a favourable trend with increasing corticosteroid exposure. The incidence of RDS decreased significantly from 60.0% in the no-dose group to 13.5% in the four-dose group ($p<0.001$). Significant reductions were also observed for IVH (20.0% vs. 3.8%; $p=0.042$), NEC (16.7% vs. 1.9%; $p=0.038$), early-onset sepsis (23.3% vs. 5.8%; $p=0.047$), and overall neonatal sepsis (33.3% vs. 7.7%; $p=0.019$). Although late-onset sepsis decreased numerically across the exposure groups, the difference did not reach statistical significance ($p=0.089$).

Among metabolic complications, the incidence of hypoglycaemia increased significantly with increasing corticosteroid exposure, from 16.7% in the no-dose group to 25.0% in the four-dose group ($p=0.042$). However, hyperbilirubinaemia occurred at similar rates across all groups ($p=0.138$).

Duration of NICU stay decreased progressively with increasing antenatal corticosteroid exposure, falling from 18.1±6.3 days in the no-dose group to 10.4±4.1 days among neonates receiving four doses ($p<0.001$). Neonatal mortality also declined significantly, from 20.0% in the no-dose group to 3.8% in the four-dose group ($p=0.043$), while the survival rate increased correspondingly from 80.0% to 96.2%.

**Table 1: Baseline maternal and neonatal characteristics according to the antenatal corticosteroid exposure, (n=200).**

| Characteristics | No dose, (n=30) (%) | 1 dose, (n=34) (%) | 2 doses, (n=40) (%) | 3 doses, (n=44) (%) | 4 doses, (n=52) (%) | Total, (n=200) (%) |
|---|---|---|---|---|---|---|
| **Maternal age (in years)** | | | | | | |
| <20 | 2 (6.7) | 3 (8.8) | 3 (7.5) | 4 (9.1) | 4 (7.7) | 16 (8.0) |
| 20-25 | 11 (36.7) | 12 (35.3) | 14 (35.0) | 15 (34.1) | 18 (34.6) | 70 (35.0) |
| 26-30 | 10 (33.3) | 11 (32.4) | 14 (35.0) | 15 (34.1) | 17 (32.7) | 67 (33.5) |
| >30 | 7 (23.3) | 8 (23.5) | 9 (22.5) | 10 (22.7) | 13 (25.0) | 47 (23.5) |
| **Maternal comorbidity** | | | | | | |
| PIH/ pre-eclampsia | 6 (20.0) | 6 (17.6) | 8 (20.0) | 8 (18.2) | 10 (19.2) | 38 (19.0) |
| Gestational diabetes mellitus | 4 (13.3) | 4 (11.8) | 5 (12.5) | 5 (11.4) | 6 (11.5) | 24 (12.0) |
| PROM/ PPROM | 7 (23.3) | 8 (23.5) | 9 (22.5) | 10 (22.7) | 11 (21.2) | 45 (22.5) |
| Other comorbidity | 3 (10.0) | 4 (11.8) | 4 (10.0) | 5 (11.4) | 5 (9.6) | 21 (10.5) |
| No comorbidity | 10 (33.3) | 12 (35.3) | 14 (35.0) | 16 (36.4) | 20 (38.5) | 72 (36.0) |
| **Gestational age (in weeks)** | | | | | | |
| 24-28 | 8 (26.7) | 8 (23.5) | 8 (20.0) | 8 (18.2) | 8 (15.4) | 40 (20.0) |
| 28-30 | 8 (26.7) | 9 (26.5) | 10 (25.0) | 11 (25.0) | 12 (23.1) | 50 (25.0) |

Continued.

| Characteristics | No dose, (n=30) (%) | 1 dose, (n=34) (%) | 2 doses, (n=40) (%) | 3 doses, (n=44) (%) | 4 doses, (n=52) (%) | Total, (n=200) (%) |
|---|---|---|---|---|---|---|
| 30-32 | 7 (23.3) | 8 (23.5) | 10 (25.0) | 11 (25.0) | 15 (28.8) | 51 (25.5) |
| 32-34 | 7 (23.3) | 9 (26.5) | 12 (30.0) | 14 (31.8) | 17 (32.7) | 59 (29.5) |
| **Sex of the child** | | | | | | |
| Male | 17 (56.7) | 18 (52.9) | 22 (55.0) | 24 (54.5) | 28 (53.8) | 109 (54.5) |
| Female | 13 (43.3) | 16 (47.1) | 18 (45.0) | 20 (45.5) | 24 (46.2) | 91 (45.5) |
| **Mode of delivery** | | | | | | |
| Vaginal delivery | 13 (43.3) | 15 (44.1) | 17 (42.5) | 18 (40.9) | 20 (38.5) | 83 (41.5) |
| LSCS | 17 (56.7) | 19 (55.9) | 23 (57.5) | 26 (59.1) | 32 (61.5) | 117 (58.5) |

*PIH-pregnancy-induced hypertension; PROM/PPROM-(pre-labour) premature rupture of membranes; LSCS-lower-segment caesarean section. P values are for comparison across the five exposure groups within each characteristic block (Chi-square test).

**Table 2: Neonatal birth characteristics, care requirements, and respiratory, infective, metabolic and survival outcomes according to antenatal corticosteroid exposure, (n=200).**

| Domains | Outcomes | No dose, (n=30) (%) | 1 dose, (n=34) (%) | 2 doses, (n=40) (%) | 3 doses, (n=44) (%) | 4 doses, (n=52) (%) | P value |
|---|---|---|---|---|---|---|---|
| **Birth characteristics (mean±SD)** | Birth weight (g) | 1385±310 | 1468±295 | 1558±272 | 1635±255 | 1722±238 | <0.001 |
| | APGAR score at 1 minute | 5.7±1.4 | 6.2±1.3 | 6.7±1.1 | 7.1±1.0 | 7.5±0.8 | <0.001 |
| | APGAR score at 5 minutes | 6.5±1.3 | 7.1±1.2 | 7.5±1.0 | 7.9±0.9 | 8.3±0.8 | <0.001 |
| **Neonatal care** | NICU admission | 30 (100) | 32 (94.1) | 36 (90.0) | 38 (86.4) | 42 (80.8) | 0.018 |
| | CPAP required | 15 (50.0) | 13 (38.2) | 10 (25.0) | 7 (15.9) | 5 (9.6) | 0.003 |
| | Mechanical ventilation | 10 (33.3) | 8 (23.5) | 6 (15.0) | 4 (9.1) | 3 (5.8) | 0.006 |
| | Surfactant therapy | 11 (36.7) | 9 (26.5) | 7 (17.5) | 4 (9.1) | 3 (5.8) | 0.005 |
| | Small for gestational age (in weeks) | 8 (26.7) | 7 (20.6) | 9 (22.5) | 6 (13.6) | 7 (13.5) | 0.312 |
| **Respiratory and infective morbidity** | RDS | 18 (60.0) | 16 (47.1) | 13 (32.5) | 10 (22.7) | 7 (13.5) | <0.001 |
| | IVH | 6 (20.0) | 5 (14.7) | 4 (10.0) | 3 (6.8) | 2 (3.8) | 0.042 |
| | NEC | 5 (16.7) | 4 (11.8) | 3 (7.5) | 2 (4.5) | 1 (1.9) | 0.038 |
| | Early-onset sepsis | 7 (23.3) | 6 (17.6) | 5 (12.5) | 4 (9.1) | 3 (5.8) | 0.047 |
| | Late-onset sepsis | 3 (10.0) | 2 (5.9) | 2 (5.0) | 1 (2.3) | 1 (1.9) | 0.089 |
| | Overall neonatal sepsis | 10 (33.3) | 8 (23.5) | 7 (17.5) | 5 (11.4) | 4 (7.7) | 0.019 |
| **Metabolic complications** | Hypoglycaemia | 5 (16.7) | 6 (17.6) | 7 (17.5) | 10 (22.7) | 13 (25.0) | 0.042 |
| | Hyperbilirubinaemia | 9 (30.0) | 11 (32.4) | 12 (30.0) | 13 (29.5) | 14 (26.9) | 0.138 |
| **Hospital outcome** | NICU stay (days), mean±SD | 18.1±6.3 | 15.8±5.7 | 13.7±5.2 | 11.9±4.7 | 10.4±4.1 | <0.001 |
| **Survival outcome** | Mortality | 6 (20.0) | 5 (14.7) | 4 (10.0) | 3 (6.8) | 2 (3.8) | 0.043 |
| | Survival | 24 (80.0) | 29 (85.3) | 36 (90.0) | 41 (93.2) | 50 (96.2) | - |

**Table 3: Multivariate logistic regression analysis of independent predictors of neonatal mortality.**

| Variables | Adjusted OR | 95% CI | P value |
|---|---|---|---|
| **Gestational age <30 weeks** | 3.24 | 1.41-7.48 | 0.006 |
| **Birth weight <1500 gm** | 2.89 | 1.27-6.57 | 0.011 |
| **Incomplete steroid exposure (≤2 doses)** | 2.52 | 1.17-5.42 | 0.018 |
| **RDS** | 2.31 | 1.08-4.95 | 0.031 |
| **Neonatal sepsis** | 3.76 | 1.39-10.18 | 0.009 |
| **IVH** | 2.14 | 1.02-4.51 | 0.044 |

***Multivariate logistic regression analysis of neonatal mortality***

The multivariate logistic regression model identified several independent predictors of neonatal mortality (Table 3). Neonates delivered before 30 weeks of gestation had more than a threefold increased risk of mortality (adjusted OR=3.24, 95% CI: 1.41-7.48; p=0.006). Birth weight below 1500 g was also independently associated with mortality (adjusted OR=2.89, 95% CI: 1.27-6.57; p=0.011).

Incomplete antenatal corticosteroid exposure (≤2 doses) increased odds of neonatal death by approximately 2.5-

fold (adjusted OR=2.52, 95% CI: 1.17-5.42; p=0.018). Furthermore, RDS (adjusted OR=2.31, 95% CI: 1.08-4.95; p=0.031), neonatal sepsis (adjusted OR=3.76, 95% CI: 1.39-10.18; p=0.009), and IVH (adjusted OR=2.14, 95% CI: 1.02-4.51; p=0.044) remained significant independent predictors of neonatal mortality after adjustment for potential confounding variables.

## DISCUSSION

Despite substantial progress in obstetric and neonatal care, preterm birth remains a leading cause of neonatal death, and antenatal corticosteroids remain among the most effective interventions for improving outcomes in this population by accelerating fetal lung maturation, surfactant synthesis and the maturation of other fetal organ systems.[11,27] The relative benefit of a partial versus a completed corticosteroid course, however, is less clearly established, and this prospective observational study was designed to address that gap by comparing outcomes across preterm neonates stratified by the exact number of antenatal dexamethasone doses received.

### *Distribution of corticosteroid exposure and baseline comparability*

Most neonates in our cohort belonged to the four-dose group, reflecting that the majority of mothers were able to complete the recommended course before delivery-a distribution consistent with that reported in the WHO Antenatal Corticosteroid Trial by Althabe et al and in other pragmatic, population-based implementation studies, where completion of the full course was likewise associated with more favourable neonatal outcomes.[20] Importantly, the five exposure groups in our study were well balanced for maternal age, comorbidities, gestational age, neonatal sex and mode of delivery, minimising confounding and strengthening the validity of the outcome comparisons; pregnancy-induced hypertension/pre-eclampsia and PROM/PPROM were the leading maternal risk factors identified, consistent with their recognised role as major antecedents of spontaneous and indicated preterm birth.[4]

### *Birth weight and APGAR scores*

Birth weight increased progressively with increasing corticosteroid exposure. This gradient most plausibly reflects that mothers who progress further through a corticosteroid course tend to remain pregnant for longer, allowing further fetal growth, rather than a direct fetal growth-promoting effect of the drug itself-a distinction supported by pharmacological and clinical reviews of antenatal corticosteroid regimens.[16] The parallel, significant improvement in 1-and 5-minute APGAR scores with increasing exposure is consistent with enhanced cardiorespiratory adaptation at birth attributable to greater lung maturity and surfactant production, in keeping with outcomes reported from large steroid-exposed preterm cohorts.[27]

### *Small for gestational age*

The proportion of SGA neonates did not differ significantly across groups. This finding is reassuring and argues against a clinically important adverse effect of a completed four-dose dexamethasone course on fetal growth in this cohort, in line with data from major repeat-course corticosteroid trials that found no consistent excess of growth restriction with standard-course regimens.[19]

### *NICU admission and respiratory support*

NICU admission fell from 100% in the no-dose group to 80.8% in the four-dose group, and the requirement for CPAP, mechanical ventilation and surfactant therapy declined in parallel with increasing corticosteroid exposure. These findings mirror the well-established effect of ACS in reducing the severity, rather than necessarily the occurrence, of NICU-level care requirements, as documented in Cochrane-level evidence syntheses of antenatal corticosteroids for fetal lung maturation.[12,13] Mechanistically, this reflects two complementary glucocorticoid actions on the immature lung: induction of surfactant protein (SP-A, SP-B, SP-C) gene expression and phospholipid synthesis by type II pneumocytes, which lowers alveolar surface tension, and upregulation of epithelial sodium-channel (ENaC) activity, which accelerates clearance of fetal lung fluid at birth-together improving lung compliance and gas exchange enough to reduce, though not abolish, the need for CPAP, ventilation and surfactant replacement. Even in the four-dose group, a proportion of neonates still required NICU admission and respiratory support, underscoring that corticosteroids substantially reduce, but do not eliminate, respiratory morbidity in neonates born at the extremes of prematurity.[28]

### *RDS*

RDS was the most common morbidity observed and fell from 60.0% to 13.5% with increasing corticosteroid exposure ($p<0.001$), a magnitude of benefit consistent with the original Liggins and Howie trial and subsequent Cochrane reviews that established antenatal corticosteroids as standard therapy for RDS prevention.[11,13] The physiological basis for this reduction-accelerated proliferation of type II pneumocytes, increased surfactant phospholipid synthesis and improved lung compliance-is well described.[7,29] Nonetheless, a residual burden of RDS persisted even after a complete four-dose course, reflecting the limits of pharmacological maturation in extremely preterm lungs.[30]

### *IVH and NEC*

IVH fell from 20.0% to 3.8%, and NEC from 16.7% to 1.9%, with increasing corticosteroid exposure. Antenatal corticosteroids are thought to reduce IVH risk by stabilising cerebral vascular tone and reducing fluctuation

in cerebral blood flow, and to reduce NEC risk through accelerated intestinal epithelial maturation and improved gut barrier integrity.[8,9,31,32] Both complications nonetheless occurred even among neonates who received the complete four-dose course, confirming that corticosteroids substantially reduce, but do not abolish, risk of these severe morbidities of extreme prematurity.

***Neonatal sepsis***

Early-onset sepsis fell from 23.3% to 5.8%, and overall neonatal sepsis from 33.3% to 7.7%, with increasing corticosteroid exposure, while the reduction in late-onset sepsis (10.0% to 1.9%) did not reach statistical significance. This pattern is biologically plausible: reduced respiratory morbidity lessens the need for invasive ventilatory support and prolonged vascular access, both recognised risk factors for early neonatal infection, whereas late-onset sepsis is driven predominantly by the duration of NICU stay, indwelling devices and nosocomial exposure rather than antenatal factors.[10,33]

***Hypoglycaemia and hyperbilirubinaemia***

Hypoglycaemia increased with increasing corticosteroid exposure (16.7% to 25.0%, p=0.042), a pattern also reported from the ALPS trial, in which antenatal betamethasone was associated with a higher rate of transient neonatal hypoglycaemia manageable with routine glucose monitoring and early feeding.[21] The biological basis for this association is reasonably well understood: repeated fetal glucocorticoid exposure transiently suppresses fetal pancreatic beta-cell insulin secretion in utero, and once this suppressive effect wanes after birth, a rebound surge in insulin release-coupled with corticosteroid-driven depletion of hepatic glycogen stores laid down late in gestation-leaves the neonate briefly unable to mobilise glucose fast enough to match demand, producing the early, transient hypoglycaemia observed with increasing dose exposure in our cohort. Hyperbilirubinaemia did not differ significantly across groups, consistent with the understanding that neonatal jaundice in preterm infants is driven mainly by hepatic enzymatic immaturity and increased red-cell turnover rather than by antenatal corticosteroid exposure.[34]

***Duration of NICU stay and neonatal mortality***

Duration of NICU stay fell significantly with increasing corticosteroid exposure, most plausibly reflecting the cumulative reduction in respiratory and infective morbidity documented above. Neonatal mortality likewise fell progressively, from 20.0% to 3.8% (p=0.043), a finding consistent with large steroid-exposed extremely-preterm cohorts demonstrating improved survival with more complete antenatal corticosteroid coverage.[27,35] Biologically, this graded survival benefit is best understood not as a single mechanism but as the cumulative product of simultaneous maturational effects across several vulnerable organ systems-accelerated surfactant synthesis and lung fluid clearance lowering the risk of fatal respiratory failure, stabilisation of cerebral blood flow autoregulation reducing catastrophic IVH, and enhanced gut barrier integrity limiting NEC and its septic sequelae-each dose completing a further increment of this multi-organ maturation programme; because glucocorticoid-responsive gene induction in the fetal lung, gut and brain requires sustained receptor occupancy over 24-48 hours to reach its full effect, a partial course likely captures only part of this maturational benefit, which would explain why incomplete exposure remained an independent predictor of death even after adjusting for gestational age and birth weight. Two deaths nonetheless occurred even in the four-dose group, underscoring that extreme prematurity, very low birth weight and severe neonatal illness continue to drive mortality despite optimal antenatal corticosteroid exposure.[36]

***Predictors of neonatal mortality***

On multivariate analysis, gestational age below 30 weeks, birth weight below 1500 g, incomplete corticosteroid exposure (≤2 doses), RDS, neonatal sepsis and IVH independently predicted neonatal mortality, with neonatal sepsis showing the strongest association. These findings closely parallel those of large multicentre studies of extremely preterm infants, which similarly identify low gestational age, low birth weight, severe respiratory disease and neonatal infection as the dominant determinants of neonatal death.[33,37] The independent association of incomplete corticosteroid exposure with mortality, even after adjustment for gestational age and birth weight, lends further support to prioritising completion of the full antenatal corticosteroid course wherever clinically feasible. In practical terms, this suggests that in busy referral hospitals such as ours, even brief administrative or transport delays that truncate a dexamethasone course to two doses or fewer carry a measurable mortality cost independent of how sick or immature the neonate already is-a modifiable factor that obstetric and neonatal teams can directly target through closer inter-departmental coordination and dose-tracking at the bedside.

***Rescue corticosteroid considerations***

Current international guidance permits a single rescue course of antenatal corticosteroids in women who remain at ongoing risk of preterm delivery more than seven days after an initial course, on the basis that this improves respiratory outcomes without evident adverse neonatal effects; routine weekly repeat dosing beyond this, however, is not recommended because of concerns regarding fetal growth and neurodevelopment.[18,24] Our findings, showing a graded benefit up to a complete four-dose course without an associated excess of SGA, are consistent with the safety margin implied by this guidance, though they do not by themselves establish the safety of dosing beyond the standard four-dose protocol.

Reassuringly, the most recent long-term follow-up of a repeat-dose corticosteroid trial, extending to 20 years of age, found no excess of asthma, adverse neuro-developmental, cardiovascular or metabolic outcomes among offspring exposed to repeat antenatal corticosteroids compared with placebo, lending further support to long-term safety of judicious additional dosing in women who remain at ongoing risk of preterm birth.

### *Strengths and limitations*

The principal strengths of this study are its prospective design, structured and standardised outcome ascertainment, and stratification across the complete range of corticosteroid exposure from none to a full four-dose course, which allowed a graded dose–response relationship to be characterised. Several limitations should be acknowledged. The precise interval between the final corticosteroid dose and delivery was not captured for all participants, precluding assessment of the well-recognised interaction between treatment-to-delivery interval and efficacy. The study was conducted at a single tertiary-care centre, which may limit generalisability, and neurodevelopmental follow-up of survivors beyond the neonatal period was not undertaken. Allocation to exposure group was determined by clinical circumstance rather than randomisation, so residual confounding by indication cannot be entirely excluded despite the balanced baseline characteristics observed. Future multicentre studies with larger sample sizes, documented treatment-to-delivery intervals, capture of rescue-course administration, and long-term neurodevelopmental follow-up are needed to further refine optimal antenatal corticosteroid strategy in resource-limited settings.

## CONCLUSION

In this prospective observational study of 200 preterm neonates, completion of the standard four-dose antenatal dexamethasone course was associated with a consistent, graded reduction in neonatal mortality and major morbidity-including RDS, IVH, NEC and neonatal sepsis-together with higher birth weight, better APGAR scores, reduced requirement for respiratory support and shorter NICU stay, compared with partial or no antenatal corticosteroid exposure. Transient hypoglycaemia was more common with increasing exposure but was clinically manageable. Gestational age <30 weeks, birth weight <1500 g, incomplete corticosteroid exposure, RDS, neonatal sepsis and IVH were independent predictors of mortality. These findings support prioritising timely initiation and completion of the recommended antenatal corticosteroid course in women at risk of preterm birth, particularly in resource-limited settings where treatment interruption is common.

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