Retraction

Retracted: The Relationship between Antenatal Corticosteroid Administration-to-Delivery Intervals and Neonatal Respiratory Distress Syndrome and Respiratory Support

Journal of Healthcare Engineering

This article has been retracted by Hindawi following an investigation undertaken by the publisher [1]. This investigation has uncovered evidence of one or more of the following indicators of systematic manipulation of the publication process:

(1) Discrepancies in scope

(2) Discrepancies in the description of the research reported

(3) Discrepancies between the availability of data and the research described

(4) Inappropriate citations

(5) Incoherent, meaningless and/or irrelevant content included in the article

(6) Peer-review manipulation

The presence of these indicators undermines our confidence in the integrity of the article's content and we cannot, therefore, vouch for its reliability. Please note that this notice is intended solely to alert readers that the content of this article is unreliable. We have not investigated whether authors were aware of or involved in the systematic manipulation of the publication process.

In addition, our investigation has also shown that one or more of the following human-subject reporting requirements has not been met in this article: ethical approval by an Institutional Review Board (IRB) committee or equivalent, patient/participant consent to participate, and/or agreement to publish patient/participant details (where relevant).

Wiley and Hindawi regrets that the usual quality checks did not identify these issues before publication and have since put additional measures in place to safeguard research integrity.

We wish to credit our own Research Integrity and Research Publishing teams and anonymous and named external researchers and research integrity experts for contributing to this investigation.

The corresponding author, as the representative of all authors, has been given the opportunity to register their agreement or disagreement to this retraction. We have kept a record of any response received.

References

[1] L. Li, H. Li, Y. Jiang, B. Yu, X. Wang, and W. Zhang, "The Relationship between Antenatal Corticosteroid Administration-to-Delivery Intervals and Neonatal Respiratory Distress Syndrome and Respiratory Support," *Journal of Healthcare Engineering*, vol. 2022, Article ID 2310080, 7 pages, 2022.

Hindawi

Research Article

The Relationship between Antenatal Corticosteroid Administration-to-Delivery Intervals and Neonatal Respiratory Distress Syndrome and Respiratory Support

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Background. Administration of antenatal corticosteroids (ACSs) is an effective strategy for managing preterm infants, which improves neonatal respiratory distress syndrome (NRDS) and attenuates the risk of neonatal mortality. However, many preterm infants are not exposed to a complete course of ACS administration, and the effects of different ACS-to-delivery intervals on NRDS and respiratory support remain unclear. Therefore, this study explored the relationship between ACS-to-birth intervals and NRDS and respiratory support in preterm infants. *Methods.* In this retrospective cohort study, the preterm infants born between 240/7 and 316/7 wks of gestation were recruited from January 2015 to July 2021. All participants were categorised based on the time interval from the first ACS dose to delivery: <24 h, 1-2 d, 2–7 d, and >7 d. Multivariable logistic regression analysis examined the relationships between the ACS-to-birth interval and primary or secondary outcome while adjusting for potential confounders. *Results.* Of the 706 eligible neonates, 264, 83, 292, and 67 received ACS-to-delivery intervals of <24 h, 1-2 d, 2–7 d, and >7 d, respectively. After adjusting these confounding factors, the multivariable logistic analysis showed a significantly increased risk of NRDS (aOR: 1.8, 95% CI: 1.2–2.7), neonatal mortality (aOR: 2.8, 95% CI: 1.1–6.8), the need for surfactant use (aOR: 2.7, 95% CI: 1.7–4.4), endotracheal intubation in the delivery room (aOR: 1.9, 95% CI: 1.0–3.7), and mechanical ventilation (aOR: 1.9, 95% CI: 1.1–3.4) in the ACS-to-delivery interval of <24 h group when compared with the ACS-to-birth interval of 2–7 d group. *Conclusions.* Neonatal outcomes such as NRDS, neonatal mortality, the need for surfactant use, intubation in the delivery room, and the risk of mechanical ventilation are higher when the neonates are exposed to an ACS interval for less than 24 h before delivery.

1. Background

Neonatal respiratory distress syndrome (NRDS) is a common problem in premature neonates due to inadequate surfactant activities in the immature fetal lungs, which is the most common cause of respiratory failure in the first few days after birth resulting in neonatal death. Other complications such as bronchopulmonary dysplasia, intraventricular haemorrhage (IVH), and necrotising enterocolitis (NEC) are also at increased risk for preterm infants. Administration of antenatal corticosteroids (ACS) is an effective treatment strategy for pregnant women at high risk of preterm birth. It accelerates lung maturation and reduces the incidence of NRDS, IVH, NEC, and neonatal death risk after a complete course of ACS. Therefore, a complete course of

ACS between 24 and 34 wks of pregnancy is recommended for women at risk of premature labour [1–4]. Previous studies showed that the incidence of NRDS and neonatal mortality rates were significantly reduced after a complete course of ACS [5–9], while the effect of ACS on the need for respiratory support in the delivery room and neonatal intensive care unit (NICU) among preterm infants has been sparsely investigated. The effect of a single course of ACS appears more pronounced when a premature birth occurs between 2 and 7 d, and its effectiveness is markedly declined at ACS-to-birth intervals of less than 48 h and more than 7 d [10–15]. In contrast, women admitted for progressive labour tended not to receive ACS or only received a partial course of ACS before delivery. A study found that only 40.7% of infants received ACS 1–7 d before delivery and 24.2% within

24 h before delivery [6]. A retrospective analysis of the Canadian Neonatal Network data revealed that 41.5% of infants were not exposed to a complete course of ACS [12]. However, whether exposure to ACS at different time intervals can affect the risk of bronchopulmonary dysplasia (BPD) and neonatal death and whether endotracheal ventilation at birth, mechanical ventilation, and surfactant administration is required remain largely unknown. Moreover, the effects of different ACS-to-birth intervals on NRDS and respiratory support (intubation-mechanical ventilation) have not been adequately studied, particularly within <24 h ACS-to-birth intervals. Hence, this study aimed to determine the effects of different ACS-to-delivery intervals on NRDS and the need for respiratory support in preterm infants and determine the optimal timing of ACS administration before preterm birth.

2. Materials and Methods

2.1. Study Design and Subjects. In this retrospective cohort study, the preterm infants born between 240/7 and 316/7 wks of gestation were recruited from January 1, 2015, to July 31, 2021, in Shaoxing Maternity and Child Health Care Hospital, a tertiary hospital in Zhejiang Province. Gestational age (GA) was described by ultrasonography before 20 weeks of pregnancy or the first day of the woman's last menstrual period. The inclusion criteria were infants who were inborn and transferred to the neonatal intensive care unit (NICU) within 2 h of birth and had GA <32 wks. Infants who died in the delivery room or were not admitted to the NICU or discharged due to the high-cost burden on family members were not included in this study. Those admitted to the NICU after birth, 2 hrs after birth, who had major congenital malformations, had not been exposed to ACS before delivery, or had repeated use of ACS before delivery were also excluded from this study. The ethical approval for this study was obtained from the Hospital Research and Ethics Committee.

2.2. Exposure and Outcomes. A complete course of ACS was defined as an intramuscular administration of 6 mg of dexamethasone every 12 h for a maximum of four doses. The interval was determined from the first ACS dose to delivery. All infants were categorised into four groups: <24 h, 1-2 d, 2–7 d, and >7 d. Maternal and infant health data were acquired from electronic medical records. The maternal data include maternal age, ACS-to-birth interval (hours from the first of ACS dose to delivery), mode of delivery, maternal complications such as gestational diabetes mellitus, gestational hypertension (e.g., gestational hypertension and preeclampsia), placental abruption, placenta previa, preterm prelabour rupture of membranes (PPROM) > 18 h, oligohydramnios, and fetal intrauterine distress. Neonatal data, such as GA at birth, gender, birth weight, multiple births, the need for endotracheal intubation in the delivery room, BPD (defined as the need for respiratory support or supplemental oxygen at 36 wks postmenstrual age) [16], NRDS (diagnosed by chest radiography and at least clinical signs of respiratory distress (e.g., respiratory grunting and retracting) and increased oxygen requirement (fraction of inspired oxygen of greater than 0.3) or the administration of exogenous pulmonary surfactant) [11], the need for pulmonary surfactant (both in the delivery room and in the NICU), the need for invasive mechanical ventilation, the duration of ventilatory support (invasive or noninvasive), the duration of hospital stay, and neonatal mortality (defined as death before discharge), were collected. Invasive mechanical ventilation includes high-frequency and conventional ventilation. Noninvasive respiratory support includes noninvasive positive pressure ventilation, noninvasive high-frequency ventilation, high-flow oxygen, and nasal continuous positive airway pressure.

The primary outcome was the overall incidence of NRDS (mild, moderate, or severe). The secondary outcomes included the need for pulmonary surfactant use, invasive mechanical ventilation, BPD, intubation at birth, surfactant use or invasive mechanical ventilation, and neonatal mortality.

2.3. Statistical Analyses. Data were expressed as median (interquartile range, IQR) for variables that did not follow a normal distribution, as mean ± standard deviation (SD) for normally distributed data, and as frequencies for categorical variables. The baseline characteristics were compared with the Kruskal–Wallis H test for continuous variables with nonnormal distribution or one-way ANOVA for those with normal distribution. Categorical variables were compared with the chi-square test. Univariate and multivariate logistic regression analyses assessed the relationships between ACS-to-delivery intervals and respiratory outcome rates. For multivariate analysis, the covariates used were as follows: birth weight, GA at birth, delivery mode, premature rupture of membranes >18 h, placenta previa, and pregnancy-induced hypertension disorders. The infants exposed to ACS within 2–7 d before birth were regarded as the reference group. And the secondary outcome of ventilation duration was not included in the multivariate analysis. All statistical tests were conducted using STATA 15.0. Odds ratio (OR) and 95% confidence interval (CI) were estimated for binary outcomes. A two-sided p value of <0.05 was considered statistically significant.

3. Results

3.1. Characteristics of the Study Population. Eight hundred and sixty-one infants were delivered between 240/7 and 316/7 wks of gestation. Neonates with major neonatal malformations or congenital diseases ($n = 2$), admitted to the NICU after 2 hrs of birth ($n = 11$), not admitted to the NICU ($n = 53$), and discharged due to family financial difficulties or concerns about prognosis ($n = 43$) were excluded. Moreover, 6 infants received multiple courses of ACS, 40 infants did not receive ACS before birth, and 1 infant with a maternal diagnosis of systemic lupus erythematosus was also excluded. Finally, 706 infants were included in the study: 264, 83, 292, and 67 infants were born at ACS-to-delivery intervals of <24 h, 1-2 d, 2–7 d, and >7 d, respectively (Figure 1).

Maternal infant baseline characteristics are summarised in Table 1. Of the 706 neonates, 66 (9.35%), 203 (28.75%),

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Total admission at 24-316/7 weeks of
gestation during the study
period, (n=861)
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Excluded (n=155)
neonatal with congenital disease (n=2)
Neonates not admitted to NICU (n=53)
discharged from NICU (n=43)
admitted to NICU after 2 hours of
birth (n=11)
repeated course of ACS (n=5)
non-exposed to ACS (n=40)
mother with systemic lupus
erythematosus (n=1)
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Eligible participants
(n=706)
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ACS<24 hours
(n=264,27.39%)
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ACS 24-48 hours
(n=83,11.76%)
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ACS 2-7days
(n=292,41.36%)
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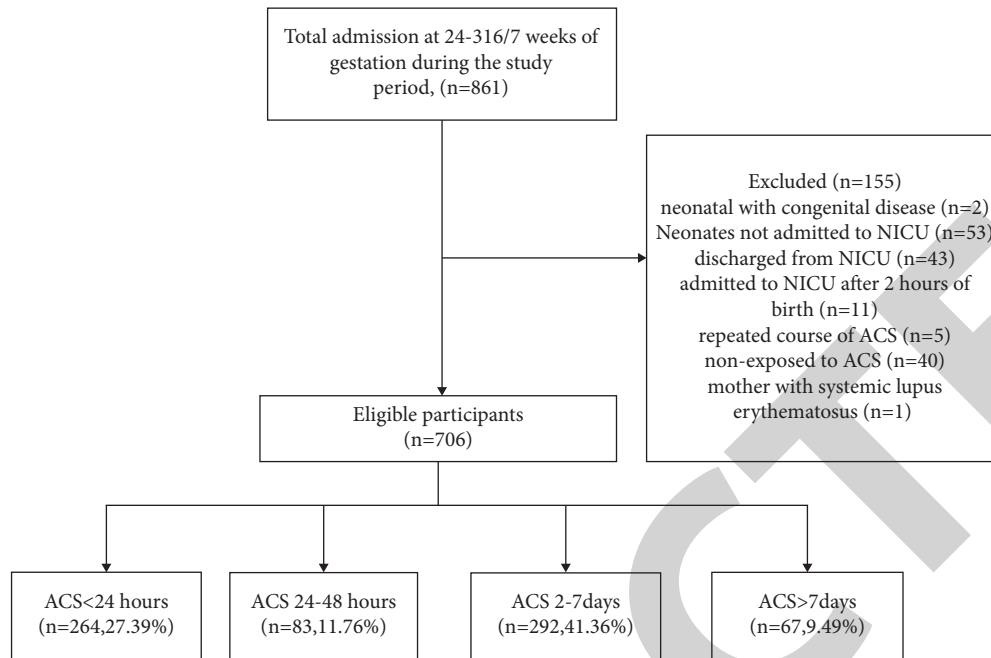```
ACS>7days
(n=67,9.49%)
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Figure 1: Flowchart of the inclusions and study groups.

Table 1: Baseline characteristics of the study population (intervals from steroid therapy to delivery).

| Characteristics | ACS < 24 h $n = 264$ (37.39%) | ACS 1-2 d $n = 83$ (11.76%) | ACS 2–7 d $n = 292$ (41.36%) | ACS > 7 d $n = 67$ (9.49%) | p value |
|---|---|---|---|---|---|
| Infant | | | | | |
| GA at delivery, wks, (IQR) | 30.0 (28.6, 31.1) | 30.5 (29.4, 31.3) | 30.4 (29.3, 31.1) | 30.4 (29.3, 31.1) | 0.009 |
| Birth weight, g, (IQR) | 1415 (1230, 1640) | 1550 (1300, 1730) | 1480 (1235, 1700) | 1520 (1300, 1700) | 0.052 |
| Gender ($n$, %), male | 141/264 (53.41) | 49/83 (59.04) | 172/292 (58.90) | 43/67 (64.18) | 0.342 |
| Twin ($n$, %) | 69/264 (26.14) | 11/83 (13.25) | 56/292 (19.18) | 16/67 (23.88) | 0.048 |
| Duration of ventilation (d, IQR) | 10 (2, 23) | 7 (0, 14) | 7 (0, 20) | 4.5 (1, 13) | 0.01 |
| Duration of hospitalisation (d, IQR) | 31 (20, 42) | 28 (22, 38) | 30.5 (22, 40.5) | 30 (22, 39) | 0.85 |
| ACS interval before delivery (h, IQR) | 4 (1.5, 11) | 34 (27, 42) | 76 (62.5, 102.5) | 264 (209, 360) | < 0.001** |
| Maternal | | | | | |
| PPROM ($n$, %) | 27/264 (10.23) | 42/83 (50.60) | 123/292 (42.12) | 20/67 (29.85) | < 0.001** |
| Mode of delivery ($n$, %), vaginal | 130/264 (49.24) | 25/83 (30.12) | 104/292 (35.62) | 20/67 (29.85) | < 0.001** |
| Placenta previa ($n$, %) | 16/264 (6.06) | 5/83 (6.02) | 19/292 (6.51) | 12/67 (17.91) | 0.019* |
| Placental abruption ($n$, %) | 15/264 (5.68) | 2/83 (2.41) | 10/292 (3.42) | 5/67 (7.46) | 0.278 |
| Gestational diabetes mellitus ($n$, %) | 35/264 (13.26) | 14/83 (16.87) | 38/292 (13.01) | 6/67 (8.96) | 0.579 |
| Fetal intrauterine distress ($n$, %) | 23/264 (8.71) | 14/83 (16.87) | 32/292 (10.96) | 8/67 (11.94) | 0.214 |
| Hypertension disorder in pregnancy ($n$, %) | 19/264 (7.20) | 13/83 (15.66) | 47/292 (16.10) | 9/67 (13.43) | 0.007 |

* $p < 0.05$ and ** $p < 0.01$. ACS: antenatal corticosteroid; IQR: interquartile range; PPROM: preterm prelabour rupture of membranes. Data were analysed by the Kruskal–Wallis $H$ test or $\chi^2$ test.

and 437 (61.90%) were born at the GA of 24–276/7, 28–296/7, and 30–316/7 wks, respectively. Women receiving ACS <24 h before delivery were less likely to have PPROM >18 h, placenta previa, hypertension disorders, vaginal delivery, and twins while more likely to have a low GA and a low birth weight. Significant differences in the maternal characteristics such as hypertensive disorders, placenta previa, GA at delivery, PPROM >18 h, and mode of delivery were observed among the 4 groups (Table 1). The incidence of placental abruption, gestational diabetes, and fetal intrauterine distress before delivery was relatively similar among the 4 groups. The median duration of ventilation (invasive and noninvasive support) was 10 d (IQR: 2,

23 d) in the ACS interval of <24 h group and 4.5 d (IQR: 1, 13 d) in the ACS interval of >7 d group ($p = 0.01$). The intervals from the first corticosteroid dose to delivery were remarkably different among the 4 groups, while the length of hospitalisation was quite similar among the 4 groups (Table 1). Figure 2 shows the distribution of GA at birth for the 4 groups.

3.2. Relationships between ACS-to-Birth Intervals and Neonatal Outcomes. The infants exposed to ACS at 2–7 d before birth tended not to use surfactant and required intubation-mechanical ventilation (17.1% and 10.3%) compared to
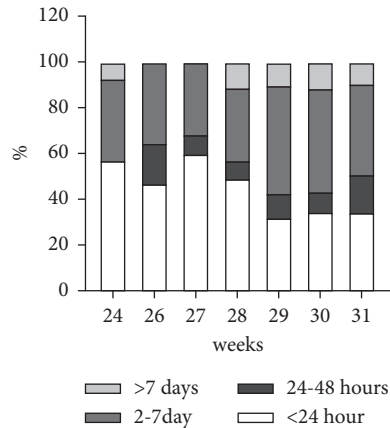
Figure 2: Distribution of the gestational age at birth in the four groups.

those exposed <24 h (37.1% and 18.9%), 1-2 d (18.1% and 10.8%), and >7 d (22.4% and 13.4%) before delivery, respectively. Unadjusted cumulative incidence rates and ORs testing the associations between ACS intervals and neonatal outcomes are shown in Table 2. The unadjusted incidence of NRDS, death, need for intubation in the delivery room, surfactant use, and mechanical ventilation were significantly higher in the ACS interval of <24 h compared with the administration-to-birth interval of 2–7 d, and there was no increased risk in the ACS interval of the 1-2 d group and >7 d group in comparison with the ACS interval of 2–7 d. There were no differences in the BPD incidences among the 4 groups.

After adjusting these confounding factors, multivariable logistic regression analysis revealed a significantly increased risk of NRDS (aOR: 1.8, 95% CI: 1.2–2.7) observed in the ACS-to-birth interval of <24 h group compared with the ACS-to-birth interval of 2–7 d group.

The secondary outcomes include neonatal mortality rate (aOR: 2.8, 95% CI: 1.1–6.8), the need for surfactant use (aOR: 2.7, 95% CI: 1.7–4.4), invasive mechanical ventilation rate (aOR: 1.9, 95% CI: 1.1–3.4), and surfactant use or invasive mechanical ventilation rate (aOR, 2.8; 95% CI, 1.7–4.4) which were significantly higher in the ACS-to-birth interval of <24 h group compared with the ACS-to-birth interval of 2–7 d group (Table 2). The risk of endotracheal intubation at birth (aOR: 1.9, 95% CI: 1.0–3.7) was also significantly higher when preterm infants were exposed to the ACS-to-birth interval of <24 h. Compared with the ACS-to-birth interval of 2–7 d group, the rates of NRDS, surfactant use, invasive mechanical ventilation, and mortality were relatively similar in the ACS intervals of 1-2 d and >7 d groups with no statistical differences among these groups (Table 2). However, no remarkable difference in BPD rate was found among the 4 groups after adjusting the variables.

## 4. Discussion

### 4.1. Main Findings of the Study. In the present study, we assessed the effects of different ACS-to-delivery intervals on NRDS incidences and respiratory support in preterm infants

(n = 706). Approximately 49.15% of preterm infants did not receive a complete course of ACS, while 37.39% of preterm infants received ACS at an interval of <24 h. Our findings demonstrated that the infants with the ACS-to-delivery interval of <24 h had a higher risk of NRDS, neonatal mortality, the need for surfactant use, and mechanical ventilation when compared to those with an ACS-to-delivery interval of 2–7 d. Administration of ACS >7 d before delivery was not significantly associated with an increased risk of these complications compared with the infants exposed to ACS 2–7 d before delivery.

### 4.2. Comments on the Results. The incidence of NRDS, death, surfactant use, the need for mechanical ventilation, and delivery room intubation were significantly higher in the ACS-to-birth interval of <24 h group than in the ACS-to-birth interval of 2–7 d group. These results are in good agreement with those of previously reported studies on the effects of ACS-to-birth intervals on neonatal morbidity. A study of preterm lambs found that the physiological parameters of the respiratory system improved after 15 h of a single dose of betamethasone. At the same time, no improvements were observed after an 8 h treatment-to-delivery interval [17]. Hence, the authors suggested that the optimal interval from fetal corticosteroid treatment to delivery was between 8 and 15 h to improve postnatal lung functional responses [17], consistent with our results. Our findings were also supported by a prospective cohort study of pregnant women with GA between 24 and 31 wks [6]. The study found that the ACS-to-birth interval of >12 h was related to a significant decrease in neonatal mortality, while there was no noticeable difference in mortality rates between the ACS-to-delivery intervals of 12 h and 18–48 h groups. Thus, it is speculated that ACSs may be effective even if they are administered a few hours before delivery.

In a recent retrospective study, Norberg et al. [18] found that extremely preterm infants born <24 h after ACS as well as those born more than 7 days after ACS administration had lower HRs for survival (HR: 0.53; 95% CI: 0.33–0.87 and HR: 0.56; 95% CI: 0.32–0.97, respectively) than infants born 48 h to 7 days after ACS administration. In that study, the survival rate of infants born at 24–47 h did not differ from infants born 48 h to 7 d after ACS administration [18], which was similar to our study. Moreover, the NRDS and respiratory outcomes were not significantly different between the ACS-to-delivery intervals of 1-2 d and 2–7 d groups. There were no observed differences between the ACS-to-delivery intervals of >7 d and 2–7 d groups. In another study of the Neonatal Research Network of Japan at 24–31 wks gestation, Ushida et al. [19] found that ACS treatment was associated with significant decreases in neonatal death, NRDS, and IVH in both hypertensive disorders of pregnancy (HDP) and non-HDP groups which were in line with our study. However, neonates were grouped as exposed to and non-exposure to ACS groups, and no further classification was performed in that study. In contrast to our findings, a recent study found no differences in respiratory, cerebral, and composite outcomes for ACS intervals of the ≤2 d, 2–7 d,

Table 2: Relationships between ACS-to-birth intervals and neonatal outcomes.

| | | ACS < 24 h n = 264 (37.39%) | | | ACS 1-2 d n = 83 (11.76%) | | | ACS 2–7 d n = 292 (41.36%) | | | ACS>7 d n = 67 (9.49%) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | No./total (%) | OR (95% CI) | | No./total (%) | OR (95% CI) | | No./total (%) | OR (95% CI) | | No./total (%) | OR (95% CI) | |
| | | | COR | aOR | | COR | aOR | | COR | aOR | | COR | aOR |
| Primary outcome | NRDS | 174/264 (65.9) | 2.3 (1.6–3.3)** | 1.8 (1.2–2.7)** | 40/83 (48.2) | 1.1 (0.7–1.8) | 1.4 (0.8–2.4) | 133/292 (45.6) | — | — | 29/67 (43.3) | 0.9 (0.5–1.6) | 0.8 (0.4–1.4) |
| | Neonatal mortality | 28/263 (10.6) | 3.0 (1.5–6.2)** | 2.8 (1.1–6.8)* | 3/83 (3.6) | 0.9 (0.3–3.5) | 1.5 (0.4–6.1) | 11/292 (3.8) | | | 2/67 (3.0) | 0.8 (0.2–3.6) | 1.3 (0.2–7.1) |
| | Surfactant use/ mechanical ventilation | 106/264 (40.2) | 2.7 (1.8–3.9)** | 2.8 (1.7–4.4)** | 19/83 (22.9) | 1.2 (0.7–2.2) | 1.6 (0.8–3.1) | 58/292 (19.9) | | | 16/67 (23.9) | 1.3 (0.7–2.4) | 1.2 (0.6–2.5) |
| Secondary outcomes | Pulmonary surfactant use | 98/264 (37.1) | 2.9 (1.9–4.2)** | 2.7 (1.7–4.4)** | 15/83 (18.1) | 1.1 (0.6–2.0) | 1.4 (0.7–2.8) | 50/292 (17.1) | | | 15/67 (22.4) | 1.4 (0.7–2.7) | 1.3 (0.6–2.7) |
| | Intubation at birth | 41/264 (15.5) | 2.5 (1.4–4.4)** | 1.9 (1.0–3.7)* | 7/83 (8.4) | 1.3 (0.5–3.1) | 1.6 (0.6–4.3) | 20/292 (6.9) | — | — | 8/67 (11.9) | 1.8 (0.8–4.4) | 1.8 (0.7–4.7) |
| | Mechanical ventilation | 50/264 (18.9) | 2.0 (1.3–3.3)** | 1.9 (1.1–3.4)* | 9/83 (10.8) | 1.1 (0.5–2.3) | 1.3 (0.6–3.1) | 30/292 (10.3) | | | 9/67 (13.4) | 1.4 (0.6–3.0) | 1.5 (0.6–3.6) |
| | BPD | 29/228 (12.7) | 1.2 (0.7–2.0) | 1.3 (0.7–2.6) | 7/76 (9.2) | 0.8 (0.3–1.9) | 1.4 (0.5–3.7) | 30/275 (10.9) | — | — | 2/67 (3.1) | 0.3 (0.1–1.1) | 0.4 (0.1–1.8) |

*$p < 0.05$ and **$p < 0.01$. COR: crude odds ratio; aOR: adjusted odds ratio; CI: confidence interval; BPD: bronchopulmonary dysplasia; NRDS: newborn respiratory distress syndrome. Univariate and multivariate logistic regression analyses analysed the data. aORs: adjusted for maternal age, birth weight, gestational age at birth, premature rupture of membranes >18 h, mode of delivery, and placenta previa hypertension disorders in pregnancy. The infants exposed to ACS within 2–7 d before birth were regarded as a reference group.

8–14 d, and >14 d groups [20]. In that study, the percentage of surfactant use and ventilation risk decreased with increasing time intervals [20]. However, the authors only reported association estimates, and no extensive multivariate regression analysis was performed [20].

Taking into account the pharmacological mechanism of ACS, the fetus can respond differentially to corticosteroids at the primary (0–24 h) and secondary (>24 h) phases compared with the first dose. Studies showed an increase in fetal heart rate (FHR) variability for both dexamethasone and betamethasone at the primary phase, in which antenatal betamethasone increased the expression of $Na^+$, $K^+$-ATPase, and ENaC subunits in the airway and respiratory epithelium, thus contributing to beneficial pulmonary effects of ACS [21–24]. This may be the reason for its more rapid action.

There is conflicting evidence on the effect of the ACS-to-birth interval of >7 d in neonatal death. In a large retrospective cohort study of infants born at 24–33 wks of gestation from the Canadian Neonatal Network, neonatal morbidity and mortality rates were significantly higher in the ACS-to-delivery interval of >7 d [12]. A secondary analysis of 2259 infants between 230/7 and 336/7 wks of gestation showed that the ACS-to-delivery interval of 7–14 d was associated with severe neonatal morbidity, and the risk of severe neonatal morbidity (aOR: 1.57, 95% CI: 1.12–2.19) was higher in the ACS-to-birth interval of >14 d group than in the ACS-to-birth interval of 2–7 d group [10].

Another study showed that the twins in the ACS-to-delivery interval of >7 d group (39.4%) had a decreased risk of NRDS (aOR: 2.205, 95% CI: 0.773–6.292) compared to those in the nonexposure group (50.8%). Still, the difference was not statistically significant [11]. This may be due to the fact that the transient effect of ACS may persist for a longer time [6, 25]. Another possible explanation is the small sample size of our study. Therefore, further multicenter, prospective cohort studies should be carried out in the near future.

The rates of BPD did not differ significantly among the 4 groups. This could be explained by that the sample size of infants delivered at <28 wks of gestation ($n = 66$) was relatively small in our study. Moreover, BPD occurs almost exclusively in premature infants (born at 28 wks or less) as they are more vulnerable to lung anomalies in the postnatal environment. The most substantial risk factors for BPD are prematurity and low birth weight [26]. Other studies also reported no significant association between BPD and the timing of ACS administration [5, 27]. Therefore, the potential relationship between the ACS-to-delivery interval and BPD risk needs further investigation.

*4.3. Strengths and Limitations.* In this study, the ACS-to-delivery intervals (in hours) of preterm infants were acquired without data loss. We assessed the effects of different ACS intervals of <24 h on neonatal mortality, which were

sparsely investigated in previous studies. The existing evidence on the association between ACS administration and neonatal outcomes focuses mainly on high-income countries and hospital settings where antenatal betamethasone is primarily applied for perinatal care. However, antenatal dexamethasone is mainly used for perinatal management in developing countries. Therefore, the findings of the antenatal dexamethasone-to-delivery interval and neonatal respiratory support are more applicable to preterm birth in developing countries.

Several limitations should be noted. First, the ACS used in our hospital was dexamethasone; thus, the results of this study should be interpreted with caution. Second, there is a potential postnatal bias in which some infants did not receive intensive care. To reduce this effect, the infants did not receive delivery room resuscitation. Those admitted to the NICU after 2 h of delivery were excluded from the analysis because of the impact of hypothermia on neonatal morbidity and mortality [28–30]. Third, the infants not exposed to ACS were not included in this study, although we believed that excluding infants unexposed to ACS might not affect the rates of neonatal mortality and/or respiratory outcomes with the administration-to-birth interval of 2–7 d as a reference. Fourth, the risk of BPD could not be assessed in preterm infants who died before 36 wks postmenstrual age or were transferred to another hospital, which might lead to a certain bias in the interpretation of BPD findings. However, it may not affect the rates of surfactant use and the need for invasive mechanical ventilation, which are employed in the early stage of preterm life and the incidence of neonatal mortality. Fifth, as the study period spanned over 7 years, some unmeasured risk factors and clinical practice changes may occur, affecting our primary and secondary outcome rates. Lastly, the data of this study were collected from a single centre, and we only included pregnant women of <32 wks GA. Therefore, our findings are not generalisable to the entire population. Although we adjusted the potential confounders that differed among groups, some unmeasured residual confounding factors still exist due to the inadequate adjustment of baseline differences in the multivariate analysis.

## 5. Conclusions and Clinical Implications

This study demonstrates that preterm infants exposed to ACS <24 h are associated with a higher risk of NRDS and neonatal mortality in preterm infants born at 240/7–316/7 wks of gestation compared to those with the ACS-to-birth interval of 2–7 d. This study also points out that the severity of NRDS could be reduced by ACS administration at least 24 h before delivery in preterm infants. A multicenter, prospective study is needed to assess the differences in ACS administration rates among preterm infants in the future. Well-designed randomised controlled trials should be conducted to verify the effects of ACS administration on NRDS and respiratory support in larger population-based cohorts.

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