Prediction of preterm delivery

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Relationship between the time interval from antenatal corticosteroid administration until preterm birth and the occurrence of respiratory morbidity.

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Abstract

Objective The purpose of this study was to assess the relationship between neonatal respiratory morbidity and the interval between antenatal corticosteroids (ACS) administration and birth.

Study design We performed a retrospective cohort study among women who had received ACS and delivered at < 34 weeks of gestation. We categorized these women in four groups: ACS - delivery interval 0-7 days, 8-14 days, 15-21 days, and 22-28 days. Multivariable logistic regression analysis assessed the association between the ACS-to-delivery interval and neonatal respiratory morbidity.

Results We included 254 neonates. Eighty-two neonates (32%) were intubated. In comparison with neonates with an ACS-delivery interval 0-7 days, the risk for intubation was increased in all other groups (OR 2.3 (95%-CI 1.1 to 5.4), 5.6 (95%-CI 1.8 to 18), and 4.8 (95%-CI 0.71 to 32, not statistically significant, respectively).

Conclusion The effect of ACS decreases when the ACS-to-delivery interval exceeds 7 days. The first administration of ACS should be considered carefully.
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Introduction

Preterm delivery occurs in 7-10% of all pregnancies and is a major cause of infant death and morbidity. Respiratory distress syndrome (RDS) is often the most acute problem of the premature neonate because of insufficient surfactant production in the immature fetal lung.

Antenatal corticosteroids (ACS) treatment, to enhance fetal lung maturity in pregnant women who are at risk for premature birth, was first introduced in 1972 by Liggins and Howie, who reported a significant reduction of RDS in premature neonates whose mothers had received ACS. Since this first randomized controlled trial, many studies have assessed the effectiveness of ACS in women who are at risk for preterm birth. Meta-analysis of these studies showed a significant reduction in the incidence of RDS and the risk of intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and neonatal death.

Although the effectiveness of ACS is beyond doubt, the optimal timing between the administration of the ACS course and premature birth remains uncertain. In a review, Crowley showed the most marked benefit in neonatal outcome when delivery occurred between 24 hours and 7 days after the initiation of corticosteroid treatment. Peaceman et al reported an increased need for short-term respiratory support among premature infants born >7 days after exposure to a single course of ACS; however, no significant differences were found in other measures of neonatal morbidity and death.

Data that determine whether the effect of ACS really diminishes from 7 days after initiation of the treatment are scarce. Knowledge of the duration of effectiveness of ACS is of particular interest in the decision whether to repeat ACS administration, because the effects of a repeated dose are still debatable and because harmful effects on neonatal length, weight, and head circumference at birth have been reported.

We therefore studied whether the effectiveness of a single complete course of ACS in the prevention of neonatal respiratory and composite neonatal morbidity depends on the time interval between ACS administration and delivery.
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Materials and methods

We performed a retrospective cohort study in 2 Dutch perinatal centers. All neonates who were born alive at a gestational age (GA) between 24 5/7 and 34 weeks in 2006 and whose mothers completed a single course of ACS (2 doses of 12-mg Celestone Chronodose [Merck Sharp & Dohme bv, Brussels, Belgium] intramuscularly with a 24-hour interval) were included. We excluded neonates whose mother did not complete a full course of ACS or whose mother had multiple courses of steroids. Neonates who died within 24 hours after birth because pediatric intervention was not desired because of extreme prematurity were excluded as well. The maternal medical charts were reviewed for characteristics such as age, obstetric history, GA at initiation of corticosteroids, and delivery. Neonatal charts were reviewed for death and morbidity. Each neonate who was born from a multiple pregnancy was analyzed separately. If women were discharged to other hospitals before delivery, we contacted those hospitals to complete the missing data. A case was lost to follow up and excluded from further analysis if information concerning the neonatal admission was untraceable.

The primary outcome, severe neonatal respiratory morbidity, was defined as the need for intubation of the neonate at the neonatal intensive care unit. Neonates were intubated if they were in need of at least 40% oxygen. Secondary end points were RDS (graded in 4 stadia according to abnormalities on X-thorax: grade 1, slight reticular (slight granular) decrease in transparency of the lung; grade 2, soft decrease in transparency and air-bronchograms, which overlaps the cardiac borders; grade 3, unclear cardiac borders; grade 4, white lung), continuous positive airway pressure (CPAP; given if the neonate needed 21-40% oxygen), and chronic lung disease (CLD; diagnosed if the need for oxygen persisted from 28 days after birth).

For the analysis, patients were categorized in 4 groups: ACS-to-delivery interval from 0-7 days, from 8-14 days, from 15-21 days, and from 22-28 days. The interval was calculated from the day that the first dose of the ACS course was given. First, we constructed spline functions to visualize the association between the need for intubation and the ACS-to-delivery interval in 4 different GA groups: delivery from 26-27 6/7 weeks, from 28–29 6/7 weeks, from 30–31 6/7 weeks, and from 32–33 6/7 weeks. A spline function is the kind of estimate produced by a spline regression in which the slope varies for different ranges of the regressors. The association between the variables on the X- and Y-axes is not fixed by a pre-specified formula;
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instead the line of the spline regression graft approaches the observed relationship in our study. We performed a multivariable logistic regression analysis to assess the relationship between the ACS-to-delivery interval and neonatal intubation. The association with the ACS-to-delivery intervals was further analyzed separately for the following outcomes: CPAP, RDS, and CLD.

Finally, we used another multivariable logistic regression analysis to assess whether the interval between ACS and delivery also influenced composite neonatal morbidity. All logistic regression analyses were corrected for GA. Composite neonatal morbidity was defined as the presence of ≥1 of the following grades: CLD, IVH grades 3 and 4 (diagnosed by ultrasound: grade 3, hemorrhage with ventricle dilatation; grade 4, intraparenchymal hemorrhage), NEC, proven sepsis and periventricular leukomalacia grades 2, 3, and 4 (diagnosed by ultrasound: formation of cysts 4 weeks after the cerebral incident). Statistical analysis was performed with SPSS software (version 17.0; SPSS Inc, Chicago, IL).

Results

We identified 522 neonates, whose mothers had received ACS and/or delivered preterm in 2006. Of these neonates, 131 were excluded for being born before the ACS course was completed (of which 1 neonate was 1 of a twin pregnancy) or for receiving multiple courses. We excluded 101 neonates because they were born after a GA of 33 6/7 weeks and 22 neonates because they were born >28 days after the first dose of ACS. Data for 4 other neonates were not retraceable; therefore, they were excluded from the study. Of the remaining 264 neonates, 3 fetuses died before delivery (2 of them were 1 of a twin pregnancy); 5 neonates died during delivery, and 2 neonates died within 24 hours after birth because further pediatric intervention was not desired because of extreme prematurity. Thus, 254 neonates of 220 mothers were included in the analysis (Figure 1).
The mean age of the mothers was 32 years (range, 17–44 years), with a mean body mass index of 24.7 kg/m² (range, 15.4–48.0 kg/m²). Ninety-three women (42%) were multiparous, of whom 36 women (39%) had had a previous preterm delivery. In our cohort, 185 women (84%) were pregnant of a singleton. Thirty-three (15%) and 2 (1%) of the pregnancies concerned twins and triplets, respectively; 3 neonates who were part of a twin pregnancy were excluded (as described earlier) because of antepartum death (n=2) and an incomplete ACS course (n=1). The multiple pregnancies were spread out among the different groups of GA and ACS-to-delivery intervals. The mean GA at which the first dose of ACS was administrated was 29 0/7; the mean GA at delivery was 30 1/7 weeks (Table 1).
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Table 1 Baseline characteristics mothers (N=220)

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Measurement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>31.6 (7 - 44)</td>
</tr>
<tr>
<td>Body mass index, kg/m²#</td>
<td>24.7 (15 - 48)</td>
</tr>
<tr>
<td>Smoking, n (%)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>39 (18%)</td>
</tr>
<tr>
<td>No</td>
<td>100 (45%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>81 (37%)</td>
</tr>
<tr>
<td>Primiparous women, n (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>127 (58%)</td>
</tr>
<tr>
<td>Pregnancies, n (%)</td>
<td></td>
</tr>
<tr>
<td>Singleton pregnancies</td>
<td>185 (84%)</td>
</tr>
<tr>
<td>Twin pregnancies</td>
<td>33 (15%)</td>
</tr>
<tr>
<td>Triplet pregnancies</td>
<td>2 (0.9%)</td>
</tr>
<tr>
<td>History of preterm labor, n (%)</td>
<td>36 (16%)</td>
</tr>
<tr>
<td>Gestational age 1st antenatal corticosteroid dose, wks*</td>
<td>29 0/7 (24 3/7 - 33 2/7)</td>
</tr>
<tr>
<td>Gestational age at delivery, wks*</td>
<td>30 1/7 (25 0/7 - 33 6/7)</td>
</tr>
</tbody>
</table>

*a Data are given as mean (range). y: years, wks: weeks

Intubation

Of the 254 neonates, 82 were intubated (32%). All 11 neonates (100%) who were born at a GA of <26 weeks had to be intubated; 28 of 37 of the neonates (74%) who were born at a GA of 26–27 6/7 weeks, 30 of 66 the neonates (22%) who were born at a GA of 28–29 6/7 weeks, 10 of 75 neonates (13%) who were born at a GA of 30–31 6/7 weeks, and 3 of 65 neonates (5%) who were born at a GA of 32–33 6/7 weeks had to be intubated. Thirty-two percent of the neonates who were born within 7 days after ACS administration (49/154) were intubated; 33% of the neonates (20/60) who were born at an ACS-to-delivery interval between 8 and 14 days were intubated; 39% of the neonates (11/28) who were born at an ACS-to-delivery interval of 15–21 days were intubated; and 17% of the neonates (2/12) who were born at an ACS-to-delivery interval of 22-28 days were intubated. Table 2 gives an overview on the intervals between ACS delivery and the need for intubation within the different gestational ages.

The effect of the time interval between the first ACS dose and delivery in the different GA groups (26–27 6/7, 28–29 6/7, and 30–31 6/7 weeks) was visualized by spline functions (Figures 2–4). No spline could be made for the GA group between 32 and 33 6/7 weeks because only 3 of 65 neonates were intubated. In the neonates who were born at <28 weeks of gestation, the ACS-to-delivery interval had limited impact on the risk for intubation, because most children who were born at < 28 weeks of gestation were intubated (Figure 2).
### Table 2 Need for intubation in correlation to gestational age and ACS-to-delivery interval

<table>
<thead>
<tr>
<th>Gestational age, wks</th>
<th>Total</th>
<th>Interval between ACS dose and delivery, days</th>
<th>0-7</th>
<th>8-14</th>
<th>15-21</th>
<th>22-28</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 26</td>
<td>11</td>
<td>11 (100%)</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 – 27 6/7</td>
<td>37</td>
<td>28 (74%)</td>
<td>20</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>28 – 29 6/7</td>
<td>66</td>
<td>30 (22%)</td>
<td>12</td>
<td>13</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>30 – 31 6/7</td>
<td>75</td>
<td>10 (13%)</td>
<td>6</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>32 – 33 6/7</td>
<td>65</td>
<td>3 (5%)</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>254</td>
<td>82 (32%)</td>
<td>49</td>
<td>20</td>
<td>11</td>
<td>2</td>
</tr>
</tbody>
</table>

ACS: antenatal corticosteroids, wks: weeks

### Figure 2 Risk of intubation at gestational age 26-27 6/7 weeks

The solid line represents the proportion; the dashed line represents 95% confidence interval. ACS: antenatal corticosteroids.
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Between 28 and 30 weeks of gestation, neonates whose mothers received ACS shortly before delivery seemed to be at lower risk for intubation, compared with neonates of mothers with a longer ACS-to-delivery interval (Figure 3). At more than 30 weeks of gestation, the need for intubation was low, independent of the length of the interval (Figure 4).

In comparison with the group of neonates with an ACS-to-delivery interval of 0–7 days, the risk for intubation was statistically significantly increased in neonates who were born within the ACS-to-delivery interval of 8–14 days (odds ratio [OR], 2.3; 95% confidence interval [CI], 1.1–5.4; \( P = .045 \)) and in neonates who were born within the ACS-to-delivery interval of 15–21 days (OR, 5.6; 95% CI, 1.8–18; \( P = .003 \)) and non-significantly increased in neonates who were born within the ACS-to-delivery interval of 22–28 days (OR, 4.8; 95% CI, 0.71–32; \( P = .11 \); Table 3).

Figure 3 Risk of intubation at gestational age 28-29 6/7 weeks

The solid line represents the proportion; the dashed line represents 95% confidence interval. ACS: antenatal corticosteroids.
Figure 4 Risk of intubation at gestational age 30-31 6/7 weeks

The solid line represents the proportion; the dashed line represents 95% confidence interval. ACS: antenatal corticosteroids.

CPAP

In our cohort, 174 neonates (69%) needed CPAP. In neonates with an ACS-to-delivery interval from 0–7 days, the risk of CPAP was 32% (50/154) vs 63% (38/60) in neonates who were born within the ACS-to-delivery interval of 8–14 days, 64% (18/28) in neonates who were born within the ACS-to-delivery interval of 15–21 days, and 42% (5/12) in neonates who were born within the ACS-to-delivery interval of 22–28 days. In comparison with the group of neonates with an ACS-to-delivery interval of 0–7 days, the risk for CPAP was not increased significantly in neonates who were born in the other ACS-to-delivery interval groups (Table 3).
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Table 3 Association of neonatal respiratory morbidity and the ACS-to-delivery interval

<table>
<thead>
<tr>
<th>Variable</th>
<th>8 to 14 days (N=60)</th>
<th>15 to 21 days (N=28)</th>
<th>22 to 28 days (N=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Intubation</td>
<td>2.3 (1.1-5.4)</td>
<td>0.045</td>
<td>5.6 (1.8-17.8)</td>
</tr>
<tr>
<td>CPAP</td>
<td>1.0 (0.41-2.0)</td>
<td>0.92</td>
<td>1.6 (0.54-4.8)</td>
</tr>
<tr>
<td>RDS</td>
<td>1.3 (0.58-2.8)</td>
<td>0.54</td>
<td>2.2 (0.73-6.4)</td>
</tr>
<tr>
<td>CLD</td>
<td>1.4 (0.46-41)</td>
<td>0.56</td>
<td>4.0 (1.1-15)</td>
</tr>
<tr>
<td>Composite outcomea</td>
<td>1.4 (0.60-3.2)</td>
<td>0.45</td>
<td>3.2 (1.0-9.7)</td>
</tr>
</tbody>
</table>

Data have been corrected for gestational age at delivery. Odds ratios compared to women with an ACS-to-delivery interval < 7 days (n = 154).

ACS: antenatal corticosteroids; CI: confidence interval; NA: not available; OR: odds ratio. CPAP: Continuous Positive Airway Pressure, RDS: Respiratory Distress Syndrome, CLD: Chronic Lung Disease.
a Chronic lung disease, intraventricular hemorrhage, necrotizing enterocolitis, proven sepsis, and periventricular leukomalacia.

RDS
Information concerning the development of RDS was traceable in 231 cases (91%); this information was missing for 23 neonates. Of the 231 neonates, 36% (83/231) had RDS. Among neonates with an ACS-to-delivery interval of 0–7 days, 37% (55/147) had RDS vs 27% of the neonates (17/62) who were born within the ACS-to-delivery interval of 8–14 days, 39% of the neonates (9/23) who were born within the ACS-to-delivery interval of 15–21 days, and 22% of the neonates (2/9) who were born within the ACS-to-delivery interval of 22–28 days. In comparison with the group of neonates with an ACS-to-delivery interval between 0–7 days, the risk of the development of RDS was not increased in neonates who were born within an ACS-to-delivery interval of 8–14 days and not significantly increased in neonates who were born within an ACS-to-delivery interval of 15–21 days and 22–28 days (Table 3).

CLD
Information concerning the development of CLD was missing for 22 neonates. Thirty-three of the 232 neonates (14%) had CLD. Among the neonates with an ACS-to-delivery interval of 0–7 days, 15% (22/146) had CLD vs 11% of the neonates (6/53) who were born within the ACS-to-delivery interval of 8–14 days and 32% (5/24) of the neonates born within the ACS-to-delivery interval of 15–21 days. CLD
was not diagnosed among neonates for whom the ACS-to-delivery interval was 22–28 days. In comparison with the group of neonates with an ACS-to-delivery interval of 0–7 days, no difference was found in the risk of the development of CLD in neonates who were born within the ACS-to-delivery interval of 8–14 days. We did find a significant increase in the risk of the development of CLD in neonates who were born within the ACS-to-delivery interval of 15–21 days (Table 3).

**Subgroup analysis of neonates who were born at a GA of 28–29 6/7 weeks**

Because the spline functions of the effect of the time interval between the first ACS dose and delivery in the different GA groups showed an effect mainly in the neonates who were born at a GA of 28–29 6/7 weeks, a subgroup analysis was performed in this group that consisted of 66 neonates. A multivariable regression analysis showed a significant increase of the intubation outcome in neonates who were born within the ACS-to-delivery time interval of 8–14 days, compared with the group of neonates with an ACS-to-delivery interval of 0-7 days and of the CLD outcome in neonates who were born within the ACS-to-delivery time interval of 15–21 days (Table 4).

**Table 4 Association of neonatal respiratory morbidity and the ACS-to-delivery interval at GA 28-29 6/7 weeks**

<table>
<thead>
<tr>
<th>Variable</th>
<th>8 to 14 days (N=19) OR (95% CI)</th>
<th>15 to 21 days (N=6) OR (95% CI)</th>
<th>22 to 28 days (N=1) OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubation</td>
<td>5.1 (1.6-16.5)</td>
<td>4.7 (0.76-29.0)</td>
<td>NA</td>
</tr>
<tr>
<td>CPAP¹</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>RDS²</td>
<td>2.7 (0.85-8.7)</td>
<td>6.8 (0.72-63.3)</td>
<td>NA</td>
</tr>
<tr>
<td>CLD³</td>
<td>1.1 (0.28-4.1)</td>
<td>8.0 (1.2-51.7)</td>
<td>NA</td>
</tr>
<tr>
<td>Composite outcomea</td>
<td>0.98 (0.33-3.0)</td>
<td>6.8 (0.72-63.3)</td>
<td>NA</td>
</tr>
</tbody>
</table>

Data have been corrected for gestational age at delivery. Odds ratio compared to women with an ACS-to-delivery interval <7 days (n = 40).

ACS: antenatal corticosteroids; CI: confidence interval; NA: not available; OR: odds ratio. CPAP: Continuous Positive Airway Pressure, RDS: Respiratory Distress Syndrome, CLD: Chronic Lung Disease.
a: Chronic lung disease, intraventricular hemorrhage, necrotizing enterocolitis, proven sepsis, and periventricular leukomalacia.
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Comment

We studied whether the effectiveness of a single complete course of ACS in the prevention of neonatal respiratory morbidity was related to the time interval between ACS administration and delivery. Virtually all neonates who were born at <28 weeks of gestation needed intubation; therefore, the length of the interval between ACS and delivery had limited impact. Between 28 and 30 weeks of gestation, neonates whose mothers received ACS shortly before delivery seemed to have less need for intubation, whereas neonates who were delivered after a longer time interval had a higher risk of intubation. At >30 weeks of gestation, the need for intubation was low, independent of the length of the time interval. Similar trends were found for need for CPAP and the development of RDS, CLD, and severe neonatal morbidity.

A limitation of our study is its retrospective character. However, the primary endpoint is well-defined and not subject to large differences in interpretation. Decisions for CPAP and intubation were made by protocol on clinical grounds, independent of the ACS-to-delivery interval. Furthermore, we analyzed each neonate of a multiple pregnancy separately, if they were clustered in 1 of the interval groups or GA groups, this might have influenced the results. In our study, the multiple pregnancies were spread out among the different groups of GA and ACS-to-delivery intervals; an unpublished subgroup analysis revealed no remarkable differences in the results.

Finally, we point out that the incidence of respiratory failure and RDS depends on multiple prenatal risk factors, such as maternal hypothyroidism, preeclampsia, and prolonged premature rupture of membranes, which we were not able to take along as confounders in our analyses. Previously, the outcomes of neonates who were born before and > 7 days after ACS treatment have been compared.\textsuperscript{6,12,13}

Sehdev et al\textsuperscript{12} studied very low birth weight infants (500-1500 g) who were exposed to a partial or 1 complete course of ACS. No significant differences were presented among 4 time interval groups (<24 hours, 24–48 hours, 48 hours to 7 days, and >7 days) with respect to RDS, IVH, NEC, and deaths. Similarly, Vermillion et al\textsuperscript{13} found no significant differences in frequencies of RDS or grades 3–4 IVH among 3 time interval groups (1–2, 3–7, and 8–14 days). Frequencies of selected perinatal infectious outcomes also were similar among groups.
Chapter 6

Peaceman et al\textsuperscript{6} demonstrated an increased need for short-term respiratory support among neonates who are born at >7 days of ACS treatment compared with neonates who are born within 7 days (81\% vs 62\%; \(P = 0.01\)). However, no differences were found in surfactant treatment, use of mechanical ventilation, NEC, IVH, oxygen dependence at 28 days after delivery or at a GA of 36 weeks, estimated GA, length of stay, or death. These results were not different when only the neonates who were delivered before a GA of 30 weeks were evaluated.

Ring et al\textsuperscript{14} showed that an ACS-to-delivery time interval of >14 days increased the risk for ventilator support (58\% vs 46\%; \(P = .02\)) and surfactant use (60\% vs 48\%; \(P = 0.02\)) in neonates who were born at a GA >28 weeks. No differences in ventilator support, surfactant use, RDS, or IVH were found in neonates born at a GA less than 28 weeks. No comparison was made between neonates who were delivered ≤7, 7–14, and >14 days after ACS administration.

Similar to Peaceman et al\textsuperscript{6}, we found that neonates who are born at <30 weeks of gestation seem to benefit from ACS, but that this benefit diminishes at higher GAs. Although we did not find a significant higher risk for RDS or CPAP, the point estimates of the odds ratios were all increased in children who were born after a longer ACS-to-delivery interval, compared with children who were born ≤7 days after ACS administration. We did observe that the risk for CLD increased significantly if the time interval between ACS and delivery is >14 days. Peaceman et al suggested a rescue course of ACS, but this suggestion may not be justified. The timing of the administration of ACS seems to be of great importance, because ACS does not have to be repeated if the timing is accurate. Measurement of fetal fibronectin and cervical length in women with threatened preterm labor might be helpful to estimate the risk of an actual preterm delivery within 7 days after admission and therefore may help to improve the timing of ACS administration\textsuperscript{15-18}.

In view of the current evidence, including our study, we conclude that the effect of ACS diminishes only in neonates who are born at a GA of 28 and 30 weeks, when the time interval between a complete ACS course and delivery becomes >7 days, which results in a higher need for intubation and higher chances for the development of CLD. Consequently, the first administration of ACS should be considered carefully.
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References