Prediction of preterm delivery
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Time to delivery after the first course of antenatal corticosteroids: a cohort study.

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Abstract

Objective The optimal time-interval between administration of antenatal corticosteroids and delivery is 1 to 7 days. This study evaluates the timing of the first course of antenatal corticosteroids in clinical practice.

Study Design A retrospective cohort study of consecutive women who had received antenatal corticosteroids and/or delivered between 24 and 34 weeks of gestation. Time between administration of corticosteroids and delivery was compared between women with different causes of anticipated preterm deliveries: symptomatic preterm labor with intact membranes, preterm prelabor rupture of membranes, (pre)eclampsia and HELLP syndrome, intra uterine growth restriction, vaginal blood loss and suspected fetal distress.

Results We included 439 women of whom 348 women (79%) completed the course of corticosteroids. In women with a complete course, 143 women (41%) delivered within 7 days. The median time interval between the course and delivery was 11 days, and varied between 41 days in women with vaginal blood loss, 25 days in women with spontaneous preterm labor with intact membranes, and 8 days in women with preeclampsia (p < 0.001).

Conclusion In women with spontaneous preterm labor with intact membranes and in women with vaginal blood loss, we can benefit substantially from a more accurate discrimination of women who need corticosteroids immediately and who do not.
**Introduction**

Preterm delivery is a major contributor to neonatal morbidity and mortality. The risk of respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis and neonatal death in infants born before 34 weeks of gestation can be reduced by administration of antenatal corticosteroids (ACS).1

It is thought that the positive effects of ACS are optimal if birth takes place between 24 hours and seven days after the administration of ACS.2;3 If the time interval exceeds 7 days, it is possible to repeat ACS, but it is unknown whether the infants would profit from repeated courses.4 Although repeated courses of ACS may decrease the risk of severe neonatal lung disease and other causes of infant morbidity, it may also have harmful effects, such as decreased neonatal length, weight, and head circumference at birth as was shown by the MACS trial.5

Uncertainty about the effects of repeating ACS may lead to a dilemma in the initial ACS administration. On the one hand we want to be sure that a woman who delivers preterm has received ACS to reduce the risk of respiratory distress syndrome. In clinical practice this might result in a low threshold for the administration of ACS and therefore a high probability of unnecessary administration of ACS in women who will not proceed into subsequent preterm delivery. On the other hand, if subsequent preterm delivery does not occur and the threat of preterm labor continues, those women who have received unnecessary administration of ACS will become at risk for potentially harmful repeated courses. Alternatively, if ACS will not be repeated, there may be no benefit from the protective effects of ACS if women deliver after the effective period of ACS.

The difficult choice whether to repeat courses of ACS, can be circumvented if the first course is accurately timed. To evaluate in which women the timing of the first course of ACS can be improved we assessed the time interval between the first course of ACS and delivery in women with different medical indications for ACS.

**Methods**

We performed a retrospective cohort study in two Dutch perinatal centers. These centers function as tertiary referral hospitals for all pregnant women below 32 weeks of gestation who are at high risk for preterm delivery in the near future. The protocols in the two hospitals in this study were to administer ACS between 24 and
34 weeks of gestation if preterm delivery is likely to occur. These protocols were in consensus with the guidelines of the Dutch Society of Obstetrics and Gynecology and the Dutch Society of Paediatrics.6-8

We collected the medical charts of all women who delivered between 24 and 34 weeks of gestation in 2006, and of all women who received ACS between 24 and 34 weeks of gestation in 2006, but who delivered later. We excluded women with an elective preterm delivery based on fetal loss in previous pregnancies. The medical charts were reviewed for maternal characteristics, the medical indication for ACS administration and the time of ACS administration and delivery. If the delivery date was untraceable a case was lost to follow up and excluded from analysis.

We assessed the following maternal characteristics: smoking, parity, previous preterm delivery and the number of fetuses. Smoking was defined as ‘yes’ if smoking occurred during any part of the pregnancy. Previous preterm delivery was defined as a former delivery between a gestational age of 24 and 37 weeks. The primary indication for ACS administration was assessed through consensus amongst two or more researchers. We classified women under one of the following groups of primary indications: symptomatic preterm labor with intact membranes (PTL), preterm prelabor rupture of membranes (PPROM), (pre) eclampsia and HELLP syndrome (PE/HELLP), intra uterine growth restriction (IUGR), vaginal blood loss (VBL) and suspected fetal distress (FD). FD was diagnosed in case of CTG or Doppler abnormalities. If ACS was administered for more than one clinically relevant indication, women were grouped under the category multiple indications. We assessed when the first ACS were given and whether the course of ACS was completed, defined as two given doses of 12 mg Celestone Chronodose intramuscular with a 24 hour interval.

Statistical analysis was performed using SPSS software version 16.0 and R version 2.10.1. We calculated how often a course of ACS was started and completed in groups of women with different characteristics and medical indications. Pearson Chi-Square tests were used to evaluate whether there was a significant difference in the proportion of completed courses between the groups. The median time from the first ACS administration to delivery was calculated for women who had completed a course of ACS. A Kaplan-Meier plot was derived to express time to delivery. Data were censored after 28 days, since administration of ACS is unlikely to be beneficial if delivery occurs after this period. We evaluated the proportional
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hazards assumption by testing the scaled Schoenfeld residuals after fitting a Cox model that estimated the hazard ratios between the different medical indications for ACS.\textsuperscript{9}

Because the proportional hazards assumption was rejected (the p-value was below 0.05), we compared the time to delivery (censored after 28 days) between different groups using the Peto & Peto modification of the Gehan-Wilcoxon test.\textsuperscript{10} This test is more conservative than the log-rank test if the proportional hazards assumption is invalid.

**Results**

We identified 445 women, 221 in the Maxima Medical Center and 224 in the Academic Medical Center. Four women were lost to follow up and were excluded from further analysis and two women were excluded because they had an elective preterm delivery solely based on their obstetrical history (Figure 1). Of the remaining 439 women, there were 25 women (6%) who delivered before 34 weeks without receiving ACS, 66 women (15%) who received only an incomplete course of ACS and 348 women (79%) who received a complete course of ACS (Figure 1). The mean gestational age of women with a complete course was 28 6/7 weeks at the time of ACS administration and 32 0/7 weeks at delivery.

The maternal characteristics of our cohort are shown in Table 1. The mean age of the women was 31 years, the mean BMI was 24.3 kg/m\(^2\) and 26% of the women smoked. There were 190 multiparous women (43%), of which 74 women (39%) had a previous preterm birth before 37 weeks. The cohort contained 78 women (18%) with twin or triplet pregnancies. The maternal characteristics were not significantly related to the proportion of completed courses in the cohort. Among the women with completed courses, median time to delivery only deviated slightly between smokers and non-smokers and between women with and without a previous preterm delivery (Table 2).
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Figure 1 Inclusion flow chart of number of women who received ACS or delivered between 24 to 34 weeks of gestation.

ACS = antenatal corticosteroids, PTL = symptoms of spontaneous preterm labor with intact membranes, PPROM = premature prelabor rupture of membranes, PE = pre-eclampsia or HELLP-syndrome, IUGR = fetal intra-uterine growth restriction, VBL = vaginal blood loss, FD = suspected fetal distress.

Table 1 Maternal characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n (%) or mean (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Group</td>
<td>439 (100)</td>
</tr>
<tr>
<td>Age</td>
<td>31 (5.5)</td>
</tr>
<tr>
<td>BMI *</td>
<td>24.3 (6.6)</td>
</tr>
<tr>
<td>Smoking **</td>
<td>70 (26)</td>
</tr>
<tr>
<td>Multiparous</td>
<td>190 (43)</td>
</tr>
<tr>
<td>Previous labor &lt; 37 wks</td>
<td>74 (18)</td>
</tr>
<tr>
<td>Twins / triplets</td>
<td>78 (18)</td>
</tr>
</tbody>
</table>

* 40% missing, ** 60% missing
### Table 2 Proportion of completed courses of ACS in women with different maternal characteristics and time to delivery in women with a complete course of ACS.

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>No ACS</th>
<th>Incomplete course</th>
<th>Complete course</th>
<th>Labor &lt;7 d N (%)</th>
<th>Labor &lt;34 w N (%)</th>
<th>GA + ACS mean (SD)</th>
<th>GA at delivery mean (SD)</th>
<th>Days to delivery (median, IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women</td>
<td>25 (6)</td>
<td>66 (15)</td>
<td>348 (79)</td>
<td>143 (41)</td>
<td>257 (74)</td>
<td>28.6/7 (-2+2)</td>
<td>32.0/7 (-3+5)</td>
<td>11 (4-35)</td>
</tr>
<tr>
<td>Smoking* yes</td>
<td>5 (7)</td>
<td>10 (14)</td>
<td>55 (79)</td>
<td>28 (51)</td>
<td>43 (78)</td>
<td>28.5/7 (-2+3)</td>
<td>31.1/7 (-3+1)</td>
<td>7 (4-27)</td>
</tr>
<tr>
<td>Smoking* no</td>
<td>11 (6)</td>
<td>26 (13)</td>
<td>158 (81)</td>
<td>64 (41)</td>
<td>119 (75)</td>
<td>29.0/7 (-2+2)</td>
<td>32.1/7 (-3+4)</td>
<td>11 (4-33)</td>
</tr>
<tr>
<td>Parity primi</td>
<td>12 (5)</td>
<td>45 (18)</td>
<td>192 (77)</td>
<td>80 (42)</td>
<td>150 (78)</td>
<td>29.0/7 (-2+1)</td>
<td>31.6/7 (-3+3)</td>
<td>10 (4-31)</td>
</tr>
<tr>
<td>Parity multi</td>
<td>13 (7)</td>
<td>21 (11)</td>
<td>156 (82)</td>
<td>63 (40)</td>
<td>107 (69)</td>
<td>28.5/7 (-2+3)</td>
<td>32.1/7 (-3+6)</td>
<td>12 (4-41)</td>
</tr>
<tr>
<td>Previous delivery &lt;37wks** yes</td>
<td>7 (10)</td>
<td>5 (7)</td>
<td>62 (84)</td>
<td>21 (34)</td>
<td>43 (69)</td>
<td>28.3/7 (-2+3)</td>
<td>32.3/7 (-3+4)</td>
<td>14 (5-49)</td>
</tr>
<tr>
<td>Previous delivery &lt;37wks** no</td>
<td>16 (5)</td>
<td>60 (17)</td>
<td>273 (78)</td>
<td>114 (42)</td>
<td>202 (74)</td>
<td>29.9/7 (-2+2)</td>
<td>32.9/7 (-3+5)</td>
<td>11 (4-32)</td>
</tr>
<tr>
<td>Pregnancy 1 baby</td>
<td>21 (6)</td>
<td>46 (13)</td>
<td>293 (81)</td>
<td>122 (42)</td>
<td>217 (74)</td>
<td>28.6/7 (-2+2)</td>
<td>32.0/7 (-3+5)</td>
<td>11 (4-34)</td>
</tr>
<tr>
<td>Pregnancy &gt;1 baby</td>
<td>4 (5)</td>
<td>19 (24)</td>
<td>55 (71)</td>
<td>21 (38)</td>
<td>40 (73)</td>
<td>28.4/7 (-2+1)</td>
<td>31.6/7 (-3+3)</td>
<td>11 (4-40)</td>
</tr>
</tbody>
</table>

ACS = antenatal corticosteroids, primi = primiparous, multi = multiparous, GA = gestational age, d = days, w = weeks, IQR = interquartile range, SD = standard deviation.

* 40% missing, ** 4% missing.

The proportion of complete courses differed significantly between the groups of women with different indications for ACS administration (p < 0.001). The highest proportion of complete courses was found in the group of women with PE/HELLP (98%), VBL (94%) and women with multiple indications (86%). In contrast, only 50% of the women with suspected FD completed the course [Table 3].

Of the 348 women with a complete course, 143 women (41%) delivered within 7 days and 257 women (74%) delivered before 34 weeks (Table 3). The highest incidences of delivery before 34 weeks were found in women with PE/HELLP (98%), IUGR (92%) and multiple indications (94%). Women with PTL with intact membranes or VBL delivered in resp. 58% and 44% of the cases before 34 weeks (Table 3). The median time to delivery was 11 days (IQR 4-35). Time to delivery differed significantly between the groups (p < 0.001), as is also illustrated in the Kaplan–Meier plot in Figure 2. The longest median time to delivery was found in the women with PTL with intact membranes and in women with VBL, with a median time interval of 25 (IQR 5-54) and 41 (IQR 12-60) days respectively.
the women with VBL, none of the 6 women with an unknown cause for their VBL delivered within 7 days.

Table 3 Proportion of completed courses of ACS in women with different medical indications and time to delivery in women with a complete course of ACS.

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>Women with a complete course</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No ACS N (%)</td>
</tr>
<tr>
<td>All women</td>
<td>25 (6)</td>
</tr>
<tr>
<td>PTL</td>
<td>8 (4)</td>
</tr>
<tr>
<td>PPROM</td>
<td>4 (4)</td>
</tr>
<tr>
<td>PE/HELLP</td>
<td>1 (2)</td>
</tr>
<tr>
<td>IUGR</td>
<td>2 (6)</td>
</tr>
<tr>
<td>VBL</td>
<td>1 (6)</td>
</tr>
<tr>
<td>FD</td>
<td>5 (31)</td>
</tr>
<tr>
<td>Multiple indications</td>
<td>4 (11)</td>
</tr>
</tbody>
</table>

ACS = antenatal corticosteroids, PTL = symptoms of spontaneous preterm labor and intact membranes, PPROM = premature prelabor rupture of membranes, PE/HELLP = pre-eclampsia or HELLP-syndrome, IUGR = fetal intra-uterine growth restriction, VBL = vaginal blood loss, FD = suspected fetal distress.
Figure 2 Kaplan-Meier plot showing the time to delivery in women with different medical indications who all received a complete course of ACS.

ACS = antenatal corticosteroids, VBL = vaginal blood loss, PTL = symptoms of spontaneous preterm labor and intact membranes, PPROM = premature prelabor rupture of membranes, FD = suspected fetal distress, IUGR = fetal intra-uterine growth restriction, PE = pre-eclampsia and/or HELLP-syndrome.
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Discussion

The aim of the study was to assess the time to delivery after the first course of ACS administration in women with different medical indications for ACS administration. We found that the overall timing of the first course of ACS was fairly acceptable, as 41% of women with a completed course delivered within 7 days. In women with symptoms of preterm labor with intact membranes and in women with vaginal blood loss, timing can be improved, thus reducing the dilemma of repeating ACS later on.

We did not see any remarkable influence of the maternal characteristics on the time to delivery. That such a correlation was absent might be due to the wide range of medical indications, which has resulted in a very heterogeneous group. Another explanation might be that physicians take these risk factors into account and prescribe ACS earlier to patients with a higher perceived risk of preterm delivery, resulting in a similar time to delivery. Furthermore, because of the retrospective nature of this study, some maternal characteristics could not be identified.

It is uncertain whether the results of this study can be applied to other centers. The Dutch infrastructure only provides neonatal facilities in tertiary perinatal hospitals for neonates born at a gestational age below 32 weeks. This policy results in clustering of all patients in tertiary centers who are below 32 weeks of gestation and at high risk for preterm delivery in the near future. In this study we did not register patients who were not transferred to a tertiary center and kept for observation in secondary hospitals. It is therefore unknown how the results of this study are transferable to other countries, although the proportion of women with a completed course of ACS who delivered within 7 days (41%) is comparable to a recent cohort of women in a center in Houston, Texas (38%). Secondly, this study did not include patients with a (low) risk of preterm labor who did not receive ACS, nor delivered before 34 weeks. Therefore we could not assess whether our study population differed from those women who received expectant management and delivered after 34 weeks of gestation.

The timing of ACS administration might differ between physicians, hospitals and countries, as the timing is foremost the result of a decision of an individual physician. We did not find any evidence that suggests a systematic difference in timing of ACS administration between the hospitals, or between secondary or tertiary centers that started the course of ACS.
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An accurate timing is easier to accomplish if we also influence the moment of delivery, as is more often the case in women with PE/HELLP, IUGR and FD. Having diagnosed such a severe complication that requires termination of pregnancy, the completion of a course of ACS may prompt an indicated delivery. If the moment of delivery is subject to natural pathways, as is the case in women with VBL, PPROM and PTL with intact membranes, a balanced timing of ACS is more difficult. Attempts to prevent unnecessary administration of ACS, particular in these women, should not increase the rate of premature neonates that are born without a proper course of ACS.

The time from ACS administration until delivery is the longest in women with VBL and PTL with intact membranes. Presently, the decision to administer ACS in women with VBL is sometimes initiated by the fear for placental abruption. Apart from the provision of accurate data, tools to improve the timing of ACS administration in these women are limited. Yet, in women with PTL with intact membranes, fetal fibronectin tests and cervical length measurements could be useful to optimize treatment decisions. At the time of our study, fetal fibronectin tests were not used in the Netherlands. If fibronectin can accurately predict which women will not deliver in the next 7-10 days, either by itself or in combination with other prognostic information, we might be able to prevent unnecessary early administration of ACS in these women, without increasing the rate of premature neonates without proper preparation with ACS.

In conclusion, the results of this study show that there is room for improvement in the timing of the first course of ACS in women with symptomatic preterm labor and intact membranes and in women with vaginal blood loss. It is essential to estimate the time to delivery accurately, as a better timing may result in better therapeutic results (e.g. less neonatal morbidity and mortality). Therefore, it is important to develop better tools to predict preterm deliveries. Furthermore, if we want to optimize the timing, it is important to gain better understanding of duration and optimum of the therapeutic effects of ACS.
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References

5. Murphy KE. Multiple courses of antenatal corticosteroids for preterm birth (MACS): a randomised controlled trial. 2008.