Prediction of preterm delivery
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Time to delivery after the first course of antenatal corticosteroids in preterm labor.

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Submitted
Chapter 8

Abstract

Objective To assess the impact of cervical length (CL) measurement and fetal fibronectin testing (fFN) on the clinicians’ decision to prescribe antenatal corticosteroids (ACS) to women with symptoms of preterm labor.

Methods This is a secondary analysis of a prospective cohort study including women with symptoms of PTL and intact membranes between a gestational age of 24 and 34 weeks. We compared the proportion prescribed and completed ACS courses at study enrollment, preterm delivery within seven days and median intervals from administration of a complete course to delivery in four groups: group 1 CL < 10 mm, group 2 CL 10-30 mm and positive fFN, group 3 CL 10-30 mm and negative fFN and group 4 CL> 30 mm.

Results ACS were prescribed to 63/65 (97%) women in group 1, 176/192 (91%) in group 2, 111/172 women (65%) in group 3 and 55/242 (23%) in group 4. In group 1, 42 (65%) women delivered within seven days, compared to 34 (18%) in group 2, 6 (3%) in group 3 and 3 (1%) in group 4. Two of the women who did not receive ACS at enrollment (n=266) delivered within seven days. The median intervals between study enrollment and delivery were 6 days (IQR 3 to 61 days), 44 days (IQR 17 to 69 days), 53 days (IQR 37 to 77 days) and 66 days (IQR 43 to 78 days) in group 1, 2, 3 and 4 respectively.

Conclusion The negative predictive value of both cervical length >30 mm as well as that of fibronectin are not fully exploited.
Introduction

Preterm delivery (PTD) is a major contributor to neonatal morbidity and mortality.\(^1\,2\) Antenatal corticosteroids are known to improve the outcome of premature neonates born before 34 weeks of gestation\(^3\,6\).

The effect of corticosteroids was incidentally discovered in preterm lambs by Graham Liggins, in the late 1960’s. Together with pediatrician Ross Howie he published in 1972 a randomized controlled trial (RCT), in which they described a significant reduction of the incidence of respiratory distress syndrome (RDS).\(^7\) Furthermore, a reduction in mortality and in the risk of IVH were found in preterm neonates whose mothers received two 12-mg injections of betamethasone administered 24 hours apart.\(^8\)

It took, however, over 2 decades before the administration of antenatal corticosteroids to mothers at risk of a PTD was implemented.\(^9\) A strong increase of the use of ACS was seen after a consensus conference in 1994 by the National Institutes of Health (NIH). Endorsed by the American College of Obstetricians and Gynecologist (ACOG), this meeting resulted in the recommendation to administrate of ACS to all women at risk of PTD between 24 and 34 weeks’ gestation.\(^10\)

A possible diminishing effect of the initial course ACS over time, the optimal interval of 7 to 14 days between the administration of the first course ACS and delivery and the difficulty to accurately predict which women with symptoms of preterm labor (PTL) actually will deliver in the short term, created a clinical dilemma,\(^11\,15\) which resulted in routinely repetition of ACS courses in the 1990’s.\(^16\,18\)

Seven years after the first consensus conference, the NIH held a second one which concluded that repeat courses should be reserved for patients enrolled in randomized controlled trials.\(^19\) The results of these trials, published in the beginning of the 21\(^{st}\) century, showed a reduction in occurrence and severity of neonatal lung disease en serious infant morbidity after repeat courses.\(^20\,22\) Although a lower birth weight and smaller head circumference were reported after repeat courses,\(^23\) the long-term outcomes at 2-3 years of age seemed to be reassuring. However, no evidence was found for long-term benefit of repeat doses ACS.\(^24\,25\)

More than 4 decades after the initial trial that showed a beneficial effect of ACS, to strike the golden mean, a “rescue” course of ACS could be considered if the antecedent treatment was given more than 2 weeks prior, the gestational age is less than 32 6/7 weeks, and the women are judged by the clinician to be likely to give birth within the next week.\(^26\,28\)
The question whether or not to repeat a course of ACS would not rise if the timing of the first course of ACS would be optimal. On the other hand, we want to be sure that women who deliver preterm have received ACS, which might result in a low threshold to administer ACS in clinical practice. Obviously, the dilemma on when to administer ACS is guided by the ability to predict the risk of preterm delivery. In women with symptoms of PTL, measurement of the cervical length (CL) by vaginal ultrasound in combination with fetal fibronectin (fFN) testing might improve the identification of those women who actually will deliver within seven days after the onset of symptoms. In women with a CL above 30 mm or a CL between 10-30 mm combined with a negative fFN test the risk of PTD within seven days is small. 29-32

In this cohort study, we assessed clinicians’ prescribing patterns of ACS in relation to the test results the CL and fFN. The cohort consisted of women with symptoms of PTL. The decision to administer ACS was left to the clinician although the treatment with tocolytics was fixed in a treatment protocol depending on the fFN CL between 10 and 30 mm combined with a negative fFN test are at low risk for PTD within seven days.29-32 We hypothesize that clinicians prescribe ACS too liberally and therefore inadequately timed to these low risk women.

Materials and methods

This study was a secondary analysis of data collected in the APOSTEL-1 study. The APOSTEL-1 study was a prospective cohort study performed in all ten perinatal centers in The Netherlands between December 2009 and August 2012. The principal aim of the study was the accuracy of fFN testing and CL measurement in a triage of women with symptoms of PTL between 24-34 weeks of gestation and intact membranes. The study protocol received IRB-approval (MEC 08/363), and methods have been reported previously. 33

Participants and interventions

In short, the APOSTEL-1 study included women with symptoms of PTL between 24-34 weeks of gestation and intact membranes. Women who received tocolytic treatment within the previous seven days were excluded. Women who received only a single dose of tocolytic treatment for transportation to a tertiary hospital were not excluded. Other exclusion criteria were contra-indications for tocolysis, such
as lethal congenital abnormalities, suspected intra-uterine infection or suspected fetal distress and more than 3 cm dilatation diagnosed at digital examination. At admission a fFN test (Rapid fetal fibronectin TL1IQ analyser (Hologic Benelux B.V.® Almere, the Netherlands) with a 0.050 μg/mL cut-off) was taken from the posterior fornix, the CL was measured by transvaginal ultrasound and a digital examination was performed to assess cervical changes. Women were treated with tocolytics according to local protocol in case of a CL under 10 mm (group 1) or a CL between 10 and 30 mm and a positive fFN test (group 2). Women with a CL between 10 and 30 mm and a negative fFN (group 3) test were eligible for randomisation for the embedded double-blinded randomised controlled trial, and received placebo or nifedipine for 48 hours. Women with a CL above 30 mm (group 4) were monitored, without receiving tocolytic treatment. Administration of ACS was based on the clinician’s decision. The results of this trial will be published elsewere, concluding a non-inferiority of placebo relative to nifedipine, suggesting expectant management in fFN negative women.

Outcomes
In the APOSTEL I study, there was no fixed protocol concerning the treatment with ACS. We therefore assessed, in women with symptoms of PTL, the impact of the CL and the fFN result on the clinician’s decision to administer ACS. We differentiated four groups of the fixed protocol to prescribe tocolytics: CL < 10 mm (group 1), CL 10-30 mm and positive fFN (group 2), CL 10-30 mm and negative fFN (group 3), CL > 30 mm (group 4).
Among these four groups, we evaluated whether ACS were prescribed optimally at study enrollment, i.e. that women who received a complete course of ACS delivered within the optimal interval between 48 hours and seven days after administration of ACS. While women, to whom initially no ACS were prescribed, indeed did not deliver within 7 days.
We therefore evaluated among the four groups, the proportion prescribed and the proportion completed courses of ACS at study enrollment, the PTD rates within seven days after study enrollment and before a gestational age of 34 weeks and the interval between ACS treatment and delivery. A complete course ACS was defined as two doses of 12 mg Celestone Chronodose (Merck Sharp & Dohme bv, Brussels, Belgium) intramuscularly.
Chapter 8

Statistical analysis
To evaluate the prescribing patterns of ACS at study enrollment, we analyzed women who received no ACS treatment at study enrollment, but were treated later on in pregnancy, as if they received no ACS treatment.

We assessed the following characteristics since they might influence the risk assessment of PTD and therewith the proportion of completed ACS courses: parity, ethnicity (Caucasian vs non-Caucasian), smoking, previous preterm delivery, singleton vs multiple pregnancy and referral from midwifery or secondary care center.

We analyzed the proportion prescribed courses and the proportion of complete ACS courses at study enrollment, within the four groups. And for women who received no, an incomplete course or a complete course of ACS at study enrollment in these four groups we calculated the median gestational age at delivery, median gestational age at ACS treatment and the median interval from enrollment to delivery, all with interquartile ranges (IQR). Kaplan-Meier plots was derived to illustrate the interval from enrollment to term and preterm delivery (before 34 weeks gestation) of women who received no, an incomplete or a complete course of ACS at enrollment for the total population. Separate plots were made to illustrate the interval between the first ACS dose and delivery of the women within the four CL and fFN groups to whom a complete course of ACS was administered at study enrollment. Data were censored after 28 days, since administration of ACS is unlikely to be beneficial if delivery occurs after this period.

To evaluate prescribing patterns of ACS during the course of pregnancy we analyzed the proportion of postponed incomplete and complete courses of ACS in women who initially received no ACS treatment. Among these women, delivery within seven days after study enrollment and PTD before a gestational age of 34 weeks were evaluated.

Categorical variables were analyzed with Pearson Chi-Square tests. Normality of continuous variables was assessed with tests for skewness/kurtosis and the Shapiro-Wilk tests. Normally distributed continuous variables were compared with the use of the Student t test and in nonparametric data the Mann-Whitney U or Kruskal-Wallis tests were used as appropriate. Statistical analyses were performed using SPSS software, version 21.0 (SPSS Inc. Chicago, Illinois, USA). A probability value (p-value) of < 0.05 was considered statistically significant.
Results

Between December 2009 and August 2012, 758 women were approached for the APOSTEL-1 study. Five women did not meet the inclusion criteria, 23 had one or more exclusion criteria and 16 did not sign an informed consent form. From the remaining 714 women, fFN results were invalid in 21 women, while in nine women the fFN results were not recorded while in 13 women the CL results were missing (n =43) (Figure 1). Therefore, 671 women were included in the analysis. The median gestational age at enrollment was 29.4 weeks (IQR 27 to 31.3). Of the included women, 347 (52%) were nulliparous, and 324 (48%) were multiparous, and 145 (45%) of the latter group had previously delivered premature. The cohort contained 104 (14%) multiple pregnancies. Further baseline characteristics can be found in Table 1.

Table 1 Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>n = 671</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparous</td>
<td>347 (51.7%)</td>
</tr>
<tr>
<td>Maternal age (years)</td>
<td>29.2 (+/- 5.3)</td>
</tr>
<tr>
<td>Gestational age at study enrollment (weeks)</td>
<td>29.4 (IQR 27 to 31.3)</td>
</tr>
<tr>
<td>Caucasian ethnicity</td>
<td>448 (66.8%)</td>
</tr>
<tr>
<td>Maternal smoking† (n =625)</td>
<td>90 (14.4%)</td>
</tr>
<tr>
<td>Body-mass index† (first antenatal visit, kg/m²)</td>
<td>22.3 (IQR 20.3 to 25.1)</td>
</tr>
<tr>
<td>Previous preterm delivery</td>
<td>145 (21.6%)</td>
</tr>
<tr>
<td>Singleton</td>
<td>567 (84.5%)</td>
</tr>
<tr>
<td>Twin</td>
<td>102 (14.1%)</td>
</tr>
<tr>
<td>Triplet</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Referral from peripheral hospital or midwife</td>
<td>425 (63%)</td>
</tr>
<tr>
<td>Fetal fibronectin</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>306 (45.6%)</td>
</tr>
<tr>
<td>Negative</td>
<td>365 (54.4%)</td>
</tr>
<tr>
<td>Digital examination † (n = 624)</td>
<td></td>
</tr>
<tr>
<td>Cervical dilation &lt; 3 cm</td>
<td>606 (97.1%)</td>
</tr>
</tbody>
</table>

Data are number of patients (%), mean (+/- SD) or median (IQR). † Data are missing for some participants.

Of the characteristics, parity and singleton or multiple pregnancy were significantly related to the proportion completed courses of ACS and had a significant different interval between the first dose of ACS and delivery in those women who completed a course of ACS (Table 2).
Figure 1 Flow diagram

Women eligible for study (n=758)
- No inclusion (n=5)
  - No gestational age between 24-34 weeks (n=3)
  - Ruptured membranes (n=1)
  - No signs of preterm labor (n=1)

Women eligible for study (n=753)
Exclusion (n=23)
- Tocolysis for more than 12 hours (n=15)
- More than 3 cm dilatation (n=6)
- Lethal congenital abnormality (n=2)
- Intra-uterine infection (n=2)

No informed consent (n=16)

Women included in cohort (n=714)
Either fetal fibronectin or cervical length result not available (n=43)

Women analyzed (n=671)
- CL < 10 mm (n=65)
- CL 10-30 + fFN + (n=192)
- CL 10-30 + fFN (n=172)
- CL > 30 mm (n=242)
Table 2: Completion of ACS courses at study enrollment in relation to baseline characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total</th>
<th>No ACS N (%)</th>
<th>Incomplete ACS course N (%)</th>
<th>Complete ACS course N (%)</th>
<th>p-value*</th>
<th>Women with completed ACS course</th>
<th>p-value*</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
<td>PTD &lt; 7 days N (%)</td>
<td></td>
<td>Days between ACS and delivery Median (IQR)</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nulliparous</td>
<td>347</td>
<td>112 (33%)</td>
<td>22 (6%)</td>
<td>213 (61%)</td>
<td>&lt;0.001</td>
<td>41 (19%)</td>
<td>0.005</td>
<td>45 (17 to 73) 0.04</td>
</tr>
<tr>
<td>Multiparous</td>
<td>324</td>
<td>154 (48%)</td>
<td>12 (4%)</td>
<td>158 (48%)</td>
<td></td>
<td></td>
<td></td>
<td>54 (29 to 75)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>448</td>
<td>166 (37%)</td>
<td>27 (6%)</td>
<td>255 (57%)</td>
<td>0.068</td>
<td>36 (14%)</td>
<td>0.57</td>
<td>46 (26 to 72) 0.99</td>
</tr>
<tr>
<td>Non-Caucasian</td>
<td>223</td>
<td>100 (45%)</td>
<td>7 (3%)</td>
<td>116 (52%)</td>
<td></td>
<td></td>
<td></td>
<td>51 (23 to 72)</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>505</td>
<td>210 (42%)</td>
<td>28 (5%)</td>
<td>267 (53%)</td>
<td>0.31</td>
<td>40 (15%)</td>
<td>0.84</td>
<td>49 (28 to 74) 0.39</td>
</tr>
<tr>
<td>Stopped</td>
<td>30</td>
<td>7 (23%)</td>
<td>1 (3%)</td>
<td>22 (73%)</td>
<td></td>
<td>4 (18%)</td>
<td>46 (22 to 77)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>90</td>
<td>34 (38%)</td>
<td>3 (3%)</td>
<td>53 (59%)</td>
<td></td>
<td>6 (11%)</td>
<td>41 (23 to 73)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>46</td>
<td>15 (33%)</td>
<td>2 (4%)</td>
<td>29 (63%)</td>
<td></td>
<td>5 (17%)</td>
<td>39 (16 to 63)</td>
<td></td>
</tr>
<tr>
<td>Previous PTD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>145</td>
<td>56 (39%)</td>
<td>5 (3%)</td>
<td>84 (58%)</td>
<td>0.60</td>
<td>7 (8%)</td>
<td>0.06</td>
<td>54 (27 to 79) 0.07</td>
</tr>
<tr>
<td>No</td>
<td>525</td>
<td>209 (40%)</td>
<td>29 (6%)</td>
<td>287 (54%)</td>
<td></td>
<td>48 (17%)</td>
<td>46 (24 to 72)</td>
<td></td>
</tr>
<tr>
<td>Singleton</td>
<td>567</td>
<td>244 (43%)</td>
<td>28 (5%)</td>
<td>295 (52%)</td>
<td>&lt;0.001</td>
<td>40 (14%)</td>
<td>0.18</td>
<td>53 (29 to 79) &lt;0.001</td>
</tr>
<tr>
<td>Multiple</td>
<td>104</td>
<td>22 (21%)</td>
<td>6 (6%)</td>
<td>76 (72%)</td>
<td></td>
<td>15 (20%)</td>
<td>35 (14 to 54)</td>
<td></td>
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<tr>
<td>Referral</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>425</td>
<td>156 (37%)</td>
<td>23 (5%)</td>
<td>246 (58%)</td>
<td>0.66</td>
<td>38 (15%)</td>
<td>0.64</td>
<td>49 (25 to 76) 0.20</td>
</tr>
<tr>
<td>No</td>
<td>246</td>
<td>110 (45%)</td>
<td>11 (4%)</td>
<td>125 (51%)</td>
<td></td>
<td>17 (14%)</td>
<td>45 (25 to 71)</td>
<td></td>
</tr>
</tbody>
</table>

ACS: antenatal corticosteroids, PTD: preterm delivery

*p Determined by χ² for categoric variables and nonparametric tests of medians for continuous variables.

Parity was the only maternal factor related to an increased frequency of PTL within seven days after enrollment, meaning that nulliparous women with a complete course ACS delivered significantly more frequent within seven days after enrollment (Table 3).

Of the 671 women with symptoms of PTL, at enrollment 371 (55%) received a complete course ACS, 34 (5%) received an incomplete course consisting of 1 dose ACS and 266 (40%) did not receive ACS treatment (Table 3). Among women who received a complete course of ACS, the median time between the first dose of ACS at enrollment to delivery was 46 (IQR 25 to 72) days, among women who received one dose, the median time from ACS to delivery was 1 day (IQR 0 to 3,25 days). Among women who did not receive initial treatment with ACS at study enrollment, the interval from enrollment to delivery was 62 days (46 to 80 days) (p< 0.001). The Kaplan Meier curve in figure 2 illustrates the interval from study enrollment to delivery and PTD before a gestational age of 34 weeks of women who received no, an incomplete course or a complete course of ACS at study enrollment.
Figure 2 Kaplan Meier curves illustrating the time from study enrollment to (preterm) delivery

ACS: antenatal corticosteroids

Table 3 Completion of ACS courses at study enrollment and preterm delivery rates according to CL and fFN

<table>
<thead>
<tr>
<th></th>
<th>Total (n=671)</th>
<th>CL &lt; 10 mm (n=65)</th>
<th>CL 10-30 mm + fFN pos (n=192)</th>
<th>CL 10-30 mm + fFN neg (n=172)</th>
<th>CL &gt; 30 mm (n=242)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No ACS at study enrollment</td>
<td>266 (40%)</td>
<td>2 (3%)</td>
<td>16 (8%)</td>
<td>61 (35%)</td>
<td>187 (77%)</td>
</tr>
<tr>
<td>PTD &lt; 7 days</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (2%)</td>
<td>1 (0.5%)</td>
</tr>
<tr>
<td>PTD &lt; 34 weeks</td>
<td>12 (5%)</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>7 (11%)</td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Incomplete course ACS at study enrollment</td>
<td>34 (5%)</td>
<td>18 (28%)</td>
<td>10 (5%)</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>PTD &lt; 7 days</td>
<td>28 (82%)</td>
<td>18 (100%)</td>
<td>7 (70%)</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>PTD &lt; 34 weeks</td>
<td>28 (82%)</td>
<td>18 (100%)</td>
<td>7 (70%)</td>
<td>2 (67%)</td>
<td>1 (33%)</td>
</tr>
<tr>
<td>Complete course ACS at study enrollment</td>
<td>371 (51%)</td>
<td>45 (69%)</td>
<td>166 (86%)</td>
<td>108 (63%)</td>
<td>52 (21%)</td>
</tr>
<tr>
<td>PTD &lt; 7 days</td>
<td>55 (15%)</td>
<td>24 (53%)</td>
<td>27 (16%)</td>
<td>3 (3%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>PTD &lt; 34 weeks</td>
<td>100 (27%)</td>
<td>29 (64%)</td>
<td>48 (29%)</td>
<td>14 (13%)</td>
<td>9 (17%)</td>
</tr>
<tr>
<td>Total</td>
<td>85 (13%)</td>
<td>42 (65%)</td>
<td>34 (18%)</td>
<td>6 (3%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>PTD &lt; 34 weeks</td>
<td>140 (21%)</td>
<td>47 (72%)</td>
<td>56 (29%)</td>
<td>23 (13%)</td>
<td>14 (6%)</td>
</tr>
</tbody>
</table>

ACS: antenatal corticosteroids, CL: cervical length, fFN: fetal fibronectin, PTD: preterm delivery

Figure 1 further shows the distribution of the included women over the four groups and the proportion completed ACS courses. The proportion completed ACS courses differed significantly between the four groups. (p=0.001) (Table 3).
Group 1 CL < 10 mm

Group 1 consisted of 65 women. The median gestational age of these women at study enrollment was 28 1/7 weeks (IQR 26 1/7 to 30 2/7 weeks). The median gestational age at delivery was 30 4/7 weeks (IQR 28 0/7 to 34 1/7 weeks). ACS were prescribed to 63 women (97 %) at study enrollment (Table 3). PTD within seven days after study enrollment occurred in 42 (65%) of the women in this group. Delivery within seven days occurred in 24 (53%) of the 45 (69%) women who received a complete course and all of the 18 (28%) women who received an incomplete course. To two women (3%) no ACS was prescribed, these women did not deliver within seven days and received no ACS treatment further on in pregnancy (Table 4). Of the women in this group who completed the ACS course, the median interval between study enrollment and delivery was 6 days (IQR 3 to 61 days), compared to a half day (IQR 0 to 1.3 days) in women who received an incomplete course and 75 days (IQR 58 to 91 days) in those women who received no ACS. Of the 21 women who received a complete course but did not deliver within seven days, 6 (29%) received a second course of ACS (1 incomplete and 5 complete). Only the women (17%) who received a second incomplete course delivered within seven days.

Group 2 CL 10 to 30 mm and a positive fFN test

Group 2 consisted of 192 women. The median gestational age of these women at study enrollment was 29 3/7 weeks (IQR 27 0/7 to 31 0/7 weeks). The median gestational age at delivery was 36 4/7 weeks (IQR 31 3/7 to 38 2/7 weeks). ACS were prescribed to 176 women (91 %). PTD within seven days after study enrollment occurred in 34 (18%) of the women in this group. Delivery within seven days occurred in 27 (16%) of the 166 (86%) women who received a complete course of ACS and 7 (70%) of the 10 (5%) women who received an incomplete course. None of the 16 (8%) women who received no ACS treatment at study enrollment delivered within seven days (Table 3). Of the women in this group who completed the ACS course, the median interval between study enrollment and delivery was 44 days (IQR 17 to 69 days), compared to 1 day (IQR 0 to 36 days) in women who received an incomplete course and 63 days (IQR 38 to 79 days) in those women who received no ACS. To three (19%) of the 16 women to whom initially no ACS were prescribed, ACS was administered further on in pregnancy, of whom 1 delivered within seven days after treatment. One woman delivered before a gestational age of 34 weeks without being treated with ACS (Table 4). Of the 139 women who received a complete course but did not deliver within seven days, 15 (11%) received a second
course of ACS (3 incomplete and 12 complete). Six (40%) women delivered within seven days after this second course, one of these courses could not be completed.

**Group 3 CL 10 to 30 mm and a negative fFN test**

Group 3 consisted of 108 women. The median gestational age of these women at study enrollment was 29 6/7 weeks (IQR 26 6/7 to 31 5/7 weeks). The median gestational age at delivery was 37 6/7 weeks (IQR 36 1/7 to 39 5/7 weeks). ACS were prescribed to 111 (65%) women. PTD within seven days after enrollment occurred in 6 (3%) of the women in this group. Delivery within seven days occurred in 3 (3%) of the 108 (63%) women who received a complete course of ACS at study enrollment and in 2 (67%) of the 3 (2%) women who received an incomplete course. One (2%) of the 61 (35%) women who received no ACS treatment at study enrollment delivered within seven days, at a gestational age of 34 4/7 weeks (Table 3). Of the women in this group who completed the ACS course, the median interval between study enrollment and delivery was 53 days (IQR 37 to 77 days), compared to 1 day (IQR 0.5 to 19 days) in women who received an incomplete course and 62 days (IQR 39 to 80 days) in those women who received no ACS. To 15 (24%) of the 61 women to whom initially no ACS were prescribed a complete course of ACS was administered further on in pregnancy, of whom 2 (13%) delivered within seven days (Table 4). Of the 105 women who received a complete course but did not deliver within seven days, 11 (10%) received a second course of ACS (5 incomplete and 6 complete). Three (27%) women delivered within seven days after this second course, two of these courses could not be completed.

**Group 4 CL > 30 mm**

Group 4 consisted of 242 women. The median gestational age of these women at study enrollment was 29 4/7 weeks (IQR 27 1/7 to 31 1/7 weeks). The median gestational age at delivery was 38 4/7 weeks (IQR 37 3/7 to 40 0/7 weeks). ACS were prescribed to 55 (23%) women. PTD within seven days after study enrollment occurred in 3 (1%) of the women in this group. PTD within seven days occurred in 1 (2%) of the 55 (21%) women who received a complete course of ACS at study enrollment and 1 (33%) of the 3 (2%) women who received an incomplete course. One (0.5%) of the 187 (77%) women who received no ACS treatment at study enrollment delivered within seven days after receiving an incomplete course further on in pregnancy (Table 3). Of the women in this group who completed the ACS course, the median interval between study enrollment and delivery was
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66 days (IQR 43 to 78 days), compared to 68 days (IQR 1 to 95 days) in women who received an incomplete course and 62 days (IQR 48 to 80 days) in those women who received no ACS. Eleven of the 187 women (6%) to whom initially no ACS were prescribed received ACS further on in pregnancy, of whom 4 (36%) delivered within seven days after treatment. One woman of the 176 (0.6%) women who did not receive ACS at all, delivered before a gestational age of 34 weeks (Table 4). Of the 51 women who received a complete course but did not deliver within seven days, 4 (8%) received a second course of ACS (1 incomplete and 3 complete). Two (50%) women delivered within seven days after this second course, both could complete the course.

Table 3 further contains the PTD rates before a gestational age of 34 weeks for the four groups.

The Kaplan Meier curve in figure 3 illustrates the time from the first ACS gift of a complete course to delivery and PTD before a gestational age of 34 weeks among the four groups.

**Table 4** Completion of ACS courses in the course of pregnancy and preterm delivery rates after no prescription of ACS at study enrollment

<table>
<thead>
<tr>
<th></th>
<th>Total (n=266)</th>
<th>CL &lt; 10 mm (n=2)</th>
<th>CL 10-30 mm + fFN pos (n=16)</th>
<th>CL 10-30 mm fFN neg (n=61)</th>
<th>CL &gt; 30 mm (n=187)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>No ACS</td>
<td>237 (89%)</td>
<td>2 (100%)</td>
<td>13 (81%)</td>
<td>46 (75%)</td>
<td>176 (94%)</td>
</tr>
<tr>
<td>PTD &lt; 7 days</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>PTD &lt; 34 weeks</td>
<td>2 (1%)</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>Postponed incomplete</td>
<td>3 (1%)</td>
<td>0 (0%)</td>
<td>1 (6%)</td>
<td>0 (0%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>PTD &lt; 7 days</td>
<td>3 (100%)</td>
<td>1 (100%)</td>
<td>1 (100%)</td>
<td>2 (100%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>PTD &lt; 34 weeks</td>
<td>2 (66%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (100%)</td>
<td>2 (100%)</td>
</tr>
<tr>
<td>Postponed complete</td>
<td>26 (10%)</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
<td>15 (25%)</td>
<td>9 (5%)</td>
</tr>
<tr>
<td>PTD &lt; 7 days</td>
<td>4 (15%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>2 (13%)</td>
<td>2 (22%)</td>
</tr>
<tr>
<td>PTD &lt; 34 weeks</td>
<td>8 (31%)</td>
<td>0 (0%)</td>
<td>7 (47%)</td>
<td>1 (11%)</td>
<td></td>
</tr>
</tbody>
</table>

ACS: antenatal corticosteroids, CL: cervical length, fFN: fetal fibronectin, neg: negative, pos: positive, PTD: preterm delivery
Discussion

The aim of this study was to assess the impact of cervical length measurement and fetal fibronectin testing on the clinicians’ decision to administer antenatal corticosteroids to women with symptoms of preterm labor. ACS were prescribed to 97% of the women with CL < 10 mm, to 91% of the women with a CL between 10 and 30 mm and a positive fFN test, to 65% of the women with a CL between 10 and 30 mm and a negative fFN test and to 23% of the women with a CL > 30 mm. Delivery within seven days occurred in 65% of the women with a CL < 10 mm, in 18% of the women with a CL between 10 and 30 mm and a positive fFN test, in 3% of the women with a CL between 10 to 30 mm and a negative fFN test and in 1% of the women with a CL > 30 mm. Two (1%) of the women who did not receive ACS at enrollment (n = 266) delivered within seven days. The median intervals between study enrollment and delivery were 6 days (IQR 3 to 61 days), 44 days (IQR 17 to 69 days), 53 days (IQR 37 to 77 days) and 66 days (IQR 43 to 78 days) in group 1, 2, 3 and 4 respectively.

In the Netherlands the care for the premature neonate born before a gestational age of 32 weeks is centralized in tertiary perinatal centers. Women in secondary care centers who are thought to be of high risk of PTD in the short term will therefore be transferred to one of these tertiary centers. We did not find any difference in ACS
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administration between women with symptoms of PTL referred from a secondary care center or primary care midwifery to the participating tertiary centers and women who were primarily hospitalized in these tertiary hospitals. We did not, however, register the patients with symptoms of PTL admitted in a secondary care center, who were not transferred to a perinatal center. Therefore we could not compare our results to the proportion completed ACS and the time from ACS administration to delivery in women hospitalized in secondary care centers with early symptoms of PTL but a (low) risk of PTD or a higher risk of PTD after 32 weeks' gestation.

Only in nulliparous women and in multiple pregnancies we found a significant higher proportion of completed courses. One explanation might be that clinicians might perceive a higher risk of PTD in these women and therefore have a lower threshold to prescribe ACS. The interval between ACS prescription and delivery is women with these characteristics did have a significant shorter interval between ACS prescription and delivery, but this still by far exceeds the recommended 7 day interval.

A recent retrospective chart review focused on the undertreatment with ACS of women who delivered without receiving or completing their ACS course and found possibilities to improve administration rates, with shorter intervals between the presentation of the women and administration of ACS. They found that within the group of women who delivered before 34 weeks of gestation 17.8% did not deliver within two weeks of the administration of the complete course ACS and emphasized that caution must be used in these women to balance the uncertainty of whether a PTD will be experienced within the next week to limit under- or overuse of this medication. A prospective audit of the use of fFN in women diagnosed with PTL, has shown that patients with negative fFN results who were not transferred to tertiary care still received ACS therapy in 34% of the cases, which indicates a concern in clinicians about the possibility of ongoing PTL.

Negative findings concerning the clinical utility of fFN have been reported. In these studies women were allocated to a treatment strategy with or without the availability of fFN results. The lack of benefit of the use of fFN might be explained by the absence of a fixed protocol in relation to the fFN results, and therefore clinicians might not have incorporated the test results into their decision making. The combination of CL measurement and fFN testing improves the prediction of PTD, allowing to improve the timing of ACS administration. The
absence of a fixed protocol in our study concerning the administration of ACS in correlation to the CL and fFN results, might explain the inadequate timing and overuse of ACS in women with symptoms of PTL and a low risk of preceding PTD. Meta-analyses have shown that the combination of fFN testing and CL measurement may reduce unnecessary costs. Studies included in these analyses combined CL and fFN testing in different ways, so it remains unclear from these studies how to combine both tests to maximize cost reduction without compromising neonatal outcomes. A recent model-based cost-effectiveness analysis to evaluate 7 test-treatment strategies in women with threatened PTL conducted in the Netherlands, found that additional fFN testing in the case of a CL between 10 and 30 mm, and only treating women with a CL < 10 mm or a CL between 10-30 mm with a positive fFN test, is cost saving without compromising neonatal health outcomes, compared with a treat-all strategy or single CL testing.

A recent retrospective study has shown that none of the included women admitted and treated for PTL with a CL > 30 mm delivered preterm and concluded that health care cost could be lowered significantly without jeopardizing outcome. Our results show that of the women with a CL between 10 and 30 mm and a negative fFN test, 13% delivered before 34 weeks of gestation, but only 3% within 7 days after presentation. Six percent of the women with a CL > 30 mm delivered before a gestational age of 34 weeks, one percent delivered within seven days. In the Netherlands midwives in primary care and obstetricians in secondary care centers preselect which women with symptoms of PTL will be transferred to a tertiary center, which might explain the PTD rates in our study compared to the retrospective study mentioned above.

ACS administration could initially be omitted in women with a CL 10-30 mm and a negative fFN test and in women with a CL > 30 mm. In case of persisting or recurrent threat of PTD, treatment can be reconsidered to optimize timing. Of the 248 low risk women in our study who received no ACS at study enrollment, one (0.4%) delivered before a gestational age of 34 weeks without receiving ACS. The other women were treated further on in pregnancy. In case of recurrent threat of PTD, reassessment by measuring the CL and fFN testing might be considered. There is no clear strategy to identify initially low-risk women who will deliver preterm later on in pregnancy. This might explain overuse of ACS in this group at first presentation of symptoms, possibly due to concerns of the clinician about the possibility of proceeding PTD and therewith the risk of suboptimal preparation of the neonate due to withdrawal of ACS treatment.
In conclusion, this study shows that there is room for improvement in the prescribing patterns of ACS to women with symptoms of PTL in women with a CL of 10-30 mm and a negative fFN test or a CL > 30 mm. Although clinicians were informed about the CL en fFN status, and therefore could assess the risk of PTD within seven days, to a large portion of these low risk women ACS were prescribed directly after presentation with PTL. The interval between ACS prescription and delivery by far exceeded the recommended maximum of seven days. Better prescribing patterns and timing may result in better therapeutic results, avoids the question whether or not to repeat ACS and might prevent overtreatment and therewith lower health care costs. Consensus about ACS administration is needed and a fixed treatment protocol based on the CL and fFN result, might help clinicians to decide whether or not to prescribe ACS.
Chapter 8

References

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