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Prescribing patterns of antenatal corticosteroids in women with threatened preterm labor

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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.

Study design: This is a secondary analysis of a prospective cohort study including women with symptoms of preterm labor and intact membranes between 24 and 34 weeks' gestation. We compared the proportion prescribed and completed ACS courses, preterm delivery within seven days and median intervals from ACS 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, 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. Median intervals between ACS and delivery were 6 days (IQR 3–61 days), 44 days (IQR 17–69 days), 53 days (IQR 37–77 days) and 66 days (IQR 43–78 days) in group 1, 2, 3 and 4 respectively.

Conclusion: ACS were prescribed frequently to women with a CL of 10–30 mm and a negative fFN test or a CL > 30 mm. There is room for improvement in the prescription of ACS in these low risk women.

Introduction

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

Two decades have passed since the first publication on the reduction of the incidence of respiratory distress syndrome (RDS) by ACS before ACS were implemented following a recommendation by the National Institutes of Health (NIH) to administer ACS to all women at risk of PTD between 24 and 34 weeks' gestation [7–9].

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Difficulty in accurate prediction of preterm delivery in the short term and a possible diminishing effect of ACS over time, with an optimal interval of 7–14 days between ACS and delivery, resulted in routinely repetition of ACS in the 1990s [10–17]. However no long-term benefit of repeat courses were found [18–24]. Furthermore a lower neonatal birth weight and smaller head circumference were reported, although the long-term outcomes at 2–3 years of age seemed to be reassuring. Nowadays a "rescue" course of ACS can be considered [25–27].

Optimal timing of the first course of ACS can prevent the rise of the question whether or not to repeat a course. 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 recognition of women at low risk of PTD within the next seven days [28–32].

In this cohort study, we assessed clinicians' prescribing patterns of ACS in relation to CL and fFN results in women with symptoms of PTL. We hypothesize that clinicians inadequately time treatment of women at low risk for PTD.

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 to access the accuracy of fFN testing and CL measurement in women with symptoms of PTL. The study protocol received IRB-approval (MEC 08/363), and methods have been reported previously [33].

Participants and interventions

The APOSTEL-1 study included women with symptoms of PTL, such as contractions (>3 per 30 min), vaginal bleeding, or abdominal/back pain between 24 and 34 weeks of gestation and intact membranes. Women who received tocolytic treatment within the previous seven days were excluded, except for those who received a single dose of tocolytic treatment for transportation to a tertiary hospital. Other exclusion criteria were more than 3 cm dilatation diagnosed at digital examination and contra-indications for tocolysis, such as lethal congenital abnormalities, suspected intra-uterine infection or non-reassuring fetal status. At admission a fFN test (rapid fetal fibronectin TLI_{IQ} 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.

No strict protocol was available for treatment decisions, but recommendations were provided. Tocolysis was recommended according to local protocol in women with a CL below 10 mm (group 1) or a CL between 10 and 30 mm and a positive fFN test (group 2). In women with a CL between 10 and 30 mm and a negative fFN test (group 3) the clinician on call decided whether to start tocolysis. We recommended to withhold tocolytic treatment in women with a CL above 30 mm (group 4). Clinicians could prescribe nifedipine, indomethacin, atosiban and/or ritodrine. Corticosteroids were given to women at the discretion of the clinician on call [32].

Outcomes and statistical analysis

A complete course ACS was defined as two doses of 12 mg Celestone Chronodose (Merck Sharp & Dohme bv, Brussels, Belgium) intramuscularly with a 24-h interval.

For women who received a complete, an incomplete (1 dose) or no ACS course we calculated median gestational age at delivery, median gestational age at ACS treatment and the median interval from study enrollment to delivery, all with interquartile ranges (IQR). A Kaplan–Meier plot was derived to illustrate the interval from enrollment to preterm delivery (before 34 weeks). To evaluate the influence of a prolonged interval between a complete course ACS at enrollment and preterm delivery before 34 weeks gestation on the neonatal respiratory outcome, we compared intubation rate of neonates born alive within or beyond seven days after administration of ACS and calculated the odds ratios (OR) with 95% confidence intervals (95% CI). Since the gestational age at which neonates are born is of influence on the respiratory outcome, we evaluated the intubation rates per two weeks gestation.

Among the four groups based on CL and fFN result we evaluated the proportion prescribed and the proportion completed courses of ACS at study enrollment, the PTD rates within seven days after study enrollment and before 34 weeks gestation and the interval between ACS treatment and delivery. Mode of delivery was described for the women who delivered prematurely. A Kaplan–Meier plot was made to illustrate the interval from the time from the first ACS gift of a complete course to preterm delivery (before 34 weeks). Data were censored after 28 days, since ACS are unlikely to be beneficial if delivery occurs after this period.

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. To evaluate prescribing patterns during the course of pregnancy we analyzed the proportion postponed and repeated ACS courses and PTD rates after a postponed or repeated course.

Finally, we assessed the following characteristics: parity, ethnicity, smoking, previous preterm delivery, singleton vs. multiple pregnancy and referral from primary care midwifery practice or secondary care center. Stratified analyses were performed since these characteristics might influence the risk assessment of PTD and therewith the prescribing patterns of ACS.

Statistical analyses were performed using SPSS software, version 21.0 (SPSS Inc. Chicago, IL, USA).

Results

Between December 2009 and August 2012, 758 women were approached for the APOSTEL-1 study. We included 671 women in the analysis (Fig. 1). The median gestational age at study enrollment was 29.4 weeks (IQR 27–31.3). Of the included women, 324 (48%) were multiparous of whom 145 (45%) had a previous premature delivery. The cohort contained 104 (14%) multiple pregnancies. A cesarean section was performed in 144 (21%) women. Further baseline characteristics can be found in Table 1.

Total population

Of the 671 women with symptoms of PTL, 371 (55%) received a complete ACS course, 34 (5%) an incomplete course and 266 (40%) received no ACS treatment at enrollment (Table 2). The median interval from enrollment to delivery among women who received a complete course, an incomplete course or no ACS at study enrollment was 46 days (IQR 25–72) days, 1 day (IQR 0–3.25) and 62 days (IQR 46–80) days respectively ($p < 0.001$). The Kaplan–Meier curve in Fig. 2 illustrates the interval from study enrollment to delivery and PTD before 34 weeks. Out of the 100 women who completed an ACS course and delivered before 34 weeks of gestation 124 neonates were born alive. Table 3 shows the intubation rate of neonates born before 34 weeks of gestation within or beyond seven days after administration of a complete course of ACS, categorized per two weeks of gestation. No significant odds ratios were found. Virtually all neonates born