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Review

Antepartum and intrapartum interventions to prevent preterm birth and its sequelae

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SUMMARY

Preterm birth is the main cause of neonatal morbidity and mortality. This review provides an overview of antepartum and intrapartum management of threatened preterm birth. The most effective method to identify women at high risk of delivering within seven days is the combination of cervical length and fetal fibronectin test. Antenatal corticosteroids administered for 48 h improve neonatal outcome. Although tocolysis has been shown to prolong pregnancy, there is no evidence that tocolytic therapy improves neonatal outcomes. Intrapartum administration of magnesium sulfate improves neurologic outcomes, such as cerebral palsy and gross motor function. In women with preterm premature rupture of membranes, prophylactic antibiotic treatment with erythromycin improves short-term neonatal outcomes, but proof of long-term benefit is lacking. In threatened preterm birth with intact membranes, prophylactic antibiotic treatment is thought to be harmful. Critical appraisal of the long-term benefits and harms of all these treatments questions their use.

1. Introduction

Preterm birth complicates 5–13% of all pregnancies worldwide and is the most important cause of neonatal morbidity and mortality [1]. Although disability-free survival rates have increased over the years as a result of improved facilities and treatments, preterm birth is still accountable for 75% of all perinatal deaths and >50% of morbidities [2,3]. Morbidity and mortality are strongly related to gestational age; of those infants born <30 weeks of gestation, only 25% are free of disabilities at the age of five years [3,4]. Many treatments have been investigated to improve neonatal outcomes. The aim of this article is to review current evidence-based practice of antepartum and intrapartum interventions in threatened preterm birth to improve neonatal outcome. We discuss the most accurate method of diagnosing threatened preterm birth. Treatments including the use of tocolytic drugs, corticosteroids, magnesium sulfate as neuroprotective agent, and antibiotics are discussed.

2. Diagnosis of threatened preterm birth

Pregnant women with symptoms of threatened preterm birth are a frequent problem in obstetric care. In women with intact membranes and contractions, 12–17% deliver within seven days, whereas around 40–60% of women with preterm premature rupture of membranes (PPROM) deliver within seven days [5,6]. Therefore, to minimize the risk of overtreatment, and to maximize timing of interventions, identification of women at high risk of delivery within seven days is of utmost importance.

Historically, risk assessment was based on digital vaginal examination. The addition of transvaginal sonographic measurement of the cervical length is of value in the prediction of preterm birth within one week (sensitivity/specificity: cervical length: 78.1%/82.7% vs vaginal examination: 65.6%/72.4%) [7]. Identification of women at high risk of delivery can be improved by adding fetal fibronectin testing to cervical length measurement. Fetal fibronectin is a protein produced by fetal cells and can found at the border of the chorion and the decidua. Fetal fibronectin is released into the vagina when a preterm delivery is likely to occur and may be measured using a vaginal swab [8]. A recent prospective cohort study showed that women with symptoms of preterm labor and cervical length >30 mm or with cervical length between 15 and

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30 mm with negative fetal fibronectin test result have a low risk (<5%) of spontaneous preterm delivery within seven days [9]. A randomized trial, allocating women at low risk of delivering within seven days (intact membranes, cervical length between 10 and 30 mm, and negative fetal fibronectin test) to tocolysis with nifedipine or placebo, showed no differences in prolongation of pregnancy or neonatal outcomes, thereby confirming that these women do not benefit by treatment with tocolysis [10]. Women with symptoms of preterm labor and cervical length <15 or 15–30 mm and positive fetal fibronectin test have a high risk of delivery within seven days (11–52%), therefore treatment is justified [9]. A cost-effectiveness analysis of the use of cervical length in combination with fetal fibronectin testing showed a possible saving in costs between −1.6 and −8.0 million per 100,000 deliveries [11].

2.1. Conclusion

The use of cervical length measurement in combination with fetal fibronectin test is most accurate and cost-effective to discriminate between women at high and low risk of delivering within seven days.

3. Antenatal corticosteroids

In the late 1960s Graham Liggins, University of Auckland, coincidentally found in his investigation on involvement of corticosteroids on preterm birth that preterm lambs exposed to antenatal corticosteroids had structurally more mature lungs than expected. Furthermore these lambs were viable at lower gestational age and had fewer respiratory problems at birth [12].

In 1972 Liggins and his partner Ross Howie published their landmark randomized trial comparing corticosteroids with placebo in women with threatened preterm birth <37 weeks of gestational age [13]. Liggins and Howie found an improvement in respiratory distress syndrome and neonatal mortality. They recruited 282 women in 22 months starting in 1969. The study was approved by the general staff of the National Women's Hospital, Auckland, New Zealand. Interestingly, they continued to randomize a total of 1142 women until 1974 [14]. Subsequent trials confirmed the findings of Higgins and Howie. The first structured review was published in 1990 and showed that corticosteroids are effective in reducing respiratory distress syndrome and neonatal mortality [15]. In 1994 the American College of Obstetricians and Gynecologists and the National Institutes of Health (NIH) published their consensus statement, recommending the use of antenatal corticosteroids in threatened preterm birth [16]. In retrospect, it took 22 years to translate the results of the trial by Liggins and Howie into international clinical practice.

3.1. Single course of antenatal corticosteroids

A Cochrane review (2006) showed that in women with gestational age between 26^{+0} and 34^{+6} weeks treatment with a single course of antenatal corticosteroids for 48 h is associated with a decrease in neonatal death (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.58–0.81; 18 studies, 3956 infants), respiratory distress syndrome (0.66, 0.59–0.73, 21 studies, 4038 infants), intraventricular hemorrhage (0.54, 0.43–0.69; 13 studies, 2872 infants), necrotizing enterocolitis (0.46, 0.29–0.74; eight studies, 1675 infants), respiratory support, intensive care admissions (0.80, 0.65–0.99; two studies, 277 infants), and systemic infections within the first 48 h of life (0.56, 0.38–0.85; five studies, 1319 infants) [14]. A recent cluster-randomized trial, comparing a strategy for improvement of antenatal corticosteroid therapy with standard therapy in six countries with low-resource setting, found no decrease in neonatal mortality despite increasing use of corticosteroids. In the overall population using the strategy there was even an increase in mortality (RR 1.12, 95% CI 1.02–1.22) [17]. The recent World Health Organization (WHO) guideline concerning preterm birth recommends to administer antenatal corticosteroids between 24 and 34 weeks of gestational age; without signs of infection and adequate childbirth care is available [18].

3.2. Repeat course of antenatal corticosteroids

Timing of the administration of antenatal corticosteroids is crucial. While the period of 48 h is arbitrary, the effect of antenatal corticosteroids on neonatal respiratory morbidity decreases after seven days of administration [19]. When women do not deliver within seven days after the initial course of antenatal corticosteroids, and remain at risk for preterm birth, a repeat course of antenatal corticosteroids may be considered.

A recent Cochrane review showed that a repeat course reduced the risk of respiratory distress syndrome compared with women not receiving a repeat course (RR 0.83, 95% CI 0.75–0.91; eight trials, 3206 infants) and adverse neonatal outcome (0.84, 0.75–0.94; seven trials, 5094 infants). A reduction in mean birth weight was found in women treated with a repeat course (mean difference (MD) −75.79 g, 95% CI −117.63 to 33.96; nine trials, 5626 infants). However, adjusted birth weight for gestational age did not differ between treatment groups [20]. In long-term follow-up (early childhood) no statistically significant differences were found in infants exposed to repeat antenatal corticosteroids compared with unexposed infants for the primary outcomes (total deaths; survival free of any disability or major disability; disability; or serious adverse outcome) or in the secondary outcome growth assessments [21]. The WHO preterm birth guideline recommends a single repeat course of antenatal corticosteroids when preterm birth does not occur within seven days after the initial dose, and when a subsequent clinical assessment shows that there is a high risk of preterm birth in the next seven days [18].

3.3. Type of corticosteroids

The glucocorticoids used for antenatal administration are dexamethasone and betamethasone. A recent Cochrane review on different types and regimens of corticosteroids showed that dexamethasone was associated with a decreased risk of intraventricular hemorrhage compared with betamethasone (RR 0.44, 95% CI 0.21–0.92; four trials, 549 infants). No statistically significant differences were seen for other primary outcomes such as infant respiratory distress syndrome (1.06, 0.88–1.27; five trials, 753 infants) and perinatal death (1.41, 0.54–3.67; four trials, 596 infants). In secondary outcomes small differences were found, such as rate of admission to the neonatal intensive care unit. However, one trial found that infants in the dexamethasone group had a significantly shorter length of neonatal intensive care unit (NICU) admission (MD −0.91 days, 95% CI −1.77 to 0.05; 70 infants) [22].

3.4. Long-term outcomes

A recent meta-analysis examined long-term neurologic outcomes after a single course of antenatal corticosteroids. Results showed that a single course of antenatal corticosteroids was associated with a decreased risk for cerebral palsy (RR 0.68, 95% CI 0.56–0.82; seven studies), poor psychomotor development (0.83, 0.74–0.93), and severe disability (0.79, 0.73–0.85). Steroid treatment increased the rates of intact survival (1.19, 1.06–1.33) [23]. A single course of antenatal corticosteroids appears to have no adverse effects on children's health. However, follow-up of a trial