F1000Prime REPORTS

Published: 02 April 2015

Recent advances in the prevention and management of preterm birth

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F1000Prime Reports 2015, **7**:40 (doi:10.12703/P7-40)

Abstract

The management of preterm birth has seen major transformations in the last few decades with increasing interest worldwide, due to the impact of preterm birth on neonatal morbidity and mortality. The prevention strategies currently available for asymptomatic women at risk of preterm birth include progesterone, cervical cerclage and cervical pessary. Each approach has varying effects depending on the patient's prior history of preterm birth, cervical length and the presence of multiple gestations. There is a shift in the focus of antenatal treatment, with the use of prenatal magnesium sulphate and corticosteroids, to reduce neonatal intensive care admissions and longer-term disabilities associated with preterm birth, consequently relieving emotional and economical burden. This article provides an update on the recent advances in prevention and management approaches available for women at risk of preterm birth.

Introduction

Preterm birth is the leading cause of perinatal morbidity and mortality, and remains one of the biggest challenges in modern obstetrics [1]. It is estimated that more than one million children in the world die every year because of preterm birth [2]. The neonatal complications are closely related to the gestational age at delivery and include respiratory distress syndrome, intraventricular hemorrhage, periventricular leukomalacia, sepsis, and necrotizing enterocolitis. Severe long-term complications include cerebral palsy and neurodevelopmental delay [3,4].

Preterm birth refers to delivery before 37 weeks' gestation, which occurs in 5–8% of all pregnancies, but most mortality and morbidity relates to early preterm birth before 32 weeks, which occurs in about 1% of singletons and 9% of twin pregnancies [5,6]. Preterm birth can either be spontaneous, following premature labor with intact membranes, or preterm premature rupture of membranes (PPROM), or the consequence of iatrogenic delivery for maternal and/or fetal indications [7].

In this article, we will focus on recent advances in the prevention of spontaneous preterm birth and antenatal management strategies to reduce the neonatal complications of pregnancies delivering prematurely.

Prevention of spontaneous preterm birth

Cervical pessary

Several retrospective studies showed promising results in the use of a cervical pessary for the reduction of spontaneous preterm birth in high-risk pregnancies [8–10]. Subsequent prospective randomized controlled trials (RCTs) provided conflicting results. The Pesario Cervical para Evitar Prematuridad (PECEP) study of cervical pessary vs. expectant management in 385 women with singleton pregnancies and sonographically defined short cervix (≤25 mm) at 18–22 weeks' gestation, reported that the pessary was associated with significant reduction in the rate of preterm birth <34 weeks (6% vs. 27%; odds ratio (OR) 0.18, 95% confidence interval (CI) 0.08–0.37) [11]. Analysis of secondary outcomes also identified a decrease in respiratory distress syndrome (3% vs. 12%; OR 0.20, 95% CI 0.06–0.55) and a reduction

in neonates with a birth weight <1500 g (5% vs. 14%; OR 0.31, 95% CI 0.13–0.72). Although the results appear promising, the generalizability of the results of this study has been questioned, due to the unexpectedly high rate of preterm birth in the control arm [12]. Another smaller trial of 108 singleton pregnancies with cervical length of <25 mm at 20–24 weeks' gestation did not demonstrate any significant differences in the rate of preterm birth <34 weeks (9.4% vs. 5.5%, $P = 0.46$) [13]. Neither study reported any serious adverse effects associated with the use of the pessary.

In multiple pregnancies, the use of cervical pessary was examined in the Pessaries in Multiple Pregnancy as a Prevention of Preterm Birth (ProTwin) trial, where 813 women with multiple pregnancies were randomized either to receive the pessary at 16–20 weeks' gestation or to have routine care [14]. Overall, there was no difference between the two groups in the rate of preterm birth (<28, 32, 37 weeks' gestation) or poor perinatal outcome. However, in a subgroup analysis of women with a cervical length of <38 mm (less than the 25th percentile), the pessary significantly reduced the rate of very preterm birth <28 weeks (relative risk [RR] 23, 95% CI 0.06–0.87) and preterm birth <32 weeks (RR 0.49, 95% CI 0.24-0.97), and composite poor perinatal outcome (RR 0.40, 95% CI 0.19–0.83). The results for the subgroup of women with a short cervix are consistent with those of the PECEP trial; nevertheless, these findings need to be replicated before definitive recommendations can be made.

Progesterone

Several studies have suggested that the prophylactic use of progesterone reduces the rates of preterm birth in women with a singleton pregnancy and a history of spontaneous preterm birth [15,16], or a short cervix identified on transvaginal ultrasound at 19–25 weeks' gestation [17,18]. Both natural vaginal micronized preparation and synthetic intramuscular 17 alpha-hydroxyprogesterone (17-OHPC) have been investigated. The FDA approved progesterone use in 2011 and the American College of Obstetricians and Gynecologists (ACOG) and the Society for Maternal-Fetal Medicine recommended it in their 2012 treatment guidelines [19,20]. The algorithms created in these guidelines support the use of 17-OHPC but not vaginal progesterone in women with a prior spontaneous preterm birth. The reverse is true for women with a short cervix (<20 mm) where vaginal progesterone is the preferred option.

A Cochrane review published in 2013 summarized the effects of progesterone in women with a prior history of preterm birth based on 11 RCTs that included 1899 patients. Progesterone was associated with a reduced risk of preterm birth at <34 weeks (RR 0.31, 95% CI 0.14–0.69) and perinatal mortality (RR 0.50, 95% CI 0.33–0.75). There were also decreased rates of infants with a low birth weight <2500 g, necrotizing enterocolitis, neonatal death, and admission to a neonatal intensive care unit [21]. There were no observed disparities in outcomes when subgroup analyses were performed with different routes (intramuscular/vaginal/oral) and doses of progesterone administration, but the number of patients in each subgroup was small.

In asymptomatic singleton pregnancies with a sonographic short cervix ≤25 mm, vaginal progesterone appears to be beneficial in reducing preterm birth and neonatal morbidity and mortality. In an individual patient data meta-analysis of five RCTs (775 women, 827 infants), the rate of early preterm birth at <33 weeks was significantly lower in women who received vaginal progesterone (12.4% vs. 22.0%; RR 0.58; 95% CI 0.42–0.80; numbers needed to treat [NNT] 11), the effect being evident regardless of a history of previous preterm birth [22]. Infants of treated women had significantly reduced the risk of respiratory distress syndrome (6.1% vs. 12.5%; RR 0.48; 95% CI 0.30–0.76), composite neonatal morbidity and mortality (9.7% vs. 17.3%; RR 0.57), and birth weight <1500 g (8.8% vs. 16.5%; RR 0.55). There was no increased risk of adverse maternal events or congenital anomalies between the treatment and placebo groups. Almost 90% of subjects in this meta-analysis were attributable to two trials [17,18] that used different cervical length cut-offs of <15 mm [17] and 10-20 mm [18] and doses of vaginal progesterone 200 mg/day [17] and 90 mg/day [18]. Despite these variations, the results from both studies were consistent with a 42% and 45% reduction in early preterm births.

There has only been one RCT that evaluated the effects of 17-OHPC vs. placebo in asymptomatic women with singleton pregnancies and a short cervix of <30 mm [23]. There was no difference in the rate of preterm birth at <37 weeks (25.1% vs. 24.2%; RR 1.03, 95% CI 0.79–1.35) or the rate of composite adverse neonatal outcome (7.0% vs. 9.1%; RR 0.77, 95% CI 0.46–1.30).

In multiple pregnancies, several RCTs have reported the failure of both vaginal micronized progesterone and 17-OHPC to lower the rates of preterm birth in twins [24-27], and triplets [28,29]. A recently published individual participant data meta-analysis (13 trials; 3768 women/7536 infants) confirmed the lack of benefit in preventing preterm birth at <34 weeks when progestogens were used in unselected twin pregnancies

(17-OHPC RR 1.1, 95% CI 0.94–1.2; vaginal progesterone RR 0.97, 95% CI 0.85–1.1) and also confirmed there were no differences in adverse perinatal outcome (17-OHPC RR 1.2, 95% CI 0.87–1.5; vaginal progesterone RR 0.96; 95% CI 0.83–1.1) [30]. However, in the subgroup of women with a cervical length of ≤25 mm, vaginal progesterone was associated with a reduction in adverse perinatal outcome (15/56 vs. 22/60; RR 0.57; 95% CI 0.47–0.70). The authors concluded that, although promising, these results should be interpreted with caution, due to the post hoc nature of the analysis and the small numbers involved. A recent RCT, comparing 17-OHPC to placebo in a 2:1 ratio, reported that there were no significant differences in the rates of preterm birth, but there were reductions in the rate of very low birth weight neonates (7.6% vs. 14.3%; RR 0.5; 95% CI 0.3–0.9), composite neonatal morbidity (19.1% vs. 30.9%; OR 0.53; 95% CI 0.31–0.90), and respiratory distress syndrome (14.4% vs. 23.4%; OR 0.55; 95% CI 0.31–0.98) [31].

The mechanism of preterm birth in multiple pregnancies is likely to be related to uterine distension, which appears to be unresponsive to progesterone unless there is already cervical shortening (which may be an early sign of the onset of parturition). Some authors have suggested that asymptomatic twin pregnancies may require increased doses of vaginal progesterone in order for it to be effective at reducing preterm birth in a similar way to singleton pregnancies. However, one RCT found that vaginal progesterone did not reduce preterm birth at either 200 or 400 mg [32].

Recently, safety concerns have been raised about the use of 17-OHPC. In an RCT involving women with triplet pregnancies, the group receiving weekly injections of 250 mg 17-OHPC experienced 13 mid-trimester fetal losses vs. none in the placebo group ($P<0.02$) [29]. In another study of asymptomatic twin pregnancies in women with a short cervix, treatment with 17-OHPC was associated with a significant increase in the rate of preterm birth at <32 weeks (29% vs. 12%; $P = 0.007$) [33]. Furthermore, in a recent meta-analysis, in the subgroup of women with a cervical length of >25 mm treated with 17-OHPC there was a worrying trend towards increased adverse perinatal outcome (RR 2.1, 95% CI 1.9–2.2) [30].

Cervical cerclage vs. progesterone

Cervical cerclage appears to be beneficial in reducing spontaneous preterm birth in high-risk groups (women with >3 preterm births and women with >1 preterm births with cervical length <25 mm at <24 weeks) [34,35]. However, no RCTs have been performed that compare the relative efficacy of vaginal progesterone with cervical cerclage in high-risk women. An indirect patient meta-analysis suggested that both interventions are equally effective both in the reduction of preterm birth and in adverse perinatal outcomes in singleton pregnancies of women with prior preterm birth and cervical length <25 mm in mid-trimester [36].

It is not known whether the effects of cerclage and progesterone are additive if used in combination. However, a secondary analysis of an RCT evaluating cerclage vs. expectant management for women with singleton pregnancies, prior spontaneous preterm birth and short cervix, found that the administration of 17-OHPC did not have an additional benefit to cerclage in reducing preterm birth, but actually increased the rates of miscarriage and perinatal mortality [37].

Antenatal management strategies to reduce neonatal complications of preterm birth

Antenatal corticosteroids

Maternal administration of corticosteroids reduces the rates of respiratory distress syndrome, intraventricular hemorrhage and death in neonates born prematurely, and the maximum benefit occurs if the drug is given at <7 days from preterm birth [38]. Although the administration of a single course of corticosteroids is not associated with adverse effects on the mother or baby [39], the use of repeated courses is controversial.

A systematic review and meta-analysis on the use of multiple courses reported that such treatment was associated with improved neonatal respiratory function but also with adverse effects on brain function and fetal growth [40]. Similarly, an earlier Cochrane review reported that multiple courses of corticosteroids resulted in a reduction in birth weight in one trial of 1144 infants, and an increase in the number of small for gestational age babies in two trials with 602 infants [41]. However, a more recent Cochrane review, including 10 RCTs, reported that the treatment of women who remain at risk of preterm birth seven or more days after an initial course of prenatal corticosteroids with repeat dose(s), compared with no repeat corticosteroid treatment, reduced the risk of their infants experiencing the primary outcomes respiratory distress syndrome (RR 0.83, 95% CI 0.75–0.91, eight trials, 3206 infants, NNT 17, 95% CI 11 to 32) and serious infant outcome (RR 0.84, 95% CI 0.75 to 0.94, seven trials, 5094 infants, NNT 30, 95% CI 19 to 79), without an effect on birth weight where outcomes were adjusted for gestational age. At early childhood follow-up, the primary outcomes (mortality, survival free of disability, serious outcome) and secondary growth assessments did not reveal any significant

differences between those with and without repeated doses of antenatal corticosteroids [42]. The lack of longer-term benefits of multiple courses vs. a single course of steroids has been replicated in the recently reported MACS-5 study, where no difference in a primary outcome of death or neurodisability at 5 years of age was seen in any preterm gestational age category [43]. However, of potential concern, for infants born ≥37 weeks gestation, there was a statistically significant increase in the risk of the primary outcome in multiple antenatal corticosteroid therapy: 48/213 (22.5%) compared to 38/249 (15.3%) in the single antenatal corticosteroid therapy; OR = 1.69 95% CI: 1.04, 2.77; $P = 0.037$. This difference was primarily driven by a four-fold increase in neurosensory disability, which in turn appears largely due to an increase in the need for visual aids. This should be interpreted with caution given that the gestational age windows were determined post-randomization, hence making it possible there were pre-existing differences to account for the findings [43].

Magnesium sulphate

Magnesium sulphate ($MgSO_4$) is widely used for seizure prophylaxis in pre-eclampsia and the treatment of eclampsia but, when used as a tocolytic, appears to confer no clear benefit in prevention of preterm delivery or serious infant outcome, when compared with placebo or other tocolytics [44]. However, when used with the primary intention of neuroprotection, there appears to be a significant benefit over placebo. An association between mothers who received $MgSO_4$ and a lower risk of cerebral palsy was first observed in a case control study in 1995 [45]. This finding was supported by five subsequent RCTs [46–50]. A meta-analysis of five RCTs (5235 infants) concluded that prenatal exposure to $MgSO_4$ significantly reduced the rates of cerebral palsy of any severity (RR 0.70, 95% CI 0.55–0.89) and moderate-severe cerebral palsy (RR 0.60, 95% CI 0.43–0.84), without increased risk of mortality (RR 1.01 95% CI 0.89–1.14) [51]. The number needed to treat to prevent one case of cerebral palsy among infants who survive until the age of 18–24 months was 46 (95% CI 26–187) and 56 (95% CI 34–164) in infants exposed to $MgSO_4$ *in utero* before 30 weeks and between 32 and 34 weeks, respectively.

Another meta-analysis of six RCTs (4796 women and 5357 infants delivered before 34 weeks), reported a significant reduction in the risk of cerebral palsy (RR 0.69, 95% CI 0.55–0.88), and substantial gross motor dysfunction (RR 0.60, 95% CI 0.43–0.83) with no difference in perinatal mortality [52]. The Cochrane review reported similar results, confirming the neuroprotective role of $MgSO_4$ with a significant lower risk of cerebral palsy (3.4% vs. 5%; RR 0.68, 95% CI 0.54–0.87; 6145 infants) and also substantial gross motor dysfunction (RR 0.61, 95% CI 0.44–0.85; 5980 infants) [53]. These findings prompted professional bodies to issue recommendations in favor of using $MgSO_4$ in anticipated early preterm birth [54–56]. However, the optimal gestation and dosage of MgSO4 for neuroprotection remain to be determined, as it was reported that many women ceased therapy due to these adverse effects (8% vs. 2.4%; RR 3.26, 95% CI 2.46–4.31) [53]. The previous RCTs used 4 or 6 g, as loading dose, with some continuing with a maintenance dose of 1 or 2 g/hour.

More recently, the authors of one of the original RCTs of MgSO4 for neuroprotection in women at risk of delivery <30 weeks, reported on neurological, cognitive, behavioral, growth and functional outcomes in school age children (6–11 years) and found no benefit over placebo. These results may be unsurprising given that the original study did not show a reduction in cerebral palsy, although there was a reduction in gross motor dysfunction (3.4% vs. 6.6%; RR 0.51; 95% CI, 0.29–0.91). Further data are required to be certain of these recent findings which, as the authors point out, may have been affected by sub-optimal follow-up rates (77%) and low rates of gross motor dysfunction (3.5%) in the placebo group [57].

Conclusions

Progesterone has been shown to reduce the risk of preterm birth both in low-risk women with a short cervix and high-risk women with a history of prior preterm birth. There is some evidence that progesterone may also improve perinatal outcomes, but this needs to be studied in larger RCTs. Progesterone does not have any clear benefit in unselected twin pregnancies, but its role in those women with a short cervix warrants further investigation. There is concern about the safety of 17-OHPC but no adverse effects from natural progesterone have been reported. The evidence for the use of the cervical pessary in singleton and twin pregnancies remains unclear, but further RCTs, particularly in women with short cervix, are warranted.

Maternal administration of corticosteroids reduces the rates of mortality and morbidity for neonates born prematurely. Although significant short-term benefits for the neonate have been seen with repeat courses compared with a single course, there appears to be less evidence that this translates to improved long-term outcomes. Whilst there is cumulative evidence for the neuroprotective role of $MgSO_4$ in reducing the risk of moderate-severe cerebral palsy in early childhood, the long-term benefits remain to be proven.

For all the therapies discussed, further studies addressing mechanisms of action, as well as those designed to determine the long-term outcome, are needed to help us understand the true risks and benefits of these interventions. Such data are now being reported for $MgSO_4$ and repeated doses of antenatal steroids. In both circumstances, the evidence suggests that the long-term benefits may be limited.

Abbreviations

17-OHPC, 17 alpha-hydroxyprogesterone; CI, confidence interval; NNT, numbers needed to treat; OR, odds ratio; PECEP, Pesario Cervical para Evitar Prematuridad; RCT, randomized controlled trial; RR, relative risk.

Disclosures

The authors declare that they have no disclosures.

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