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The Essence of Tocolysis

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Introduction

Preterm birth, defined as birth before 37 weeks gestation, is a major contributor to perinatal morbidity and mortality. It occurs in 12,000 pregnancies in the Netherlands per year. Of all perinatal mortality, 50-70% can be attributed to preterm birth. Preterm birth can be iatrogenic due to the condition of the mother or the child, but the majority occurs spontaneously, either starting with preterm rupture of membranes (PROM) or with spontaneous contractions [1-3]. As such, spontaneous preterm birth is the leading cause of perinatal mortality and neonatal morbidity, mostly due to respiratory immaturity, intracranial hemorrhage and infections. These conditions can have long-term neuro developmental sequelae such as intellectual impairment, cerebral palsy, chronic lung disease, deafness and blindness. Death due to complications of prematurity is ranked 7th in the global deaths rank and together with communicable, maternal, and nutritional causes responsible for 25% of the deaths worldwide. Hence, spontaneous preterm birth is one of the largest single conditions in the Global Burden of Disease analysis given the high mortality and the considerable risk of lifelong impairment.

The costs of preterm delivery are enormous and mainly driven by intensive care admission for neonates at a cost of €2,500 per day (with an average duration of admission of 14 days) [4]. Estimated costs of disabled children are €80,000 and €20,000 yearly for severely and moderately disabled children, respectively. Additionally, a substantial part of the costs is also caused by antenatal care for mothers at increased risk for preterm delivery [5].

An important breakthrough in the treatment of imminent preterm delivery was antenatal administration of steroids for fetal lung maturation. The first randomized controlled trial (RCT) on the subject was published in 1972 [6-8]. It was not until 1990 that the Cochrane collaboration published a review that showed that this treatment reduces the odds of the babies dying from the complications of immaturity by 30% to 50%, leading to antenatal steroids becoming the standard treatment in preterm labour.

Though the use of tocolytics to postpone delivery was already described around 1950, proof of its effectiveness is still lacking. Ideally, labor-inhibiting agents should exclusively target the myometrium or the labor stimulus itself, with a rapid onset of action and long duration and minimal maternal and fetal side effects. However, such an agent does not currently exist. Types of tocolytics described in modern literature are nitric-oxide, cyclooxygenase inhibitors, beta-mimetics, calcium channel antagonists and oxytocin antagonists. These different types of tocolytics all cause smooth muscle relaxation by engaging on slightly different mechanisms of action.

β-adrenoreceptor agonists

β-adreno receptor agonists activate adenyl cyclase to form cyclic adenosine monophosphate. By reducing intracellular calcium through increasing calcium uptake by sarcoplasmic reticulum and phosphorylation of the myosin light-chain kinase β-adrenoreceptor agonists decrease myosin light-chain kinase activity, which causes myometrial relaxation. Beta-mimetics have been compared to placebo and have shown to be effective in postponing delivery, as they decrease the number of women in preterm labour giving birth within 48 hours (relative risk (RR) 0.63; 95% confidence interval (CI) 0.53-0.75). No benefit, however, has been demonstrated on perinatal death (RR 0.84; 95% CI 0.46-1.55, 7 trials, n=1,332), neonatal death (RR 1.00; 95% CI 0.48-2.09, 5 trials, n=1,174) or respiratory distress syndrome (RR 0.87; 95% CI 0.71-1.08, 8 trials, n=1,239). Beta-mimetics have been largely abandoned from clinical practice, due to its unfavorable side effects profile [9].

Calcium channel blockers

Calcium channel blockers, such as nifedipine, prevent the influx of extracellular calcium ions into the myometrial cell. They are non-specific for the uterine muscles and mostly used for the

treatment of hypertension in adults. Calcium channel blockers are used off-label [10,11]. Two small placebo controlled trials showed a significant decrease in birth within 48 hours after start of treatment compared to no treatment (RR 0.30, 95% CI 0.21-0.43). A higher incidence of maternal adverse effects was found (RR 49.89, 95% CI 3.13-795.02, one trial, 89 women) compared to placebo. No neonatal outcomes were reported.

Comparing calcium channel blockers with β-adrenoreceptor agonists, calcium channel blockers resulted in an increase in the interval between trial entry and delivery (MD 4.38 days, 95% CI 0.25-8.52) and gestational age (MD 0.71 weeks, 95% CI 0.34-1.09). A decrease in preterm and very preterm birth was found (RR 0.89, 95% CI 0.80-0.98 and RR 0.78, 95% CI 0.66 to 0.93). Neonatal outcomes were improved with calcium channel blockers compared to β-adrenoreceptor agonists; infant respiratory distress syndrome (RR 0.64, 95% CI 0.48-0.86); necrotizing enterocolitis (RR 0.21, 95% CI 0.05-0.96); intraventricular hemorrhage (RR 0.53, 95% CI 0.34-0.84); neonatal jaundice (RR 0.72, 95% CI 0.57-0.92); and admissions to NICU (RR 0.74, 95% CI 0.63-0.87) [12].

Since calcium channel blockers are essentially designed for the treatment of hypertension, most maternal side effects are related to the effect on the blood pressure. These include hypotension, headache, flushing, nausea, tachycardia and vomiting. When compared with β-adrenoreceptor agonists, fewer maternal adverse effects were found when using calcium channel blockers (RR 0.36, 95% CI 0.24-0.53). Furthermore fewer maternal adverse effects requiring discontinuation of therapy were seen (RR 0.22, 95% CI 0.10-0.48). On the other hand, when compared with oxytocin receptor antagonists side effects were found more in the calcium channel blockers group (RR 2.61, 95% CI 1.43-4.74) 11. A large prospective cohort study showed 0.9 % serious adverse drug reaction rate and 1.1% had a mild adverse drug reaction rate. Most adverse reactions were blood pressure related. Most events occurred within two to four hours after initiation of tocolytic therapy, therefore monitoring of blood pressure is recommended [13].

Calcium channel blockers therefore have benefits over the use of placebo or no treatment concerning prolongation of pregnancy. However no large placebo controlled trials have been performed and no results on neonatal outcomes are known. Furthermore, when compared with β-adrenoreceptor agonists, calcium channel blockers have benefits regarding prolongation of pregnancy, serious neonatal morbidity, and maternal adverse effects. Compared with oxytocin receptor antagonists more side effects are found, but calcium channel blockers seem to be more effective in postponing delivery.

Oxytocin receptor antagonists

Oxytocin is a peptide hormone produced in the hypothalamus, uterus, placenta and amnion. It has a variety of functions, mainly stimulating uterine contractions, thereby playing an important role in the pathway to normal and preterm labor. Oxytocin receptor antagonists, such as atosiban and barusiban, bind to oxytocin receptors in the myometrium. They prevent a rise in intracellular calcium, thereby relaxing the myometrium. The use of oxytocin receptor antagonists is currently the only registered agent for the indication tocolysis [14,15].

When comparing oxytocin receptor antagonists with placebo, no difference was shown in birth within 48 hours after trial entry (RR 1.05, 95% CI 0.15-7.43; (two studies, 152 women), perinatal mortality (RR 2.25, 95% CI 0.79-6.38; two studies, 729 infants), or major neonatal morbidity. No differences were found in preterm birth less than 37 weeks of gestation or other adverse neonatal outcomes, except for a small reduction in birth weight (MD -138.86g, 95% CI -250.53 to -27.18; two studies, 676 infants). One study found an increase in extremely preterm birth (<28 weeks of gestation) when using atosiban (RR 3.11, 95% CI 1.02-9.51) and infant deaths (up to 12 months) (RR 6.13, 95% CI 1.38-27.13) compared with placebo. However, this might be caused by the higher number of women with a gestational age below 26 weeks in the atosiban group. Furthermore, oxytocin receptor antagonists resulted in an increase in maternal adverse drug reactions requiring end of treatment compared with placebo (RR 4.02, 95% CI 2.05-7.85).

A recent Cochrane review showed that oxytocin receptor antagonists compared with β-adrenoreceptor agonists had no statistically significant difference in birth within 48 hours after trial entry (RR 0.89, 95% CI 0.66-1.22; eight studies, 1389 women), very preterm birth (RR 1.70, 95% CI 0.89-3.23; one study, 145 women), extremely preterm birth (RR 0.84, 95% CI 0.37-1.92; one study, 244 women) or perinatal mortality (RR 0.55, 95% CI 0.21-1.48; three studies, 816 infants). Concerning major neonatal mortality, no differences were found, although numbers were small. Oxytocin receptor antagonists had fewer maternal adverse effects requiring cessation of treatment (RR 0.05, 95% CI 0.02-0.11; five studies, 1161 women) 13.

Oxytocin receptor antagonist has a superior safety profile compared with other tocolytics. A large prospective cohort study showed no serious and only 0.2 % mild adverse reactions when using atosiban as tocolytic drug (RR 0.07, 95% CI 0.01-0.4) 12.

The Cochrane review did not show superiority of oxytocin receptor antagonists (mostly atosiban) as a tocolytic agent compared to placebo, β-adrenoreceptor agonists or calcium channel blockers (mostly nifedipine) in terms of pregnancy prolongation or neonatal outcomes. However, use of oxytocin receptor antagonists was associated with less maternal adverse effects than treatment with β-adrenoreceptor agonists or calcium channel blockers.

Recently, we completed a nationwide multicenter randomized controlled trial that compared the effectiveness of the two widely used tocolytic drugs nifedipine and atosiban (APOSTEL III study; Zon MW 836011005). We randomized 511 women with signs of preterm labor between 25 and 34 weeks. This study showed that those randomized to nifedipine had

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similar adverse perinatal outcome rates compared to those who received atosiban (14% versus 15%; RR 0.91; 95% CI 0.61-1.37). Unexpectedly, children born from mothers randomized to nifedipine had a non-signicantly higher mortality rate (5.4% vs. 2.4% RR 2.20; 95% CI 0.91-5.33), questioning the safety of the drug, and tocolytic drugs in general.

The evidence of the effectiveness of the currently used tocolytic drugs nifedipine and atosiban as compared to placebo is scarce, if not absent. In addition, it is worth to realize that tocolysis in the setting of ruptured membranes, which is currently advocated by most centers, is absent. The Cochrane review on tocolysis and PPROM states that compared to no tocolysis, tocolysis was not associated with a significant effect on perinatal mortality in women with PPROM (risk ratio (RR) 1.67; 95% confidence interval (CI) 0.85 to 3.29). Tocolysis was associated with longer latency (mean difference (MD) 73.12 hours; 95% CI 20.21 to 126.03; three trials of 198 women) and fewer births within 48 hours (average RR 0.55; 95% CI 0.32 to 0.95; six trials of 354 women; random-effects, Tau^2=0.18, I^2=43%) compared to no tocolysis. However, tocolysis was associated with increased five-minute Apgar of less than seven (RR 6.05; 95% CI 1.65 to 22.23; two trials of 160 women) and increased need for ventilation of the neonate (RR 2.46; 95% CI 1.14 to 5.34; one trial of 81 women). For women with PPROM before 34 weeks, there was a significantly increased risk of chorioamnionitis in women who received tocolysis.

Conclusion

In conclusion, the widespread use of tocolytic drugs in women with threatened preterm birth cannot be justified by the available evidence in the current literature. There is no substantial evidence that the currently most used tocolytic drugs nifedipine and atosiban improve neonatal outcome. Prolongation of pregnancy in itself is not a primary goal of tocolysis. Improvement of neonatal outcome should be the primary outcome in future trials on tocolysis. A view that is supported by the WHO, as they state in their new guidelines on preterm labor that the effectiveness of tocolytics is not proven, and that placebo controlled studies are urgently needed. It is time to question our daily clinical practice of administration of tocolytic drugs to women with threatened preterm birth. We have an obligation to our patients to provide them with the best available care in order to improve the short term and long term outcome of their babies. The truth is that we don't know if tocolytic drugs will improve the outcome of their babies. We don't even know for sure that it might not harm their babies. We therefore propose to perform an urgently needed placebo controlled trial in women with threatened preterm birth with neonatal outcome as the primary outcome. In addition, long term follow-up should be part of this trial and in fact, every obstetric intervention trial.

References

1. Schaaf JM, Mol BW, Abu-Hanna A, Ravelli AC (2011) Trends in preterm birth: Singleton and multiple pregnancies in the Netherlands, 2000-2007. BJOG An Int J Obstet Gynaecol 118(10): 1196-1204.
2. Wen SW, Smith G, Yang Q, Walker M (2004) Epidemiology of preterm birth and neonatal outcome. Semin Fetal Neonatal Med 9(6): 429-435.
3. Hack M, Fanaroff A (2000) Outcomes of children of extremely low birth weight and gestational age inthe 1990's. Early Hum Dev 5(2): 89-106.
4. Moore T, Hennessy EM, Johnson SJ, Draper ES, Kate LC, et al. (2012) Neurological and developmental outcome in extremely preterm children born in England in 1995 and 2006: the Epicture Studies. The BMJ 345: e7961.
5. (2004) The global burden of disease 2004.
6. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, et al. (2012) Global and regional mortality from 235 causes of death for 20 age groups in 1990and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380(9859): 2095-2128.
7. Liggins GC, Howie RN (1972) A controlled trial of antepartum glucocorticoid treatment for prevention ofthe respiratory distress syndrome in premature infants. Pediatrics 50(4): 515-525.
8. Crowley P, Chalmers I, Keirse M (1990) The effects of corticosteroid administration before preterm delivery: an overview of the evidence from controlled trials. Br J Obstet Gynaecol 97(1): 11-25.
9. Goldenberg RL (2002) The management of preterm labor. Obstet Gynecol 100: 1020-1037.
10. Neilson JP, West HM, Dowswell T (2014) Betamimetics for inhibiting preterm labour. Cochrane Database Syst Rev 2: CD004352.
11. Flenady V, Wojcieszek AM, Papatsonis DN, Stock OM, Murray L, et al. (2014) Calcium channel blockers for inhibiting preterm labour and birth. Cochrane Database Syst Rev 6: CD002255.
12. de Heus R, Mol BW, Erwich JJ, van Geijn HP, Gyselaers WJ, et al. (2009) Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. BMJ 338: b744.
13. Flenady V, Reinebrant HE, Liley HG, Tambimuttu EG, Papatsonis DN (2014) Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database Syst Rev 6: CD004452.
14. van Vliet EO, Schuit E, Heida KY, Opmeer BC, Kok M, et al. (2014) Nifedipine versus atosiban in the treatment of threatened preterm birth (Assessment of Perinatal Outcome after Specific Tocolysis in Early Labour: APOSTEL III-Trial): a multicentrer and omised controlled trial. Lancet 387(10033): 2117-2124.
15. Mackeen AD, Seibel-Seamon J, Muhammad J, Baxter JK, Berghella V (2014) Tocolytics for preterm premature rupture of membranes. Cochrane Database Syst Rev 27(2): CD007062.

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