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Maintaining and repeating tocolysis: A reflection on evidence

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ABSTRACT

It is inherent to human logic that both doctors and patients want to suppress uterine contractions when a woman presents in threatened preterm labor. Tocolysis is widely applied in women with threatened preterm labor with a variety of drugs. According to literature, tocolysis is indicated to enable transfer to a tertiary center as well as to ensure the administration of corticosteroids for fetal maturation. There is international discrepancy in the content and the implementation of guidelines on preterm labor. Tocolysis is often maintained or repeated. Nevertheless, the benefit of prolonging pregnancy has not yet been proven, and it is not impossible that prolongation of the pregnancy in a potential hostile environment could harm the fetus. Here we reflect on the use of tocolysis, focusing on maintenance and repeated tocolysis, and compare international guidelines and practices to available evidence. Finally, we propose strategies to improve the evaluation and use of tocolytics, with potential implications for future research.

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Introduction

Preterm birth (PTB) is traditionally defined as birth before 37 weeks' gestation and represents a major cause of neonatal mortality and morbidity.[1] When spontaneous preterm labor (PTL) or preterm premature rupture of membranes (PPROM) are diagnosed, or iatrogenic preterm birth is indicated, maternal interventions, such as antenatal corticosteroids (ACS), magnesium sulfate, or antibiotic prophylaxis can improve health outcomes for both mother and newborn.[2] In the setting of spontaneous preterm labor, tocolysis, by reducing uterine contractility, aims to delay delivery, at least to

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enable administration of ACS for fetal lung maturation and to arrange transfer to a hospital with an appropriate neonatal intensive care unit (NICU).[3] Internationally, standards state that tocolytic drugs are indicated in this setting for a 48 -h duration. However, in reality, tocolysis is often maintained after this initial agreed course of 48 h (maintenance tocolysis) or repeated when a new episode of threatened preterm labor occurs (repeated tocolysis). Though prolonging the pregnancy may seem logical to both patients and their doctors, it must be remembered that PTL and PPROM can be symptoms of underlying inflammation and/or infection and potentially harmful for the fetus and the newborn.[4]

Many different agents have been used for tocolytic therapy to suppress uterine contractions, but a standard first-line drug has not emerged. Those in current use include beta-agonists, calcium channel blockers, oxytocin receptor antagonists, prostaglandin synthetase inhibitors, nitric oxide donors, and magnesium sulfate.[5–10]

A network meta-analysis by Haas et al.[11] showed that prostaglandin inhibitors and calcium channel blockers (mainly nifedipine) have the highest probability of delaying delivery and improving neonatal outcomes. Prostaglandin inhibitors can nevertheless cause fetal and neonatal complications, which limits their use after 32 weeks' gestation.[12] Nifedipine and atosiban, an oxytocin antagonist available outside of the United States, have shown comparable effectiveness in delaying birth for up to 7 days.[13] Nifedipine seems to be the first choice tocolytic. Nifedipine is not registered for use in pregnancy and therefore used off label. Compared with beta-agonists, nifedipine may be associated with improved neonatal outcomes, although there are no long-term data.[13–16]

The International Spontaneous Preterm birth Young investigators group (I-SPY) is a novel collaboration between aspiring young researchers, whose main focus is preterm birth. This group was founded by 2 senior researchers (Bo Jacobsson, Department of Obstetrics and Gynecology in the University of Gothenburg in Sweden, and Ben Mol, University of Adelaide) and a junior researcher (Lina Bergman, co-author). The goal of the group is to form an international network of young researchers in preterm birth, with high approachability for juniors and close guidance and mentorship from senior researchers. The group currently consists of members from 11 European countries and works towards improved international collaboration, identifying gaps in current knowledge, and thinking within the field of preterm birth. In the first article resulting from this collaboration, we set out to collate the current guidelines and practices of our international members, as well as critically appraise the best available evidence for maintenance and repeated tocolytic therapy.

Methods

We carried out a PubMed literature search using the term "tocolysis," "repeat(ed) tocolysis," "maintenance tocolysis," "sustained tocolysis," "preterm labor," and/or "preterm birth." We extracted reviews and meta-analyses (before 2000) and randomized controlled trials (RCTs) and individual participant data meta-analyses (IPD-MA) (from 2000 to 2016). We withheld only RCTs and IPD-MAs comparing active drug to placebo or no treatment. We only took into account the "classic" tocolytics (beta-agonists, calcium channel blockers, oxytocin receptor antagonists, prostaglandin synthetase inhibitors, nitric oxide donors, and magnesium sulfate) and excluded studies evaluating progesterone as a tocolytic. We also excluded reviews since our goal was to critically appraise the original, most recent, studies.

We conducted a survey amongst I-SPY members attending the European Spontaneous Preterm Birth Congress in Gothenburg, Sweden (2016) to collect the respective national guidance of participating countries, as well as clinicians day-to-day practice using tocolysis, and compared guidelines and practice.

Results

Maintenance and repeated tocolysis: a critical appraisal of evidence from RCTs and IPD-MAs

We found no reviews, meta-analyses (before 2000), placebo-controlled RCTs or IPD-MAs (2000–2016) on repeated tocolysis. A meta-analysis carried out by Sanchez-Ramos et al., compared maintenance tocolysis to placebo or no treatment in women who had acute tocolysis and ACS. In 12 RCTs, a total of 1590 women from studies published between 1980 and 1998, were included.[17] In an updated review, the authors added 8 RCTs, for a total of 1981 patients.[18] In 4 of these studies (275 patients); however, a tocolytic drug was compared to another tocolytic drug, not to placebo. Outcomes included were rate of and interval to recurrent threatened preterm labor, incidence of preterm delivery, Apgar scores, rate of admission to NICU, and perinatal mortality. In both types of studies (drug/placebo and drug/drug), maintenance tocolysis was not associated with reductions in preterm delivery or recurrent preterm labor, nor with improved perinatal outcomes.

Since 2000, 6 RCTs on maintenance tocolysis meeting our inclusion criteria have been published[19–24] (Table 1). Matijević et al.[19] published an RCT comparing an oral beta-agonist (ritodrine) with no therapy. Oral treatment was started after 48 h of intravenous (IV) ritodrine treatment and continued to 34 weeks' gestation. Oral beta-agonists did not decrease the frequency of recurrent episodes of preterm labor within 72 h after IV treatment [$n = 8/62$ in the ritodrine group vs $n = 6/58$ in the control group, $p = 0.879$, 95% confidence interval (CI) not available].

Lyell et al.[20] compared nifedipine to placebo. Treatment was started after 48 hours treatment with IV magnesium sulfate ($MgSO_4$), and was continued until 37 weeks of gestation. When recurrent threatened preterm labor occurred, IV tocolysis ($MgSO_4$) was restarted; women who did not deliver continued the study drug. Investigators studied not only maintenance tocolysis, but also repeated tocolysis. The primary outcome was delivery before 37 weeks. For calculation of the sample size (66 patients), the authors assumed that 75% of placebo-users would deliver before 37 weeks of gestational age. Interestingly, Hackney et al. reported that the upper maximum of patients with preterm labor not using

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