Royal College of Obstetricians and Gynaecologists

Setting standards to improve women's health

Clinical Guideline No. 1(B)
October 2002
(Replaces Guideline No.1A Beta-agonists *and* No.1 Ritodrine)

TOCOLYTIC DRUGS FOR WOMEN IN PRETERM LABOUR

1. Purpose and scope

Preterm birth is the most important single determinant of adverse infant outcome, in terms of both survival and quality of life. Although preterm birth is defined as being before 37 completed weeks, most mortality and morbidity is experienced by babies born before 34 weeks. Prevention and treatment of preterm labour is important, not as an end in itself, but as a means of reducing adverse events for the child.[1] For many women in preterm labour it may not be appropriate to consider attempting tocolysis. Labour may be too advanced, for example, or prolonging the pregnancy may be hazardous because of intrauterine infection or placental abruption. As it is the woman who receives the intervention, there is also a responsibility to ensure that she is not harmed.

A wide variety of agents have been advocated as suppressing uterine contractions. Those in current use include beta-agonists, calcium channel blockers, prostaglandin synthetase inhibitors, nitric oxide donors and oxytocin receptor antagonists. There is little reliable information about current clinical practice but it is likely that ritodrine hydrochloride, a beta-agonist, remains the most widely used. Magnesium sulphate is popular for tocolysis in the USA and some other parts of the world, but is rarely used for this indication in the UK.

Tocolysis has also been advocated for the management of intrapartum fetal distress, impaired fetal growth and to facilitate external cephalic version at term. These uses will not be considered further here. The aim of this guideline is to summarise the evidence about the effectiveness of tocolytic drugs for preterm labour and to provide guidance as to how to incorporate this evidence into clinical practice.

2. Identification and assessment of evidence

The Cochrane Library and the *Cochrane Controlled Trials Register* Issue 1, 2001, were searched for relevant systematic reviews. Where there were no reviews, or if the reviews had not been recently updated, the search included relevant trials. The search for reviews was updated on Issue 3, 2002. A similar search was conducted for Medline, 1966–2000.

The definitions of the types of evidence used in this guideline originate from the US Agency for Healthcare Research and Quality. Where possible, recommendations are based on and explicitly linked to the evidence that supports them. Areas lacking evidence are highlighted and annotated as 'Good practice points.'

3. Is tocolysis better than no tocolysis for preterm labour?

A **It is reasonable not to use tocolytic drugs, as there is no clear evidence that they improve outcome. However, tocolysis should be considered if the few days gained would be put to good use, such as completing a course of corticosteroids, or *in utero* transfer.**

A systematic review identified 17 trials with a total of 2284 women comparing tocolysis with no treatment or placebo.[2] Many trials included maintenance treatment if and after contractions stopped. Some trials excluded women with ruptured membranes but in others they were included. The most frequently evaluated agent was ritodrine. Ritodrine has predominantly β2-receptor effects, relaxing muscles in the uterus, arterioles and bronchi. Other tocolytic drugs evaluated in these trials included isoxuprine, terbutaline, magnesium sulphate, indomethacin and atosiban. Overall, tocolytics were associated with a reduction in the odds of delivery within 24 hours (OR 0.47; 95% CI 0.29–0.77), 48 hours (OR 0.57; 95% CI 0.38–0.83) and seven days (OR 0.60; 95% CI 0.38–0.95). For beta-agonists, indomethacin and atosiban, these effects were statistically significant, but not for magnesium sulphate. However, there was no statistically significant reduction in births before 30 weeks (OR 1.33; 95% CI 0.53–3.33), before 32 weeks (OR 0.81; 95% CI 0.61–1.07) or before 37 weeks of gestation (OR 0.17; 95% CI 0.02–1.62).

Evidence level Ia

Tocolysis was not associated with any clear effects on perinatal death (OR 1.22; 95% CI 0.84–1.78) or on any measure of neonatal morbidity related to being born too early, such as respiratory distress syndrome (OR 0.82; 95% CI 0.64–1.07) or intraventricular haemorrhage (OR 0.73; 95% CI 0.46–1.15).

Since this review, one trial comparing glyceryl trinitrate with placebo has been reported (33 women) but was too small for any firm conclusions.[3] Another trial, comparing atosiban with placebo (501 women), included in the review as an abstract, has now been published in full.[4] The additional data reported included stillbirths and infant deaths (13/288 [4.5%] with atosiban versus 5/295 [1.7%] with placebo; RR 2.66; 95% CI 0.96–7.37). Overall, data from these studies are consistent with the systematic review discussed above. There are no placebo-controlled trials of calcium channel blockers.

Evidence level Ib

Taken together, these studies show that tocolytic agents reduce the proportion of births occurring up to seven days after beginning treatment. This is not reflected in clear evidence of an effect on perinatal or infant mortality or on serious morbidity, although moderate increases or decreases in these outcomes remain possible. To demonstrate reliably such moderate effects would require large high-quality randomised trials. There are three plausible explanations for this lack of a major effect on substantive perinatal outcomes. First, the trials may have included too many women who were so advanced in gestation that any further prolongation of pregnancy would have little potential to benefit the baby. Second, the time gained by tocolytic treatment may not have been used to implement potentially beneficial measures, such as corticosteroids or transfer to a unit with better neonatal health services. Third, there may be direct or indirect adverse effects of tocolytics which counteract their potential gain, including prolongation of pregnancy when this is detrimental to the baby.

In the absence of clear evidence that tocolytic drugs improve outcome following preterm labour, it is reasonable not to use them.[5] The women most likely to benefit from tocolysis are those who are still very preterm, those needing transfer to a hospital that can provide neonatal intensive care or those who have not yet completed a full course of corticosteroids to promote fetal lung maturation. For these women, tocolytic drugs should be considered.

4. Choice of tocolytic drug

A **If a tocolytic drug is used, ritodrine no longer seems the best choice. Atosiban or nifedipine appear preferable as they have fewer adverse effects and seem to have comparable effectiveness. Atosiban is licensed for this usage in the UK but nifedipine is not.**

Once a decision is made to use a tocolytic drug, which is the best choice? Ritodrine remains widely

used and has been the most thoroughly evaluated but, like all beta-agonists, has a high frequency of unpleasant and sometimes severe adverse effects. In recent years there has therefore been considerable interest in identifying a safe alternative with equal, or greater, effectiveness and fewer adverse effects.

Common adverse effects when beta-agonists are compared to no treatment or placebo include palpitations (48% with beta-agonists versus 5% with control), tremor (39% versus 4%), nausea (20% versus 12%), headache (23% versus 6%) and chest pain (10% versus 1%).[2] Rare but serious and potentially life threatening adverse effects have been reported following beta-agonist use and there have been a small number of maternal deaths associated with use of these drugs. Pulmonary oedema is a well-documented complication, usually associated with aggressive intravenous hydration. A systematic review[2] reported one case of pulmonary oedema among 852 women (1/425 with beta-agonists versus 0/427 placebo). For the other tocolytic drugs (magnesium sulphate, indomethacin and atosiban), fewer types of adverse effects were reported and they occurred less frequently.[2] For example, with magnesium sulphate 7% of women discontinued treatment compared to none on placebo and no women allocated indomethacin discontinued treatment (0/18 with indomethacin versus 0/18 with control). For atosiban, the only clearly documented adverse effect is nausea (11% with atosiban versus 5% with placebo).[4] This study reported no increase in vomiting (3% with atosiban versus 4% with placebo), headache (5% versus 7%) chest pain (1% versus 4%), or dyspnoea (0.4% versus 3%).[4]

Atosiban has been compared with three different beta-agonists (ritodrine, salbutamol and terbutaline) in a large multicentre study (733 women).[6–8] There seems to be little difference in the effect of these agents on delayed delivery. For women allocated atosiban 317/361 (88%) were undelivered at 48 hours, compared with 330/372 (89%) allocated beta-agonists ([RR 0.99; 95% CI 0.94–1.04), while, at seven days, 287/361 (80%) were undelivered compared with 288/372 (77%) (RR 1.03; 95% CI 0.95–1.11).[6] Data on gestation at birth were not reported, however, and there were too few perinatal deaths for any reliable conclusions (RR 0.53; 95% CI 0.20–1.40). Atosiban was associated with fewer maternal adverse effects than beta-agonists, such as chest pain (1% with atosiban versus 5% with beta-agonists), palpitations (2% versus 16%), tachycardia (6% versus 76%), hypotension (3% versus 6%), dyspnoea (0.3% versus 7%), nausea (12% versus 16%), vomiting (7% versus 22%) and headache (10% versus 19%).[6] There was one case of pulmonary oedema in the atosiban group (in a woman who also received salbutamol for seven days), and two in the beta-agonists group.

Evidence level Ia

Ritodrine has been compared with atosiban, nifedipine, glyceryl trinitrate and indomethacin in randomised trials. Two systematic reviews of nifedipine versus beta-agonists (nine trials, 607 women,[9] nine trials, 679 women[10]) came to similar conclusions. In both, there was insufficient evidence for any conclusions about the effect on neonatal mortality. Nifedipine was associated with a better chance of delivery being delayed for over 48 hours (RR 1.13; 95% CI 1.01–1.26[10]), a lower risk of respiratory distress syndrome or admission to a special care unit and fewer maternal adverse effects than the beta-agonists, largely ritodrine. Analysis of adverse effects was limited due to inconsistent reporting in individual trials. However, one review[10] reported fewer interruptions of treatment due to adverse effects with nifedipine rather than beta-agonists (0% versus 7%). The other[9] reported fewer adverse effects among women allocated nifedipine rather than ritodrine (16% versus 45%). A recent Cochrane systematic review (11 trials, 870 women)[11] has compared calcium channel blockers with any other tocolytic agent, mainly beta-agonists. This also showed that calcium channel blockers were associated with a reduction in the number of women giving birth within 48 hours (RR 0.73; 95% CI 0.54–0.98) and within seven days (RR 0.76; 95% CI 0.59–0.99). However, this was not reflected in a statistically significant effect on birth before 34 weeks (RR 0.84; 95% CI

0.70–1.02) or before 37 weeks (RR 0.91; 95% CI 0.79–1.06) and there was no clear effect on perinatal death (RR 1.39; 95% CI 0.60–3.24). Calcium channel blockers did seem to reduce the risk of neonatal respiratory distress syndrome (RR 0.64; CI 0.45–0.91) and neonatal jaundice (RR 0.73; 95% CI 0.57–0.93), compared with alternative agents. A theoretical risk of adverse effects on fetal or placental circulation following nifedipine exposure has been suggested.[12] Although this has not been confirmed with clinical data, further information about its safety, in terms of both short-term and long-term outcomes, is required.

Evidence level Ia

Another recent review compared nitric oxide donors (primarily glyceryl trinitrate) with other agents, ritodrine, magnesium sulphate and a beta-blocker (4 trials, 433 women).[13] Although there is insufficient evidence for any conclusions about the comparative effectiveness of these agents, nitric oxide donors did seem to be associated with fewer maternal adverse effects.

Three trials (209 women) have compared indomethacin with beta-agonists (ritodrine and nylidrin).[14–16] Overall, there is insufficient evidence for any firm conclusions about any differential effect on delay in delivery, but indomethacin does seem to have fewer maternal adverse effects than the beta-agonists. Concern has been raised about the safety of indomethacin for the fetus and newborn, however, with suggestions of a possible increased risk of premature closure of the ductus, renal and cerebral vasoconstriction and necrotising enterocolitis associated with high dose and prolonged exposure.[17,18] A large placebo-controlled trial involving glyceryl trinitrate is underway in North America. These agents however cannot be recommended for clinical practice until further data from large trials are available.

Evidence level Ib

If the decision is made to use a tocolytic drug, ritodrine no longer seems the best choice. Alternatives such as atosiban or nifedipine appear to have comparable effectiveness in delaying delivery for a few days, with fewer maternal adverse effects and less risk of rare serious adverse events. It is unclear whether they have any substantive advantage in terms of fetal or neonatal outcome.

Evidence level Ia/b

Atosiban is licensed in the UK for treatment of threatened preterm labour. The recommended dosage and administration schedule for atosiban is a three-step procedure.[19] The initial bolus dose is 6.75 mg over one minute, followed by an infusion of 18 mg/hour for three hours and then 6 mg/hour for up to 45 hours. Duration of treatment should not exceed 48 hours and the total dose given during a full course should preferably not exceed 330 mg of atosiban.[19] The purchase price of atosiban is substantially higher than alternatives such as nifedipine or the beta-agonists. Drug costs for a 19-hour treatment are £240 (June 2000 prices),[19] compared with £40–80 for an equivalent length of treatment with ritodrine and £17–25 for nifedipine.[20] A full comparison of cost has not been reported but this should also take into account the cost of administering each drug and any benefits or adverse effects.

Nifedipine has the advantage of oral use and it is cheap. However, it is not licensed in the UK for use as a tocolytic agent and so responsibility for its use lies with the prescribing doctor. There is no consensus about the appropriate regimen for nifedipine: the optimal dose has not been defined and the different release characteristics of the formulations available may affect the dosage required. Dosage in the largest trial[21] was 10 mg sublingually every 15 minutes for the first hour, until contractions stopped, then 60–160 mg/day of slow release nifedipine depending on uterine activity.

5. Maintenance treatment after threatened preterm labour

A **Maintenance tocolysis is not recommended for routine practice.**

Data from systematic reviews provide insufficient evidence to show whether or not oral beta-

agonists (220 women),[22] oral magnesium therapy (100 women)[23] or any maintenance therapy (1590 women)[24] will prevent preterm birth and its consequences after threatened preterm labour. In addition, one trial has compared subcutaneous atosiban with placebo (513 women).[25] Although atosiban delayed the next episode of threatened labour, there is insufficient evidence for firm conclusions about effects on other more substantive outcomes.

There is insufficient evidence for any firm conclusions about whether or not maintenance tocolytic therapy following threatened preterm labour is worthwhile. Therefore maintenance therapy cannot be recommended for routine practice.

Evidence level Ia

6. Summary

There is still no clear evidence that tocolytic drugs improve outcome following preterm labour and so it is reasonable not to use them. The main effect of tocolytic drugs when used for women in preterm labour is to reduce the numbers who deliver within seven days of commencing the drug. There is insufficient evidence for reliable conclusions about more substantive effects on perinatal or infant mortality or on serious neonatal morbidity. It remains plausible that, for selected women, such as those who require transfer for neonatal care or time to complete a course of corticosteroids, there may be benefit associated with tocolysis. However, this benefit has not been formally evaluated in randomised trials.

If a tocolytic agent is used, ritodrine no longer seems the best choice. Alternatives such as atosiban or nifedipine appear to have comparable effectiveness in terms of delaying delivery for up to seven days and are associated with fewer maternal adverse effects. Atosiban is licensed for use as a tocolytic but the purchase price is relatively expensive. Nifedipine is not licensed for use as a tocolytic and the ideal dosage and formulation are unclear. For both these agents, further evidence is required about their relative effects on substantive outcomes such as neonatal mortality and morbidity, and on safety and long-term outcome for the child.

In view of the current lack of evidence for any substantive benefit for the baby from tocolysis, and the possibility of hazard for the mother, the available evidence should be discussed with the woman and her partner and their preferences taken into account in determining her care.

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APPENDIX

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No 1: *Guidance for the Development of RCOG Green-top Guidelines* (available on the RCOG website http://www.rcog.org.uk/medical/greentopguide.html). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

Ia	Evidence obtained from meta-analysis of randomised controlled trials.
Ib	Evidence obtained from at least one randomised controlled trial.
IIa	Evidence obtained from at least one well-designed controlled study without randomisation.
IIb	Evidence obtained from at least one other type of well-designed quasi-experimental study.
III	Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.
IV	Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities.

Grades of recommendations

A Requires at least one randomised controlled trial as part of a body of literature of overall good quality and consistency addressing the specific recommendation. (Evidence levels Ia, Ib)

B Requires the availability of well-controlled clinical studies but no randomised clinical trials on the topic of recommendations. (Evidence levels IIa, IIb, III)

C Requires evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities. Indicates an absence of directly applicable clinical studies of good quality. (Evidence level IV)

Good practice point

✓ Recommended best practice based on the clinical experience of the guideline development group.

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The guideline review process will commence in January 2008
unless evidence requires earlier review