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Green-top Guideline No. 1b

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Tocolysis for Women in Preterm Labour

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This is the second edition of this guideline, which was first published in October 2002 under the same title.

1. Background

Preterm birth, defined as birth at less than 37^{+0} weeks of gestation, is the most important single determinant of adverse infant outcome in terms of both survival and quality of life.[1] In the UK, infant mortality among preterm births was 42/1000 live births in 2005, compared with 5/1000 live births overall.[2] For very preterm births (at less than 32^{+0} weeks of gestation), mortality in the first year was 144/1000 live births, compared with 1.8/1000 live births for babies born at term (38^{+0} to 41^{+6} weeks).[2] Very preterm birth accounts for 1.4% of UK births but 51% of infant deaths. Although birth at 32^{+0} to 37^{+0} weeks of gestation is associated with less risk than very preterm birth, there is growing recognition that even this moderately preterm birth is associated with increased risk of infant death.[2,3] Risk of death or neurosensory disability increases with decreasing gestational age.[1] Preterm birth may have huge psychosocial and emotional effects on the family, as well as being costly for health services.

Prevention and treatment of preterm birth is important, not as an end in itself but as a means of improving outcome for the child. Cervical cerclage is one strategy for prevention of preterm birth and this topic is covered in a separate Green-top Guideline.[4] 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 for the woman or her baby 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 by any treatment.

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

2. Purpose and scope

This guideline summarises evidence about the effectiveness and safety of tocolytic drugs for treatment of preterm labour and provides guidance on incorporating this evidence into clinical practice.

Tocolysis has been advocated for the management of intrapartum fetal distress and impaired fetal growth and to facilitate external cephalic version at term. These uses will not be considered further here. Also outside the scope of this guideline are interventions aimed at preventing the onset of preterm labour, for women at risk of preterm birth, and interventions to improve outcome for children at risk of being born preterm, such as use of antenatal corticosteroids and of magnesium sulphate for neuroprotection.

3. Identification and assessment of evidence

This RCOG guideline was developed in accordance with the standard methodology for producing RCOG Green-top Guidelines. The Cochrane library (including the Database of Systematic Reviews and the Cochrane Control Register of Controlled Trials), the Database of Abstracts of Reviews and Effects, Embase, ACP Journal Club and Medline, including in-process and other non-indexed citations, were searched from

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2000 to September 2010 to identify all relevant randomised controlled trials (RCTs), systematic reviews and meta-analyses published since the previous edition of the guideline. The databases were searched using the relevant MeSH terms including all sub-headings. Search terms included were: 'preterm labour', 'preterm birth', 'tocolysis', 'tocolytic', 'beta-agonist', 'calcium channel blocker', 'magnesium sulphate', 'nitric oxide donor', 'oxytocin receptor antagonist', 'prostaglandin synthetase inhibitor', 'magnesium sulphate' and 'uterine contraction + suppression'. The search was limited to humans and the English language. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines and reviews.

4. Uses of tocolysis for women in preterm labour.

4.1 Does tocolysis prevent preterm birth?

Use of a tocolytic drug is associated with a prolongation of pregnancy for up to 7 days but with no significant effect on preterm birth and no clear effect on perinatal or neonatal morbidity.

There is no clear evidence that tocolytic drugs improve outcome and therefore it is reasonable not to use them. 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**

A systematic review identified 17 trials (2800 women) comparing tocolysis with no treatment or placebo.[5] Many trials included maintenance treatment if and after contractions stopped. Some trials excluded women with ruptured membranes but they were included in others. The most frequently evaluated agent was ritodrine. Ritodrine has predominantly beta 2-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 birth within 24 hours (odds ratio [OR] 0.47; 95% confidence interval [CI] 0.29–0.77), 48 hours (OR 0.57; 95% CI 0.38–0.83) and 7 days (OR 0.60; 95% CI 0.38–0.95). For the beta-agonists indomethacin and atosiban these effects were statistically significant, but not for magnesium sulphate. However, use of any tocolytic drug was not associated with a statistically significant reduction in births before 30 weeks of gestation (OR 1.33; 95% CI 0.53–3.33), before 32 weeks of gestation (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 1+

Since this review, three further placebo-controlled trials have been reported. The largest compared atosiban with placebo (531 women).[6] Data from this study are consistent with the results of the systematic review above as, although time to delivery was not reported for all women (it was reported only for the subset of women who did not have an alternative tocolytic drug), there was no clear effect on birth before 37 weeks of gestation (relative risk [RR] 1.17; 95% CI 0.99–1.37) or before 28 weeks of gestation (RR 2.25; 95% CI 0.80–6.35).[6,7] The second study recruited 158 women and compared glyceryl trinitrate skin patches with placebo patches.[8] There was no clear difference in birth within 48 hours (RR 0.92, 95% CI 0.53–1.58) or before 37 weeks of gestation (RR 1.01; 95% CI 0.73–1.40). The third study compared glyceryl trinitrate with placebo (33 women) but was too small for any firm conclusions about the possible benefits or hazards of glyceryl trinitrate to be drawn.[9] Evidence level 1+

A more recent review included ten trials (904 women) comparing tocolysis with placebo.[10] This review restricted inclusion to studies in which the mean gestation at randomisation was between 28 weeks and 32 weeks of gestation but the methodology used did not allow calculation of an overall event rate. Nevertheless, it was concluded that use of a tocolytic drug, rather than placebo or no tocolytic drug, increased delay to delivery at 48 hours and at 7 days. Evidence level 1+

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Taken together, these studies show that tocolytic drugs reduce the proportion of births occurring up to 7 days after beginning treatment. Most women in these studies had singleton pregnancies.

4.2 Does the use of any tocolytic drug prevent perinatal or neonatal death and neonatal morbidity?

Use of a tocolytic drug is not associated with a clear reduction in perinatal or neonatal mortality, or neonatal morbidity. **A**

Tocolysis was not associated with a clear reduction in perinatal mortality (OR 1.22; 95% CI 0.84– 1.78) nor in neonatal morbidity was it 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).[5]

Evidence level 1+

Of the three studies published after this review, in the trial comparing atosiban with placebo there was no clear difference between the groups in perinatal mortality (RR 2.25; 95% CI 0.79–6.40).[6] Follow-up to 1 year was subsequently reported and, although the confidence remained wide, this showed an increase in deaths in the first year of life associated with atosiban rather than placebo (RR 6.15; 95% CI 1.39–27.22).[7] Possible explanations for this increase are an imbalance in allocation with more women at very early gestation (under 26 weeks) allocated to atosiban or fetal vasopressin receptor blockade by atosiban, which could lead to changes in amniotic fluid volume, with resultant alterations to fetal renal development and fetal lung development.[7] Although atosiban is licensed in the UK for the treatment of threatened preterm labour, there are insufficient data on long-term outcome for children exposed to atosiban in utero.

Evidence level 1+

The trial comparing glycerol trinitrate patches with placebo reported few perinatal deaths (0/74 with glycerol trinitrate compared with 3/79 with placebo). The primary outcome in this study was a composite outcome (occurrence of one or more of chronic lung disease, necrotising enterocolitis, significant intraventricular haemorrhage, periventricular leucomalacia or perinatal death). There was a reduction in this outcome associated with glycerol trinitrate which was borderline for statistical significance (RR 0.29; 95% CI 0.09–1.00).

Evidence level 1+

Although tocolytic drugs reduce the proportion of births occurring within 7 days, this is not reflected in clear evidence for any overall effect on perinatal mortality or serious neonatal morbidity; moderate increases or decreases in these outcomes remain possible. The increase in mortality at age 1 year associated with use of atosiban rather than placebo is also a concern. To demonstrate reliably small to moderate short-term effects requires large randomised trials, with follow-up of the children for several years to assess the potential effects on subsequent mortality and neurodevelopment. Follow-up data are not available for other tocolytic drugs.

There are four plausible explanations for the lack of a major effect of tocolytic drugs 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 trials may have included too many women who were not genuinely in preterm labour or at risk of preterm birth. Third, 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. Fourth, there may be direct or indirect adverse effects of tocolytic drugs (including prolongation of pregnancy when this is detrimental to the baby), which counteract their potential gain.

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5. When should tocolytic drugs be used?

Tocolysis may be considered for women with suspected preterm labour who have had an otherwise uncomplicated pregnancy. It is reasonable not to use any tocolytic drug. B

Women most likely to benefit from use of a tocolytic drug are those who are in very preterm labour, those needing transfer to a hospital which can provide neonatal intensive care and those who have not yet completed a full course of corticosteroids. ✓

Tocolysis should not be used where there is a contraindication to prolonging pregnancy. ✓

In the absence of clear evidence that tocolytic drugs improve outcome following preterm labour, it is reasonable not to use them.[11] The women most likely to benefit from use of a tocolytic drug are those who are in very preterm labour, those needing transfer to a hospital that can provide neonatal intensive care and those who have not yet completed a full course of corticosteroids. For these women, tocolytic drugs should be considered, provided that there is no contraindication to prolonging the pregnancy.

Evidence level 1+

Tocolysis may be considered for women with suspected preterm labour who have had an otherwise uncomplicated pregnancy. Any contraindication to prolonging pregnancy is a contraindication to tocolytic therapy; for example, known lethal congenital or chromosomal malformation, intrauterine infection, severe pre-eclampsia, placental abruption, advanced cervical dilatation and evidence of fetal compromise or placental insufficiency. Relative contraindications include mild haemorrhage due to placenta praevia, non-reassuring cardiotocograph, fetal growth restriction and multiple pregnancy.

In view of the current lack of evidence for any substantive short-term benefit to the baby from tocolysis, the possibility of hazard for the mother and the lack of reliable information about long-term outcome, the available evidence should be discussed with the woman and her partner and their preferences taken into account in determining her care. A senior obstetrician should be involved in the decision to offer tocolysis.

6. Is one tocolytic drug more effective in preventing preterm birth than another?

Nifedipine and atosiban have comparable effectiveness in delaying birth for up to seven days. A

Compared with beta-agonists, nifedipine is associated with improvement in neonatal outcome, although there are no long-term data. A

Ritodrine and atosiban are licensed in the UK for the treatment of threatened preterm labour. Although the use of nifedipine for preterm labour is an unlicensed indication,[12] it has the advantages of oral administration and a low purchase price.

The comparative effects of alternative tocolytic drugs have been evaluated in a range of trials. Beta-agonists reduce the risk of giving birth within 48 hours (11 trials, 1320 women; RR 0.63; 95% CI 0.53–0.75) compared with placebo,[13] but there is no clear evidence that they are any more effective at preventing preterm birth than other tocolytic drugs.[14,15]

Evidence level 1+

A Cochrane review comparing calcium channel blockers with other tocolytic drugs included 12 trials with 1029 women.[14] In ten of these trials, oral nifedipine was the calcium channel blocker and in eight the comparator was intravenous ritodrine. The use of calcium channel blockers, rather than other tocolytic drugs, was associated with a reduction in the number of women giving birth within 7 days of receiving treatment (RR 0.76; 95% CI 0.60–0.97) and before 34 weeks of gestation (RR 0.83; 95% CI 0.69–0.99) compared with other tocolytic drugs.

Evidence level 1+

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The oxytocin receptor agonist atosiban has been compared with beta-agonists in four trials with 1044 women.[7] There was no clear difference between the groups either in birth within 48 hours (RR 0.98; 95% CI 0.68–1.41) or birth within 7 days (RR0.91; 95% CI 0.69–1.20). Atosiban has not been compared with calcium channel blockers in randomised trials. A systematic review using adjusted indirect comparison between nifedipine and atosiban concluded that nifedipine was associated with a non-significant trend towards increased delay in delivery by 48 hours.[16]

Evidence level 1+

Cyclo-oxygenase (COX) enzymes contribute to production of prostaglandins, which are important in the onset and maintenance of labour. It has been hypothesised that inhibitors of the inducible COX-2 enzyme might be effective tocolytics with fewer fetal side effects. Indomethacin is the COX inhibitor most commonly used for tocolysis. The Cochrane review identified eight trials with 557 women comparing COX inhibitors with other tocolytic drugs (beta-agonists or magnesium sulphate).[17] COX inhibition reduced birth before 37 weeks of gestation (3 trials, 168 women; RR 0.53; 95% CI 0.31–0.94). Short-term use of NSAIDs in the third trimester of pregnancy is associated with a significant increase in the risk of premature ductal closure.[18] There have been two RCTs comparing COX-2 inhibitors with magnesium sulphate for acute tocolysis,[19,20] each of which showed no difference between oral COX-2 inhibitor and intravenous magnesium sulphate in delaying preterm labour. However, there is a lack of evidence that magnesium sulphate itself reduces the risk of preterm birth. The COX-2 inhibitor rofecoxib has been compared with placebo for prophylaxis in one RCT,[21] which showed that it has a significant but reversible effect on fetal renal function and the ductus arteriosus but does not decrease the risk of preterm labour before 32 weeks of gestation and increases the risk after treatment is withdrawn at 32 weeks of gestation. There is therefore no good evidence that COX-2 inhibitors reduce the risk of preterm birth.

Evidence level 1+

The nitric oxide donor nitroglycerine has been compared with ritodrine, albuterol and magnesium sulphate.[22] Although there was a reduction in births before 37 weeks of gestation (three trials, 391 women; OR 0.53; 95% CI 0.35–0.81), there was no clear impact on birth before 32–34 weeks of gestation.

Evidence level 1+

Magnesium sulphate for prevention of preterm birth has been evaluated in 23 trials with 2036 women.[15] There is no clear evidence that magnesium sulphate reduces the risk of preterm birth. However, administration of magnesium sulphate to women considered at risk of preterm birth reduces the risk of cerebral palsy (RR 0.68; 95% CI 0.54–0.87; five trials; 6145 infants).[23] If a woman is at risk of preterm birth, she should receive magnesium sulphate for 24 hours to reduce the risk of cerebral palsy.

Evidence level 1+

7. What are the comparative adverse effects for the woman of alternative tocolytic drugs for preterm labour?

Beta-agonists have a high frequency of adverse effects. Nifedipine, atosiban and the COX inhibitors have fewer types of adverse effects, and they occur less frequently than for beta-agonists but how they compare with each other is unclear.

A

Using multiple tocolytic drugs appears to be associated with a higher risk of adverse effects and so should be avoided.

B

Once a decision is made to use a tocolytic drug, the best choice of drug would be the most effective with the fewest adverse effects, both immediate and long-term. Ritodrine was widely used in the past in the UK and is still in common use in some parts of the world. It has been the most thoroughly evaluated in trials but, like all beta-agonists, it has a high frequency of unpleasant and sometimes severe or potentially life-threatening adverse effects for the woman.[13,24] In recent years there has therefore been considerable interest in identifying a safer alternative.

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Common adverse effects when beta-agonists are compared with placebo include palpitations (38% for beta-agonists compared with 4% for placebo), tremor (39% compared with 4%), nausea or vomiting (21% compared with 12%), headache (19% compared with 5%), chest pain (10% compared with 1%) and dyspnoea (14% compared with 3%).[13] Women allocated beta-agonists were far more likely to stop treatment because of adverse effects than those allocated placebo (five trials, 1081 women; RR 11.38; 95% CI 5.21–24.86).[13] Rare but serious and potentially life-threatening adverse effects have been reported following beta-agonist use and there are case reports of 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 reported one case of pulmonary oedema among 852 women (1/425 beta-agonists compared with 0/427 placebo).[13]

Evidence level 1+

Fewer types of adverse effects are reported for the other tocolytic drugs and they occur less frequently. No trials have compared calcium channel blockers with placebo for treatment of preterm labour.[14] When compared with other tocolytic drugs (ritodrine in most of the trials), calcium channel blockers are associated with fewer adverse effects (RR 0.32; 95% CI 0.24–0.41) and less need to stop treatment because of adverse effects (RR 0.14; 95% CI 0.05–0.36).[14] Reported adverse effects for nifedipine, the most widely used calcium antagonist, include flushing, palpitations, nausea and vomiting and hypotension.[25,26] Nifedipine is contraindicated if the woman has cardiac disease and should be used with caution if she has diabetes or multiple pregnancy, owing to the risk of pulmonary oedema.[12]

Evidence level 1+

With atosiban, reported adverse effects are nausea (11% for atosiban compared with 5% for placebo), vomiting (3% compared with 4%), headache (5% compared with 7%), chest pain (1% compared with 4%) and dyspnoea (0.4% compared with 3%).[5] Only nausea was statistically significantly increased (OR 2.28, 95% CI 1.26–4.13).[5] Women allocated atosiban were also more likely to stop treatment because of adverse effects than those allocated placebo (two trials, 613 women; RR 4.02; 95% CI 2.05–7.85).[7] A common reason for stopping treatment was injection-site reactions.[6] Compared with beta-agonists, however, fewer women allocated atosiban stop treatment because of adverse effects (RR 0.04; 95% CI 0.02–0.11; number needed to treat 6; 95% CI 5–7). Atosiban has not been compared with calcium antagonists in randomised trials. Diabetes and cardiac disease are not contraindications to atosiban.

Evidence level 1+

COX inhibitors are well tolerated by the women and, when compared with placebo, there is no clear effect on the need to discontinue treatment (three trials, 101 women; RR 1.58; 95% CI 0.66–3.78).[17] When compared with other tocolytic drugs, COX inhibitors were associated with fewer women needing to stop treatment because of adverse effects (five trials, 355 women; RR 0.07; 95% CI 0.02–0.29).[17]

Evidence level 1+

Adverse effects (other than headache) were reduced in women who received the nitroglycerine, a nitric oxide donor, rather than ritodrine, albuterol or magnesium sulphate but headache was increased.[22]

Magnesium sulphate is associated with adverse effects for the woman but, as it is ineffective in delaying preterm birth, it should not be used.[15]

Using more than one type of tocolytic in combination with another appears to increase the risk of adverse effects and so should be avoided.[24]

Evidence level 2++

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8. What are the comparative effects for the baby of alternative tocolytic drugs for preterm labour?

The comparative effects for the baby of alternative drugs are unclear. Most drugs have been compared with beta-agonists. There are insufficient data on long-term follow-up for reliable conclusions about the effects on the baby for any of these tocolytic drugs.

B

Calcium channel blockers were associated with less neonatal respiratory distress syndrome (RR 0.63; 95% CI 0.46–0.88), less necrotising enterocolitis (RR 0.21; 95% CI 0.05–0.96) and less intraventricular haemorrhage (RR 0.59; 95% CI 0.36–0.98) than other tocolytic drugs.[14] There was no clear difference between the treatment groups either in stillbirths (RR 3.00; 95% CI 0.13–71.07) or in neonatal deaths (RR 1.40; 95% CI 0.63–3.12).[14]

Evidence level 1+

Nifedipine, the most commonly used calcium channel blocker, crosses the placenta, but whether it has any long-term effect on the child is uncertain. Animal studies with very high doses have reported abnormalities of fetal and placental blood flow and abnormal digital development.[14] No specific congenital defects have been associated with its use in humans.

Evidence level 2+

The oxytocin receptor agonist atosiban has been compared with beta-agonists in four trials with 1044 women.[7] There was no clear difference between the groups in neonatal deaths (RR 0.70; 95% CI 0.27–1.81) or neonatal morbidity. The only difference was that atosiban was associated with an increase in birth weight under 1500 g (RR 1.96; 95% CI 1.15–3.35).[7] Oxytocin receptor agonists have not been compared with calcium channel blockers in randomised trials. A systematic review using adjusted indirect comparison between nifedipine and atosiban concluded that nifedipine was associated with a reduction in respiratory distress syndrome but there were insufficient data for reliable conclusions about other measures of morbidity and mortality.[16]

Evidence level 1–

COX inhibitors cross the placenta and potential adverse effects for the baby include premature closure of the ductus arteriosus with consequent pulmonary hypertension, persistent patent ductus arteriosus, necrotising enterocolitis and intraventricular haemorrhage. The trials conducted to date are too small to provide reliable information about the potential effects on the baby.[17,27]

Magnesium sulphate for prevention of preterm birth has been evaluated in 23 trials with 2036 women.[15] In these trials, exposure to magnesium sulphate was associated with an increased risk of fetal, neonatal or infant death (seven trials, 727 infants; RR 2.82; 95% CI 1.20–6.62).

Evidence level 1+

9. What are the recommended dose regimens for nifedipine and atosiban?

The suggested dose of nifedipine is an initial oral dose of 20 mg followed by 10–20 mg three to four times daily, adjusted according to uterine activity for up to 48 hours. A total dose above 60 mg appears to be associated with a three- to four-fold increase in adverse events.

✓

A suggested dose of atosiban of an initial bolus dose of 6.75 mg over 1 minute, followed by an infusion of 18 mg/hour for 3 hours, then 6 mg/hour for up to 45 hours (to a maximum of 330 mg).

✓

There is no clear consensus on the ideal dose regimen for nifedipine when used for tocolysis. A sensible recommendation is for an initial oral dose of 20 mg followed by 10–20 mg three to four times daily adjusted according to uterine activity.[12] Total dose above 60 mg appears to be associated with a three- to four-fold increase in adverse events such as headache and hypotension.[26]

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For atosiban, the recommended regimen is a three-step procedure: an initial bolus dose of 6.75 mg over 1 minute, followed by an infusion of 18 mg/hour for 3 hours, then 6 mg/hour for up to 45 hours (to a maximum of 330 mg).[12] For both, duration of treatment is 48 hours.

10. What is the cost effectiveness of tocolysis for preterm labour?

Cost effectiveness has not been reported but the purchase price of atosiban is nearly ten times that of nifedipine.

The purchase price of atosiban is substantially higher than nifedipine or other tocolytic agents such as COX inhibitors and beta-agonists. The purchase price of the drug for a standard 48 hours of treatment with atosiban is £494,[12] compared with £1 for nifedipine[12] and £50 for ritodrine.[18] Cost effectiveness analysis has not been reported but this should also take into account the cost of administering each drug and any benefits or adverse effects.

A cost decision analysis in the USA comparing terbutaline, magnesium sulphate, indomethacin and nifedipine concluded that indomethacin and nifedipine were the least expensive options.[28] A similar analysis in Germany compared atosiban with beta-agonists and concluded atosiban was the cheaper option.[29] The relevant comparison for the UK would be of atosiban with nifedipine.

11. Should tocolysis by used in multiple pregnancy?

There is insufficient evidence for any firm conclusions about whether or not tocolysis leads to any benefit in preterm labour in multiple pregnancy. ✓

There is no specific evidence for a beneficial role for tocolytic drugs in preterm labour in multiple pregnancy, although both nifedipine and atosiban have been widely used in this context. A series of case reports has suggested an association between nifedipine use in multiple pregnancy and pulmonary oedema,[30] suggesting that atosiban may be preferable to nifedipine in this context, although this association was not confirmed in a prospective cohort study.[24]

12. Is maintenance tocolytic therapy worthwhile?

There is insufficient evidence for any firm conclusions about whether or not maintenance tocolytic therapy following threatened preterm labour is worthwhile. Thus, maintenance therapy is not recommended. A

A systematic review of any maintenance tocolytic therapy compared with placebo or no treatment after threatened preterm labour found no clear evidence of an effect on preterm birth or its consequences (12 trials, 1590 women).[31] A Cochrane review of oral beta-agonists for maintenance therapy following threatened preterm labour compared with placebo or no treatment identified eight trials with 994 women.[32] There was no clear difference in preterm birth (before 37 weeks of gestation) (four trials, 384 women; RR 1.08; 95% CI 0.88–1.32), nor in any other measure of perinatal morbidity or mortality. One trial with 513 women has compared maintenance therapy with oxytocin receptor antagonists (in this trial subcutaneous atosiban) with placebo (513 women).[33] There was no clear difference between the groups in preterm birth (RR 0.89; 95% CI 0.71–1.12) or in any other substantive outcome. Only one trial with 74 women has evaluated calcium channel blockers for maintenance therapy, which provides insufficient evidence for any reliable conclusions.[34] Similarly, the one trial (100 women) evaluating magnesium sulphate for maintenance therapy is too small for any reliable conclusions.[35]

Evidence level 1+

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13. Summary

Use of a tocolytic drug is not associated with a clear reduction in perinatal or neonatal mortality or neonatal morbidity. The main effect of tocolytic drugs when used for women in preterm labour is to reduce the numbers who deliver within 48 hours or within 7 days of commencing the drug. Data on long-term outcome are sparse. 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 reliable prediction of which women in suspected preterm labour are likely to have a preterm birth were possible, the use of tocolysis could be reserved for these women. Unfortunately, few tests offer useful predictive value.[36] Fetal fibronectin has been advocated as a promising predictive test[36] but it may have limited accuracy in predicting preterm birth within 7 days for women with symptoms of preterm labour.[37] Ultrasound assessment of cervical length is also a promising predictive test for symptomatic women.[36] It remains unclear whether any predictive test, or combination of tests, is sufficiently accurate to be cost effective.[36,38]

If the decision is made to use a tocolytic drug, nifedipine and atosiban appear to have comparable effectiveness in delaying delivery, with fewer maternal adverse effects and less risk of rare serious adverse events than alternatives such as ritodrine or indomethacin. There is limited evidence that use of nifedipine, rather than a beta-agonist, is associated with improved short-term neonatal outcome. There is little information about the long-term growth and development of the child for any of the drugs.

Ritodrine and atosiban are licensed in the UK for the treatment of threatened preterm labour. Although the use of nifedipine for preterm labour is an unlicensed indication,[12] it has the advantages of oral administration and a low purchase price.

The available evidence should be discussed with the woman and her partner and their preferences taken into account in determining her care.

14. Auditable standards

- Number of women who received a tocolytic drug for suspected preterm birth.
- Documented involvement of a consultant obstetrician in the decision to commence a tocolytic drug.
- Choice and duration of tocolytic drug.
- Proportion of women on local first-line tocolytic drug and on multiple drugs.
- Number of women receiving a course of antenatal corticosteroids births before 34 weeks of gestation.
- Proportion of women and babies with adverse effects associated with tocolytic drugs.
- Number of babies born without exposure to antenatal corticosteroids.
- Use of a guideline on tocolysis.

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References

1. Saigal S, Doyle LW. An overview of mortality and sequelae of preterm birth from infancy to adulthood. *Lancet* 2008;371:261–9.
2. Moser K, Macfarlane A, Chow YH, Hilder L, Dattani N. Introducing new data on gestation-specific infant mortality among babies born in 2005 in England and Wales. *Health Stat Q* 2007:13–27.
3. Kramer MS, Demissie K, Yang H, Platt RW, Sauvé R, Liston R, *et al*. The contribution of mild and moderate preterm birth to infant mortality. *JAMA* 2000;284:843–9.
4. Royal College of Obstetricians and Gynaecologists. *Cervical Cerclage*. Green-top Guideline No. 60. London: RCOG; 2011.
5. Gyetvai K, Hannah ME, Hodnett ED, Ohlsson A. Tocolytics for preterm labor: a systematic review. *Obstet Gynecol* 1999;94:869–77.
6. Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela GJ, Veille JC, Tabor B, *et al*. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. *Am J Obstet Gynecol* 2000;182:1173–83.
7. Papatsonis D, Flenady V, Cole S, Liley H. Oxytocin receptor antagonists for inhibiting preterm labour. *Cochrane Database Syst Rev* 2005;(3): CD004452.
8. Smith GN, Walker MC, Ohlsson A, O'Brien K, Windrim R. Randomized double-blind placebo-controlled trial of transdermal nitroglycerin for preterm labor. *Am J Obstet Gynecol* 2007;196:37.e1–8.
9. Smith GN, Walker MC, McGrath MJ. Randomised, double-blind, placebo controlled pilot study assessing nitroglycerin as a tocolytic. *Br J Obstet Gynaecol* 1999;106:736–9.
10. Haas DM, Imperiale TF, Kirkpatrick PR, Klein RW, Zollinger TW, Golichowski AM. Tocolytic therapy: a meta-analysis and decision analysis. *Obstet Gynecol* 2009;113:585–94.
11. Hannah ME. Search for best tocolytic for preterm labour. *Lancet* 2000;356:699–700.
12. British National Formulary [http://bnf.org].
13. Anotayanonth S, Subhedar NV, Neilson JP, Harigopal S. Betamimetics for inhibiting preterm labour. *Cochrane Database Syst Rev* 2004;(4):CD004352.
14. King JF, Flenady V, Papatsonis D, Dekker G, Carbonne B. Calcium channel blockers for inhibiting preterm labour. *Cochrane Database Syst Rev* 2003;(1):CD002255.
15. Crowther CA, Hiller JE, Doyle LW. Magnesium sulphate for preventing preterm birth in threatened preterm labour. *Cochrane Database Syst Rev* 2002;(4):CD001060.
16. Coomarasamy A, Knox EM, Gee H, Song F, Khan KS. Effectiveness of nifedipine versus atosiban for tocolysis in preterm labour: a meta-analysis with an indirect comparison of randomised trials. *BJOG* 2003;110:1045–9.
17. King J, Flenady V, Cole S, Thornton S. Cyclo-oxygenase (COX) inhibitors for treating preterm labour. *Cochrane Database Syst Rev* 2005;(2):CD001992.
18. Koren G, Florescu A, Costei AM, Boskovic R, Moretti ME. Nonsteroidal antiinflammatory drugs during third trimester and the risk of premature closure of the ductus arteriosus: a meta-analysis. *Ann Pharmacother* 2006;40:824–9.
19. Borna S, Saeidi FM. Celecoxib versus magnesium sulfate to arrest preterm labor: randomized trial. *J Obstet Gynaecol Res* 2007;33:631–4.
20. McWhorter J, Carlan SJ, OLeary TD, Richichi K, Obrien WF. Rofecoxib versus magnesium sulfate to arrest preterm labor: a randomized trial. *Obstet Gynecol* 2004;103:923–30.
21. Groom KM, Shennan AH, Jones BA, Seed P, Bennett PR. TOCOX: a randomised, double-blind, placebo-controlled trial of rofecoxib (a COX-2-specific prostaglandin inhibitor) for the prevention of preterm delivery in women at high risk. *BJOG* 2005;112:725–30.
22. Duckitt K, Thornton S. Nitric oxide donors for the treatment of preterm labour. *Cochrane Database Syst Rev* 2002;(3):CD002860.
23. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. *Cochrane Database Syst Rev* 2009;(1):CD004661.
24. de Heus R, Mol BW, Erwich JJ, van Geijn HP, Gyselaers WJ, Hanssens M, *et al*. Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study. *BMJ* 2009;338:b744.
25. Al-Qattan F, Omu A, Labeeb N. A prospective randomized study comparing nifedipine versus ritodrine for suppression of preterm labour. *Med Princ Pract* 2000;9:164–173.
26. Khan K, Zamora J, Lamont RF, Van Geijn Hp H, Svare J, Santos-Jorge C, *et al*. Safety concerns for the use of calcium channel blockers in pregnancy for the treatment of spontaneous preterm labour and hypertension: a systematic review and meta-regression analysis. *J Matern Fetal Neonatal Med*. 2010;23:1030–8.
27. Loe SM, Sanchez-Ramos L, Kaunitz AM. Assessing the neonatal safety of indomethacin tocolysis: a systematic review with meta-analysis. *Obstet Gynecol* 2005;106:173–9.
28. Hayes E, Moroz L, Pizzi L, Baxter J. A cost decision analysis of 4 tocolytic drugs. *Am J Obstet Gynecol* 2007;197:383.e1–6.
29. Wex J, Connolly M, Rath W. Atosiban versus betamimetics in the treatment of preterm labour in Germany: an economic evaluation. *BMC Pregnancy Childbirth* 2009;9:23.
30. Oei S. Calcium channel blockers for tocolysis: a review of their role and safety following reports of serious adverse events. *Eur J Obstet Gynecol Reprod Biol* 2006;126:137–45.
31. Sanchez-Ramos L, Kaunitz AM, Gaudier FL, Delke I. Efficacy of maintenance therapy after acute tocolysis: a meta-analysis. *Am J Obstet Gynecol* 1999;181:484–90.
32. Dodd JM, Crowther CA, Dare MR, Middleton P. Oral betamimetics for maintenance therapy after threatened preterm labour. *Cochrane Database Syst Rev* 2006;(1):CD003927.
33. Papatsonis D, Flenady V, Liley H. Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour. *Cochrane Database Syst Rev* 2009;(1):CD005938.
34. Gaunekar NN, Crowther CA. Maintenance therapy with calcium channel blockers for preventing preterm birth after threatened preterm labour. *Cochrane Database Syst Rev* 2004;(3):CD004071.
35. Han S, Crowther CA, Moore V. Magnesium maintenance therapy for preventing preterm birth after threatened preterm labour. *Cochrane Database Syst Rev* 2000;(7):CD000940.
36. Honest H, Forbes CA, Durée KH, Norman G, Duffy SB, Tsourapas A, *et al*. Screening to prevent spontaneous preterm birth: systematic reviews of accuracy and effectiveness literature with economic modelling. *Health Technol Assess* 2009;13:1–627.
37. Sanchez-Ramos L, Delke I, Zamora J, Kaunitz AM. Fetal fibronectin as a short-term predictor of preterm birth in symptomatic patients: a meta-analysis. *Obstet Gynecol* 2009;114:631–40.
38. Vis JY, Wilms FF, Oudijk MA, Porath MM, Scheepers HC, Bloemenkamp KW, *et al*. Cost-effectiveness of fibronectin testing in a triage in women with threatened preterm labor: alleviation of pregnancy outcome by suspending tocolysis in early labor (APOSTEL-I trial). *BMC Pregnancy Childbirth* 2009;9:38.

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Appendix 1

Classification of evidence levels

1++ High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias

1+ Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias

1– Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias

2++ High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal

2+ Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal

2- Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal

3 Non-analytical studies, e.g. case reports, case series

4 Expert opinion

Grades of recommendations

A At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or

A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results

B A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 1++ or 1+

C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or

Extrapolated evidence from studies rated as 2++

D Evidence level 3 or 4; or

Extrapolated evidence from studies rated as 2+

Good practice point

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

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This guideline was produced on behalf of the Guidelines Committee of the Royal College of Obstetricians and Gynaecologists by:
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The final version is the responsibility of the Guidelines Committee of the RCOG.

The guideline review process will commence in 2014 unless evidence requires earlier review.

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