WHO recommendation on the use of tocolytic treatment for inhibiting preterm labour

17 November 2015

Recommendation

Tocolytic treatments (acute and maintenance treatments) are not recommended for women at risk of imminent preterm birth for the purpose of improving newborn outcomes.

*(Conditional recommendation based on very-low-quality evidence).*

Publication history

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Assessed as up-to-date: November 2015

Remarks

- This recommendation was informed by the lack of substantive benefits of tocolytic treatment compared with no tocolytic treatment, in terms of reducing adverse perinatal and neonatal outcomes. The GDG agreed that prolongation of pregnancy for 2–7 days (which is achievable by few tocolytic agents) is an intermediate outcome that has not been demonstrated to improve critical neonatal outcomes.

- The GDG agreed that in women at risk of imminent preterm birth who have an otherwise uncomplicated pregnancy, the acute use of a tocolytic drug to prolong pregnancy (up to 48 hours) can be considered to provide a window for administration of antenatal corticosteroid and/or in-utero fetal transfer to an appropriate neonatal healthcare setting, although there is currently no direct evidence to show that this measure improves neonatal outcomes.
When tocolysis is considered in this context, nifedipine (a calcium channel blocker) is the preferred agent. There is considerable variation in the nifedipine regimens used in relevant trials. The most common regimen used in trials for acute tocolytic treatment was 10–30 mg as an initial dose, followed by 10–20 mg every 4–8 hours until contractions ceased or for up to 48 hours. The GDG suggested an initial oral dose of 20 mg followed by 10–20 mg every 4–8 hours for up to 48 hours or until transfer is completed, whichever comes first.

Although betamimetics do appear effective in delaying birth for more than 48 hours, they should not be used for tocolysis because of the higher risk of adverse drug reactions, which may sometimes be life-threatening.

There is no evidence of additional benefit of using a combination of tocolytic agents over single agents. Therefore, when tocolysis is considered, a combination of tocolytic agents should not be used.

The available evidence regarding the potential risks and the lack of information on the long-term outcomes following tocolysis should be discussed with the woman and her partner in order for them to take an informed decision regarding the woman’s care.

Consideration of the use of tocolytics should be individualized and tocolytics should not be used when there is any obstetric or medical contraindication to prolonging the pregnancy. Specifically, tocolytics may be associated with harm and should not be used in the following conditions:

- preterm prelabour rupture of membranes (PPROM)
- chorioamnionitis
- placenta abruption
- cardiac disease.

The GDG agreed that considerable uncertainty still exists around the value of tocolysis for newborns, particularly as it relates to taking advantage of the time gained for administration of antenatal corticosteroids and/or in-utero transfer, and whether a short prolongation of pregnancy of 2–7 days is more advantageous in one setting compared to another. The group considered studies on tocolytics (e.g. calcium channel blocker) + antenatal corticosteroids versus placebo + antenatal corticosteroids for improving neonatal outcomes a research priority. In addition, the GDG stressed the need for systematic collection of data on critical neonatal outcomes following tocolysis.

Background

Preterm birth, defined as birth before 37 weeks of gestation, is the single most important determinant of adverse infant outcomes, in terms of survival and quality of life. (1) Globally, it is the leading cause of perinatal and neonatal mortality and morbidity. (2) Preterm infants are particularly vulnerable to complications due to impaired respiration, difficulty in feeding, poor body temperature regulation and high risk of infection. (3-5) With the increasing contribution of neonatal deaths to overall child mortality, it is critical to address the determinants of poor outcomes related to preterm birth to achieve further reductions in child mortality. (6-8)

Infant mortality and morbidity from preterm birth can be reduced through interventions delivered to the mother before or during pregnancy, and to the preterm infant after birth. (9) Interventions can be directed at all women for primary prevention and reduction of the risk of preterm birth (e.g. smoking cessation programme) or aimed at minimizing the risk in women with known risk factors (e.g. gestational agents, cervical cerclage). (10) However, the most beneficial set of maternal interventions are those that are aimed at improving outcomes for preterm infants when preterm birth is inevitable (e.g. antenatal corticosteroids, magnesium sulfate and antibiotic prophylaxis). (9) Special care of the preterm newborn to prevent and treat
complications of prematurity is also critical to newborn survival. In high-income countries, reductions in mortality rates in infants that were born preterm have been driven largely by improved care and, more importantly, by appropriate policy changes.

Methods

The recommendations were developed using standard operating procedures in accordance with the process described in the WHO handbook for guideline development (11). Briefly, these included (i) identification of priority questions and critical outcomes, (ii) retrieval of the evidence, (iii) assessment and synthesis of evidence, (iv) formulation of recommendations, and (v) planning for the dissemination, implementation, impact evaluation and updating of the guideline.

The scientific evidence underpinning the recommendations was synthesized using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (12). Up-to-date systematic reviews were used to prepare evidence profiles for the priority questions. WHO then convened a Technical Consultation in May 2014 where an international group of experts – the Guideline Development Group (GDG) – formulated and approved the recommendations based on the evidence profiles.

In November 2014, an online consultation of the GDG was conducted to review and revise the recommendations in the light of the findings of a large implementation trial of antenatal corticosteroids in low-resource countries.

Further information on procedures for developing this recommendation are available here.

Recommendation question

For this recommendation, we aimed to answer the following question:

- among pregnant women at risk of imminent preterm birth (P), is the use of tocolytic agent(s) (I), compared with no tocolytic agent, effective in delaying preterm birth and reducing adverse newborn outcomes? If so:
  - Which population of pregnant women should be offered tocolytics? (considering gestational age at presentation or birth; interval between presentation and anticipated birth)
  - Which population of pregnant women should not be offered tocolytics? (considering potential contraindications: women with preterm prelabour rupture of membranes, multiple pregnancy, antepartum haemorrhage, fetal growth restriction and medical conditions)
  - Which tocolytic agents (and regimens) should be used for eligible women?
  - Should a tocolytic maintenance regimen be offered following successful first-line tocolysis of a preterm labour? If so, which maintenance regimen should be recommended?

Evidence summary

Any tocolytic agent versus placebo or no treatment

Evidence related to the use of tocolytic drugs versus no tocolysis for improving pregnancy outcomes in
women with threatened preterm labour was extracted from eight Cochrane reviews examining the relative effects of tocolytic therapies (13–20). Each systematic review originally examined the effectiveness of a particular class of tocolytic agent (as described below), rather than tocolysis as an intervention. Another systematic review examined the use of oral or intravenous (IV) hydration as a treatment for preterm labour (21). The methodology of many of the tocolytic studies was limited by insufficient numbers of participants, lack of comparison with a placebo, and inconsistent use of glucocorticoids. For specific subgroups (e.g. women with multiple pregnancies, PPROM), evidence was sought from commissioned systematic reviews that considered both randomized and non-randomized studies. The summary of evidence for these subgroups is not included in this document as the overall recommendation is not in favour of tocolysis.

Betamimetics versus placebo or no treatment

Twelve trials compared any betamimetics with placebo (1366 women). Eligible women were between 20 and 37 weeks of pregnancy, but the majority of women were recruited after 32 weeks. Three trials included women with PPROM and six included twin pregnancies in addition to singletons. Two trials administered steroids to women in both arms, use of steroids was not clear in one trial, and the remaining trials did not state whether or not women received steroids in addition to tocolytic therapy. Nine trials compared the betamimetic ritodrine with placebo, two compared terbutaline with placebo, and one trial compared isoxsuprine with placebo.

Maternal outcomes

*Maternal death:* There were no maternal deaths reported in trials that evaluated this outcome (2 studies, 907 women).

*Pregnancy prolongation:* While there was no observed effect on preterm birth before 37 weeks (RR 0.95, 95% CI 0.88–1.03; 10 studies, 1212 women), betamimetics reduced the chances of women in threatened preterm labour giving birth within 48 hours (RR 0.68, 95% CI 0.53–0.88; 10 studies, 1209 women) and within 7 days of entering the trial (RR 0.80, 95% CI 0.65–0.98; 5 studies, 911 women), compared with women who received placebo.

*Adverse drug reaction and side-effects:* More women on betamimetics stopped treatment due to adverse drug reaction (RR 11.38, 95% CI 5.21–24.86; 5 studies, 1081 women). Betamimetics were also associated with a number of maternal side-effects, including palpitation (RR 9.91; 95% CI 6.46–15.20; 5 studies, 1089 women) and chest pain (RR 11.29, 95% CI 3.81–33.46; 2 studies, 814 women). In addition, more women in the treatment group experienced headache (RR 4.07; 95% CI 2.60–6.35; 3 studies, 936 women), hyperglycaemia (RR 2.90, 95% CI 2.05–4.09; 1 study, 708 women), hypokalaemia (RR 6.07, 95% CI 4.00–9.20; 1 study, 708 women), dyspnoea (RR 3.86, 95% CI 2.21–6.77; 2 studies, 814 women), nausea or vomiting (RR 1.76, 95% CI 1.29–2.42; 3 studies, 932 women), nasal stuffiness (RR 2.90, 95% CI 1.64–5.12; 1 study, 708 women) and tremor (RR 10.74, 95% CI 6.20–18.59; 1 study, 708 women). There were no observed differences in women for pulmonary oedema, tachycardia, cardiac arrhythmias or hypotension. Myocardial infarction occurred in 6 out of 54 betamimetic-treated women compared with none among the 52 controls.

Infant outcomes

*Perinatal, neonatal or infant death:* There were no significant differences between comparison groups for perinatal death (RR 0.84, 95% CI 0.46–1.55; 11 studies, 1332 infants), neonatal death (RR 0.90, 95% CI 0.27–3.00; 6 studies, 1174 infants) or infant death (RR 0.51, 95% CI 0.05–5.64; 1 study, 750 infants). Severe neonatal morbidity: There were no significant differences between comparison groups for any severe neonatal morbidity reported (RDS, NEC, neonatal sepsis or infection, neonatal hypoglycaemia or cerebral palsy). In a small trial, fetal tachycardia was significantly increased in the treatment group (RR 2.40, 95% CI
1.12–5.13; 30 infants).

**Calcium channel blocker versus placebo or no treatment**

Only two studies (173 women) compared calcium channel blockers (nifedipine) with placebo and only three relevant outcomes were reported. One study included women carrying singleton pregnancies between 30 and 34 weeks of gestation and with intact membranes; the second included women between 28 and 35 weeks, with no further details given.

**Maternal outcomes**

*Pregnancy prolongation:* Both studies reported on the rate of preterm birth. In one study, birth before 37 weeks of gestation was significantly reduced in the calcium channel blockers group (RR 0.44, 95% CI 0.31–0.62; 84 women), while in another study, all but 2 of the 89 women included had given birth before 37 weeks (RR 0.96, 95% CI 0.89–1.03). Overall, there was no difference between groups (pooled average RR 0.65, 95% CI 0.18–2.43). Compared with placebo, calcium channel blockers were associated with a significant reduction in the number of women giving birth within 48 hours of recruitment (RR 0.30, 95% CI 0.21–0.43; 2 studies, 173 women).

*Adverse drug reaction and side-effects:* One study with 89 women reported maternal adverse drug reactions, and these were increased in the calcium channel blockers group compared with placebo: more than half of the women in the tocolysis group had side-effects (flushing, headache and vertigo) compared with none in the placebo group (RR 49.89, 95% CI 3.13–795.02).

**Infant outcomes**

Infant outcomes were not reported in these studies.

**Cyclo-oxygenase (COX) inhibitors versus placebo or no treatment**

Three studies involving 106 women included comparisons of indomethacin (a COX inhibitor) with placebo. In two trials, indomethacin was administered orally and in the third as a rectal suppository. Women recruited to these trials were in labour between 23 and 35 weeks of gestation. Women with ruptured membranes were excluded from all three trials and those with multiple pregnancies from two of the trials.

**Maternal outcomes**

*Pregnancy prolongation:* In trials comparing COX inhibitors with placebo, findings on pregnancy prolongation were inconsistent. In one study with a small sample size, fewer women who received COX inhibitors gave birth before 37 weeks (RR 0.21, 95% CI 0.07–0.62; 36 women). There were no differences between treatment groups for delivery within 48 hours or within 7 days of initiation of treatment (RR 0.20, 95% CI 0.03–1.28, 2 studies, 70 women; RR 0.41, 95% CI 0.1–1.66, 2 studies, 70 women, respectively). Mean gestational age at birth was increased by 3.53 days in the COX inhibitors group compared with controls (95% CI 1.13–5.92; 2 studies, 67 women).

*Maternal morbidity:* No significant differences were observed between comparison groups for maternal infection (chorioamnionitis or endometritis: RR 1.94, 95% CI 0.44–8.60; 2 studies, 64 women).
**Adverse drug reaction and side-effects:** There were no significant differences between women receiving COX inhibitors versus placebo for maternal adverse drug reactions (RR 1.58, 95% CI 0.66–3.78; 3 studies, 101 women).

**Infant outcomes**

**Perinatal death or severe neonatal morbidity:** There were no significant differences between groups for perinatal mortality or serious infant morbidity including IVH, neonatal sepsis, NEC, RDS, persistent pulmonary hypertension of the newborn, or chronic neonatal lung disease; for all of these outcomes, studies lacked sufficient power to demonstrate differences between groups. Admission to NICU was comparable in the two groups (RR 0.80, 95% CI 0.56–1.15; 1 study, 39 infants), as was low infant Apgar score (<7) at 5 minutes (RR 0.53, 95% CI 0.05–5.34; 1 study, 39 infants). In two studies with a total sample size of 67, mean infant birth weight was 716.34 g greater in the COX inhibitors group (95% CI 425.52–1007.16).

**Magnesium sulfate versus placebo or no treatment**

Four trials compared magnesium sulphate with placebo or no tocolytic treatment (346 women). The loading dose of IV magnesium sulfate was 4–5 g and the maintenance dose was 2–4 g per hour. In two of the trials, women with ruptured membranes were explicitly excluded.

**Maternal outcomes**

**Pregnancy prolongation:** There was limited evidence that magnesium sulfate was effective in prolonging pregnancy, as compared with no treatment. There was no significant evidence that birth within 24 or 48 hours of trial entry was reduced in the magnesium sulfate group (RR 1.05, 95% CI 0.64–1.74, 1 study, 156 women; RR 0.57, 95% CI 0.28–1.15; 3 studies, 190 women, respectively). There was also no significant difference between groups for the mean interval between trial entry and birth (MD 0.08 days, 95% CI -4.08 to 4.24; 3 studies, 281 women). One trial with a small sample size (65 women) showed a reduction in preterm birth (before 37 weeks of gestation) in the group receiving magnesium sulfate (RR 0.62, 95% CI 0.46–0.83). However, the mean gestational age at birth was higher (approximately 5 days) in the group receiving no active treatment (MD -0.78 weeks, 95% CI -1.40 to -0.17; 3 studies, 281 women).

**Maternal morbidity:** Serious maternal complications were evaluated in one study and there were no events reported in either comparison group. Three studies reported the frequency of caesarean birth and there were no differences observed between the groups (RR 1.08, 95% CI 0.63–1.85; 280 women).

**Adverse drug reaction and side-effects:** Four trials reported maternal adverse effects leading to treatment discontinuation and there were no significant differences between groups (RR 1.31, 95% CI 0.01–221.68; 310 women). Maternal tachycardia and hypotension were assessed in one study (156 women) but no events were reported.

**Infant outcomes**

**Perinatal death:** Infant mortality was low in these trials and the trials lacked power to identify any possible differences between groups. There were no significant differences between groups receiving magnesium sulfate or no active treatment in terms of fetal deaths (RR 5.70, 95% CI 0.28–116.87; 2 studies, 257 infants), neonatal deaths (RR 1.37, 95% CI 0.48–3.97; 3 studies, 290 infants) or in terms of a composite outcome, including serious neonatal outcomes and death (RR 1.74, 95% CI 0.63–4.77; 3 studies, 292 infants). For all deaths (fetal, neonatal and infant) there was no significant difference between groups, although there was a trend towards fewer deaths in the group not receiving magnesium sulfate (RR 4.56, 95% CI 1.00–20.86; 2 studies, 257 infants).
Severe neonatal morbidity: There was no statistically significant difference between the group receiving magnesium sulfate and the group receiving no active treatment for any of the measures of serious infant morbidity reported: RDS (RR 1.09, 95% CI 0.98–1.22; 3 studies, 289 infants), proven neonatal infection (RR 6.25, 95% CI 0.32–121.14; 1 study, 34 infants), severe IVH (Grade 3 or 4) or periventricular leukomalacia (no events, 1 study, 90 infants), any grade IVH (RR 0.86, 95% CI 0.28 to 2.62; 3 studies, 289 infants), NEC (RR 1.19, 95% CI 0.33 to 4.29; 3 studies, 289 infants), respiratory arrest (RR 3.16, 95% CI 0.13–76.30; 2 study, 156 infants) or use of mechanical ventilation (RR 1.17, 95% CI 0.61–2.24; 2 study, 165 infants). There was also no significant difference between groups for admission to NICU (RR 0.49, 95% CI 0.18–1.32; 2 study, 165 infants).

Oxytocin receptor antagonists versus placebo or no treatment

Three studies involving 691 women compared the use of the oxytocin receptor antagonist atosiban with placebo. The minimum gestational age at recruitment was 20 weeks in all three studies and the maximum varied between 34 and 36 weeks. All three studies excluded women with ruptured membranes and one excluded women with multiple pregnancies.

Maternal outcomes

Pregnancy prolongation: There was an observed reduction in extremely preterm birth, defined as birth before 28 weeks of gestation (RR 3.11, 95% CI 1.02–9.51; 1 study, 501 women), but not preterm birth, defined as birth before 37 weeks (RR 1.17, 95% CI 0.99–1.37; 1 study, 501 women). Compared with placebo there was no observed reduction in birth within 48 hours using oxytocin receptor antagonists for tocolysis (RR 1.05, 95% CI 0.15–7.43; 2 studies, 152 women).

Maternal morbidity or death: There were no maternal deaths reported in any of the studies.

Maternal adverse drug reaction: Maternal side-effects requiring cessation of treatment were significantly increased in those women using oxytocin receptor antagonists (RR 4.02, 95% CI 2.05–7.85; 2 studies, 613 women). There was also a significant increase in maternal drug reactions in the treated arm (RR 1.54, 95% CI 1.02–2.32; 2 studies, 613 women).

Infant outcomes

Perinatal or infant death: There was no difference between treatment groups for neonatal death (RR 4.10, 95% CI 0.88–19.13; 1 study, 583 infants). However, the use of the atosiban was associated with an increase in infant deaths (up to 12 months of age) in one study (RR 6.15, 95% CI 1.39–27.22; 583 infants).

Severe neonatal morbidity: There was no difference in adverse infant outcomes (RDS, IVF, NEC, admission to intensive care).

Nitric oxide donors versus placebo or no treatment

Three trials compared nitric oxide donors with placebo (336 women). One trial used sublingual isosorbide dinitrate and two used glycerine trinitrate transdermal patches. In two of the trials, women with singleton pregnancies were recruited, and in two trials women with ruptured membranes were explicitly excluded. The lowest gestational age at recruitment in the trials was between 24 and 33 weeks and the maximum was between 32 and 36 weeks. For most outcomes a single trial contributed data.
Maternal outcomes

_Prolongation of pregnancy:_ Use of nitric oxide donors was not associated with prolongation of pregnancy for more than 48 hours (RR 1.19, 95% CI 0.74–1.90; 2 studies, 186 women) nor reduced frequency of birth before 28, 34 or 37 completed weeks of gestation (RR 0.50, 95% CI 0.23 to 1.09, 1 study, 153 women; RR 0.93, 95% CI 0.61–1.41, 1 study, 153 women; RR 0.57, 95% CI 0.16 to 2.01, 2 studies, 303 women, respectively).

_Adverse drug reaction and side-effects:_ Two studies (186 women) reported adverse drug reactions. Compared with controls, women in the nitric oxide donors group were more likely to experience adverse reactions (RR 1.49, 95% CI 1.14–1.94). Frequency of individual side-effects, including dizziness, flushing and hypotension, were similar in the two groups, although there was a higher incidence of headache in women in the nitric oxide donors group (RR 1.95, 95% CI 1.31–2.90; 1 study, 153 women).

_Severe maternal morbidity:_ Other relevant outcomes reported included rate of caesarean section – which was not significantly different in women receiving nitric oxide donors (RR 0.47, 95% CI 0.14–1.57; 1 study, 33 women) – and whether women had completed a full course of antenatal corticosteroids – again, there was no significant difference between groups (RR 1.04, 95% CI 0.90–1.20).

Infant outcomes

_Perinatal death or severe neonatal morbidity:_ There were no significant differences between groups for any outcomes relating to serious infant morbidity or mortality. One study with data for 153 infants reported stillbirths unrelated to congenital abnormality – and reported a single event with no significant difference between groups. The rate of neonatal death was also not significantly different in the nitric oxide and control groups (RR 0.43, 95% CI 0.06–2.89; 2 studies, 186 infants). For serious neonatal morbidity, there was no significant difference between groups for RDS (RR 0.47, 95% CI 0.14–1.57; 1 study, 33 infants), IVH (RR 2.14, 95% CI 0.20–23.06; 1 study, 153 infants) or chronic lung disease (RR 0.15, 95% CI 0.02–1.21; 1 study, 153 infants). There was no significant difference between groups in terms of mean infant birth weight (MD 327.00 g, 95% CI -272.13 to 926.13; 1 study, 33 infants).

Progestational agents versus placebo or no treatment

Four studies involving 300 women considered the effects of progestational agents on preterm labour and birth. Evidence for this question was extracted from a Cochrane systematic review that included eight studies, although four of these did not report the critical outcomes of interest. Women received adjuvant tocolysis in all trials; that is, a progestational agent was offered in addition to a tocolytic agent. The included studies varied in the form of progesterone used, dosage, method of administration, and additional tocolytic agents used.

Maternal outcomes

_Prolongation of pregnancy:_ Fewer mothers who had received progestational agents delivered babies before 37 weeks of gestation (RR 0.62, 95% CI 0.39–0.98; 4 studies, 293 infants). There were no differences between groups for birth within 48 hours of intervention (RR 0.76, 95% CI 0.38–1.50; 1 study, 110 women). There was no significant difference in the number of babies born before 34 weeks (RR 0.62, 95% CI 0.30–1.27; 1 study, 62 infants) or 35 weeks (RR 0.43, 95% CI 0.12–1.5; 1 study, 60 infants).

Infant outcomes

_Perinatal death or severe neonatal morbidity:_ There were no significant differences in perinatal mortality (RR 0.31, 95% CI 0.01–7.41; 1 study, 83 infants), RDS (RR 0.93, 95% CI 0.06–14.38; 1 study, 83 infants),
low birth weight (<2500 g) (RR 2.0, 0.43 to 9.32; 1 study, 30 infants).

**Intravenous or oral hydration versus bed rest alone or no treatment**

A Cochrane systematic review examined the evidence for the use of IV or oral hydration therapy as a treatment for preterm labour (21). Included trials recruited women less than 37 weeks pregnant with intact membranes, preterm contractions and cervical changes to receive oral or IV hydration therapy versus bed rest alone. The review included two studies involving 228 women. Approximately 30% of women from both the intervention and control groups in these trials were treated with tocolytic drugs. There were no significant differences between groups for any relevant outcome reported.

**Maternal outcomes**

*Pregnancy prolongation:* There were no differences between groups for rates of preterm birth before 32, 34 or 37 weeks of gestation (RR 0.76, 95% CI 0.29–1.97, 1 study, 110 women; RR 0.72, 95% CI 0.20–2.56, 1 study, 118 women; RR 1.09, 95% CI 0.71–1.68, 2 studies, 228 women, respectively). Hydration had no significant effect on time to delivery in days (MD -0.99 days, 95% CI -7.85 to 5.87; 2 studies, 228 women).

**Infant outcomes**

*Severe neonatal morbidity:* For infants, the rates of NICU admission were comparable between the intervention and control groups (RR 0.99, 95% CI 0.46–2.16; 1 study, 118 infants). Other critical outcomes were not reported.

**Tocolytic maintenance therapy for preterm labour after first-line tocolysis**

Available evidence related to the use of tocolytic drugs as maintenance therapy to improve pregnancy outcomes after initial treatment of preterm labour consisted of five systematic reviews of 27 RCTs, each evaluating a particular class of tocolytic agent: oral betamimetics (13 RCTs, 1551 women) (22), terbutaline pump (3 RCTs, 166 women) (23), magnesium as magnesium sulfate, chloride or oxide (4 RCTs, 422 women) (24), calcium channel blockers (6 RCTs, 794 women) (25) and oxytocin antagonists (1 RCT, 513 women) (26). The interventions in these studies used different doses, regimens and drug, within each class of tocolytic agent. Most compared maintenance therapy with no treatment or placebo, while others conducted within-class and between-class comparisons of tocolytic agents. All studies were hospital based. Twenty-six were conducted in high-income countries (Croatia, Japan, Netherlands, New Zealand, Turkey, the United Kingdom and the USA) and one in a low-income country (Malaysia).

**Tocolytic maintenance therapy versus placebo or no treatment**

**Maternal outcomes**

*Severe maternal morbidity or death:* Maternal deaths were generally not reported and in those that did report maternal deaths, there were no deaths observed. Serious maternal morbidity was rare, and when reported there were no significant differences between groups for any of the maintenance therapies evaluated.

*Pregnancy prolongation:* There were no significant differences in the rates of preterm birth before 37 weeks of gestation for women receiving oral betamimetics, magnesium, nifedipine (calcium channel blocker) or atosiban (oxytocin antagonist) as maintenance therapy when compared with placebo or no treatment.
betamimetics (ritodrine and terbutaline; 6 studies, 644 women): RR 1.11, 95% CI 0.91–1.35
magnesium (2 studies, 99 women): RR 1.05, 95% CI 0.80–1.40
calcium channel blockers (nifedipine; 5 studies, 681 women): RR 0.97, 95% CI 0.87–1.09
oxytocin antagonists (atosiban; 1 study, 510 women): RR 0.89, 95% CI 0.71–1.12.

Compared with placebo or no treatment, none of the maintenance therapies led to a significant reduction in the rates of birth before 28 weeks or 32 weeks of gestation. There was no significant difference in mean gestational age at birth (weeks) for women receiving tocolytic maintenance therapy compared with placebo or no treatment (magnesium: MD -0.55, 95% CI -1.34 to 0.25, 2 studies, 183 women; nifedipine: MD 0.32, 95% CI -0.61 to 1.25, 5 studies, 681 women). Use of nifedipine maintenance therapy was associated with a prolongation of pregnancy after recruitment by 5.35 days on average (95% CI 0.49–10.21), but this therapy did not appear to affect any other measure of pregnancy prolongation. There were no significant effects on frequency of birth within 24 or 48 hours of commencing oral betamimetic maintenance therapy when compared with no active treatment or with nifedipine.

**Adverse drug reaction and side-effects:** Side-effects (tachycardia, tachypnea, hypotension and palpitations) were more likely to occur in women receiving oral betamimetics (RR 2.13, 95% CI 1.52–2.98, 4 studies, 414 women; RR 3.52, 95% CI 1.20–10.33, 2 studies, 260 women; RR 1.89, 95% CI 1.13–3.19, 2 studies, 166 women; and RR 5.67, 95% CI 1.32–24.40, 1 study, 140 women, respectively), although in two trials only 1 woman out of 141 stopped treatment due to severe side-effects. For other side-effects, no significant differences between groups were identified.

**Maternal morbidity:** There was no difference in maternal readmission for a repeat episode of preterm labour in groups receiving active treatment.

**Infant outcomes**

**Perinatal death or severe neonatal morbidity:** There was no statistically significant difference in perinatal mortality between groups receiving maintenance tocolytic therapy and placebo or no treatment.

- betamimetics (ritodrine and terbutaline; 6 studies, 681 infants): RR 2.41, 95% CI 0.86–6.74
- magnesium therapy (1 study, 50 infants): RR 5.00, 95% CI 0.25–99.16
- calcium channel blockers (nifedipine; 2 studies, 466 infants): RR 1.48, 95% CI 0.45–4.86
- oxytocin antagonist (atosiban; 1 study, 512 infants): RR 0.77, 95% CI 0.21–2.83.

There was no observed reduction in severe morbidity for infants receiving any type of maintenance therapy (including rates of RDS, NEC, neonatal sepsis, periventricular haemorrhage, admission to NICU or mean length of NICU stay). The frequency of low birth weight (< 2500 g) and mean birth weight were not significantly different for infants whose mothers had received maintenance therapy (betamimetics, magnesium sulphate, calcium channel blockers or oxytocin antagonists) compared with infants whose mothers had received placebo or no treatment.

Further information and considerations related to this recommendation can be found in the WHO guidelines, available at:

http://apps.who.int/iris/bitstream/handle/10665/183037/9789241508988_eng.pdf?sequence=1

http://apps.who.int/iris/bitstream/handle/10665/183038/WHO_RHR_15.17_eng.pdf?sequence=1

**Implementation considerations**
The successful introduction of this recommendation into national programmes and health-care services depends on well-planned and participatory consensus-driven processes of adaptation and implementation. The adaptation and implementation processes may include the development or revision of existing national guidelines or protocols based on this recommendation.

- The recommendation should be adapted into a locally appropriate document that can meet the specific needs of each country and health service. Any changes should be made in an explicit and transparent manner.
- A set of interventions should be established to ensure that an enabling environment is created for the use of the recommendations, and that the behaviour of the healthcare practitioner changes towards the use of this evidence-based practice.
- In this process, the role of local professional societies is important and an all-inclusive and participatory process should be encouraged.

**Research implications**

The GDG identified this priority question related to tocolytic treatment for inhibiting preterm birth recommendation:

- What are the effects on neonatal mortality and morbidity, and on maternal mortality and morbidity, of tocolytics in combination with antenatal corticosteroids versus placebo + antenatal corticosteroids? (Consider calcium channel blockers versus placebo to improve outcomes, including dosing regimens)

**Related links**

WHO recommendations on interventions to improve preterm birth outcomes (2015) – [full document](#) and [evidence tables](#)

Supporting systematic reviews:


References


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