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The safety of tocolytics used for the inhibition of preterm labour

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ABSTRACT

Introduction: Preterm birth is the major cause of neonatal mortality and morbidity worldwide and a huge cost burden on healthcare. Between 22 and 26 completed weeks of gestation, for every day that delivery is delayed, survival increases by 3%.

Areas covered: Following a systematic review of the literature, we have provided an overview of the use of tocolytics for the prevention of preterm birth and have examined the fetal and maternal adverse effects of the various tocolytic agents currently in use.

Expert opinion: No tocolytic currently in use was developed specifically to treat preterm labour so most have multi-organ side effects. β2-agonists are relatively safe for the fetus but have rare and potentially serious maternal adverse effects. In contrast, prostaglandin synthetase inhibitors have potentially serious side effects for the fetus and neonate but have mild maternal gastrointestinal side effects. In Europe, the choice of first line therapy is either atosiban or nifedipine. The evidence base for atosiban is much more robust than for nifedipine. While their efficacy is similar, atosiban has placebo level side effects and is safer than nifedipine but is much more expensive.

1. Introduction

Preterm birth (PTB), particularly at early gestations, is the major cause of death and handicap in newborn babies worldwide.[1–3] About 13 million PTBs occur annually (9.6% of all births), 85% of which occur in Africa and Asia. Compared to Europe (6.2%), the rate of PTB is higher in the USA (10.6%) where the rate of PTB has risen by 36% in the last 25 years, particularly at later gestations (34–36 weeks). It is estimated that 28% of the 4,000,000 neonatal deaths that occur annually worldwide are due to PTB. The United Nations Millennium Development Goals numbers 4 (child survival) and 5 (improvement of women’s health) are directly related to reducing death and disability through PTB. The morbidity and mortality associated with PTB are inversely related to gestational age at birth. While 50% of PTBs occur after 35 completed weeks of gestation, 99% of the morbidity and mortality associated with PTB occur before this time. In the UK and Ireland, approximately 65% of babies born between 22 and 26 completed weeks of gestation will die on the labor ward or neonatal intensive care unit (NICU), and at follow-up aged 2.5 years, 50% will be handicapped, and in 50% of these, the handicap is severe. This means that at 30 months of age, only 13% are alive and neurologically intact.[3]

The Swedish EXPRESS (Extremely Preterm Infants in Sweden Study) study demonstrated that babies born at 22, 24, and 26 completed weeks of gestation have respective infant mortality rates of 54%, 21%, and 2% and at 1 year and have respective survival rates without major morbidity of 0.02%, 14.1%, and 45.9%.[2] In 2007, the Institute of Medicine in the USA calculated that the cost of PTB was $26.2 billion annually. This comprises medical costs for the baby ($16.9 billion), the mother ($1.9 billion), children with disabilities and developmental delays ($611 million), special education needs ($1.1 billion), and loss of earnings for those born preterm ($5.7 billion).[4] In the UK, the cost of hospital readmission during the first 5 or 10 years of life is 20 times greater for babies born before 28 weeks compared to those born after 37 weeks.[5] While the daily cost of NICU care is approximately £800–£1000, the psychosocial cost of PTB is incalculable. Since this review pertains to the use of tocolytics for the treatment of preterm labor, teratogenicity will not be considered and efficacy/effectiveness of tocolytics will not be discussed in depth as this has been previously reviewed.[6]

2. Tocolytics for the prevention of PTB

The main indications for the use of tocolytics to delay delivery are (i) to administer a full course of antepartum glucocorticoids and (ii) to arrange in utero transfer to a center with NICU facilities. In addition, between 23 and 26 completed weeks of gestation, each day of prolongation of pregnancy increases the survival rate by 3%.[7] Accordingly, tocolytics are also used to prolong gestation to achieve fetal maturation and a putative increase in survival and a decrease in handicap though no tocolytic study has been powered sufficiently to demonstrate such an effect.
2.1. Historical aspects

Prior to the introduction of pharmacological interventions, the treatment of spontaneous preterm labor (SPTL) was maternal bed rest, sedation, or analgesia. The mechanism of action of maternal hydration was not fully appreciated at the time but has a basis in fact. The myometrium contains not only oxytocin (OT) receptors but also type V1a vasopressin receptors, the stimulation of which results in uterine contractions. Maternal hydration causes a reduction in vasopressin secretion with less stimulation of V1a and OT receptors (which have crossover affinity). Alcohol also inhibits OT and vasopressin secretion from the posterior pituitary and was also used to treat SPTL in the 1980s, but had unacceptable maternal side effects. In 1982, the US Food and Drug Administration (US FDA) permitted the introduction of ritodrine for the treatment of SPTL.[8] This more specific β2-agonist replaced isoxsuprine, a β1-agonist that was developed for the treatment of peripheral vascular disease. Over the next decade, β2-agonists such as ritodrine, terbutaline, salbutamol, and fenoterol became established worldwide as first-choice treatment for SPTL.[9] In 1992, the Canadian Preterm Labor Group[10] reported their findings and, in the same issue, Leveno and Cunningham[11] called for a reappraisal of the use of β2-agonists. Together with concerns about the serious side effects of β2-agonists,[12,13] this led to a reduction in the use of β2-agonists in the USA and elsewhere. With no tocolytic alternative (atosiban was not registered for use in Europe until 1999), their use became limited and resulted in a drift toward the use of other tocolytic agents with a poor evidence base. These are covered separately in another review.[14] For a fuller account of the development and introduction of anti-oxytocic tocolytics, the reader is referred to another review.[15]

2.2. Tocolytics currently available for use

The tocolytics currently available for use in the treatment of SPTL differ with respect to their evidence base for safety, efficacy, and cost. Some are licensed for use (β2-agonists and vasopressin/oxytocin [VOT] receptor antagonists), but most are not (nitric oxide donors, prostaglandin synthetase inhibitors [PGSIs], magnesium sulfate, and calcium channel blockers [CCBs]). Off-label (unlicensed) use of drugs is common,[16] and approximately 75% of drugs used in obstetrics and 90% of drugs used in neonates are used off-label. This is not because these drugs have been demonstrated to be of harm but that the pharmaceutical companies have not carried out the research to demonstrate their safety and efficacy in these contexts. Only VOT receptor antagonists were developed specifically to treat SPTL albeit that at discovery these were thought to be a treatment for dysmenorrhea. The remainder (nitric oxide donors, PGSIs, CCBs, β2-agonists, and magnesium sulfate) were developed and introduced for other reasons, but were found to have possible tocolytic effects. Accordingly, since they are not uterospecific, these drugs have multi-organ side effects. Though the use of β2-agonists is decreasing worldwide, they are still widely used though more often now as second-line therapy. To illustrate this, some international preterm labor guidelines and tocolytic treatment recommendations from a selection of Western European Countries are shown in Table 1.

2.3. Currently rarely used tocolytics

2.3.1. Magnesium sulfate

Magnesium sulfate is considered ineffective as a tocolytic, potentially harmful to infants and unpleasant for women such that there have been calls for a ‘time to quit’ its use as a tocolytic.[17] Despite this, the drug is still used as a tocolytic in the USA. The risk of fetal and infant death is higher for babies exposed to magnesium sulfate (relative risk [RR]: 2.82; 95% confidence interval [CI]: 1.20–6.62) when seven trials involving 727 infants were analyzed.[18] This result was consistent with the Magnesium and Neurological Endpoints Trial (MagNET) which led to early suspension of the study albeit that much of the mortality seen in the MagNET trial was potentially attributable to other factors such as twin–twin transfusion syndrome.[19] Mortality in this trial was associated with higher doses of magnesium sulfate.[20] Antenatal exposure to higher levels of magnesium sulfate may also be associated with an increased risk of neonatal intraventricular hemorrhage (IVH).[21] A recent Cochrane review demonstrated that magnesium sulfate is ineffective in delaying or preventing PTB and has no apparent advantage for a range of neonatal and maternal outcomes. In addition, the use of magnesium sulfate as a tocolytic may be associated with an increased risk of total fetal, neonatal, or infant mortality.[18] This is in contrast to its use in appropriate groups of women for fetal, neonatal, and infant neuroprotection where beneficial effects have been demonstrated.[22]

In a systematic review of 143 publications, compared with placebo or no treatment, magnesium sulfate significantly increased the risk of ‘any adverse effects’ (RR: 4.62; 95% CI: 2.42–8.83; four trials, 13,322 women) and the need to cease treatment due to adverse effects (RR: 2.77; 95% CI: 2.32–3.30; five trials, 13,666 women).[23] To evaluate the tolerability and safety of ‘high-dose’ magnesium sulfate for the treatment of SPTL, a retrospective cohort study of 456 women was conducted. Of these, 417 (91.4%) experienced side effects. Severe side effects (pulmonary edema, respiratory arrest, intensive care...
Table 1. International preterm labor guidelines and tocolytic treatment recommendations from a selection of Western European countries (Presented at Ninth World Conference in Perinatal Medicine. Symposium on Uterine Contractility (Berlin) 2009).

<table>
<thead>
<tr>
<th>Countries</th>
<th>Guidelines and organizations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>Royal College of Obstetricians and Gynaecologists (RCOG)</td>
<td>If tocolytics are to be used, atosiban or nifedipine is preferable.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atosiban is licensed and nifedipine is not. β2-agonists should not be used.</td>
</tr>
<tr>
<td>Germany</td>
<td>German Society of Gynecologists &amp; Obstetricians (DGGG)</td>
<td>No first-line recommendation. Atosiban, fenoterol, and nifedipine are equivalent. Atosiban has less side effects.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β-Agonists or atosiban. Atosiban first line for certain patient groups.</td>
</tr>
<tr>
<td>Austria</td>
<td>Austrian Society for Gynecology and Obstetrics (OEJGG)</td>
<td>Not applicable.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>G GolF: Atosiban first-line treatment (48 h) with options of 3× repetitive treatments. VVOG: Atosiban is preferred treatment of choice.</td>
</tr>
<tr>
<td>Switzerland</td>
<td>No national guidelines</td>
<td>Both atosiban and nifedipine are at ‘first place’ position.</td>
</tr>
<tr>
<td>Belgium</td>
<td>GGOLFB and VVOG</td>
<td>(1) Atosiban; (2) nifedipine; (3) indomethacin; (4) terbutaline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recommendation. Ritonide and nifedipine are equivalent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atosiban first line for ‘risk patient’.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80% of the guidelines at level III hospitals are recommending atosiban as first line.</td>
</tr>
<tr>
<td>Norway</td>
<td>Norwegian Society of Obstetrics and Gynaecology (NGF)</td>
<td>(1) Atosiban; (2) nifedipine; (3) indomethacin; (4) terbutaline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recommendation of atosiban as first line of treatment.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80% of the guidelines at level III hospitals are recommending atosiban as first line.</td>
</tr>
<tr>
<td>Sweden</td>
<td>No national guidelines.</td>
<td>80% of the guidelines at level III hospitals are recommending atosiban as first line.</td>
</tr>
<tr>
<td></td>
<td>Work in progress</td>
<td>80% of the guidelines at level III hospitals are recommending atosiban as first line.</td>
</tr>
<tr>
<td>Spain</td>
<td>SPTL guideline No. 10</td>
<td>Atosiban to be used as first choice</td>
</tr>
<tr>
<td></td>
<td>Spanish Society of Gynecology and Obstetrics (SEGO)</td>
<td></td>
</tr>
<tr>
<td>Portugal</td>
<td>No national guidelines</td>
<td>Hospitals implemented internal SPTL guidelines. Atosiban or nifedipine are the most prescribed tocolytic drugs. Atosiban for diabetic patients, multiple pregnancies, and women with cardiac pathology.</td>
</tr>
</tbody>
</table>

GGOLFB: Groupement des Gynécologues Obstétriciens de Langue Française de Belgique; VVOG: Voetbal Vereniging Ons Genoegen; SPTL: spontaneous preterm labor; SIGO: Società Italiana di Ginecologia e Ostetricia.

unit transfer, cardiac arrest, or death) occurred in 24 (5.3%) cases. Those with severe side effects were less likely to have a singleton and more likely to have a higher order multifetal pregnancy (p < 0.001), received more magnesium sulfate, and more likely to have received multiple concurrent tocolytic therapy (p = 0.04). ‘High-dose’ magnesium sulfate tocolysis resulted in side effects in 9 of 10 patients treated, and severe side effects occurred in 1 in 20 patients.[24]

2.3.2. Nitric oxide donors

There are also insufficient data to support the use of nitric oxide donors for the treatment of SPTL.[25] The action of nitric oxide on maternal vascular tone may lead to changes in uterine blood flow and fetal side effects. Vasodilatation may also lead to maternal side effects such as flushing, headache, hypotension, and tachycardia.[25] The randomized controlled trial by Lees et al. [26] found headache to be the commonest maternal adverse effect, but other side effects such as tachycardia, palpitations, and nausea were less common with glyceryl trinitrate therapy than with ritodrine therapy. While headache was increased, adverse effects other than headache were reduced in women who received glyceryl trinitrate, rather than ritodrine, albuterol, or magnesium sulfate.[25]

3. Methods

We carried out a search based on ‘the safety of tocolytics used in the management of preterm labor’ limited in time from 1 January 2008 to 3 December 2015. This was because our group had published two reviews on this subject in 2008, and the intention was to update the safety aspect of these reviews.[6,27] The databases used were NICE Evidence, TRIP Database, Cochrane Library, AMED, BNI, CINAHL, EMBASE, HMIC, MEDLINE, PsychINFO, Google Scholar, and Google Advanced Search. The database search terms were tocolytic*; exp TOCOLYTIC AGENTS; β-agonists or atosiban. The randomized controlled trial by Lees et al. [26] found headache to be the commonest maternal adverse effect, but other side effects such as tachycardia, palpitations, and nausea were less common with glyceryl trinitrate therapy than with ritodrine therapy. While headache was increased, adverse effects other than headache were reduced in women who received glyceryl trinitrate, rather than ritodrine, albuterol, or magnesium sulfate.[25]

3.1 Search results

3.1.1. Guidelines and policy documents

3.1.2. Evidence reviews
Six evidence reviews were found in the search, three of which were from the Cochrane Database of Systematic Reviews [18,32,33] and three from quality-assessed reviews from the Database of Abstracts of Reviews of Effects.[34–36] All six of these documents contributed to the review.

3.1.3. Published research
From published research, 73 articles were found further during the search procedure, and these were scrutinized for new information to contribute to the review. C.D.L. scanned the abstracts of the 73 articles and listed 34 as relevant, 19 as irrelevant, and 20 as potentially relevant. R.F.L. reviewed the abstracts and agreed with the assessment. R.F.L. considered that 5 of the 20 potentially relevant articles added additional information and these were added to the text.[23,24,37–39] Of the 34 articles considered relevant, 2 were already cited, 1 was an abstract of a later publication, 14 were reviews, and 13 were small sample size, investigator-led studies, which added nothing new to the existing literature and supported the existing evidence base. This left four papers that added new information [40–43] and these were included in the review.

4. Fetal effects of tocolytic agents
4.1. β2-Agonists
β2-Agonists cross the placenta and may induce fetal tachycardia by directly stimulating the myocardium.[9] They cause an increased left ventricular stroke volume and cardiac output, a decreased umbilical artery, and an increased middle cerebral artery pulsatility index,[44] but the clinical significance of these changes in the fetus is unclear and it is difficult to measure the extent of any myocardial ischemia in neonates.[45] β2-Agonists induce hyperinsulinemia and hypoglycemia in the neonate, which is reactive in response to maternal hyperglycemia.[46]

4.2. Vasopressin/oxytocin receptor antagonists
Since the development and introduction of atosiban culminating in the worldwide randomized comparative trial [47] and clinical use, no substantiated safety concerns of VOT receptor antagonists for the fetus have emerged. Atosiban therapy was associated with an increased incidence of perinatal death when compared to placebo in one study,[48] but this was due to inequality between treatment and placebo groups at baseline due to imbalances of randomization at early gestational ages (<26 completed weeks) in women who were also significantly more advanced in SPTL (assessed by the modified Bishop score). Vasopressin is secreted by the fetus exposed to stress,[49] and it was thought that vasopressin antagonism by atosiban may have led to excess deaths in the treatment group compared to placebo. However, the authors explained that it was unlikely that atosiban had contributed to these deaths, as higher doses of atosiban had previously been associated with an improved perinatal outcome and experimental toxicity studies in animals had not revealed any adverse events. Fetal plasma atosiban levels have been shown to be negligible or undetectable.[50] Following approval in the European Union in 2000, in June 2007, atosiban was approved in 67 countries, and the calculated cumulative patient response to atosiban in an estimated 156,468 treatment cycles has revealed no significant safety issues.[6]

4.3. Calcium channel blockers
A report of fetal death associated with nifedipine tocolysis [51] was followed by anecdotal evidence that cases of maternal hypotension severe enough to cause fetal compromise occurred at a higher rate than would have been expected.[52,53] In pregnant women, nifedipine hypotension may lead to severe hypotension and has led to fetal distress requiring emergency cesarean section [54] and fetal death.[51] The only long-term follow-up study of children who were exposed in utero to nifedipine tocolysis compared the behavioral–emotional outcomes, quality of life, motor function, parenting distress, and childhood education of children exposed to nifedipine with those exposed to ritodrine in utero.[55] No significant differences in long-term outcome were observed. A long-term comparison to placebo would have been more meaningful, but to date, no such follow-up study has been performed.

4.4. Prostaglandin synthetase inhibitors
PGSIs reduce the volume of amniotic fluid, cause closure of the fetal ductus arteriosus, and can cause sudden fetal death. Fetal prostaglandins have an important role in renal development, coagulation, and vascular regulation. Intrapartum, the fetal ductus arteriosus remains dilated, and both the splanchic and the cerebral blood flow is regulated by prostaglandins.[56] Indeed, indomethacin is used to try to close a persistent patent ductus arteriosus in the neonate. Accordingly, PGSIs cause transient and reversible effects such as reduction of flow in the ductus arteriosus and impairment of fetal renal function.[57] Neonatal periventricular hemorrhage, premature closure of the ductus arteriosus, impaired renal function, necrotizing enterocolitis, and bronchopulmonary dysplasia have been reported by other investigators.[58–60] A meta-analysis assessing the neonatal safety of indomethacin tocolysis concluded that the extent of these risks is unknown due to the limited statistical power of published randomized controlled trials.[61] In a systematic review with meta-analysis, 27 studies included 1731 infants who were exposed to antenatal indomethacin. Antenatal indomethacin was associated with an increased risk of severe IVH (grades III to IV based on Papile’s criteria; RR: 1.29; 95% CI: 1.06–1.56), necrotizing enterocolitis (RR: 1.36; 95% CI: 1.08–1.71), and periventricular leukomalacia (RR: 1.59; 95% CI: 1.17–2.17).[62]

In a meta-analysis and decision analysis of tocolytic therapy, concerns have been expressed about premature closure of fetal ductus arteriosus after 32 weeks gestation and necrotizing enterocolitis and IVH before 30 weeks.[63]
5. Maternal effects of tocolytic agents

5.1. β2-Agonists

β2-Adrenergic receptors are widely distributed in extrauterine tissues, particularly, in the cardiovascular system. Stimulation of these receptors results in peripheral vasodilatation, decreased peripheral vascular resistance, and reflex tachycardia to compensate for systemic hypotension and causes symptoms such as tachycardia, headache, palpitations, sweating, tremor, and dyspnea. The rate of occurrence of common adverse effects caused by β2-agonists compared with placebo is shown in Table 2. Accordingly, women given β2-agonists were far more likely to stop treatment because of adverse effects than those allocated to placebo (five trials, 1081 women; RR: 11.38; 95% CI: 5.21–24.86).[30] There is also an increased risk of arrhythmias, angina, and myocardial ischemia in susceptible women.[9] By their metabolic and cardiovascular effects, β2-agonists have the potential to cause life-threatening pulmonary edema through a number of pathophysiological factors. The normal physiological adaptations to pregnancy result in plasma expansion and iatrogenic fluid overload or the use of smaller volumes of hyperosmotic fluids may precipitate pulmonary edema. Retention of sodium and water occurs due to physiological and drug-induced changes in the renin–angiotensin–aldosterone system.[12] While there have been many reports of pulmonary edema occurring in women who received β2-agonists, the incidence varies between 0.01% and 9% of women,[11,64] and the real figure is probably around 0.5%.[12]

5.1.1. Cardiovascular effects

The tachycardia associated with β2-agonist therapy often results in a very short cardiac cycle in which there is insufficient time for filling of the left ventricle in diastole. This causes pulmonary venous congestion, which increases the risk of pulmonary edema. Finally, many cases of SPTL, particularly at early gestations, are due to infection[65] and the associated tissue permeability predisposes to pulmonary edema. Women with pulmonary edema caused by β2-agonist therapy usually respond to treatment, but maternal deaths have been reported,[66–69] and, at one stage, 5% of obstetricians in the USA had witnessed a maternal death attributable to β2-agonist use.[66]

5.1.2. Metabolic effects

β2-Agonists are diabetogenic and result in hyperglycemia due to gluconeogenesis and glycogenolysis stimulated by glucagon release from the pancreas. In response, insulin is produced to counteract the hyperglycemia, and, in diabetic women, insulin therapy has been necessary to treat ketoacidosis.[67–70] β2-Agonists also cause reactive hypokalemia[71–73] following hyperglycemia caused by insulin-induced potassium influx into the cells,[74–76] and rebound hyperkalemia after cessation of terbutaline[77] and ritodrine therapy[78,79] has been reported. Hypokalemia causes arrhythmias, which increase the risk of pulmonary edema.[12,72–74]

5.2. Vasopressin/oxytocin receptor antagonists

Atosiban has placebo-level fetomaternal and neonatal side effects (Table 3). Only nausea was statistically significantly more common with atosiban, and this was mainly related to the bolus injection. Atosiban has only one-tenth of the cardiovascular side effects of β2-agonists (81% vs. 8%), and β2-agonists have a 15-fold increased risk (15% vs. 1%) of the need to discontinue therapy due to unacceptable side effects.[47] Atosiban has a much higher affinity for vasopressin receptors (V1a, V1b, and V2) than OT receptors but is marketed as an OT receptor antagonist to stress its uterospecificity. Despite its vasopressin affects, no dangerous maternal complications pertaining to this have been reported to date, with no significant renal, cardiovascular, or neurological complications. Unlike β2-agonists, atosiban is not contraindicated in diabetes or cardiac disease. Theoretically, OT antagonism in tissues that express OT receptors may inhibit milk release or postpartum uterine contractions, but the short half-life and readily reversible effect of atosiban make these risks negligible.[80] There has been one reported case of maternal pulmonary edema with the use of atosiban, but this was non-cardiogenic and thought to be due to micronized progesterone used as a tocolytic. Arachis oil is one of the excipients used to prepare micronized progesterone, and if the patient had a peanut allergy, this might explain the unusual outcome.[81]

5.3. New information on safety of OT receptor antagonists

Retosiban, a specific, high-affinity OT receptor antagonist, is now in development for the inhibition of uterine contractions in SPTL. In a phase II, randomized, double-blind, placebo-controlled proof-of-concept study to confirm the efficacy and safety of intravenous retosiban in women experiencing SPTL between 30 and 35 completed weeks gestation, the maternal, fetal, and neonatal adverse events were comparable between the retosiban and placebo groups.[43]
5.4. Calcium channel blockers

Nifedipine is an antihypertensive, causing vasodilatation by its effect on vascular smooth muscle.[83] The vascular to cardiac ratio of nifedipine effects is about 10:1. While the vascular effects of nifedipine are vasodilatation, the cardiac effects are negatively chronotropic and negatively inotropic which predisposes to cardiodepression.[84] In healthy individuals, vasodilatation by nifedipine leads to baroreceptor stimulation in the carotid arteries and an increase in sympathetic tone in the carotid sinus and arch of the aorta, which compensates for the cardiodepression. In the presence of infection/inflammation where vasodilatation may already be maximal, with the addition of nifedipine, baroreceptor stimulation, increase in sympathetic tone and cardiac compensation, may not occur and may lead to cardiodepression. If there is coexisting cardiac disease such as pulmonary hypertension or cardiomyopathy and nifedipine is added, hypotension, negative inotropic, and negative chronotropic may cause further cardiodepression by diminishing cardiac output. In a more recent study, the placental and fetal circulation was assessed using Doppler ultrasound examination prior to nifedipine administration and then after 24 and 48 h. Oral administration of nifedipine seems not to seriously alter uterine nor fetal arterial blood flow pattern. The authors concluded that, since significant changes were observed by different authors, further studies should be performed to verify the optimal total dose of nifedipine and its influence on hemodynamic conditions [85] which supports the findings of Khan et al.[86]

In a retrospective study, the hemodynamic effects of nifedipine tocolysis in 138 non-hypertensive women were studied. Over the 8-h study period, mean systolic blood pressure ($p < 0.001$) and mean diastolic blood pressure ($p < 0.001$) decreased by 5 mmHg and heart rate increased by 4 bpm ($p < 0.001$). The authors concluded that nifedipine tocolysis was associated with hemodynamic changes in non-hypertensive women.[37]

Accordingly, nifedipine is contraindicated in woman with cardiac disease and should be used with caution in diabetes or multiple pregnancy, due to the risk of pulmonary edema.[30] Nifedipine has been reported to cause maternal pulmonary edema,[87,88] myocardial infarction,[89,90] hypoxia,[91] and atrial fibrillation.[92] Since nifedipine is not licensed for use in SPTL or for any indication in pregnancy, ‘near misses’ where nifedipine tocolysis (used off-license) has resulted in severe maternal hypotension without lasting morbidity or mortality may be underreported.[93] In a systematic review of 269 relevant reports, including 5607 women, adverse fetomaternal events associated with the use of CCBs in pregnancy varied according to the total dose and study design. Adverse events were highest among women given >60 mg/day total dose of nifedipine (odds ratio [OR]: 3.78; 95% CI: 1.27–11.2; $p = 0.017$) and in reports from case series compared to controlled studies (OR: 2.45; 95% CI: 1.17–5.15; $p = 0.018$).[86]

We could find only one study of CCBs versus placebo.[94] This was a poor-quality, small sample size study in which the conclusions differed from the presented data. In the Cochrane review of CCBs,[32] Analysis 1.3 entitled ‘Calcium channel blockers compared with placebo or no treatment, Maternal adverse effects’, this study was cited.[94] The review reported maternal adverse effects in 25/45 women who received CCBs compared to 0/44 in women who received placebo. However, in their conclusions in The Bangladesh Journal of Obstetrics and Gynecology, the authors stated ‘Nifedipine is a well tolerated tocolytic drug with fewer side-effects’.[94]

When compared with other tocolytic drugs (mainly ritodrine), CCBs (mainly nifedipine) 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).

5.5. Prostaglandin synthetase inhibitors

PGSIs cause nausea, vomiting, esophageal reflux, and gastritis. Platelet dysfunction occurs but is rarely of clinical significance in patients without an underlying bleeding disorder.[28]

5.6. Comparative adverse effects of different tocolytic drugs

In a prospective cohort study of 1920 women from 28 hospitals in the Netherlands and Belgium, the incidence of serious maternal complications after the use of various tocolytic drugs for the treatment of SPTL in a routine clinical setting was evaluated independently. Of the 1920 women treated with tocolysis, 1327 received a single course of treatment (69.1%), 282 sequential courses (14.7%), and 311 combined courses (16.2%). Fourteen women developed serious side effects that required cessation of treatment, with an overall incidence of 0.7%. Four were considered to be possibly, seven probably, and three certainly due to the use of tocolytics.[95] Six women developed dyspnea, four developed hypotension, two developed pulmonary edema, and one each developed heart failure and hypoxia. The three cases where causality was considered a certainty with respect to tocolytic use were all cases of hypotension with sole use of nifedipine. Four of the 14 cases occurred in twin pregnancies. With single tocolytic therapy, serious adverse drug reaction occurred in 3/175 (1.7%) of women who received β2-agonists and 5/542 (0.9%) of women who received nifedipine. The RR of an adverse effect following the use of β2-agonists, nifedipine, and atosiban was 3.8 (95% CI: 1.6–9.2), 1.7 (95% CI: 0.8–4.8), and 0.07 (95% CI: 0.01–0.4), respectively. Compared with atosiban, the RR of an adverse drug reaction for single treatment with a β2-agonist was 22.0 (95% CI: 3.6–138.0) and for single treatment with a calcium antagonist was 12 (95% CI: 1.9–69). Multiple drug tocolysis led to five serious adverse drug reactions (1.6%). The authors concluded that the use of β2-agonists or multiple tocolytics was associated with a high incidence of serious adverse drug reactions. Indomethacin and atosiban were the only drugs not associated with serious adverse drug reactions.[95]

In a randomized comparative study of nifedipine versus progesterone for maintenance tocolysis after arrested preterm labor, the efficacy and safety of nifedipine (20 mg three times daily) and progesterone (400 mg daily) was compared. Nifedipine was significantly associated with side effects, and
the authors concluded that when compared with nifedipine, progesterone significantly prolonged pregnancy in women with arrested SPTL with better neonatal outcomes and fewer side effects.[38] In a retrospective case-control study, the effect of magnesium sulfate and nifedipine on the risk of developing pulmonary edema in PTB was assessed. Magnesium sulfate treatment was strongly associated with the development of pulmonary edema when used either as a tocolytic agent or for seizure prophylaxis.[39]

5.6.1. Atosiban versus nifedipine
In the UK and Western Europe, nifedipine and atosiban are generally first-line choices. Atosiban is not licensed for use in the USA and Australia. In their assessment, the US FDA relied heavily on the US multicenter study,[48] which showed an excess of neonatal mortality in the placebo group. However, in the US multicenter study, unlike subsequent studies,[47] randomization was not stratified by gestational age and so the mean gestational age at study entry was significantly earlier in the atosiban group and twice as many women (10% vs. 5%) in the atosiban group were recruited before 26 completed weeks of gestation. The study design was a randomized placebo-controlled trial with tocolytic rescue and the US FDA demanded a placebo-controlled trial. While many centers boast their policy of not using tocolytics, it is still notoriously difficult to recruit patients to a placebo-controlled trial. It was for this reason and the fact that Tractocile®(Ferring Pharmaceuticals, Saint-Prex, Switzerland; atosiban) only had a short duration before it was out of patent that the parent drug company decided not to pursue licensing in the USA. Since that time, the evidence base for atosiban has become more robust than any other tocolytic, and without doubt, atosiban has the best all-round fetomaternal safety profile of all tocolytics. Nifedipine is still widely used because it is inexpensive and is administered orally, but the evidence base is less robust than with atosiban. There are no well-conducted placebo-controlled studies,[30] and all the studies are small and investigator led with the potential for bias.[14] Many of the studies were unblinded, with no intention to treat analysis, carried out at late gestations, with no account of randomization, and nifedipine was often used as second-line treatment. Since the studies lacked sufficient power, the evidence for safety and efficacy is based on a meta-analysis.

Of the four studies cited in the Cochrane systematic review of CCBs,[96] three showed no benefit of nifedipine and one study that showed benefit constituted 60% of the weighting and was published by one of the co-authors of this review, a practice that Cochrane discourages. Adverse fetomaternal events associated with CCB use vary according to the total dose of nifedipine and study design.[86] The original Cochrane review of OT receptor antagonists [97] (effectively atosiban) was heavily criticized in the feedback by opinion leaders with experience of the drug. They were concerned that the review *inter alia* may have been unintentionally biased in favor of CCBs and that the analysis was ‘flawed’ and ‘not up to the high standards of Cochrane reviews’. The review has been recently updated [98] but by the same group who appear to have made the same errors for which the original review was criticized.[14]

5.6.2. APOSTEL III trial
The Assessment of Perinatal Outcome after Specific Tocolysis in Early Labour (APOSTEL) III trial has just been reported.[99] This was a trial of nifedipine versus atosiban for the treatment of threatened preterm labor. The trial was a nationwide multicenter, randomized controlled study. Women in threatened preterm labor between 25 and 34 weeks gestation with a positive fetal fibronectin test or ruptured membranes were randomly allocated to treatment with nifedipine or atosiban. Primary outcome was a composite measure of severe neonatal mortality and morbidity. Secondary outcomes were time to delivery, gestational age at delivery, days on ventilatory support, admission to NICU, length of stay in NICU, total days in hospital until 3 months corrected age, convulsions, apnea, asphyxia, proven meningitis, pneumothorax, and maternal side effects. An economic evaluation of the treatment was also performed. This trial provides evidence for the optimal tocolytic drug (between nifedipine and atosiban) in the treatment of threatened preterm labor. Primary outcome data were available for 248 women and 297 babies in the nifedipine group and 255 women and 294 babies in the atosiban group. The primary and secondary outcome rates were comparable between the groups, and the authors concluded that, in women in threatened preterm labor, nifedipine and atosiban had similar adverse rates of perinatal outcome, but there was a nonsignificant but possibly clinically relevant increase in mortality in the nifedipine group that questioned its safety and required further analysis.[42]

6. Conclusions
A perfect tocolytic that is 100% effective with no side effects does not exist. No tocolytic currently in use was developed specifically for the inhibition of preterm labor. Even atosiban, the most uterospecific tocolytic, was initially investigated as a treatment for dysmenorrhea. Accordingly, most tocolytics have multi-organ side effects, though some more than others. Compared to placebo, β₂-agonists, nifedipine, PGSIs, and atosiban are effective at inhibiting uterine contractions and prolonging labor and hence gestation.[82] β₂-Agonists are relatively safe for the fetus, but have rare and potentially serious maternal adverse effects. In contrast, PGSIs have potentially serious side effects for the fetus and neonate, but have mild gastrointestinal maternal side effects. As nifedipine use as a tocolytic has increased since the demise of β₂-agonists, increasing fetomaternal concerns have emerged. Atosiban has placebo-level side effects, and combined tocolytic use is discouraged.

The choice of first-line therapy will be a balance of efficacy, safety, and cost. Efficacy and cost are not part of the remit of this review but are intimately associated and so will be briefly addressed. For magnesium sulfate and nitric oxide donors such as glyceryl trinitrate, the balance of efficacy versus safety should render their use as a tocolytic redundant. Nevertheless, magnesium sulfate is still used around the world, particularly in the USA. This leaves β₂-agonists, nifedipine, PGSIs, and atosiban for consideration. Following the report of the Canadian Preterm Labour Investigators (1992),[10] and the contemporaneous call
for a reappraisal of the use of $\beta_2$-agonists in the USA,[11] the use of $\beta_2$-agonists declined worldwide. During the vacuum that occurred until atosiban became available in 1999, the use of nifedipine or no tocolytic use became a significant option. $\beta_2$-Agonists and PGSIs, mainly because of their side-effect profile, are still used as tocolytics but mainly as second-choice agents, and the choice of first-line therapy lies mainly between nifedipine and atosiban. Other OT receptor antagonists are being developed but are not yet commercially available.

7. Expert opinion

7.1. Weaknesses in the research done so far in this field

Prior to the worldwide comparative study of atosiban versus $\beta_2$-agonists,[47] the quality of tocolytic studies was poor. Since 50% of PTBs occur after 35 completed weeks of gestation, this was an easy target for recruitment yet probably contained many women in physiologically slightly early term labor. In contrast to the worldwide comparative study of atosiban versus $\beta_2$-agonists, the inclusion criteria of early tocolytic trials used only contractions rather than some measure of cervical change such as cervical dilatation/length or Bishop score. Since 50% of pregnant women and 30% of attendants (midwives and obstetricians) will be wrong in their diagnosis of SPTL on the basis of contractions alone, this means that many women included in studies were not in genuine SPTL. All tocolytic research has used PTB as an outcome parameter, yet this is only a surrogate for neonatal outcome.

7.2. Comments on the APOSTEL trial

Khan et al. demonstrated that the safety of nifedipine was compromised when >60 mg/24 h was used.[86] From the protocol, it appears that 80–100 mg/24 h of nifedipine could have been administered in the APOSTEL trial. This could account for the unexpectedly higher perinatal mortality (5.4% vs. 2.4%) mentioned in the results. The study is unusual if not unique in using perinatal outcome as the primary outcome variable rather than PTB per se, and this should be maintained for future tocolytic studies. The secondary outcomes were maternal and neonatal. The maternal outcomes were mortality and the need to discontinue study medication. While a necessary outcome parameter, maternal mortality is a blunt measure and most of the reasons for discontinuation of therapy were for progression of labor rather than adverse effects. It would have been more helpful to list specific serious maternal adverse effects like those cited by de Heus et al. (dyspnea, hypotension, hypoxia, pulmonary edema, and cardiac failure).[95] The findings of the APOSTEL study are counterintuitive to the findings of de Heus et al. and may be because such specific adverse effects were not sought. Birth weight and gestational age were similar between the two groups as was the composite perinatal outcome, yet significantly more in the atosiban group were admitted to NICU (62% vs. 52%). This may be a manifestation of different neonatal management protocols across the different NICUs across the 19 centers involved in the study.

7.3. Future research

The ultimate goal is to develop safer and more effective tocolytics, which improve neonatal outcome. Recruitment to tocolytic studies should be stratified below 34, 30, and 26 completed weeks of gestation. The diagnosis of SPTL should include some measures of cervical change as well as contractions and perhaps cervical length measurement and/or fetal fibronectin (qualitative/quantitative). Primary outcome variables should focus on fetomaternal outcome rather than the categorical variable of PTB per se. Within neonatal outcome, composite neonatal outcomes might be better replaced by more focused subtypes of neonatal outcome variables. While the likely sample size of future tocolytic studies may not be sufficient to demonstrate a difference in rates of respiratory distress syndrome (RDS), if RDS was subdivided into mild (headbox oxygen only), moderate (the need for continuous positive airway pressure), and severe (intermittent positive pressure ventilation), a difference with small numbers may become evident. This could be applied to other neonatal outcome for which neonatologists should be involved (Table 4), which also stresses the need for future studies to carry out long-term follow up.

7.4. Licensing

In various regions of the world, $\beta_2$-agonists and atosiban are licensed for use as tocolytics, but nifedipine and PGSIs are not. Licensing is not a major issue because it is estimated that 75% of drugs used in pregnancy and 90% of drugs used in neonates are used off-label. This is not because the drugs are contraindicated. Rather, it is because the research to demonstrate that the use of the drug is safe and efficacious for that environment has not been carried out. Nevertheless, with increased medical litigation, emphasis on evidence-based medicine, and scrutiny with respect to consent, there may be pressure in future on clinicians to make patients aware of the licensing limitations of some drugs.

7.5. Cost considerations

When considering cost and safety, two questions must be asked: (i) how costly does a drug have to be before purchasers are willing to compromise on safety and (ii) how safe does a drug have to be before cost no longer becomes an issue? In addition, if drug A is 10 times more expensive than drug B,
and drug B is extremely cheap, then 10 times the cost of drug B may still be very cheap, particularly when the comparative cost is measured against other pharmacy budgets such as oncology, cardiology, fertility, and psychiatry and the total cost of PTB (see Section 1). Apart from the medicolegal implications, savings on midwifery time due to reduced need for monitoring with safer tocolytics should be considered when assessing the cost. Two recent cost analysis studies in Germany and Italy demonstrated that owing to its superior safety profile, atosiban is cost-saving when compared to β2 agonists in the treatment of SPTL from the payer’s, hospital’s, and combined perspectives.[40,41]

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R.F.L accepted the commission, and with J.S.J., proposed a framework for the manuscript and provided guidance for the search strategy. C.D.L carried out the search, extracted the data, synthesized the evidence and provided the first draft of the manuscript. R.F.L wrote the Expert Opinion Section and all three co-authors contributed to the subsequent drafts and the final version.

Declaration of interest

In the past, RF.Lamont has advised or given lectures on conferences organised or supported by Glaxo-Smith-Klein, Sanofi-Synthelabo and Ferring Pharmaceuticals pertaining to PTB in general and tocolytics in particular. Currently RF.Lamont is a member of an Independent Drug Monitoring Committee for a randomised controlled trial of a tocolytic agent. Currently, J.S.Jørgensen is an advisor to and has lectured on conferences organised or supported by Ferring Pharmaceuticals. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

References

Papers of special note have been highlighted as:

- of interest
- of considerable interest


- Discusses the mechanisms of pulmonary edema with the use of β2-agonists.


- Highly critical commentary on the Cochrane reviews on CCBs and oxytocin receptors antagonists.


This study demonstrated a higher mortality in the atosiban group compared to the placebo (with tocolytic rescue therapy) group by randomization was not stratified at lower gestations. Accordingly, the excess of neonatal deaths in the atosiban group was probably due to greater numbers at earlier gestations in more advanced labor in this group compared to placebo with tocolytic rescue therapy.


European guidelines for the management of spontaneous preterm labor.


- An important systematic review on the safety of CCBs demonstrating that adverse outcomes are related to total daily dose of nifedipine.

- A tocolytic study which addresses neonatal outcome rather than the surrogate outcome of preterm birth.