Tocolytics and preterm labour -- Carlin et al. 338: b195 -- BMJ

Published 5 March 2009, doi:10.1136/bmj.b195
Cite this as: BMJ 2009;338:b195

Editorials

Tocolytics and preterm labour

Whether to treat or not is the real dilemma, not which drug to use

Preterm labour is still the main cause of perinatal morbidity and mortality in the developed world. Despite a better understanding of the pathophysiology, and the recognition that it is a syndrome with multiple causes, rates continue to rise.1 In the linked cohort study (doi:10.1136/bmj.b744), de Heus and colleagues assess the incidence of serious maternal complications with the use of tocolytic drugs for the treatment of preterm labour.2

Corticosteroids given to women at risk of preterm birth increase fetal lung maturity and can reduce fetal death, intraventricular haemorrhage, and respiratory distress by up to 50%.3 In contrast, it is still unclear whether tocolysis improves neonatal or longer term outcomes.4 Thus, the Royal College of Obstetricians and Gynaecologists' clinical guideline on tocolysis concludes that, "it is reasonable not to use tocolytic drugs."5

Despite the lack of evidence, several tocolytic drugs are commonly used worldwide. They are used primarily to delay delivery for up to 48 hours to allow for administration of corticosteroids or transfer to a unit with neonatal intensive care facilities (or both). Little consensus exists as to which tocolytic agent is the best. Beta agonists, atosiban, and indometacin all reduce the incidence of delivery within 48 hours compared with placebo, but none has been shown to improve neonatal outcomes.4 Nifedipine has not been studied in placebo controlled trials, but it is more effective at delaying delivery than β agonists, and has been associated with improved neonatal outcomes.6 Atosiban and nifedipine have not been directly compared.

The study by de Heus and colleagues assesses maternal safety. They recorded adverse maternal effects in an unselected population of 1920 consecutive women given tocolytic drugs in routine clinical settings in the Netherlands and Belgium over an 18 month period. The most commonly used agent was atosiban (42%), followed by nifedipine (34%), β agonists (14%), and indometacin (8%).

The overall incidence of adverse effects was reassuringly low, but the study highlights the dangers of multidrug regimens, which have no proven benefit either sequentially or in combination. Four women needed intensive care after being subjected to such regimens—three of which included β agonists. But before such practices are condemned outright, a thorough analysis of each case is warranted, so that further research into safer combination treatments is not compromised.

Because of the definitions used in the study design, postpartum haemorrhage was not included as a maternal adverse event. Some people may think this a surprising omission considering the basic mechanism of action of all tocolytics.

Consistent with previous studies, the β agonists had a higher incidence of serious adverse drug reactions (1.7%) than nifedipine (0.9%); no such reactions were reported for atosiban.

Hypotension was the most serious adverse drug reaction associated with nifedipine, which is not surprising considering its licensed indication. Hypotension was defined as a systolic blood pressure of <100 mm Hg and a drop of more than 20%. Associated symptoms did not need to be treated. It is debatable whether this reaction would be considered "life threatening" according to the Council for International Organizations for Medical Science definition used as a guideline in the article, and no justification is given for using these particular values. Indeed, the authors themselves question the importance of these events and point out that no associated episodes of fetal compromise occurred.

These findings highlight the relative maternal safety of tocolytics, although β agonists have the highest adverse event rate and
their continued use is hard to justify. Atosiban stands out as the drug with the safest maternal adverse event profile, but it has not been shown to improve neonatal outcomes and is considerably more expensive than nifedipine. Using the number needed to treat analysis provided in the article, we calculated that 108 patients would need to be treated with atosiban to prevent one serious adverse drug reaction associated with nifedipine. This means that, allowing for the spread across the confidence intervals, an extra £30 000 (€33 000; $44 000) to £45 000 would need to be spent for each serious adverse drug reaction prevented (costs sourced from British National Formulary, September 2008). Clearly a detailed cost-benefit analysis is warranted.

This study also serves as a timely reminder that the decision to use tocolysis should not be taken lightly, especially as we have no good test for differentiating "true" from "spurious" preterm labour, so many women are treated unnecessarily.4

After more than 30 years of research we still do not know whether tocolysis benefits the fetus, so the choice of which drug to use remains a secondary question. The real dilemma is whether or not we should treat at all. Not only may tocolysis lack any real benefit, but it could be harmful, as highlighted in the recent publication of the long term outcomes of the ORACLE II trial.7 In the original study, antibiotics were given to women with intact membranes who were at risk of preterm labour, and no improvement was seen in neonatal outcomes. But of major concern is the increased incidence of cerebral palsy at 7 years seen in the recently published follow-up data.

We agree with de Heus and colleagues that a randomised controlled trial of nifedipine and atosiban is needed; however, any such study should include a placebo arm. Accumulating evidence such as that from the ORACLE II trial and from groups examining the associations between infection, inflammation, preterm labour, and brain injury,8 9 10 11 alongside improvements in neonatal care, mean that the old assumption that "keeping the baby inside longer must be a good thing" can no longer go unchallenged.

Cite this as: BMJ 2009;337:b195

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Research, doi:10.1136/bmj.b744

Competing interests: RS and JN have received grants from government Research, doi:10.1136/bmj.b744

Provenance and peer review: Commissioned; not externally peer reviewed.

References


### Relevant Article

**Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study**

Roel de Heus, Ben Willem Mol, Jan-Jaap H M Erwich, Herman P van Geijn, Wilfried J Gyselaers, Myriam Hanssens, Linda Härmark, Caroline D van Holsbeke, Johannes J Duvekot, Fred F A M Schobben, Hans Wolf, and Gerard H A Visser

*BMJ* 2009 338: b744. [Abstract] [Full Text] [PDF]
Adverse drug reactions to tocolytic treatment for preterm labour: prospective cohort study

Roel de Heus, registrar of obstetrics and gynaecology,1 Ben Willem Mol, professor of perinatology and clinical epidemiology,2, 3 Jan-Jaap H M Erwich, gynaecologist and perinatologist,4 Herman P van Geijn, professor of obstetrics,5 Wilfried J Gyselaers, gynaecologist and perinatologist,6 Myriam Hanssens, professor of obstetrics,10 Linda Härmack, pharmacologist,7 Caroline D van Holsbeke, gynaecologist and perinatologist,11 Johannes J Duvekot, gynaecologist and perinatologist,6 Fred F A M Schobben, professor of pharmacology,8 Hans Wolf, gynaecologist and perinatologist,1 Gerard H A Visser, professor of obstetrics1

ABSTRACT

Objective To evaluate the incidence of serious maternal complications after the use of various tocolytic drugs for the treatment of preterm labour in routine clinical situations.

Design Prospective cohort study.

Setting 28 hospitals in the Netherlands and Belgium.

Participants 1920 consecutive women treated with tocolytics for threatened preterm labour.

Main outcome measures Maternal adverse events (those suspected of being causally related to treatment were considered adverse drug reactions) leading to cessation of treatment.

Results An independent panel evaluated the recorded adverse events, without knowledge of the type of tocolytic used. Of the 1920 women treated with tocolytics, 1327 received a single course of treatment (69.1%), 282 sequential courses (14.7%), and 311 combined courses (16.2%). Adverse drug reactions were categorised as serious or mild in 14 cases each. The overall incidence of serious adverse drug reaction was 0.7%. Compared with atosiban, the relative risk of an adverse drug reaction for single treatment with a β adrenoceptor agonist was 22.0 (95% confidence interval 3.6 to 138.0) and for single treatment with a calcium antagonist was 12 (1.9 to 69). Multiple drug tocolysis led to five serious adverse drug reactions (1.6%). Multiple gestation, preterm rupture of membranes, and comorbidity were not independent risk factors for adverse drug reactions.

Conclusions The use of β adrenoceptor agonists or multiple tocolytics for preventing preterm birth is associated with a high incidence of serious adverse drug reactions. Indomethacin and atosiban were the only drugs not associated with serious adverse drug reactions. A direct comparison of the effectiveness of nifedipine and atosiban in postponing preterm delivery is needed.

INTRODUCTION

Preterm labour is the most reported cause of perinatal morbidity and mortality in the Western world. Tocolytic drugs have not been shown to improve fetal outcome, but are used to postpone delivery for 48 hours to allow for maximal effect of parenteral steroids administered to the mother and to enable the mother to be transferred to a centre with a neonatal intensive care unit. In the absence of any clear evidence that one tocolytic is more efficacious than another, relative safety is the main reason for choosing one over the other. The drugs registered for tocolysis include the β adrenoceptor agonist ritodrine hydrochloride (United States and Europe) and the oxytocin receptor antagonist atosiban (Europe). Cyclo-oxygenase inhibitors and calcium channel blockers are also used for inhibiting preterm labour, although they are not currently registered for this indication.

β adrenoceptor agonists cause adverse effects in women more often than any other tocolytic drug. In a clinical trial setting the oxytocin receptor antagonist atosiban was associated with fewer adverse effects than β adrenoceptor agonists (relative risk 0.04, 95% confidence interval 0.02 to 0.11) with comparable effectiveness (proportion of women with birth delayed for 48 hours; relative risk 1.1, 0.9 to 1.2). When compared with placebo, however, atosiban was not associated with a reduction in the incidence of neonatal respiratory distress syndrome, a serious complication of prematurity.5 Small studies using cyclo-oxygenase inhibitors have suggested that indomethacin reduces the proportion of women delivering preterm compared with placebo (relative risk 0.2, 0.1 to 0.6); but its use has been limited because of concerns about adverse effects of cyclo-oxygenase inhibitors on fetal kidneys and ductus arteriosus and the increased risk of intraventricular haemorrhage and necrotising enterocolitis. Calcium channel blockers seem to be more effective in postponing preterm delivery (relative risk 0.8, 0.6 to 0.9) and reducing neonatal respiratory distress (0.6, 0.4 to 0.9) than do β adrenoceptor agonists. However, placebo controlled trials assessing calcium channel blockers are not available and recent reports have raised concerns about women’s safety with use of these tocolytic drugs. The choice of first line tocolytic drug for the
treatment of preterm labour is therefore controversial because of inconclusive information on the relative safety of the various agents. For example, most randomised trials on the efficiency and side effects of tocolytic drugs have generally been restricted to well defined (low risk) populations, excluding women with multiple gestation, preterm rupture of membranes, vaginal bleeding, diabetes, or a history of cardiovascular diseases. No prospective study has compared the adverse reactions of women to different tocolytic drugs in a routine clinical setting. We carried out a prospective cohort study in the Netherlands and Belgium to evaluate the incidence of serious maternal complications with the use of the various tocolytic drugs to treat preterm labour in routine clinical situations.

METHODS

We carried out an open label, prospective, cohort study. The cohort comprised consecutive women who were treated with tocolytic drugs according to local protocol for preterm labour in 28 hospitals in the Netherlands and Belgium during January 2006 to July 2007. We excluded women who were treated with tocolytic drugs for other reasons, such as external cephalic version for breech presentation or intrauterine resuscitation in case of suspected fetal distress during term labour. Potential participants were identified by the attending doctor or a study nurse and registered through a study website, which was accessible to participating clinics using centre specific access codes. We recorded the personal and obstetrical characteristics for each woman, including the date of birth, gestational age, parity, cervical dilatation, blood loss, intact versus ruptured membranes, number of fetuses, and the presence of comorbidities such as cardio-pulmonary disease, pre-eclampsia, hypertension, diabetes, placenta abnormalities, or polyhydramnios. We also recorded the type of tocolytic treatment and any maternal adverse event that required cessation of treatment. The attending obstetrician decided when to stop treatment in case of an adverse event. We carried out quality control of patient registration by checking the dispensing lists for tocolytics from the pharmaceutical department at each participating hospital. In all cases of possible adverse events the principal investigator completed a standard case report. If necessary, we retrieved additional data from the patients’ files.

Data assessment

At the end of the registration period all adverse events were evaluated and classified by a panel of five members; three obstetricians (J-JHME, HW, MH) and two pharmacologists (LH, FFAMS). Four members of the panel worked in university hospitals and the fifth was an administrator at the Dutch Pharmaco-vigilance Centre.

The panel was initially asked to establish whether the registered adverse events satisfied the criteria of occurring during tocolysis and requiring discontinuation of tocolytic treatment in the opinion of the attending obstetrician, and then to classify the adverse events in terms of severity (serious or mild). The members individually reviewed all cases of adverse events, blind to the type of tocolytic used. For serious adverse events, we used the definition of the Council for International Organizations of Medical Sciences as a guideline. According to the council a serious adverse event is one that results in death, is life threatening, requires admission to hospital or prolongation of existing hospital stay, results in persistent or important disability or incapacity, or is a congenital anomaly or birth defect. On the basis of this definition, a serious adverse event in the context of tocolytic drugs was any of the following: severe hypotension (systolic blood pressure <100 mm Hg and >20% drop compared with baseline values), severe dyspnoea, lung oedema, myocardial infarction, anaphylactic shock, admittance to intensive care, or maternal death. A mild adverse event was defined as an adverse event that led to cessation of tocolytic therapy (for example, tachycardia, nausea, diziness, headache) but did not meet the criteria for a serious adverse event.

Each panel member subsequently received the list of adverse events, previously categorised as mild or serious, and the tocolytic used. They were asked to assess whether the adverse events were causally related to each tocolytic, using the causality categories of the World Health Organization: certain, probable, possible, unlikely, conditional, and non-assessable. Important criteria for the assessment of causality were the association in time between administration of the tocolytic and event, pharmacological features, medical plausibility, and exclusion of other causes. In cases of rechallenge with the tocolytic and recurrence of the adverse event, the causal relation to treatment was classified as certain. In case of a reasonable relation with time, not likely to be attributable to other drugs or disease, and a reasonable clinical response to withdrawal, the causal relation to treatment was classified as probable. If the adverse event could also be explained by concomitant diseases or use of other drugs, the causal relation to treatment was classified as possible. For adverse events with an improbable time relation or a plausible explanation provided by concomitant diseases or the use of other drugs the causal relation to treatment was classified as unlikely. The cases with discrepant assessments were discussed during a plenary meeting and a consensus was reached in all cases. We defined all adverse events that were considered as possibly, probably, or certainly related to tocolytic treatment as adverse drug reactions.

Analysis

We classified the administration of tocolytics according to three courses of treatment: single (one tocolytic), sequential (multiple tocolytics given separately in sequence), or combined (multiple tocolytics given simultaneously). The primary outcome of the study was the incidence of serious adverse drug reactions to tocolytics. In each of the three treatment categories we calculated the incidence of a tocolytic related adverse
Table 1 | Obstetrical characteristics of women who received tocolytic treatment. Values are numbers (percentages) of women

<table>
<thead>
<tr>
<th>Variables</th>
<th>Single course treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Atosiban (n=575)</td>
</tr>
<tr>
<td>Singleton pregnancy</td>
<td>441 (77)</td>
</tr>
<tr>
<td>Parity 0</td>
<td>294 (51)</td>
</tr>
<tr>
<td>Preterm rupture of membranes</td>
<td>162 (28)</td>
</tr>
<tr>
<td>Cardiac history</td>
<td>15 (2.6)</td>
</tr>
<tr>
<td>Diabetes types 1 and 2 and gestational</td>
<td>5 (0.9)</td>
</tr>
</tbody>
</table>

Ten different combinations of atosiban, β adrenoceptor agonists, nifedipine, and cyclo-oxygenase inhibitors were recorded in 311 instances. In patients who received these combinations, five serious (1.6%) and one mild (0.3%) adverse drug reactions were observed. No serious adverse drug reaction was reported in

Table 2 | Serious maternal adverse events associated with tocolytic treatment

<table>
<thead>
<tr>
<th>Serious adverse event</th>
<th>Tocolytic</th>
<th>No of fetuses</th>
<th>Intensive care</th>
<th>Causality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnoea</td>
<td>Ritodrine</td>
<td>1</td>
<td>No</td>
<td>Probable</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Fenoterol</td>
<td>1</td>
<td>No</td>
<td>Probable</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Atosiban, nifedipine, and ritodrine*</td>
<td>1</td>
<td>No</td>
<td>Probable</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Fenoterol</td>
<td>1</td>
<td>No</td>
<td>Probable</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Nifedipine</td>
<td>2</td>
<td>No</td>
<td>Probable</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Atosiban and fenoterol*</td>
<td>1</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Nifedipine</td>
<td>1</td>
<td>No</td>
<td>Probable</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Nifedipine</td>
<td>1</td>
<td>No</td>
<td>Certain</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Nifedipine</td>
<td>2</td>
<td>No</td>
<td>Certain</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Nifedipine</td>
<td>1</td>
<td>No</td>
<td>Certain</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Atosiban then fenoterol†</td>
<td>1</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Nifedipine and ritodrine*</td>
<td>2</td>
<td>No</td>
<td>Probable</td>
</tr>
<tr>
<td>Lung oedema</td>
<td>Atosiban, nifedipine, and fenoterol*</td>
<td>2</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Lung oedema</td>
<td>Atosiban and nifedipine*</td>
<td>1</td>
<td>Yes</td>
<td>Probable</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Fenoterol</td>
<td>1</td>
<td>No</td>
<td>Unlikely</td>
</tr>
<tr>
<td>Deep vein thrombosis</td>
<td>Ritodrine then nifedipine†</td>
<td>2</td>
<td>No</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

*Combined courses: event occurred after simultaneous administration of all indicated tocolytics.
†Sequential courses: event occurred after administration of second tocolytic.
Table 3 | Mild maternal adverse events associated with tocolytic treatment

<table>
<thead>
<tr>
<th>Mild adverse events</th>
<th>Tocolytic</th>
<th>No of fetuses</th>
<th>Causality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension</td>
<td>Nifedipine</td>
<td>2</td>
<td>Possible</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Nifedipine</td>
<td>1</td>
<td>Probable</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Nifedipine</td>
<td>1</td>
<td>Probable</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Nifedipine</td>
<td>1</td>
<td>Probable</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Atosiban</td>
<td>1</td>
<td>Possible</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Fenoterol</td>
<td>1</td>
<td>Possible</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Nifedipine</td>
<td>1</td>
<td>Probable</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>Fenoterol</td>
<td>1</td>
<td>Certain</td>
</tr>
<tr>
<td>Nausea</td>
<td>Atosiban</td>
<td>1</td>
<td>Possible</td>
</tr>
<tr>
<td>Headache</td>
<td>Atosiban</td>
<td>1</td>
<td>Possible</td>
</tr>
<tr>
<td>Headache</td>
<td>Fenoterol</td>
<td>1</td>
<td>Probable</td>
</tr>
<tr>
<td>Headache</td>
<td>Atosiban, nifedipine</td>
<td>1</td>
<td>Probable</td>
</tr>
<tr>
<td>Syncope</td>
<td>Nifedipine</td>
<td>1</td>
<td>Unlikely</td>
</tr>
</tbody>
</table>

Sequential courses: event occurred after administration of second tocolytic.
Combined courses: event occurred after simultaneous administration of all indicated tocolytics.

The use of tocolytics was recorded in 414 women with a multiple pregnancy. Four of these women had a serious tocolytic related adverse drug reaction compared with women with a singleton pregnancy (relative risk 1.5, 95% confidence interval 0.39 to 5.0). Two of the women (2.0%) were treated with a single course of nifedipine (n=101) and two (2.4%) were treated with combined courses (n=84). Logistic regression showed that preterm rupture of membranes, blood loss, and other obstetric comorbidities were not independently related to an adverse event.

DISCUSSION

The use of β adrenoceptor agonists or multiple tocolytics to prevent preterm labour is associated with a high incidence of serious adverse drug reactions. Indometacin and atosiban were the only tocolytic drugs not associated with serious adverse reactions.

Randomised studies on the efficiency of tocolytics and adverse events associated with these drugs have generally been restricted to well defined (low risk) populations, excluding women with multiple pregnancies, preterm rupture of membranes, vaginal bleeding, diabetes, or a history of cardiovascular diseases; however, many of the case reports on adverse drug reactions to tocolytics have been associated with these conditions. We assessed the occurrence of serious maternal adverse drug reactions related to the use of different tocolytics in a routine clinical setting. Our results therefore apply to situations normally encountered in clinical practice, where both low risk and high risk cases are observed. Intense monitoring in a trial setting is, however, likely to reveal all mild and serious maternal side effects, whereas under-reporting of adverse experiences cannot be excluded in prospective multicentre cohort studies where the intensity of monitoring—especially of blood pressure—may vary between hospitals.

In our study the overall incidence of serious tocolytic related adverse drug reactions was low (0.7%). The incidence of serious adverse drug reactions in women receiving combined courses of tocolytics (16.2% of all patients) was, however, high (1.6-2.5%). As there is no evidence that treatment with combined tocolytics is superior to single or sequential treatment, we believe that combined treatment should be discouraged. In women treated with a single tocolytic, the incidence of serious adverse drug reactions was 1.7% for β mimetic agents and 0.9% for nifedipine. No serious adverse drug reaction was observed after treatment with a single course of atosiban. Most of the adverse drug reactions reported in women treated with nifedipine were related to the effects of the drug on blood pressure. In six of the seven cases, hypotension developed within two to four hours after the start of tocolysis. The treatment schedule was usually the following: two to four doses of 10 mg sublingual nifedipine every 15 minutes, followed by 20 mg slow release nifedipine every four hours. With such a regimen, plasma levels are likely to peak between 60 and 80 minutes after administration and cause a concomitant fall in blood pressure.

Table 4 | Adverse drug reactions associated with single tocolytic treatment. Values are numbers (percentages) of women unless stated otherwise

<table>
<thead>
<tr>
<th>Tocolytic</th>
<th>No of patients</th>
<th>Severity of adverse drug reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Serious</td>
</tr>
<tr>
<td>β mimetics</td>
<td>175</td>
<td>3 (1.7)</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>542</td>
<td>5 (0.9)</td>
</tr>
<tr>
<td>Atosiban</td>
<td>575</td>
<td>0</td>
</tr>
<tr>
<td>Cyclo-oxygenase inhibitors</td>
<td>35</td>
<td>0</td>
</tr>
</tbody>
</table>

NA=Not applicable.
*for total adverse drug reactions.
WHAT IS ALREADY KNOWN ON THIS TOPIC

Preterm birth is the major cause of perinatal mortality and morbidity
Tocolytics are used to postpone delivery to allow for maximal effect of steroids given to the mother and transfer of the mother to a centre with a neonatal intensive care unit
The choice of first line tocolytic drug is controversial because of inconclusive information on the mother's safety with use of various tocolytic agents

WHAT THIS STUDY ADDS

β adrenoceptor agonists or multiple tocolytics for preventing preterm birth are associated with a high incidence of adverse drug reactions
Indometacin and atosiban are the only tocolytic drugs not associated with serious adverse drug reactions in women
A direct comparison of effectiveness between nifedipine and atosiban in postponing preterm delivery is needed

mother had chewed two 10 mg nifedipine tablets at an interval of minutes.24

In most of the recent case reports that raised concerns about the safety of calcium antagonists in women, complicating factors such as multiple pregnancy, cardiovascular disease, diabetes, or infections were present.15 21 27 28 We did not find any significant association between adverse drug reactions to nifedipine and these factors. We found four serious adverse drug reactions in women with multiple pregnancy—two women receiving nifedipine (2%) and two receiving combined treatment (2.4%). These incidences were not significant. Whether this was due to lack of statistical power is uncertain.

β adrenoceptor agonists do not seem to be more effective than atosiban, nifedipine, or cyclo-oxygenase inhibitors in preventing preterm birth,4 5 7 8 12 and our results confirm the high incidence of adverse drug reactions with use of these agents for tocolysis.49 This justifies the use of alternative tocolytic drugs. In our study only a few women were treated with cyclo-oxygenase inhibitors, most likely because in Belgium and the Netherlands these drugs are restricted to women in early gestation. Moreover, concerns about fetal side effects limit the use of cyclo-oxygenase inhibitors for tocolysis.10 11 We found no adverse drug reactions, either with single treatment or with treatment using cyclo-oxygenase inhibitors combined with other tocolytics. A recent meta-analysis of cyclo-oxygenase inhibitors showed that indometacin reduced the proportion of women delivering preterm (<37 weeks’ gestation; relative risk 0.5, 95% confidence interval 0.3 to 0.9), with only one case of antenatal closure of the ductus arteriosus among 403 women treated short term (up to 48 hours).3 Nonetheless, on the basis of the volume of evidence the authors concluded that firm conclusions on the efficiency and safety for neonates when using cyclo-oxygenase inhibitors to prevent preterm delivery could not be drawn.

Large randomised controlled trials comparing atosiban with nifedipine are lacking. An indirect comparison of atosiban with nifedipine, using β adrenoceptor agonists as a common comparator, has been published.29 The analysis showed no significant differences in effectiveness in delaying delivery, but a significant reduction in neonatal respiratory distress syndrome with nifedipine. Whether this reduction is attributable to a difference in effectiveness of the drug or to differences between the analysed trials in terms of lack of blinding or concealment or of corticosteroid administration remains uncertain.

An ideal tocolytic should postpone delivery at low costs without maternal and fetal side effects. None of the tocolytics described in this study fulfils these criteria. We found that combined treatment or a single treatment using β adrenoceptor agonists led to a higher incidence of serious adverse drug reactions, and such treatments should be discouraged. The overall incidence of serious adverse drug reactions with a single course of nifedipine in a singleton pregnancy seems to be low, but not absent. Atosiban has the best maternal and fetal safety profile but at considerable cost. A direct comparison of effectiveness between oxytocin antagonists and calcium channel blockers is lacking. Moreover, larger studies with different dose regimens for nifedipine are necessary to compare efficiency and maternal side effects.

The participating hospitals were: Academic Medical Centre Amsterdam, Hans Wolf, Lucas Andreas Hospital Amsterdam, Celine M Radder; Free University Medical Centre Amsterdam, Herman P van Geijn, Anniemiek C Bolite; Sint Augustinus Hospital, Antwerp, Tina BVBA Vanderheijden; University Hospital Antwerp, Yves Jacquemyn, Gérè Hospital Apeldoorn, Anneke JM Husjes; General Hospital Kına Brasschaat, Patricia Crijs, Maas and Kempen Hospital, Dirk Lauwage; Sint Jan Hospital, Brugge, Anne Lloccufier; Bronovo Hospital, the Hague, Casper AG Holleboom; University Hospital Gent, Walter Parewijk, Marleen Temmerman; Hospital Oost-Limburg Genk, Wifried J Gyselaers, Caroline van Hulsbeke; University Medical Centre Groningen, Jan-Jaap HM Erwich, Atrium Medical Centre Heerlen, Frans JME Raumen; Sint Franciscus Hospital, Jan Schreurs; University Hospital Leuven, Myriam Hanssens; Maria Hospital Noord-Limburg Neerpelt, Bart Bollen; Sint Antonius Hospital Nieuwegein, Erik van Beek; Canisius-Wilhelmina Hospital Nijmegen, Jan MJ Sporken, Erasmus Medical Centre, Rotterdam, Hans J Duvekot; Laurensius Hospital Roermond, Chantal BM Wingen; Stintcbruinvoeg Hospital, Sint Truïnde, Christa Eerdekens; Twee Steden Hospital, Tilburg, Addy P Droogrop; Sint Jozef Hospital Turnhout, Jan Aerts, Myrih Hulsbeger, University Medical Centre Utrecht, Margo Graatsma, Gerard HA Visser; Maxima Medical Centre Veldhoven, Ben-Willem Mol, and Isala Hospital Zwolle, Jim van Eijk.

Contributors: All authors had full access to the data (including statistical reports and tables) in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Funding: This research was funded by an unconditional grant from Ferring Pharmaceuticals BV, Hoofddorp, The Netherlands.

Competing interests: WJG did a retrospective cohort study on tocolysis in 2006 (not published) which was supported by an unconditional grant from Ferring Pharmaceuticals.

Ethical approval: This study was approved by the medical review ethics committee of University Medical Centre Utrecht.


Accepted: 2 December 2008