Drugs for treatment of very high blood pressure during pregnancy (Review)

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ABSTRACT

Background
Very high blood pressure during pregnancy poses a serious threat to women and their babies. Antihypertensive drugs lower blood pressure. Their comparative effects on other substantive outcomes, however, is uncertain.

Objectives
To compare different antihypertensive drugs for very high blood pressure during pregnancy.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group Trials Register (28 February 2006) and CENTRAL (*The Cochrane Library* 2006, Issue 2).

Selection criteria
Studies were randomised trials. Participants were women with severe hypertension during pregnancy. Interventions were comparisons of one antihypertensive drug with another.

Data collection and analysis
Two review authors independently extracted data.

Main results
Twenty-four trials (2949 women) with 12 comparisons were included. Women allocated calcium channel blockers rather than hydralazine were less likely to have persistent high blood (five trials, 263 women; 6% versus 18%; relative risk (RR) 0.33, 95% confidence interval (CI) 0.15 to 0.70). Ketanserin was associated with more persistent high blood pressure than hydralazine (four trials, 200 women; 27% versus 6%; RR 4.79, 95% CI 1.95 to 11.73), but fewer side-effects (three trials, 120 women; RR 0.32, 95% CI 0.19 to 0.53) and a lower risk of HELLP (Haemolysis, Elevated Liver enzymes and Lowered Platelets) syndrome (one trial, 44 women, RR 0.20, 95% CI 0.05 to 0.81).

Labetalol was associated with a lower risk of hypotension (one trial 90 women; RR 0.06, 95% CI 0.00 to 0.99) and caesarean section (RR 0.43, 95% CI 0.18 to 1.02) than diazoxide. Data were insufficient for reliable conclusions about other outcomes.

The risk of persistent high blood pressure was lower for nimodipine compared to magnesium sulphate (two trials 1683 women; 47% versus 65%; RR 0.84, 95% CI 0.76 to 0.93), although nimodipine was associated with a higher risk of eclampsia (RR 2.24, 95% CI 1.06 to 4.73). Nimodipine was asociated with a lower risk of respiratory difficulties (RR 0.28, 95% CI 0.08 to 0.99), fewer side-effects (RR 0.68, 95% CI 0.54 to 0.86) and less postpartum haemorrhage (RR 0.41, 95% CI 0.18 to 0.92) than magnesium sulphate. Stillbirths and neonatal deaths were not reported.

There are insufficient data for reliable conclusions about the comparative effects of any other drugs.

Authors' conclusions
Until better evidence is available, the choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug, and on what is known about adverse effects. Exceptions are diazoxide, ketanserin, nimodipine and magnesium sulphate, which are probably best avoided.

PLAIN LANGUAGE SUMMARY

Pregnant women with very high blood pressure (hypertension) who take antihypertensive drugs can reduce their blood pressure, but the most effective antihypertensive drug is unknown

During pregnancy a woman's blood pressure falls then climbs slowly, reaching pre-pregnancy levels at term. Pregnant women with very high blood pressure often develop other complications such as pre-eclampsia and premature delivery. They are also at risk of having a stroke. The review of 24 trials including 2949 women found that while antihypertensive drugs lower blood pressure, there is not enough evidence to show which drug is the most effective when taken by pregnant women with hypertension. There is some evidence that diazoxide may result in the woman's blood pressure falling too quickly, and that ketanserin may not be as effective as hydralazine. Further research into the effects of antihypertensive drugs is needed.

BACKGROUND

During normal pregnancy there are considerable changes in blood pressure. Within the first weeks the woman's blood pressure falls, largely due to a general relaxation of muscles within the blood vessels (Hytten 1980). From around the middle of pregnancy it rises slowly again until, at term, blood pressure is close to the level it was before pregnancy. Blood pressure during pregnancy can be influenced by many other factors including, time of day, physical activity, position and anxiety. High blood pressure alone has little effect on the outcome of pregnancy, but rises in blood pressure may be associated with other complications. Of these, the most common is pre-eclampsia. This is a multisystem disorder of pregnancy which commonly presents with raised blood pressure and proteinuria (Roberts 1993), and occurs in between two to eight per cent of pregnancies (WHO 1988). Although the outcome for most of these pregnancies is good, women with pre-eclampsia have an increased risk of developing serious problems, such as kidney failure, liver failure, abnormalities of the clotting system, stroke, premature delivery (birth before 37 completed weeks), stillbirth or death of the baby in the first few weeks of life (Redman 1993).

In view of the many factors that can influence blood pressure, it is not surprising that there is often uncertainty about whether a specific abnormal measurement is potentially harmful for that woman. Once blood pressure rises above a certain level, however, there is a risk of direct damage to the blood vessel wall, regardless of what caused the rise. This risk is not specific to pregnancy, as it is similar for non-pregnant people with very high blood pressure. The level at which this risk merits mandatory antihypertensive therapy is usually considered to be 170 mmHg systolic blood pressure or 110 mmHg diastolic (Redman 1993). If the woman has signs and symptoms associated with severe pre-eclampsia (such as hyperreflexia, severe headache, sudden onset of epigastric pain, or lowered platelets) a lower threshold for treatment maybe advisable (CEMD-UK 2004). The possible consequences of such high blood pressure for the mother include kidney failure, liver failure and cerebrovascular haemorrhage (stroke). In the UK, for example, stoke resulting from severe hypertension was the single most common cause of maternal death associated with pre-eclampsia (CEMD-UK 2004). For the baby, risks include fetal distress due to vasoconstriction reducing the blood supply across the placenta, and placental abruption (separation of the placenta from the wall of the womb before birth).

Once blood pressure reaches 170 mmHg systolic or 110 mmHg diastolic, the woman is at increased risk of these harmful effects. There is therefore a general consensus that she should receive antihypertensive drugs, to lower her blood pressure, and that she should be in a hospital. The aim of treatment is to quickly bring about a smooth reduction in blood pressure to levels that are safe for both mother and baby, but avoiding any sudden drops that may in themselves cause problems such as dizziness or fetal distress. Once blood pressure is controlled, in many cases a decision will be made to deliver the baby fairly soon, particularly if the pregnancy is at or near to term. If the baby is very premature, the blood pressure responds well to initial treatment, and there are no other complicating factors, the pregnancy may be continued with the hope that this will improve outcome for the baby. This issue of timing of delivery is covered by a separate review (Churchill 2002).

In general, maternal side-effects are not different from those in the non-pregnant state, and are listed in pharmacological texts. All drugs used to treat hypertension in pregnancy cross the placenta, and so may affect the fetus directly by means of their action within

the fetal circulation, or indirectly by their effect on uteroplacental perfusion.

The care of women with very high blood pressure during pregnancy is often complex. For women who have pre-eclampsia, there is also the question of whether there is additional benefit from prophylactic anticonvulsant drugs, and this question is covered in the review 'Anticonvulsants for women with pre-eclampsia' (Duley 2003). In addition, other Cochrane reviews relevant to the care of women with severe hypertension include plasma volume expansion (Duley 1999), steroids for HELLP (Haemolysis, Elevated Liver enzymes and Lowered Platelets) syndrome (Matchaba 2004) and timing of delivery for severe pre-eclampsia before 34 weeks' gestation (Churchill 2002). Treatment of mild to moderate hypertension in pregnancy has been reviewed by Abalos 2001.

The aim of this review is to compare the different types of antihypertensive drugs used for women with severe hypertension during pregnancy to determine which agent has the greatest comparative benefit with the least risk.

OBJECTIVES

To compare the effects of different antihypertensive agents when used to rapidly lower very high blood pressure during pregnancy on:

(i) substantive maternal morbidity;
(ii) morbidity and mortality for the baby;
(iii) side-effects for the woman.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

Randomised trials were included. Studies with clearly inadequate concealment of allocation were excluded, as were those with a quasi-random design.

Types of participants

Women with severe hypertension (diastolic 105 mmHg or more and/or systolic 160 mmHg or more) during pregnancy, requiring immediate treatment. Postpartum women were excluded as the outcomes of interest for these women are substantially different.

Types of intervention

Any comparison of one antihypertensive agent with another regardless of dose, route of administration or duration of therapy. Comparisons of alternative regimens of the same agent and of alternative agents within the same class of drug are not included, but may be considered for future updates.

Types of outcome measures

For the woman

- Persistent high blood pressure: defined, if possible, as either the need for an antihypertensive drug other than the allocated treatment, or failure to control blood pressure on the allocated treatment;
- hypotension (low blood pressure): defined if possible as low blood pressure causing clinical problems;
- eclampsia: seizures superimposed on pre-eclampsia;
- measures of serious maternal morbidity: such as kidney failure, cardiac failure, stroke, abnormalities of the clotting system, liver failure, and respiratory depression. Either reported individually or as a composite measure;
- caesarean section;
- use of health service resources: dialysis, ventilation, admission to intensive care, length of stay;
- side-effects.

For the baby

- Fetal and neonatal death: total deaths before discharge from hospital. Deaths will also be reported by time of death (stillbirth, perinatal and neonatal) if possible;
- measures of serious neonatal morbidity: low Apgar scores, intraventricular haemorrhage (bleeding into the brain ventricles);
- use of health service resources: admission to special care nursery, ventilation, length of stay in hospital, special needs in the community;
- infant and child development: growth, cerebral palsy, significant learning disability.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group Trials Register by contacting the Trials Search Co-ordinator (28 February 2006).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
(1) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
(2) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

Details of the search strategies for CENTRAL and MEDLINE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Search strategies for identification of studies' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2006, Issue 2) using the following strategy:

1. HYPERTENSION, PREGNANCY-INDUCED:ME
2. PREECLAMP*
3. PRE-ECLAMP*
4. (PRE next ECLAMP*)
5. ECLAMP*
6. (HYPERTENS* and PREGNAN*)
7. (((((#1 or #2) or #3) or #4) or #5) or #6)
8. ((NIFEDIPINE or NIMODIPINE) or ISRADIPINE)
9. (HYDRALAZINE or DIHYDRALAZINE)
10. ((LABETALOL or ATENOLOL) or PROPRANOLOL)
11. (GTN or (GLYCEROL and TRINITR*))
12. (URAPIDIL or PRAZOSIN)
13. ((((#8 or #9) or #10) or #11) or #12)
14. (#7 and #13)

In the previous version of the review, we also searched MEDLINE (1966 to April 2002) using the MeSH terms 'pregnancy' and 'hypertension', limited to randomised controlled trials.

We did not apply any language restrictions.

METHODS OF THE REVIEW

Selection of studies

Two authors independently evaluated studies to assess eligibility. Discrepancies were resolved by discussion. If there was no agreement, the third author was asked to independently assess the study for inclusion. If agreement was still not reached, the study was excluded until clarification could be obtained from the authors.

Assessment of methodological quality of included studies

Two authors independently extracted data on trial characteristics. Discrepancies were resolved by discussion. Quality of each included study was assessed using the criteria in the Cochrane Reviewers' Handbook (Clarke 2002).

(i) Selection bias (randomisation and allocation concealment)

Method for generating the randomisation sequence was described for each trial. Studies with a quasi-random design were excluded. Concealment of allocation was assessed for each trial, with adequate concealment graded A, unclear B and clearly inadequate concealment C. Studies with clearly inadequate concealment of allocation were excluded. Where the method of allocation concealment was unclear, authors were contacted to provide further details.

(ii) Performance bias (blinding of participants, researchers and outcome assessment)

Quality scores for blinding of the assessment of outcome were assigned to each reported outcome using the following criteria (these scores are displayed in the methods column of the 'Characteristics of included studies' table):

(A) double blind, neither investigator nor participant knew or were likely to guess the allocated treatment;
(B) single blind, either the investigator or the participant knew the allocation. Or the trial may be described as double blind, but side-effects of one or other treatment mean that it is likely that for a significant proportion (more that 20 per cent) of participants the allocation could be correctly identified, or the method for blinding is not described;
(C) no blinding, both investigator and participant knew (or were likely to guess) the allocated treatment, or blinding not mentioned.

(iii) Attrition bias (loss of participants, eg withdrawals, dropouts, protocol deviations)

For completeness of follow up, scores were assigned using the following criteria:

(A) less than three per cent of participants excluded from the analysis;
(B) three per cent to 9.9 per cent of participants excluded from the analysis;
(C) 10 per cent to 19.9 per cent of participants excluded from the analysis.

Excluded: If not possible to enter data based on intention to treat or 20% or more participants were excluded from the analysis of that outcome.

Data extraction and data entry

Two review authors extracted data on outcomes, and discrepancies were resolved through discussion. If agreement was not reached, that item was excluded until further clarification was available from the authors. Data were entered onto the Review Manager software (RevMan 2000) and checked for accuracy. There was no blinding of authorship or results.

Statistical analyses

Statistical analyses were carried out using Review Manager (RevMan 2000). Results were presented as summary relative risk with 95% confidence intervals and, if relevant, as risk difference and number needed to treat to benefit. The I^2 statistic was used

to assess heterogeneity between trials. In the absence of significant heterogeneity, results were pooled using a fixed-effect model. If substantial heterogeneity was detected (I^2 more than 50%), possible causes were explored and subgroup analyses for the main outcomes performed. Heterogeneity that was not explained by subgroup analyses was modelled using random-effects analysis, where appropriate. Possible explanations for the variation, such as study quality and women's characteristics at trial entry, were explored.

Sensitivity analyses
When appropriate, in future updates, we will carry out sensitivity analysis to explore the effect of trial quality based on concealment of allocation, by excluding studies with unclear allocation concealment (rated B).

Subgroup analyses
Data are presented by class of drug. In addition, the following subgroup analyses will be conducted when sufficient data become available:

(1) treatment regimen within each class of drug;
(2) whether severe hypertension alone, or severe hypertension plus proteinuria at trial entry.

DESCRIPTION OF STUDIES

The review includes 24 trials into which 2949 women were recruited. All the trials were small, apart from one large study (1750 women) comparing nimodipine with magnesium sulphate (Nimodipine SG 2003) The women had very high blood pressure; almost all had diastolic blood pressure 110 mmHg or above at trial entry. Nine studies (2292 women) also stated that the women had either 'proteinuria' or 'pre-eclampsia'. as an inclusion criterion. Several trials specified a minimum gestational age for recruitment, and this ranged from 26 weeks to 36 weeks. Others stated that delivery was planned for soon after treatment. One small trial (30 women) (N Ireland 1991) had minimum entry criteria of a blood pressure of 140/90 mmHg but was included as most women were stated to have had labile blood pressure, proteinuria and symptoms. Another study included 150 women for whom first line therapy with methyldopa had not been successful (South Africa 2000).

The antihypertensive drugs evaluated in these trials were hydralazine, calcium channel blockers (nifedipine, nimodipine, nicardipine and isradopine), labetalol, methyldopa, diazoxide, prostacyclin, ketanserin, urapidil, magnesium sulphate, prazosin and isosorbide. There are twelve comparisons in the review. Hydralazine was the most common comparator, being compared with another drug (labetalol, calcium channel blockers, prostacyclin, ketanserin or rapidil) in five comparison. Most drugs were given either intravenously or intramuscularly except nifedipine, nimodipine, isosorbide and prazosin which were given orally. Dosage varied considerably between studies, in both amount and duration of therapy.

The primary hypothesis for the one large study (Nimodipine SG 2003) was to compare the effects on prevention of eclampsia, and this study is also included in the review of magnesium sulphate and other anticonvulsants for prevention of eclampsia (Duley 2003). It is also included here as it met the inclusion criteria for the review, and a secondary hypothesis in the trial was to compare the antihypertensive effects of these two drugs.

For further details *see* 'Characteristics of included studies' table.

Forty one studies were excluded from the review. The reasons for exclusion are described in the 'Characteristics of excluded studies' table. In summary, 10 studies were not a randomised trial, nine did not report clinical data, in seven participants were not women with very high blood pressure, in another seven the intervention was not a comparison of two antihypertensive drugs, two did not report outcome separately for women randomised before and after delivery, and in one more than 20% of women were excluded from the analysis.

METHODOLOGICAL QUALITY

Most of the included trials were small. Only three studies recruited more than 100 women; Nimodipine SG 2003 which recruited 1750 women, South Africa 2000 150 and Iran 2002 126. As discussed above, a wide variety of agents have been compared. Several trials were conducted in countries where English is not widely used, and it is possible that the search strategy may have missed other studies published in languages other than English.

Only five trials (314 women) had adequate concealment of allocation. Most of the others did not give adequate information about how or whether the allocation to treatment group was concealed. For most trials the identity of the allocated drug could only be blinded after trial entry with use of a double placebo. This was stated to have been done in one study (50 women) (Brazil 1994). In another two, the comparison was stated to have been blinded (South Africa 1995; South Africa 1997b). Only short-term outcomes were reported in these trials, but losses to follow up for reported outcomes was low. There is no information about outcome after discharge from hospital for either mother or baby.

RESULTS

This review includes 24 trials, into which 2949 women were recruited.

(1) Labetalol versus hydralazine
Three trials (69 women with outcome data) compared labetalol, with hydralazine. Only one study (20 women) reported data for

persistent high blood pressure (relative risk (RR) 3.00, 95% confidence interval (CI) 0.79 to 11.44). Data were reported for all three trials only for caesarean section and fetal or neonatal death. There are insufficient data for reliable conclusions about the comparative effects of these two agents.

(2) Calcium channel blockers versus hydralazine
Six trials (313 women) compared calcium channel blockers (nifedipine and isradipine) with hydralazine. Persistent high blood pressure was reported by five trials (263 women). Fewer women allocated calcium channel blockers rather than hydralazine had persistent high blood pressure (6% versus 18%; RR 0.33, 95% CI 0.15 to 0.70). For all other outcomes reported, confidence intervals were wide and crossed the line of no difference in effect.

(3) Prostacyclin versus hydralazine
One trial (47 women) compared prostacyclin with hydralazine. For all outcomes reported, confidence intervals were wide and crossed the line of no difference in effect.

(4) Ketanserin versus hydralazine
Four trials (200 women) compared ketanserin with hydralzine. Ketanserin was associated with a substantially higher risk of persistent high blood pressure than hydralazine (27% versus 6%; three trials 180 women; RR 4.79, 95% CI 1.95 to 11.73). However, side-effects were less common with ketanserin than hydralazine (three trials 120 women; RR 0.32, 95% CI 0.19 to 0.53). Hypotension also appeared to be less common with ketanserin rather than hydralazine, although the difference did not achieve statistical significance (two trials 76 women; RR 0.26, 95% CI 0.07 to 1.03). In the one small trial reporting HELLP syndrome, the risk of developing this complication of pre-eclampsia was lower with ketanserin compared to hydralazine (44 women, RR 0.20, 95% CI 0.05 to 0.81).

(5) Urapidil versus hydralazine
Two trials (59 women) compared urapidil with hydralazine. There are insufficient data for reliable conclusions about the comparative effects of these two agents on any outcome reported.

(6) Labetalol versus calcium channel blockers
One trial (60 women) compared labetalol with nicardipine. There are insufficient data for reliable conclusions about the comparative effects of these two agents.

(7) Labetalol versus methyldopa
One trial (74 women) compared labetalol,with methyl dopa. There are insufficient data for reliable conclusions about the comparative effects of these two agents.

(8) Labetalol versus diazoxide
One trial (90 women) compared labetalol with diazoxide. Labetalol was associated with less hypotension than diazoxide, although the confidence intervals are wide and borderline for statistical significance (RR 0.06, 95% CI 0.00 to 0.99). This was reflected in a similar comparative increase in the need for caesarean section in the diazoxide group, which was again borderline for statistical significance (RR 0.43, 95% CI 0.18 to 1.02). Data were insufficient for any reliable conclusions about other outcomes reported.

(9) Nitrates versus magnesium sulphate
One trial (36 women) compared isosorbide with magnesium sulphate. Although there was no clear difference in persistent hypertension (RR 0.14, 95% CI 0.01 to 2.58) isosorbide was associated with a lower risk of caesarean section than magnesium sulphate (RR 0.19, 95% CI 0.07 to 0.53).

(10) Nimodipine versus magnesium sulphate
Two trials (1683 women) compared nimodipine with magnesium sulphate. Both drugs were associated with high levels of persistent high blood pressure (47% versus 65%), although the risk associated with nimodipine was lower than magnesium sulphate (RR 0.84, 95% CI 0.76 to 0.93). The risk of eclampsia was higher with nimodipine compared with magnesium sulphate (RR 2.24, 95% CI 1.06 to 4.73). Nimodipine was associated with a lower risk of respiratory difficulties for the woman (RR 0.28, 95% CI 0.08 to 0.99), fewer side-effects (RR 0.68, 95% CI 0.54 to 0.86) and a lower risk of postpartum haemorrhage (RR 0.41, 95% CI 0.18 to 0.92). There were no clear differences in any other outcomes. Stillbirths and neonatal deaths were not reported.

(11) Nifedipine versus chlorpromazine
One small trial (60 women) compared nifedipine with chlorpromazine. There are insufficient data for reliable conclusions about the comparative effects of these two agents.

(12) Nifedipine versus prazosin
One trial (130 women) compared nifedipine with prazosin. There are insufficient data for reliable conclusions about the comparative effects of these two agents.

Side-effects
Few trials provide data on the specific side-effects related to the different agents. Reported side-effects included:

- for hydralazine: headache, flushing, light head, nausea and palpitations;
- for labetalol: flushing, light head, palpitations and scalp tingling;
- for nifedipine: flushing, nausea, vomiting;
- for urapidil: nausea and tinnitus;
- for magnesium sulphate: flushing.

DISCUSSION

All the drugs included in this review reduce high blood pressure, although magnesium sulphate and ketanserin appear to be substantially less effective than the others. This is unsurprising, as there is

no reason why drugs that are known to reduce blood pressure in people who are not pregnant should not also reduce blood pressure for women who are pregnant. There are additional issues during pregnancy, however, such as avoiding a precipitous drop in blood pressure that might cause problems for the unborn baby, side-effects that are similar to symptoms of worsening pre-eclampsia and so may delay recognition of the need to intervene, not lowering the blood pressure too far as this might also compromise blood supply across the placenta to the baby, and if the drug itself crosses the placenta not causing harm to the baby. There are relatively few data on the comparative effects of the alternative drugs on these other outcomes.

One trial did compare an antihypertensive, the nitrate isosorbide, with placebo for women with very high blood pressure (Mexico 2000). This study was excluded from the review, as our objective was to compare one antihypertensive drug with another. In this study 60 women with diastolic blood pressure 110 mmHg or above after 20 minutes rest were randomised to either sublingual isosorbide or placebo. Both groups had an intravenous infusion of Hartmann solution. Outcome was assessed over one hour, during which time one woman allocated isosorbide had hypotension. At the end of the one hour study mean blood pressure was substantially lower for women allocated isosorbide compared to placebo, there were no episodes of fetal distress or imminent eclampsia, and similar numbers of women in both groups complained of headache. Outcome after one hour is not reported. This study does show that isosorbide lowers blood pressure, but the clinically important question is not whether it is better than placebo, but whether it has any substantive advantages over other drugs in widespread clinical use.

Currently, for women with very high blood pressure during pregnancy there is insufficient evidence to conclude that any one antihypertensive drug is clearly better than another. Problems with interpreting the data in this review include differences in the way persistent hypertension was defined for each study, and differences in the clinical characteristics of the women. These differences are reflected in the wide range of frequency of persistent high blood pressure across studies. For example, in the five categories with hydralazine as a comparator the frequency of persistent high blood pressure amongst women allocated hydralazine ranged from 0% to 20%, whilst amongst women allocated an alternative drug it ranged from 0% to 60%. As few studies had blinding either of the intervention or the assessment of outcomes, there is considerable potential for bias in the assessment of blood pressure. Any effect on a comparative improvement in control of blood pressure would be of far greater clinical importance if it was reflected in comparative improvements in other more substantive outcomes, such as stroke, serious maternal morbidity and perinatal death. With the exception of the large trial comparing nimodipine with magnesium sulphate, all the trials to date have been small, with few outcomes other than control of blood pressure reported. The ongoing trial comparing labetalol with magnesium sulphate (Warren 2004) is also planned to be large. When available, results of this study should shed light on the potential value of labetalol for women with very high blood pressure.

Surprisingly few studies have reported maternal side-effects. Common side-effects included severe headache and nausea, symptoms which are similar to those of imminent eclampsia and so may make clinical management more difficult. There has been concern that rapid release nifedipine capsules may increase the risk of hypotension, and in some countries these have been withdrawn from use. One small trial (64 women) compared nifedipine capsules with slower and longer acting nifedipine tablets (Australia 2002). Outcome was assessed after 90 minutes; similar proportions of women had persistent high blood pressure (11% allocated capsules versus 9% allocated tablets), and there was less hypotension amongst those allocated tablets although this did not achieve statistical significance (3/31 versus 1/33; RR 3.19, 95% CI 0.35 to 29.10).

From the data presented here it is clear that four drugs (magnesium sulphate, high dose diazoxide, ketanserin and nimodipine) have serious disadvantages and so should not be used for women with very high blood pressure during pregnancy as better options are readily available. Over half the women allocated magnesium sulphate had persistent hypertension. So, although it is clearly of value for seizure prophylaxis in women with pre-eclampsia (Duley 2003), magnesium sulphate should not be used for control of very high blood pressure. Diazoxide given as repeated 75 mg bolus injections, seems to be associated with a greater risk of dropping the blood pressure so low that treatment is required to bring it back up again, with an associated increased risk of caesarean section, when compared with labetalol. Smaller doses may not have this disadvantage, and 15 mg bolus injections are being compared with hydralazine in one study due to report results soon (Hennessy 2002). Ketanserin was far more likely to be associated with persistent hypertension than hydralazine. Finally, nimodipine was also associated with high levels of persistent high blood pressure, as well as an increased risk of eclampsia compared to magnesium sulphate.

It would also seem sensible to avoid chlorpromazine. Although only one small trial has compared chlorpromazine with nifedipine, this antipsychotic drug has a complex mode of action and impacts on several organ systems. One well known side-effect is convulsions, which is a serious disadvantage for women with hypertension during pregnancy. That this concern is real, rather than theoretical, is demonstrated by the review of magnesium sulphate versus lytic cocktail (which includes chlorpromazine) for women with eclampsia (Duley 2000). This review shows a clear increase in the risk of further seizures associated with lytic cocktail compared to magnesium sulphate.

An alternative analysis of this topic concluded that the data do not support hydralazine as first line treatment for very high blood pressure in pregnancy (Magee 2003), and recommended future trials compare labetalol with nifedipine. However, that analysis

included quasi-random studies and women with very high blood pressure after delivery. Once the analysis is restricted to include only studies with less potential for bias and women with very high blood pressure during pregnancy or labour, as in our review, the data are insufficient to support the conclusion that labetalol is better than hydralazine.

AUTHORS' CONCLUSIONS

Implications for practice

There is no clear evidence that one antihypertensive is preferable to the others for improving outcome for women with very high blood pressure during pregnancy, and their babies. Until better evidence is available, the best choice of drug for an individual woman probably depends on the experience and familiarity of her clinician with a particular drug, and on what is known about adverse maternal and fetal side-effects. Probably best avoided are magnesium sulphate (although this may be indicated for prevention of eclampsia), high-dose diazoxide, ketanserin, nimodipine and chlorpromazine.

Implications for research

Well designed large trials are needed to make reliable comparisons of the maternal, fetal and neonatal effects of antihypertensives in common clinical practice. Ideally, clinicians should compare an agent they are familiar with in their routine clinical practice with a promising alternative that is available locally, or would be likely to become available if shown to be preferable. Many hospitals around the world continue to use hydralazine as the first choice for women with very high blood pressure. The priority is therefore to compare hydralzine with the most promising alternatives. The evidence from this review suggests that nifedipine would be a good choice for the comparator. Labetalol would be an alternative choice.

Future trials should measure outcomes that are important to women and their babies, rather than attempting to document relatively subtle differences in the effects on blood pressure. These outcomes should include persistent high blood pressure, need for additional antihypertensive drugs, further episodes of severe hypertension, low blood pressure, side-effects, severe maternal morbidity (such as stroke, eclampsia, renal failure, and coagulopathy) mode of delivery, length of stay in hospital, mortality for the baby, and admission and length of stay in a special/intensive care nursery. There should also be long-term follow up to assess possible effects on the woman's risk of cardiovascular problems after discharge from hospital, and on growth and development of the child. This is relevant not only because these drugs may cross the placenta, but also because too rapid lowering of blood pressure with a placenta that has marginal functional reserve could lead to ischaemic brain injury and long-term neurodevelopment problems. Alongside data from randomised trials, mechanisms need to be developed to monitor possible rare adverse events related to in utero exposure to antihypertensive agents.

Interpretation of the results of future studies would be made easier and more clinically meaningful by the use of similar definitions for key outcomes, such as persistent high blood pressure, and hypotension. Studies that recruit women both before and after delivery should report outcome data separately for these two groups of women. Outcome should also be reported separately for women with and without proteinuria at trial entry.

Once better information is available about the relative merits and hazards of agents already in widespread use, it will become possible to compare new drugs with the best of the traditional agents in well designed randomised trials.

POTENTIAL CONFLICT OF INTEREST

None known.

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Australia 1986**
Methods	Randomly allocated, no further information. CFU - A, blinding - C.
Participants	90 women with DBP > 105 mmHg after sedation with either phenobarbitone 200 mg or diazepam 10 mg 6 hourly. Delivery planned for soon after treatment.
Interventions	Labetalol: 200 mg in 200 ml 5% dextrose iv at 0.5 mg/kg/hr to a maximum of 3 mg/kg/hr, to keep DBP at 85-90 mmHg. Continued until 24 hrs after delivery. Diazoxide: 75 mg iv, repeated every 30 min until BP controlled. Continued until 24 hrs after delivery.
Outcomes	Woman: persistent high BP, low BP requiring treatment, caesarean section. Baby: death, respiratory distress syndrome, hypoglycaemia, hypothermia.
Notes	No data on which women received phenobarbitone and which received diazepam. Funding: Glaxo (makers of labetalol).
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**Brazil 1992**
Methods	'Randomly assigned' by drawing an envelope from a box, each containing active treatment and placebo. CFU - A, blinding - A.
Participants	37 primigravid women over 28 weeks' gestation with DBP 110 mmHg or more after 60 min rest, and proteinuria > 300 mg in 24 hours. Singleton pregnancy and a live fetus. Excluded: antihypertensive drug before trial entry, medical surgical or obstetric problem.
Interventions	Nifedipine: 10 mg orally. Hydralazine: 5 mg iv.
Outcomes	Woman: need for additional treatment. Baby: stillbirth.
Notes	
Allocation concealment	B – Unclear

Study	**Brazil 1994**
Methods	Sealed envelopes.
Participants	50 women with DBP > 110 mmHg after 60 min rest and > 28 weeks' gestation.
Interventions	Nifedipine: 10 mg sl and iv placebo. Hydralazine: 20 mg iv and sl placebo.
Outcomes	Woman: time to lower blood pressure, side-effects (flushing, nausea, palpitations). Baby: stillbirth, neonatal death.
Notes	
Allocation concealment	B – Unclear

Study	**England 1982**
Methods	'Randomised', no further information. Interim report on ongoing study. 2 women not delivered at time of reporting. CFU - A, blinding - C.
Participants	74 women with BP 170/110 mmHg, or above, and < 36 weeks' gestation. Excluded: multiple pregnancy, diabetes, rhesus isoimmunisation.
Interventions	Labetalol: 100 mg x 4/day. Methyldopa: 250 mg x 4/day. Oral or iv hydralzine in both groups if BP not controlled.
Outcomes	Woman: need for other drugs, side-effects, caesarean section. Baby: stillbirth, neonatal death, SCBU.
Notes	Interim analysis of an ongoing trial. Final report not published.
Allocation concealment	B – Unclear

Study	**Germany 1998**
Methods	Computer generated randomisation list. CFU - A, blinding C.
Participants	26 women with BP 160/110 mmHg after 3 hr bed rest, 1+ of proteinuria, oedema or hyperreflexia. Gestation 26-38 weeks. No iv antihypertensive before entry.
Interventions	Urapidil: 6.25 mg iv repeated after 5 min if BP not decreased. Then 2-4 mg/hr until delivery. Hydralazine: iv, mean 0.13 mg/kg/4 hrs.
Outcomes	Woman: eclampsia, side-effects, caesarean section. Baby: stillbirth, neonatal death.
Notes	Both groups of women also received iv magnesium ascorbate (4 g load and 1-2 g/hr maintenance.

	31 women reported to have been recruited in one German paper, no clinical data in that report.
Allocation concealment	B – Unclear

Study	**Iran 2002**
Methods	Consecutively numbered sealed envelopes. Randomised in blocks of 4.
Participants	126 women with BP at least 160/110 mmHg, and criteria for severe PE as defined by American College of Obstetricians and Gynecologists.
Interventions	Nifedipine: 8 mg sl, repeated until DBP 90-100 mmHg. Hydralazine: 5-10 mg iv, repeated until DBP 90-100 mmHg. Both: MgSO4, 4 g bolus IV, then 1-2 g/hr for 24 hr.
Outcomes	Woman: persistent high BP (not controlled after 20 minutes), further hypertensive crises, adverse effects. Baby: Apgar scores.
Notes	
Allocation concealment	A – Adequate

Study	**Mexico 1989**
Methods	'Randomised', no further information. 5 women excluded from chlorpromazine group because they received another antihypertensive. CFU - B, blinding C.
Participants	60 women with severe PE or eclampsia. Excluded if cardiopathy, diabetes, isoimmunisation, twin pregnancy, or antihypertensive in 48 hr before trial entry.
Interventions	Chlorpromazine: 12.5 mg iv and 12.5 mg im. 12.5 mg iv repeated every 30 min, to a total of 50 mg, until BP controlled or an additional antihypertensive. Nifedipine: 10 mg sl, repeated every 30 min to a max of 4 doses until BP controlled or an additional antihypertensive.
Outcomes	Woman: eclampsia, additional antihypertensive, caesarean section. Baby: gestation at delivery (mean).
Notes	All women received phenytoin.
Allocation concealment	B – Unclear

Study	**Mexico 1993**
Methods	Consecutively numbered sealed opaque envelopes.
Participants	27 women at 28-42 weeks with severe PE (BP 150 mmHg or more, 2/3+ protein), and one or more of epigastric pain, convulsions, headache. No chronic hypertension, or renal or cardiac disease.
Interventions	Hydralazine: 5 mg iv. Repeated every 20 min if DBP 110 mmHg or more, max x 3. If BP not controlled, chlorpromazine 12.5 mg iv plus 12.5 mg im x 2. Nifedipine: 10 mg sl. Repeated every 20 min if DBP 110 mmHg or more, max x 3. If BP not controlled, chlorpromazine 12.5 mg iv plus 12.5 mg im x2.
Outcomes	Woman: control of blood pressure, days in hospital (mean). Baby: Apgar at 1 and 5 min (mean).
Notes	All women had a diazepam infusion for 24 hr after delivery. Data not included in analysis. Mean hospital stay (days): for nifedipine n = 13, 5.5 SD [2.1] and for hydralazine n = 14, 6.0 [2.2].
Allocation concealment	A – Adequate

Study	**Mexico 1998**
Methods	Randomised, no further information.

Characteristics of included studies (*Continued*)

Participants	36 women > 36 weeks' gestation with severe PE (DBP > 110 mmHg + proteinuria). Excluded: diabetes, essential hypertension, history of drug or alcohol abuse, antihypertensive drugs in the last week.
Interventions	Isosorbide: 1.25 mg by sl aerosol. If BP dropped by < 15%, second dose 10 min later. MgSO4: infusion of 4 g in 1 hr, then 1 g/hr for 5 hrs.
Outcomes	Woman: need for additional antihypertensive, caesarean section, eclampsia. Baby: none.
Notes	
Allocation concealment	B – Unclear

Study	**N Ireland 1991**
Methods	Sequentially numbered sealed envelopes. CFU - A, blinding - C.
Participants	30 women with singleton pregnancy before labour, no previous antihypertensive. BP 140/90 or above, clinical decision to treat - usually because of labile BP, proteinuria and symptoms.
Interventions	Labetalol: 100 mg iv. Hydralazine: 10 mg iv.
Outcomes	Woman: side-effects (flushing, light head, nausea, scalp tingling). Baby: death.
Notes	Long study to delivery interval (range 0.1-11 weeks).
Allocation concealment	A – Adequate

Study	**Netherlands 1999**
Methods	Open randomised multicentre trial with 4 centres, randomisation by telephone call to answering service. CFU - A, blinding - C.
Participants	44 women at 26-32 weeks' gestation, DBP 110 mmHg or above. All women given plasma volume expansion at trial entry, 27 out of 44 monitored with a pulmonary artery catheter (12 ketanserin, 15 hydralazine). MgSO4 for women with impending eclampsia (8 ketanserin, 11 hydralazine).
Interventions	Ketanserin: 5 mg iv bolus then 4 mg/hr. Increased every 20 min until target BP. Max 10 mg/hr. Further 5 mg with every 2 mg/hr increment. Hydralazine: 1 mg/hr iv, hourly increments of 1 mg/hr until target BP. Max 10 mg/hr. Both groups, if BP not controlled given other study drug.
Outcomes	Woman: death, eclampsia, pulmonary oedema, HELLP, DIC, abruption, additional drugs (crossover, given other study drug), caesarean section. Baby: death (babies > 28 weeks' gestation only)
Notes	19 women in each group had antenatal steroids. Funding: Janssen-Cilag (manufacture ketanserin).
Allocation concealment	A – Adequate

Study	**Netherlands 2003**
Methods	'Randomised' no further information. Published as an abstract only.
Participants	56 women beyond 32 weeks' gestation with DBP 110 mmHg or above.
Interventions	Ketanserin: no information about dose. Hydralazine: no information about dose.
Outcomes	Woman: vaginal delivery, composite outcome of maternal morbidity (eclampsia, renal failure, pulmonary oedema, and/or HELLP).

	Baby: none reported.
Notes	Unpublished data provided by the authors: hypotension (defined as DBP < 75 mmHg), failure to reach target blood pressure (DBP 85-105 mmHg).
Allocation concealment	B – Unclear

Study	**Nimodipine SG 2003**
Methods	Randomisation stratified by centre, blocks of 6. Sealed opaque envelopes. Recruitment 1995-2000. 100 women (6%) excluded from analysis: 99 did not get allocated treatment, 1 withdrawn. Recruitment stopped early following interim analysis. CFU - B, blinding - C.
Participants	1750 women with PE, planned delivery and no previous MgSO4. BP >/= 140/90 and 1+ proteinuria plus one of: headache, clonus, visual disturbance, epigastric pain, oliguria, pulmonary oedema, raised liver enzymes, haemolysis, oligohydramnios, IUGR.
Interventions	Nimodipine: 60 mg 4 hrly, orally MgSO4: according to local protocol. Either 4 g iv then 1 g/hr, or 6 g iv then 2 g/hr. All continued either for 24 hr total, or until 24 hr after delivery. Serum monitoring not required.
Outcomes	Woman: eclampsia, stroke, coagulopathy, respiratory problems, cardiac failure, antihypertensive drugs, side-effects, abruption, caesarean section, PPH. Baby: RDS, hypotonia, intubation, hypotension.
Notes	Recruitment at 14 hospitals in 8 countries. Data for stillbirths and neonatal deaths not reported. This data was requested from the investigators, but has been lost.
Allocation concealment	B – Unclear

Study	**South Africa 1987**
Methods	Randomly allocated, no other information. CFU - A, blinding - C.
Participants	20 women with DBP 110 mmHg or above, not settled after 2 hrs bed rest and 200 mg phenobarbitone. At least 32 weeks' gestation, no previous hypotensive therapy, not in labour and no imminent eclampsia. No PMH of asthma, diabetes or heart disease.
Interventions	Labetalol: 200 mg in 200 ml 5% dextrose at 20 mg/hr. Increased every 20 min by 20 mg/hr until DBP 90-100 mmHg, or maximum dose of 160 mg/hr. Then continued for 1 hr. Hydralazine: 25 mg in 200 ml saline at 3.7 mg/hr. Increased every 20 min by 3.7 mg/hr until DBP 90-100 mmHg, or maximum dose of 15 mg/hr. Then continued for 1 hr.
Outcomes	Woman: failure of BP control, eclampsia, caesarean section. Baby: death, hypoglycaemia, mean Apgar scores.
Notes	
Allocation concealment	B – Unclear

Study	**South Africa 1989**
Methods	Random number table, no further information. CFU - A, blinding - C.
Participants	33 primigravid women; no hypertension, renal disease, or other medical problems; no antihypertensive therapy; DBP 110 mmHg or more for 2 hours; and at least 28 weeks' gestation. Not needing immediate delivery and no fetal distress.
Interventions	Nifedipine: 10 mg oral. Repeated after 30 minutes if no response. Hydralazine: 6.25 mg in 10 ml water IV over 5-10 minutes. Repeated after 30 minutes if no response.
Outcomes	Woman: need for second dose, low BP causing fetal distress, side-effects (headache, flushing nausea, retrosternal pain). Baby: death.
Notes	
Allocation concealment	B – Unclear

Characteristics of included studies (*Continued*)

Study	**South Africa 1992**
Methods	Random number tables, no further information. CFU - A, blinding - C.
Participants	47 women admitted to labour ward with DBP > 110 mmHg, which did not settle after phenobarbitone and bed rest. At least 1+ proteinurea, and above 33 weeks' gestation. Excluded if imminent eclampsia or requiring immediate delivery. All had a central venous line.
Interventions	Prostacyclin: 0.5 ng/kg/min IV increased at increments of 1.5 ng/kg/min to maximum of 10 ng/kg/min. Continued for 24 hr after delivery. Hydralazine: 0.5 mg/kg/min IV increased every 15 min to a maximum of 1.5 mg/kg/min. Continued for 24 hr after delivery.
Outcomes	Woman: caesarean section, need for additional antihypertensive, side-effects (headache, nausea and vomiting). Baby: death, ventilation.
Notes	Funding: Wellcome, MRC South Africa.
Allocation concealment	B – Unclear

Study	**South Africa 1995**
Methods	Sealed envelopes, no other information. Drug solutions prepared by someone not involved in clinical care, and blinded. CFU - A, blinding - A.
Participants	20 women at > 28 weeks' gestation; DBP > 110 mmHg after 5 minutes rest, or, 100 mmHg or above on 2 occasions 30 minutes apart. Excluded if fetal distress, antihypertensive therapy during previous 12 hours, or epidural anaesthesia.
Interventions	Hydralazine: 5 mg in 2 ml iv over 2 min. Repeated after 20 min if BP not below 100 mmHg. Ketanserin: 10 mg in 2 ml iv over 2 min. Repeated after 20 min if BP not below 100 mmHg.
Outcomes	Woman: need for more than one dose of drug, low BP causing fetal distress, caesarean section, eclampsia. Baby: none reported.
Notes	All women reached target blood pressure. In the hydralazine group this one achieved with a single dose for all women, 6 women in the ketanserin group needed additional doses.
Allocation concealment	B – Unclear

Study	**South Africa 1997**
Methods	Sealed sequentially numbered envelopes. 2:1 randomisation. 4 women excluded, but data on most clinical outcomes reported. CFU - A, blinding - C.
Participants	33 women with MAP > 125 mmHg x 3 at least 5 min apart in 30 min period. Excluded if antihypertensive other than single dose of methyl dopa or 1.25 mg hydralazine.
Interventions	Urapidil: 12.5 mg iv repeated every 3 min in bolus of 25 mg if MAP > 120 mmHg. Max dose of 400 mg. Hydralazine: 6.25 iv over 15 min, repeated every 30 min to maintain MAP > 120 mmHg.
Outcomes	Woman: hypotension, side-effects (headache, palpitations, nausea, tinnitus), caesarean section, treatment failure. Baby: death, Apgar (mean), cord pH (mean).
Notes	
Allocation concealment	A – Adequate

Study	**South Africa 1997a**
Methods	Women randomly allocated using a computer generated randomisation sheet. No information about concealment of allocation. CFU - A, blinding - C.

Characteristics of included studies (*Continued*)

Participants	40 primigravid women with severe hypertension (DBP 110 mmHg or more) and no signs or symptoms of imminent eclampsia. All had 200 mg phenobarbitone 2 hours before trial entry.
Interventions	Isradipine: iv infusion of 0.15 mcg/kg/min, increased by 0.0025 mcg/kg every 15 min until DBP < 95 mmHg. Hydralazine: 6.25 mg iv over 10 min, repeated once if DBP still > 95 mmHg.
Outcomes	Woman: persistent high BP, hypotension. Baby: fetal heart rate deceleration, stillbirth, neonatal death.
Notes	
Allocation concealment	B – Unclear

Study	**South Africa 1997b**
Methods	Sealed, numbered, opaque envelopes. Nursing sister not involved in clinical care then made up the allocated solution (4 ml). 8 women excluded (9%) as delivered without receiving antihypertensive therapy. CFU - B, blinding - B.
Participants	88 women at least 28 weeks' gestation, DBP > 110 mmHg or DBP > 100 mmHg for 30 minutes.
Interventions	Ketanserin: 500 ml crystalloid iv over 15 min, then bolus 10 mg ketanserin in 4 ml iv. Bolus repeated every 20 min, until DBP 90 mmHg, to a maximum of 4 doses. Hydralazine: 500 ml crystalloid iv over 15 min, then bolus 5 mg hydralazine in 4 ml iv. Bolus repeated every 20 min, until DBP 90 mmHg, to a maximum of 4 doses.
Outcomes	Woman: death, persistent high blood pressure (DBP > 90 mmHg after 4 bolus injections), delivery for fetal distress, caesarean section. Baby: death.
Notes	Trial stopped by 'monitoring committee', reason not stated.
Allocation concealment	B – Unclear

Study	**South Africa 2000**
Methods	Consecutive numbered sealed opaque envelopes. 5 women excluded; 2 postpartum, 1 delivered before treatment started, 1 randomised twice, 1 wrongly identified. CFU - B, blinding - C.
Participants	150 women with severe early onset PE, and BP not controlled by methyldopa 2 g/day. Excluded: planned termination of pregnancy, onset of PE after 34 weeks, postpartum, already on either agent.
Interventions	Prazosin: 1 mg x 3/day, to max 21 mg/day Nifedipine: 10 mg x3/day, to max 60 mg/day. If BP still not controlled, crossover.
Outcomes	Woman: death, eclampsia, HELLP, renal failure, pulmonary oedema, ICU admission, abruption, MgSO4 prophylaxis, caesarean section. Baby: stillbirth, hyaline membrane disease, septicaemia, SCBU admission.
Notes	
Allocation concealment	A – Adequate

Study	**Tunisia 2002**
Methods	Computer generated randomisation. Allocation concealment in sealed sequentially numbered opaque envelopes. CFU - A, blinding - C.
Participants	60 women aged > 18 years with severe hypertension (SBP 170 mmHg or more, or DBP 110 mmHg or more x 2 30 min apart) after 24 weeks' gestation. All women had MgSO4 for seizure prophylaxis before trial entry. Excluded: contraindication to beta blockers or calcium channel blockers, or either study drug given in the last 4 hours.

Characteristics of included studies (*Continued*)

Interventions	Nicardipine: 10 mg over 5 min, then if needed 12.5 mg at 5 min intervals. When 20% reduction in BP, infusion at 1-3 mg/hr for 1 hour. Labetalol: 1 mg/kg over 1 min, then 1.5 mg/kg after 5 min if BP not lowered. If BP not reduced by 20% in next 5 min, treatment failure. If BP does drop by 20%, infusion of 100-150 mg over next hour. At end of study period - treatment at discretion of clinicians for both groups.
Outcomes	Woman (assessed only after one hour): control of BP, hypotension, side-effects. Baby: none.
Notes	
Allocation concealment	A – Adequate

Study	**Turkey 1996**
Methods	Randomised, no further information. Drugs identically packaged and infusion rates identical. CFU - A, blinding - A.
Participants	33 women with severe PE.
Interventions	Nimodipine: 100 ml crystalloid, then infusion of 30 mg/kg/hr. MgSO4: 6 g iv in 100 ml crystalloid, then infusion of 2 g/hr.
Outcomes	Woman: eclampsia (during therapy only), caesarean section. Baby: none.
Notes	Available as abstract only.
Allocation concealment	B – Unclear

Study	**USA 1987**
Methods	Random numbers, 2:1 allocation. No information about concealment of allocation. CFU - A, blinding - C.
Participants	19 women with hypertension during pregnancy. Also, 41 women with postpartum hypertension, but these are excluded from this review.
Interventions	Labetalol: Either, 20 mg iv then 10-50 mg every 10 min until DBP 100 mmHg or less, or 20 mg iv then repeat doses of 20 mg, 40 mg, 80 mg, 80 mg every 10 min to a maximum of 300 mg or until DBP 100 mgHg or less. Hydralazine: 5 mg iv every 10 min until DBP 100 mmHg or less.
Outcomes	Woman: caesarean section, no others reported separately from the postpartum women. Baby: Apgar scores, respiratory distress syndrome, hypoglycaemia, hypothermia.
Notes	Women with postpartum hypertension excluded from this review.
Allocation concealment	B – Unclear

BP: blood pressure
CFU: completeness of follow up
DBP: diastolic blood pressure
DIC: disseminatied intravascular coagulation
HELLP: haemolysis, elevated liver enzymes, lowered platelets
hr: hours
ICU: intensive care unit
im: intramuscular
IUGR: intrauterine growth restriction
iv: intravenous
MAP: mean arterial pressure
MRC: Medical Research Council
MgSO4: magnesium sulphate
min: minutes
PE: pre-eclampsia

PPH: postpartum haemorrhage
PMH: past medical history
RDS: respiratory distress syndrome
SCBU: special care baby unit
SD: standard deviation
SBP: systolic blood pressure
sl: sublingual

Characteristics of excluded studies

Study	Reason for exclusion
Argentina 1986	No data on clinical outcomes. Available as abstract only. Study design: "randomly divided". Participants: 60 women. Interventions: comparison of atenolol with methyl dopa.
Australia 2002	Comparison of different ways of giving nifedipine. Study design: 'randomised' double blind. Capsules marked 'A' and 'B'. Participants: 64 women over 20 weeks' gestation, with SBP 170 mmHg or above and/or DBP 110 mmHg or above. Interventions: rapid release capsules nifedipine versus slow release tablets.
Bangladesh 2002	Dosage comparison. Probably not a randomised trial. Study design: 'divided' no further information. Participants: 77 women with eclampsia and severe hypertension. Interventions: 5 mg hydralazine iv followed by 2 mg at 15 min intervals versus infusion of 20 mg hydralazine in 200 ml saline at 10 drops/min, increasing at 5 drops/min at 15 min intervals. Outcomes: time to BP control, hypertensive crisis, total dose of hydralazine.
Brazil 1984	Not women with very high blood pressure. Study design: 'randomly' divided into two halves. Participants: 100 women with severe chronic hypertension, with or without super imposed pre-eclampsia. Interventions: comparison of pindolol with no antihypertensive drug.
Brazil 1988	No data on clinical outcomes. Study design: double-blind comparison. Participants: 13 women. Intervention: single dose of oral nifedipine versus single bolus IV hydralazine.
Brazil 1988a	No data on clinical outcomes. Study design: random number tables. Participants: 16 women with DBP above 120 mmHg after 120 minutes rest. Interventions: single dose hydralazine 5-10 mg iv versus single dose oral nifedipine 5-10 mg.
China 2000	Intervention to reduce postpartum blood loss. Study design: 'randomly divided'. Participants: 64 women with pregnancy-induced hypertension. Interventions: comparison of nifedipine with placebo during labour. Outcomes: postpartum blood loss.
Egypt 1989	Intervention was aimed at cervical ripening. Study design: 'allocated at random', no further information.

	Participants: 27 women at 34-40 weeks' gestation with severe pre-eclampsia (BP > 160/110 mmHg with proteinuria) who were receiving prostaglandin A1 infusion. Interventions: three-arm comparison of different timings of prostaglandin E2 gel in the cervical canal.
Egypt 1988	Not women with very high blood pressure. Available as abstract only. Study design: randomly allocated, no further information. Participants: 50 primigravid women with PE and 20 multigravid women with chronic hypertension. Interventions: three-arm comparison of bromocriptine with methyl dopa with placebo.
Egypt 1992	Intervention not an antihypertensive drug. Study design: 'randomly allocated', no further information. Participants: 30 women with severe pre-eclampsia. Interventions: comparison of prostaglandin A1 infusion with placebo.
France 1986	No data on clinical outcomes. Available as abstract only. Study design: 'randomised', no further information. Participants: 35 women with DBP > 105 mmHg after 20 weeks' gestation, and in hospital. Interventions: comparison of clonidine and labetalol.
Ghana 1995	Quasi-random study, allocation by alternate odd and even numbers. Participants: 104 women. Interventions: comparison of nifedipine with hydralazine.
India 1963	Quasi-random study, alternate allocation. Study included women without very high BP. Participants: women with 'mild to severe toxaemia'. Interventions: comparison of guanethidine with placebo.
India 2001	Unlikely to be a randomised trial. Study design: 'cases grouped as A and B', no further information. Participants: 120 women with eclampsia. Interventions: comparison of nifedipine plus magnesium sulphate with sedation plus magnesium sulphate. Outcomes: maternal death, mode of delivery, stillbirth.
Iran 1994	Available as abstract only. No clinical outcomes reported. Participants: 30 women. Interventions: comparison of nifedipine with hydralazine.
Israel 1991	Not a randomised trial, women allocated to treatment group according to week of the month. Participants: 54 women. Interventions: comparison of nifedipine with hydralazine.
Israel 1999	Not women with very high blood pressure, and no clinically useful outcomes reported. Study design: randomised trial. Participants: women with DBP 90 mmHg.
Italy 2004	Intervention not an antihypertensive drug. Study design: randomly allocated, using a computer generated randomisation list in blocks of 8. Participants: 23 women at 24-33 weeks' gestation with pre-eclampsia. Interventions: comparison of single antithrombin infusion with antithrombin infusion plus 5 days maintenance.
Jamaica 1999	Quasi-random study. Study design: "selecting numbers blindly from an envelope by assigning odd numbers to hydralazine and even to isradipine". Participants: 39 women with severe pre-eclampsia. Interventions: comparison of isradipine with hydralazine.

Japan 1999	Not a randomised trial - 'patients divided according to doctors choice'. Participants: 20 women with severe pre-eclampsia. Interventions: comparison of long-term epidural with bed rest plus diet plus antihypertensive drugs. Outcomes: caesarean section, days to delivery.
Japan 2000	Intervention not an antihypertensive drug. Study design: telephone randomisation, using minimisation. Participants: 133 women with severe PE at 24-35 weeks' gestation. Interventions: comparison of antithrombin with placebo.
Japan 2002	Not a randomised trial. Study design: women grouped according to length of treatment with nicardipine. Participants: 50 women with severe pre-eclampsia.
Japan 2003	Interventions were not antihypertensive drugs. Study design: telephone randomisation, with recruitment 1988-1990. Participants: women with PE at 24-36 weeks' gestation. Interventions: comparison of antithrombin concentrate plus heparin with heparin alone. Outcomes: caesarean section, blood loss > 500 ml, mean gestation at birth, baby death, bleeding disorder for the neonate.
Malaysia 1996	Quasi-random study. Study design: treatment allocation by odd and even numbers on identity cards. Participants: 200 women with DBP above 120 mmHg and over 28 weeks' gestation. Interventions: comparison of nifedipine and hydralazine.
Mexico 1967	Not clearly a randomised trial - 'test made in two groups with a comparable degree of toxaemia'. Abstract only available. Participants: women with toxaemia. Interventions: comparison of frusemide with chlorothiazide plus sedation plus potassium. Outcomes: mean glomerular filtration rate.
Mexico 2000	Not a comparison of one antihypertensive drug with another. Study design: "assigned randomly". Participants: women with severe PE after 28 weeks with DBP 110 mmHg or more after 20 min rest. Interventions: comparison of isosorbide with placebo. Normal clinical care after 1 hour.
Mexico 2004	Comparison of antihypertensive drugs with epidural. Study design: randomised, no further information. Participants: 24 women at > 29 weeks' gestation with pre-eclampsia, platelets above 70,000 and no other contraindication to an epidural. Interventions: comparison of usual care (plasma volume expansion, hydralazine, phenytoin, dexamethasone, dypiridamol) with epidural plus plasma volume expansion. Outcomes: haemodynamic measures.
Netherlands 2002	Intervention was not an antihypertensive drug. Study design: randomised, double blind, no further information. Participants: 38 women with early onset severe pre-eclampsia. Interventions: comparison of N-acetylcysteine with placebo. Outcomes: eclampsia.
New Zealand 1986	Clinical data not reported for > 20% of participants. Abstract only available. Study design: 'randomised' no further information. Participants: 117 women with severe hypertension, with or without proteinuria.

	Interventions: comparison of atenolol with pindolol.
New Zealand 1992	No clinical outcomes reported or available from authors. Participants: 24 women. Interventions: comparison of nifedipine with hydralazine.
Philipines 2000	Not women with very high blood pressure. Abstract only available. Study design: 'randomly assigned', no further information. Participants: 16 women with pre-eclampsia. Interventions: comparison of nitroglycerin patches with placebo. Outcomes: no clinical outcomes reported.
Scotland 1983	No clinical outcomes reported. Participants: 21 women. Interventions: comparison of labetalol with hydralazine.
Singapore 1971	Quasi-random study. Data for a case series of treatment with dihydrzinophthalazine included, not possible to separate. Study design: women allocated "in strict rotation". Participants: 285 women with BP 180/110 mmHg or above, or 160/100 mmHg and above with proteinuria. Interventions: comparison of protoveratrine with guanethidine with dihydrzinophthalazine.
South Africa 1982	Women with antepartum (6 women) and postpartum (6 women) hypertension not reported separately. Participants: 12 women with hypertension, either before delivery or immediately postpartum. Intervention: comparison of labetalol with hydralazine.
South Africa 1984	Dose comparisons. Probably not a randomised trial. Study design: women 'divided' into two groups. Participants: 21 women > 29 weeks' gestation with DBP 110 mmHg or more after 2 hours rest. Interventions: comparison of 60 mg iv diazoxide every 10 min with 150 mg iv every 10 min. Outcomes: total dose of diazoxide, hypotension.
South Africa 1993	40 women randomised. Numerators and denominators only reported for a subset of 34 women for whom an analysis of arrhythmias is reported. Denominators are not given for the clinical outcomes, and unclear whether they refer to the full 40 women or the subset of 34. Authors contacted, no further data available. Study design: 'randomly allocated' no further information. Intervention: comparison of labetalol with hydralazine.
South Africa 2002	Dose finding study. Some women did not meet eligibility criteria. Study design: randomised by consecutively numbered sealed envelopes. Computer generated random numbers in blocks of 20. Participants: 30 women with DBP 105 mmHg or more, x 2 10 min apart, or 100 mmHg or more for 30 min. Intervention: comparison of 10 mg ketanserin every 10 min with every 20 min.
Spain 1988	Available as abstract only. No clinical data. Study design: described as "double blind controlled trial", no other information about concealment of allocation. Numbers allocated to each intervention not reported. Interventions: comparison of hydralazine plus methyl dopa with labetalol.
Sweden 1993	Two studies, both quasi-random and allocated according to year of birth and both comparing labetalol with hydralazine. (a) 97 women, but outcome only reported for 22 women; (b) 20 women, three of whom were also in study (a).
USA 1999	Data not presented separately for women randomised before and after delivery. Participants: 50 women with severe PE, or with chronic hypertension and superimposed PE.

Characteristics of excluded studies (*Continued*)

	Interventions: comparison of nifedipine with labetalol.
Venezuela 2001	Women did not have very high blood pressure. Available as abstract only. Study design: randomly assigned, no further information. Participants: 30 women with pre-eclampsia. Interventions: comparison of nitroglycerin patches with placebo.

BP: blood pressure
DBP: diastolic blood pressure
IV: intravenous
min: minutes
PE: pre-eclampsia
SBP: systolic blood pressure

Characteristics of ongoing studies

Study	**Hennessy 2002**
Trial name or title	Diazoxide vs hydralazine for acute treatment of very high BP in pregnancy.
Participants	Pregnant women with BP greater than 170/110 or elevated BP > 140/90 with neurological signs (sustained clonus or severe headache) suggesting imminent eclampsia. Aiming for 64 women in each group based on 20% difference in caesarean section within 24 hrs.
Interventions	Diazoxide undiluted IV in mini-boluses of 15 mg every 2-3 mins versus hydralazine 5 mg IV every 20 mins for 3 doses followed if necessary by an infusion - until BP achieves a predetermined level.
Outcomes	Adequate lowering of BP, caesarean section within 24 hrs, fetal vs maternal indication for delivery, use of additional medication. use of additional IV therapy after initial course, side-effects.
Starting date	Recruitment 2000-2005. 124 women recruited.
Contact information	Dr Annemarie Hennessy Department of Renal Medicine, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia. ahennese@renicu.rpa.cs.nsw.gov.au
Notes	All women are given a simultaneous IV infusion of magnesium sulphate.

Study	**Warren 2004**
Trial name or title	Labetolol versus magnesium sulfate for the prevention of eclampsia trial (LAMPET).
Participants	Women with pre-eclampsia likely to deliver soon.
Interventions	MgSO4 IV versus labetolol 20 mg IV then 200 mg every 6 hours orally.
Outcomes	Eclampsia, blood pressure control, side-effects, complications, neonatal outcome.
Starting date	2004.
Contact information	Michael Belfort, University of Utah School of Medicine, Salt Lake City, Utah.
Notes	

BP: blood pressure
hrs: hours
IV: intravenous
MgSO4: magnesium sulphate
mins: minutes
vs: versus

ANALYSES

Comparison 01. Labetalol versus hydralazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Eclampsia	1	20	Relative Risk (Fixed) 95% CI	Not estimable
02 Persistent high blood pressure	1	20	Relative Risk (Fixed) 95% CI	3.00 [0.79, 11.44]
03 Hypotension	2	50	Relative Risk (Fixed) 95% CI	Not estimable
04 Caesarean section	3	69	Relative Risk (Random) 95% CI	0.71 [0.40, 1.24]
05 Side-effects for the woman	2	50	Relative Risk (Fixed) 95% CI	0.52 [0.24, 1.11]
06 Fetal heart rate decelerations	3	69	Relative Risk (Random) 95% CI	0.84 [0.01, 54.78]
07 Fetal or neonatal deaths	3	69	Relative Risk (Fixed) 95% CI	0.50 [0.05, 4.94]
08 Apgar < 7 at 5 minutes	1	19	Relative Risk (Fixed) 95% CI	0.10 [0.01, 1.81]
09 Respiratory distress syndrome	1	19	Relative Risk (Fixed) 95% CI	0.69 [0.15, 3.12]
10 Neonatal hypoglycaemia	2	39	Relative Risk (Fixed) 95% CI	1.14 [0.19, 6.94]

Comparison 02. Calcium channel blockers versus hydralazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Persistent high blood pressure	5	263	Relative Risk (Fixed) 95% CI	0.33 [0.15, 0.70]
02 Low blood pressure for the woman	3	199	Relative Risk (Fixed) 95% CI	2.83 [0.12, 64.89]
03 Further episode/s of very high blood pressure	2	163	Relative Risk (Fixed) 95% CI	0.85 [0.65, 1.11]
04 Side-effects for the woman	4	236	Relative Risk (Fixed) 95% CI	0.79 [0.50, 1.24]
05 Side-effects for the woman (specific effects)			Relative Risk (Fixed) 95% CI	Subtotals only
06 Fetal heart rate decelerations	3	203	Relative Risk (Fixed) 95% CI	0.40 [0.09, 1.83]
07 Caesarean section	1	37	Relative Risk (Fixed) 95% CI	0.85 [0.56, 1.29]
08 Fetal or neonatal death	4	161	Relative Risk (Fixed) 95% CI	1.36 [0.42, 4.41]

Comparison 03. Prostacyclin versus hydralazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Persistent high blood pressure	1	47	Relative Risk (Fixed) 95% CI	0.23 [0.01, 4.47]
02 Caesarean section	1	47	Relative Risk (Fixed) 95% CI	0.74 [0.50, 1.10]
03 Side-effects for the woman	1	47	Relative Risk (Fixed) 95% CI	1.14 [0.08, 17.11]
04 Neonatal death	1	47	Relative Risk (Fixed) 95% CI	1.14 [0.08, 17.11]
05 Ventilation of the baby	1	47	Relative Risk (Fixed) 95% CI	0.32 [0.08, 1.40]

Comparison 04. Ketanserin versus hydralazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Maternal death	2	124	Relative Risk (Fixed) 95% CI	0.32 [0.03, 2.96]
02 Eclampsia	2	64	Relative Risk (Fixed) 95% CI	0.60 [0.08, 4.24]
03 Persistent high blood pressure	3	180	Relative Risk (Fixed) 95% CI	4.79 [1.95, 11.73]
04 Hypotension	2	76	Relative Risk (Fixed) 95% CI	0.26 [0.07, 1.03]
05 Pulmonary oedema	1	44	Relative Risk (Fixed) 95% CI	0.11 [0.01, 1.95]
06 HELLP syndrome	1	44	Relative Risk (Fixed) 95% CI	0.20 [0.05, 0.81]

07 Disseminated intravascular coagulation	1	44	Relative Risk (Fixed) 95% CI	3.00 [0.13, 69.87]
08 Severe maternal morbidity	1	56	Relative Risk (Fixed) 95% CI	0.32 [0.09, 1.12]
09 Delivery due to fetal distress	1	80	Relative Risk (Fixed) 95% CI	0.45 [0.09, 2.33]
10 Placental abruption	2	64	Relative Risk (Fixed) 95% CI	0.14 [0.02, 1.10]
11 Caesarean section	3	120	Relative Risk (Random) 95% CI	0.53 [0.14, 2.06]
12 Side-effects for the women	3	120	Relative Risk (Fixed) 95% CI	0.32 [0.19, 0.53]
13 Perinatal death	2	116	Relative Risk (Fixed) 95% CI	0.27 [0.05, 1.64]

Comparison 05. Urapidil versus hydralazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Eclampsia	1	26	Relative Risk (Fixed) 95% CI	Not estimable
02 Persistent high blood pressure	2	59	Relative Risk (Fixed) 95% CI	1.38 [0.06, 31.14]
03 Hypotension	1	33	Relative Risk (Fixed) 95% CI	0.22 [0.02, 2.13]
04 Side-effects for the woman	2	59	Relative Risk (Fixed) 95% CI	0.59 [0.10, 3.58]
05 Placental abruption	1	33	Relative Risk (Fixed) 95% CI	0.15 [0.01, 3.46]
06 Caesarean section	2	59	Relative Risk (Fixed) 95% CI	0.77 [0.51, 1.16]
07 Stillbirth	1	26	Relative Risk (Fixed) 95% CI	Not estimable
08 Neonatal death	2	59	Relative Risk (Fixed) 95% CI	0.66 [0.08, 5.25]

Comparison 06. Labetolol versus calcium channel blockers

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Persistent high blood pressure	1	60	Relative Risk (Fixed) 95% CI	1.22 [0.59, 2.51]
02 Hypotension	1	60	Relative Risk (Fixed) 95% CI	Not estimable
03 Side-effects for the woman (specific effects)			Relative Risk (Fixed) 95% CI	Subtotals only

Comparison 07. Labetolol versus methyldopa

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Persistent high blood pressure	1	72	Relative Risk (Fixed) 95% CI	1.19 [0.74, 1.94]
02 Changed drugs due to side-effects	1	72	Relative Risk (Fixed) 95% CI	8.08 [0.45, 144.73]
03 Caesarean section	1	72	Relative Risk (Fixed) 95% CI	0.85 [0.56, 1.30]
04 Fetal or neonatal death			Relative Risk (Fixed) 95% CI	Subtotals only
05 Small-for-gestational age	1	72	Relative Risk (Fixed) 95% CI	0.78 [0.43, 1.39]
06 Admission to special care baby unit	1	72	Relative Risk (Fixed) 95% CI	1.06 [0.66, 1.71]

Comparison 08. Labetolol versus diazoxide

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Persistent high blood pressure	1	90	Relative Risk (Fixed) 95% CI	0.50 [0.13, 1.88]
02 Low blood pressure, requiring treatment	1	90	Relative Risk (Fixed) 95% CI	0.06 [0.00, 0.99]
03 Caesarean section	1	90	Relative Risk (Fixed) 95% CI	0.43 [0.18, 1.02]

04 Perinatal deaths	1	90	Relative Risk (Fixed) 95% CI	0.14 [0.01, 2.69]

Comparison 09. Nitrates versus magnesium sulphate

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Eclampsia	1	36	Relative Risk (Fixed) 95% CI	Not estimable
02 Persistent high blood pressure	1	36	Relative Risk (Fixed) 95% CI	0.14 [0.01, 2.58]
03 Caesarean section	1	36	Relative Risk (Fixed) 95% CI	0.19 [0.07, 0.53]

Comparison 10. Nimodipine versus magnesium sulphate

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Eclampsia	2	1683	Relative Risk (Fixed) 95% CI	2.24 [1.06, 4.73]
02 Stroke	1	1650	Relative Risk (Fixed) 95% CI	Not estimable
03 Persistant high blood pressure	1	1650	Relative Risk (Fixed) 95% CI	0.84 [0.76, 0.93]
04 Hypotension	1	1650	Relative Risk (Fixed) 95% CI	0.72 [0.23, 2.27]
05 Coagulopathy for the woman	1	1650	Relative Risk (Fixed) 95% CI	1.69 [0.41, 7.05]
06 Respiratory difficulty for the woman	1	1650	Relative Risk (Fixed) 95% CI	0.28 [0.08, 0.99]
07 Placental abruption	1	1650	Relative Risk (Fixed) 95% CI	0.76 [0.27, 2.18]
08 Side-effects for the woman (specific effects)			Relative Risk (Fixed) 95% CI	Subtotals only
09 Oliguria	1	1650	Relative Risk (Fixed) 95% CI	0.87 [0.59, 1.26]
10 Caesarean section	2	1683	Relative Risk (Fixed) 95% CI	0.97 [0.89, 1.06]
11 Postpartum haemorrhage	1	1650	Relative Risk (Fixed) 95% CI	0.41 [0.18, 0.92]
12 Baby intubated at delivery	1	1564	Relative Risk (Fixed) 95% CI	0.73 [0.49, 1.09]
13 Respiratory distress syndrome	1	1564	Relative Risk (Fixed) 95% CI	0.81 [0.55, 1.20]
14 Low blood pressure for the baby	1	1564	Relative Risk (Fixed) 95% CI	3.12 [0.63, 15.40]
15 Hypotonia for the baby	1	1564	Relative Risk (Fixed) 95% CI	0.56 [0.29, 1.10]

Comparison 11. Nifedipine versus chlorpromazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Eclampsia	1	55	Relative Risk (Fixed) 95% CI	2.52 [0.11, 59.18]
02 Persistent high blood pressure	1	60	Relative Risk (Fixed) 95% CI	0.09 [0.01, 1.57]
03 Caesarean section	1	55	Relative Risk (Fixed) 95% CI	0.80 [0.60, 1.05]

Comparison 12. Nifedipine versus prazosin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Maternal death	1	145	Relative Risk (Fixed) 95% CI	0.32 [0.01, 7.73]
02 Eclampsia	1	145	Relative Risk (Fixed) 95% CI	Not estimable
03 HELLP syndrome	1	145	Relative Risk (Fixed) 95% CI	1.15 [0.37, 3.60]
04 Renal failure	1	145	Relative Risk (Fixed) 95% CI	0.48 [0.04, 5.17]
05 Pulmonary oedema	1	145	Relative Risk (Fixed) 95% CI	0.19 [0.02, 1.60]
06 Admission to intensive care	1	145	Relative Risk (Fixed) 95% CI	0.32 [0.01, 7.73]
07 Magnesium sulphate prophylaxis	1	145	Relative Risk (Fixed) 95% CI	0.72 [0.17, 3.10]

08 Placental abruption	1	145	Relative Risk (Fixed) 95% CI	0.96 [0.40, 2.28]
09 Caesarean section	1	145	Relative Risk (Fixed) 95% CI	0.90 [0.72, 1.13]
10 Stillbirth	1	149	Relative Risk (Fixed) 95% CI	0.46 [0.18, 1.13]
11 Admission to special care baby unit	1	130	Relative Risk (Fixed) 95% CI	0.78 [0.49, 1.23]
12 Severe respiratory distress syndrome	1	130	Relative Risk (Fixed) 95% CI	1.22 [0.52, 2.82]

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [adverse effects; *therapeutic use]; Hypertension, Pregnancy-Induced [*drug therapy]; Pre-Eclampsia [drug therapy]; Randomized Controlled Trials

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Drugs for treatment of very high blood pressure during pregnancy
Authors	Duley L, Henderson-Smart DJ, Meher S
Contribution of author(s)	Methods for the review were developed by Lelia Duley and David Henderson-Smart. Lelia Duley wrote the initial text of the review, with discussion and comments from David Henderson-Smart. Data for the initial review and first update were extracted by Lelia Duley and David Henderson-Smart and then entered by Lelia Duley. For the 2005 update, the search strategy was updated by Shireen Meher. Lelia Duley and Shireen Meher selected studies for inclusion and exclusion. All three authors extracted and checked data, which were entered by Lelia Duley. Lelia Duley revised the text of the review, in consultation with David Henderson-Smart and Shireen Meher.
Issue protocol first published	1999/2
Review first published	1999/2
Date of most recent amendment	13 November 2006
Date of most recent SUBSTANTIVE amendment	31 March 2006
What's New	Search updated in February 2006. New included studies: Brazil 1992; Mexico 1998a; Netherlands 2003; Tunisia 2002; South Africa 1997a. New excluded studies: Australia 2002; Bangladesh 2002; Brazil 1984; Brazil 1988; Brazil 1988a; China 2000; Egypt 1989; Egypt 1992; India 1963; India 2001; Italy 2004; Jamaica 2004; Japan 1999; Japan 2000; Japan 2003; Mexico 1967; Mexico 2004; Netherlands 2002; New Zealand 1986; Philipines 2000; South Africa 1984; Venezuela 2001. Study ID changed: South Africa 1994 changed to South Africa 1997b. New ongoing study: Warren 2004, comparing labetolol with magnesium sulphate. Methods text expanded in line with the guidelines for the Cochrane Pregnancy and Childbirth Group. All text revised and expanded to reflect inclusion, and exclusion, of new studies.
Date new studies sought but none found	Information not supplied by author

Date new studies found but not yet included/excluded	Information not supplied by author
Date new studies found and included/excluded	28 February 2006
Date authors' conclusions section amended	29 April 2002
Contact address	Prof Lelia Duley Obstetric Epidemiologist Centre for Epidemiology and Biostatistics University of Leeds Academic Unit, Fieldhouse Bradford Teaching Hospitals Foundation Trust, Bradford Royal Infirmary, Duckworth Lane Bradford West Yorkshire BD9 6RJ UK E-mail: l.duley@leeds.ac.uk Tel: +44 1274 383079
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Editorial group	Cochrane Pregnancy and Childbirth Group
Editorial group code	HM-PREG

GRAPHS AND OTHER TABLES

Analysis 01.01. Comparison 01 Labetalol versus hydralazine, Outcome 01 Eclampsia

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 01 Labetalol versus hydralazine

Outcome: 01 Eclampsia

Study	Labetolol n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× South Africa 1987	0/10	0/10		0.0	Not estimable
Total (95% CI)	10	10		0.0	Not estimable
Total events: 0 (Labetolol), 0 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.02. Comparison 01 Labetalol versus hydralazine, Outcome 02 Persistent high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 01 Labetalol versus hydralazine

Outcome: 02 Persistent high blood pressure

Study	Labetolol n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1987	6/10	2/10		100.0	3.00 [0.79, 11.44]
Total (95% CI)	10	10		100.0	3.00 [0.79, 11.44]
Total events: 6 (Labetolol), 2 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.61 p=0.1					

Analysis 01.03. Comparison 01 Labetalol versus hydralazine, Outcome 03 Hypotension

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 01 Labetalol versus hydralazine

Outcome: 03 Hypotension

Study	Ketanserin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× N Ireland 1991	0/15	0/15		0.0	Not estimable
× South Africa 1987	0/10	0/10		0.0	Not estimable
Total (95% CI)	25	25		0.0	Not estimable
Total events: 0 (Ketanserin), 0 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

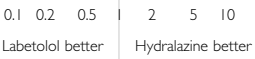
Analysis 01.04. Comparison 01 Labetalol versus hydralazine, Outcome 04 Caesarean section

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 01 Labetalol versus hydralazine

Outcome: 04 Caesarean section

Study	Labetolol n/N	Hydralazine n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
N Ireland 1991	9/15	9/15		35.8	1.00 [0.56, 1.79]
South Africa 1987	6/10	7/10		32.9	0.86 [0.45, 1.64]
USA 1987	5/13	6/6		31.3	0.38 [0.19, 0.76]
Total (95% CI)	38	31		100.0	0.71 [0.40, 1.24]
Total events: 20 (Labetolol), 22 (Hydralazine)					
Test for heterogeneity chi-square=4.72 df=2 p=0.09 I^2 =57.6%					
Test for overall effect z=1.21 p=0.2					



Analysis 01.05. Comparison 01 Labetalol versus hydralazine, Outcome 05 Side-effects for the woman

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 01 Labetalol versus hydralazine

Outcome: 05 Side-effects for the woman

Study	Labetolol n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
N Ireland 1991	6/15	8/15		64.0	0.75 [0.34, 1.64]
South Africa 1987	0/10	4/10		36.0	0.11 [0.01, 1.83]
Total (95% CI)	25	25		100.0	0.52 [0.24, 1.11]
Total events: 6 (Labetolol), 12 (Hydralazine)					
Test for heterogeneity chi-square=2.01 df=1 p=0.16 I^2 =50.4%					
Test for overall effect z=1.69 p=0.09					

Analysis 01.06. Comparison 01 Labetalol versus hydralazine, Outcome 06 Fetal heart rate decelerations

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 01 Labetalol versus hydralazine

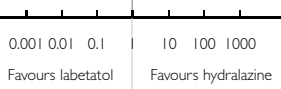
Outcome: 06 Fetal heart rate decelerations

Study	Labetatol n/N	Hydralazine n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× N Ireland 1991	0/15	0/15		0.0	Not estimable
South Africa 1987	3/10	0/10		50.2	7.00 [0.41, 120.16]
USA 1987	0/13	2/6		49.8	0.10 [0.01, 1.81]
Total (95% CI)	38	31		100.0	0.84 [0.01, 54.78]

Total events: 3 (Labetatol), 2 (Hydralazine)

Test for heterogeneity chi-square=4.23 df=1 p=0.04 I^2 =76.3%

Test for overall effect z=0.08 p=0.9



Analysis 01.07. Comparison 01 Labetalol versus hydralazine, Outcome 07 Fetal or neonatal deaths

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 01 Labetalol versus hydralazine

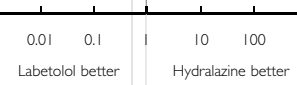
Outcome: 07 Fetal or neonatal deaths

Study	Labetolol n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
N Ireland 1991	1/15	2/15		100.0	0.50 [0.05, 4.94]
× South Africa 1987	0/10	0/10		0.0	Not estimable
× USA 1987	0/13	0/6		0.0	Not estimable
Total (95% CI)	38	31		100.0	0.50 [0.05, 4.94]

Total events: 1 (Labetolol), 2 (Hydralazine)

Test for heterogeneity: not applicable

Test for overall effect z=0.59 p=0.6



Analysis 01.08. Comparison 01 Labetalol versus hydralazine, Outcome 08 Apgar < 7 at 5 minutes

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 01 Labetalol versus hydralazine

Outcome: 08 Apgar < 7 at 5 minutes

Study	Labetolol n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 1987	0/13	2/6		100.0	0.10 [0.01, 1.81]
Total (95% CI)	13	6		100.0	0.10 [0.01, 1.81]
Total events: 0 (Labetolol), 2 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.56 p=0.1					

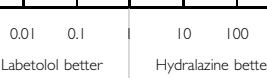
Analysis 01.09. Comparison 01 Labetalol versus hydralazine, Outcome 09 Respiratory distress syndrome

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 01 Labetalol versus hydralazine

Outcome: 09 Respiratory distress syndrome

Study	Labetolol n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
USA 1987	3/13	2/6		100.0	0.69 [0.15, 3.12]
Total (95% CI)	13	6		100.0	0.69 [0.15, 3.12]
Total events: 3 (Labetolol), 2 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.48 p=0.6					



Analysis 01.10. Comparison 01 Labetalol versus hydralazine, Outcome 10 Neonatal hypoglycaemia

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 01 Labetalol versus hydralazine

Outcome: 10 Neonatal hypoglycaemia

Study	Labetolol n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1987	1/10	0/10		26.8	3.00 [0.14, 65.90]
USA 1987	1/13	1/6		73.2	0.46 [0.03, 6.20]
Total (95% CI)	23	16		100.0	1.14 [0.19, 6.94]
Total events: 2 (Labetolol), 1 (Hydralazine)					
Test for heterogeneity chi-square=0.84 df=1 p=0.36 I^2 =0.0%					
Test for overall effect z=0.14 p=0.9					

Analysis 02.01. Comparison 02 Calcium channel blockers versus hydralazine, Outcome 01 Persistent high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 02 Calcium channel blockers versus hydralazine

Outcome: 01 Persistent high blood pressure

Study	Calcium antagonist n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Nifedipine versus hydralazine					
× Brazil 1992	0/20	0/17		0.0	Not estimable
Iran 2002	6/65	15/61		65.6	0.38 [0.16, 0.90]
× Mexico 1993	0/13	0/14		0.0	Not estimable
South Africa 1989	1/17	4/16		17.5	0.24 [0.03, 1.89]
Subtotal (95% CI)	115	108		83.0	0.35 [0.15, 0.78]
Total events: 7 (Calcium antagonist), 19 (Hydralazine)					
Test for heterogeneity chi-square=0.16 df=1 p=0.68 I^2 =0.0%					
Test for overall effect z=2.57 p=0.01					
02 Isradipine versus hydralazine					
South Africa 1997a	1/20	4/20		17.0	0.25 [0.03, 2.05]
Subtotal (95% CI)	20	20		17.0	0.25 [0.03, 2.05]
Total events: 1 (Calcium antagonist), 4 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.29 p=0.2					
Total (95% CI)	135	128		100.0	0.33 [0.15, 0.70]

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Study	Calcium antagonist n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 8 (Calcium antagonist), 23 (Hydralazine)					
Test for heterogeneity chi-square=0.25 df=2 p=0.88 I^2 =0.0%					
Test for overall effect z=2.88 p=0.004					

Analysis 02.02. Comparison 02 Calcium channel blockers versus hydralazine, Outcome 02 Low blood pressure for the woman

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 02 Calcium channel blockers versus hydralazine

Outcome: 02 Low blood pressure for the woman

Study	Calcium antagonist n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Nifedipine versus hydralazine					
× Iran 2002	0/65	0/61		0.0	Not estimable
South Africa 1989	1/17	0/16		100.0	2.83 [0.12, 64.89]
Subtotal (95% CI)	82	77		100.0	2.83 [0.12, 64.89]
Total events: 1 (Calcium antagonist), 0 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.65 p=0.5					
02 Isradapine versus hydralazine					
× South Africa 1997a	0/20	0/20		0.0	Not estimable
Subtotal (95% CI)	20	20		0.0	Not estimable
Total events: 0 (Calcium antagonist), 0 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	102	97		100.0	2.83 [0.12, 64.89]
Total events: 1 (Calcium antagonist), 0 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.65 p=0.5					

Analysis 02.03. Comparison 02 Calcium channel blockers versus hydralazine, Outcome 03 Further episode/s of very high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 02 Calcium channel blockers versus hydralazine

Outcome: 03 Further episode/s of very high blood pressure

Study	Calcium ch blocker n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Nifedipine versus hydralazine					
Brazil 1992	0/20	1/17		3.6	0.29 [0.01, 6.59]
Iran 2002	39/65	42/61		96.4	0.87 [0.67, 1.13]
Subtotal (95% CI)	85	78		100.0	0.85 [0.65, 1.11]
Total events: 39 (Calcium ch blocker), 43 (Hydralazine)					
Test for heterogeneity chi-square=0.50 df=1 p=0.48 I^2 =0.0%					
Test for overall effect z=1.21 p=0.2					
02 Isradipine versus hydralazine					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Calcium ch blocker), 0 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	85	78		100.0	0.85 [0.65, 1.11]
Total events: 39 (Calcium ch blocker), 43 (Hydralazine)					
Test for heterogeneity chi-square=0.50 df=1 p=0.48 I^2 =0.0%					
Test for overall effect z=1.21 p=0.2					

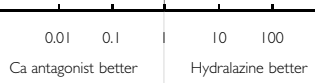
Analysis 02.04. Comparison 02 Calcium channel blockers versus hydralazine, Outcome 04 Side-effects for the woman

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 02 Calcium channel blockers versus hydralazine

Outcome: 04 Side-effects for the woman

Study	Calcium antagonist n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Nifedipine versus hydralazine					
Brazil 1992	10/20	13/17		53.2	0.65 [0.39, 1.09]
Iran 2002	11/65	10/61		39.0	1.03 [0.47, 2.26]
South Africa 1989	1/17	2/16		7.8	0.47 [0.05, 4.70]
Subtotal (95% CI)	102	94		100.0	0.79 [0.50, 1.24]
Total events: 22 (Calcium antagonist), 25 (Hydralazine)					
Test for heterogeneity chi-square=1.16 df=2 p=0.56 I^2 =0.0%					
Test for overall effect z=1.04 p=0.3					
02 Isradipine versus hydralazine					
× South Africa 1997a	0/20	0/20		0.0	Not estimable
Subtotal (95% CI)	20	20		0.0	Not estimable
Total events: 0 (Calcium antagonist), 0 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
Total (95% CI)	122	114		100.0	0.79 [0.50, 1.24]
Total events: 22 (Calcium antagonist), 25 (Hydralazine)					
Test for heterogeneity chi-square=1.16 df=2 p=0.56 I^2 =0.0%					
Test for overall effect z=1.04 p=0.3					



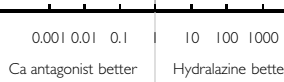
Analysis 02.05. Comparison 02 Calcium channel blockers versus hydralazine, Outcome 05 Side-effects for the woman (specific effects)

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 02 Calcium channel blockers versus hydralazine

Outcome: 05 Side-effects for the woman (specific effects)

Study	Calcium antagonist n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Palpatations					
Brazil 1992	3/20	3/17		26.5	0.85 [0.20, 3.67]
Brazil 1994	5/25	9/25		73.5	0.56 [0.22, 1.43]
Subtotal (95% CI)	45	42		100.0	0.63 [0.29, 1.39]
Total events: 8 (Calcium antagonist), 12 (Hydralazine)					
Test for heterogeneity chi-square=0.23 df=1 p=0.63 I² =0.0%					
Test for overall effect z=1.13 p=0.3					
02 Nausea and/or vomiting					
Brazil 1992	2/20	0/17		17.4	4.29 [0.22, 83.57]
Brazil 1994	7/25	0/25		16.1	15.00 [0.90, 249.30]
South Africa 1989	1/17	2/16		66.5	0.47 [0.05, 4.70]
Subtotal (95% CI)	62	58		100.0	3.48 [1.01, 11.99]
Total events: 10 (Calcium antagonist), 2 (Hydralazine)					
Test for heterogeneity chi-square=3.96 df=2 p=0.14 I² =49.5%					
Test for overall effect z=1.97 p=0.05					
03 Headache					
Brazil 1992	3/20	5/17		49.0	0.51 [0.14, 1.83]
Brazil 1994	2/25	1/25		9.1	2.00 [0.19, 20.67]
Iran 2002	7/65	2/61		18.7	3.28 [0.71, 15.20]
South Africa 1989	0/17	2/16		23.3	0.19 [0.01, 3.66]
Subtotal (95% CI)	127	119		100.0	1.09 [0.50, 2.36]
Total events: 12 (Calcium antagonist), 10 (Hydralazine)					
Test for heterogeneity chi-square=4.95 df=3 p=0.18 I² =39.4%					
Test for overall effect z=0.22 p=0.8					
04 Flushing					
Brazil 1992	2/20	2/17		41.3	0.85 [0.13, 5.41]
Brazil 1994	9/25	0/25		9.6	19.00 [1.17, 309.77]
South Africa 1989	0/17	2/16		49.1	0.19 [0.01, 3.66]
Subtotal (95% CI)	62	58		100.0	2.26 [0.83, 6.13]
Total events: 11 (Calcium antagonist), 4 (Hydralazine)					
Test for heterogeneity chi-square=6.00 df=2 p=0.05 I² =66.7%					



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Study	Calcium antagonist n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=1.60 p=0.1					
05 Dyspnoea					
Brazil 1992	1/20	1/17		100.0	0.85 [0.06, 12.59]
Subtotal (95% CI)	20	17		100.0	0.85 [0.06, 12.59]
Total events: 1 (Calcium antagonist), 1 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.12 p=0.9					

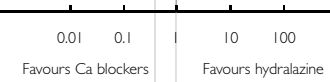
Analysis 02.06. Comparison 02 Calcium channel blockers versus hydralazine, Outcome 06 Fetal heart rate decelerations

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 02 Calcium channel blockers versus hydralazine

Outcome: 06 Fetal heart rate decelerations

Study	Calcium ch blockers n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Nifedipine versus hydralazine					
× Brazil 1992	0/20	0/17		0.0	Not estimable
× Iran 2002	0/65	0/61		0.0	Not estimable
Subtotal (95% CI)	85	78		0.0	Not estimable
Total events: 0 (Calcium ch blockers), 0 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 Isradipine versus hydralazine					
South Africa 1997a	2/20	5/20		100.0	0.40 [0.09, 1.83]
Subtotal (95% CI)	20	20		100.0	0.40 [0.09, 1.83]
Total events: 2 (Calcium ch blockers), 5 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.18 p=0.2					
Total (95% CI)	105	98		100.0	0.40 [0.09, 1.83]
Total events: 2 (Calcium ch blockers), 5 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.18 p=0.2					



Analysis 02.07. Comparison 02 Calcium channel blockers versus hydralazine, Outcome 07 Caesarean section

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 02 Calcium channel blockers versus hydralazine

Outcome: 07 Caesarean section

Study	Calcium ch blockers n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Nifedipine versus hydralazine					
Brazil 1992	13/20	13/17		100.0	0.85 [0.56, 1.29]
Total (95% CI)	20	17		100.0	0.85 [0.56, 1.29]
Total events: 13 (Calcium ch blockers), 13 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.77 p=0.4					

Analysis 02.08. Comparison 02 Calcium channel blockers versus hydralazine, Outcome 08 Fetal or neonatal death

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 02 Calcium channel blockers versus hydralazine

Outcome: 08 Fetal or neonatal death

Study	Ca channel blocker n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Nifedipine versus hydralazine					
Brazil 1992	2/20	0/17		11.7	4.29 [0.22, 83.57]
Brazil 1994	2/25	2/25		43.5	1.00 [0.15, 6.55]
South Africa 1989	1/17	1/16		22.4	0.94 [0.06, 13.82]
Subtotal (95% CI)	62	58		77.7	1.48 [0.40, 5.48]
Total events: 5 (Ca channel blocker), 3 (Hydralazine)					
Test for heterogeneity chi-square=0.77 df=2 p=0.68 I^2 =0.0%					
Test for overall effect z=0.59 p=0.6					
02 Isradapine versus hydralazine					
South Africa 1997a	1/21	1/20		22.3	0.95 [0.06, 14.22]
Subtotal (95% CI)	21	20		22.3	0.95 [0.06, 14.22]
Total events: 1 (Ca channel blocker), 1 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.04 p=1					
Total (95% CI)	83	78		100.0	1.36 [0.42, 4.41]
Total events: 6 (Ca channel blocker), 4 (Hydralazine)					
Test for heterogeneity chi-square=0.82 df=3 p=0.85 I^2 =0.0%					
Test for overall effect z=0.51 p=0.6					

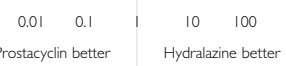
Analysis 03.01. Comparison 03 Prostacyclin versus hydralazine, Outcome 01 Persistent high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 03 Prostacyclin versus hydralazine

Outcome: 01 Persistent high blood pressure

Study	Prostacyclin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1992	0/22	2/25		100.0	0.23 [0.01, 4.47]
Total (95% CI)	22	25		100.0	0.23 [0.01, 4.47]
Total events: 0 (Prostacyclin), 2 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.98 p=0.3					



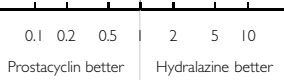
Analysis 03.02. Comparison 03 Prostacyclin versus hydralazine, Outcome 02 Caesarean section

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 03 Prostacyclin versus hydralazine

Outcome: 02 Caesarean section

Study	Prostacyclin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1992	13/22	20/25		100.0	0.74 [0.50, 1.10]
Total (95% CI)	22	25		100.0	0.74 [0.50, 1.10]
Total events: 13 (Prostacyclin), 20 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.49 p=0.1					



Analysis 03.03. Comparison 03 Prostacyclin versus hydralazine, Outcome 03 Side-effects for the woman

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 03 Prostacyclin versus hydralazine

Outcome: 03 Side-effects for the woman

Study	Prostacyclin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1992	1/22	1/25		100.0	1.14 [0.08, 17.11]
Total (95% CI)	22	25		100.0	1.14 [0.08, 17.11]
Total events: 1 (Prostacyclin), 1 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.09 p=0.9					

Analysis 03.04. Comparison 03 Prostacyclin versus hydralazine, Outcome 04 Neonatal death

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 03 Prostacyclin versus hydralazine

Outcome: 04 Neonatal death

Study	Prostacyclin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1992	1/22	1/25		100.0	1.14 [0.08, 17.11]
Total (95% CI)	22	25		100.0	1.14 [0.08, 17.11]
Total events: 1 (Prostacyclin), 1 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.09 p=0.9					

Analysis 03.05. Comparison 03 Prostacyclin versus hydralazine, Outcome 05 Ventilation of the baby

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 03 Prostacyclin versus hydralazine

Outcome: 05 Ventilation of the baby

Study	Prostacyclin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1992	2/22	7/25		100.0	0.32 [0.08, 1.40]
Total (95% CI)	22	25		100.0	0.32 [0.08, 1.40]
Total events: 2 (Prostacyclin), 7 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.51 p=0.1					

Analysis 04.01. Comparison 04 Ketanserin versus hydralazine, Outcome 01 Maternal death

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

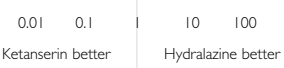
Outcome: 01 Maternal death

Study	Ketanserin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 1999	0/22	1/22		48.8	0.33 [0.01, 7.76]
South Africa 1997b	0/42	1/38		51.2	0.30 [0.01, 7.21]
Total (95% CI)	64	60		100.0	0.32 [0.03, 2.96]

Total events: 0 (Ketanserin), 2 (Hydralazine)

Test for heterogeneity chi-square=0.00 df=1 p=0.97 I^2 =0.0%

Test for overall effect z=1.01 p=0.3



Analysis 04.02. Comparison 04 Ketanserin versus hydralazine, Outcome 02 Eclampsia

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 02 Eclampsia

Study	Ketanserin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 1999	0/22	1/22		60.0	0.33 [0.01, 7.76]
South Africa 1995	1/10	1/10		40.0	1.00 [0.07, 13.87]
Total (95% CI)	32	32		100.0	0.60 [0.08, 4.24]

Total events: 1 (Ketanserin), 2 (Hydralazine)

Test for heterogeneity chi-square=0.28 df=1 p=0.60 I^2 =0.0%

Test for overall effect z=0.51 p=0.6

Analysis 04.03. Comparison 04 Ketanserin versus hydralazine, Outcome 03 Persistent high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 03 Persistent high blood pressure

Study	Ketanserin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 1999	10/22	2/22		38.1	5.00 [1.23, 20.24]
Netherlands 2003	1/32	1/24		21.8	0.75 [0.05, 11.39]
South Africa 1997b	15/42	2/38		40.1	6.79 [1.66, 27.76]
Total (95% CI)	96	84		100.0	4.79 [1.95, 11.73]

Total events: 26 (Ketanserin), 5 (Hydralazine)

Test for heterogeneity chi-square=2.02 df=2 p=0.36 I^2 =1.1%

Test for overall effect z=3.43 p=0.0006

Analysis 04.04. Comparison 04 Ketanserin versus hydralazine, Outcome 04 Hypotension

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 04 Hypotension

Study	Ketanserin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 2003	2/32	6/24		82.1	0.25 [0.06, 1.13]
South Africa 1995	0/10	1/10		17.9	0.33 [0.02, 7.32]
Total (95% CI)	42	34		100.0	0.26 [0.07, 1.03]

Total events: 2 (Ketanserin), 7 (Hydralazine)

Test for heterogeneity chi-square=0.03 df=1 p=0.87 I^2 =0.0%

Test for overall effect z=1.92 p=0.05

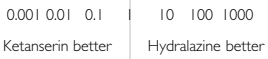
Analysis 04.05. Comparison 04 Ketanserin versus hydralazine, Outcome 05 Pulmonary oedema

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 05 Pulmonary oedema

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 1999	0/22	4/22		100.0	0.11 [0.01, 1.95]
Total (95% CI)	22	22		100.0	0.11 [0.01, 1.95]
Total events: 0 (Treatment), 4 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.50 p=0.1					



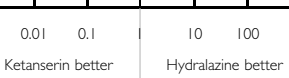
Analysis 04.06. Comparison 04 Ketanserin versus hydralazine, Outcome 06 HELLP syndrome

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 06 HELLP syndrome

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 1999	2/22	10/22		100.0	0.20 [0.05, 0.81]
Total (95% CI)	22	22		100.0	0.20 [0.05, 0.81]
Total events: 2 (Treatment), 10 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.26 p=0.02					



Analysis 04.07. Comparison 04 Ketanserin versus hydralazine, Outcome 07 Disseminated intravascular coagulation

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 07 Disseminated intravascular coagulation

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 1999	1/22	0/22		100.0	3.00 [0.13, 69.87]
Total (95% CI)	22	22		100.0	3.00 [0.13, 69.87]
Total events: 1 (Treatment), 0 (Control)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					

Analysis 04.08. Comparison 04 Ketanserin versus hydralazine, Outcome 08 Severe maternal morbidity

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 08 Severe maternal morbidity

Study	Ketanserin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 2003	3/32	7/24		100.0	0.32 [0.09, 1.12]
Total (95% CI)	32	24		100.0	0.32 [0.09, 1.12]
Total events: 3 (Ketanserin), 7 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.79 p=0.07					

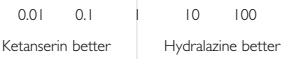
Analysis 04.09. Comparison 04 Ketanserin versus hydralazine, Outcome 09 Delivery due to fetal distress

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 09 Delivery due to fetal distress

Study	Ketanserin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1997b	2/42	4/38		100.0	0.45 [0.09, 2.33]
Total (95% CI)	42	38		100.0	0.45 [0.09, 2.33]
Total events: 2 (Ketanserin), 4 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.95 p=0.3					



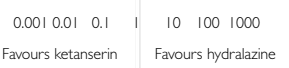
Analysis 04.10. Comparison 04 Ketanserin versus hydralazine, Outcome 10 Placental abruption

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 10 Placental abruption

Study	Ketanserin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 1999	0/22	4/22		64.3	0.11 [0.01, 1.95]
South Africa 1995	0/10	2/10		35.7	0.20 [0.01, 3.70]
Total (95% CI)	32	32		100.0	0.14 [0.02, 1.10]
Total events: 0 (Ketanserin), 6 (Hydralazine)					
Test for heterogeneity chi-square=0.08 df=1 p=0.78 I^2 =0.0%					
Test for overall effect z=1.87 p=0.06					



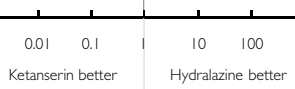
Analysis 04.11. Comparison 04 Ketanserin versus hydralazine, Outcome 11 Caesarean section

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 11 Caesarean section

Study	Ketanserin n/N	Hydralazine n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
× Netherlands 1999	22/22	22/22		0.0	Not estimable
Netherlands 2003	20/32	19/24		70.9	0.79 [0.56, 1.11]
South Africa 1995	1/10	5/10		29.1	0.20 [0.03, 1.42]
Total (95% CI)	64	56		100.0	0.53 [0.14, 2.06]
Total events: 43 (Ketanserin), 46 (Hydralazine)					
Test for heterogeneity chi-square=2.26 df=1 p=0.13 I^2 =55.7%					
Test for overall effect z=0.92 p=0.4					



Analysis 04.12. Comparison 04 Ketanserin versus hydralazine, Outcome 12 Side-effects for the women

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 12 Side-effects for the women

Study	Ketanserin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 1999	7/22	17/22		44.1	0.41 [0.21, 0.79]
Netherlands 2003	5/32	18/24		53.3	0.21 [0.09, 0.48]
South Africa 1995	1/10	1/10		2.6	1.00 [0.07, 13.87]
Total (95% CI)	64	56		100.0	0.32 [0.19, 0.53]
Total events: 13 (Ketanserin), 36 (Hydralazine)					
Test for heterogeneity chi-square=2.31 df=2 p=0.32 I^2 =13.4%					
Test for overall effect z=4.47 p<0.00001					

Analysis 04.13. Comparison 04 Ketanserin versus hydralazine, Outcome 13 Perinatal death

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 04 Ketanserin versus hydralazine

Outcome: 13 Perinatal death

Study	Ketanserin n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Netherlands 1999	0/17	3/19		61.2	0.16 [0.01, 2.87]
South Africa 1997b	1/42	2/38		38.8	0.45 [0.04, 4.79]
Total (95% CI)	59	57		100.0	0.27 [0.05, 1.64]

Total events: 1 (Ketanserin), 5 (Hydralazine)

Test for heterogeneity chi-square=0.31 df=1 p=0.58 I^2 =0.0%

Test for overall effect z=1.42 p=0.2

Analysis 05.01. Comparison 05 Urapidil versus hydralazine, Outcome 01 Eclampsia

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 05 Urapidil versus hydralazine

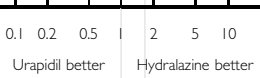
Outcome: 01 Eclampsia

Study	Treatment n/N	Control n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Germany 1998	0/13	0/13		0.0	Not estimable
Total (95% CI)	13	13		0.0	Not estimable

Total events: 0 (Treatment), 0 (Control)

Test for heterogeneity: not applicable

Test for overall effect: not applicable



Analysis 05.02. Comparison 05 Urapidil versus hydralazine, Outcome 02 Persistent high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 05 Urapidil versus hydralazine

Outcome: 02 Persistent high blood pressure

Study	Urapidil n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Germany 1998	0/13	0/13		0.0	Not estimable
South Africa 1997	1/23	0/10		100.0	1.38 [0.06, 31.14]
Total (95% CI)	36	23		100.0	1.38 [0.06, 31.14]
Total events: 1 (Urapidil), 0 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.20 p=0.8					

Analysis 05.03. Comparison 05 Urapidil versus hydralazine, Outcome 03 Hypotension

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 05 Urapidil versus hydralazine

Outcome: 03 Hypotension

Study	Urapidil n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1997	1/23	2/10		100.0	0.22 [0.02, 2.13]
Total (95% CI)	23	10		100.0	0.22 [0.02, 2.13]
Total events: 1 (Urapidil), 2 (Hydralazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.31 p=0.2					

Analysis 05.04. Comparison 05 Urapidil versus hydralazine, Outcome 04 Side-effects for the woman

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 05 Urapidil versus hydralazine

Outcome: 04 Side-effects for the woman

Study	Urapidil n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Germany 1998	0/13	1/13		51.8	0.33 [0.01, 7.50]
South Africa 1997	2/23	1/10		48.2	0.87 [0.09, 8.53]
Total (95% CI)	36	23		100.0	0.59 [0.10, 3.58]

Total events: 2 (Urapidil), 2 (Hydralazine)

Test for heterogeneity chi-square=0.24 df=1 p=0.62 I^2 =0.0%

Test for overall effect z=0.57 p=0.6

Analysis 05.05. Comparison 05 Urapidil versus hydralazine, Outcome 05 Placental abruption

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 05 Urapidil versus hydralazine

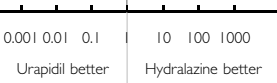
Outcome: 05 Placental abruption

Study	Urapidil n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 1997	0/23	1/10		100.0	0.15 [0.01, 3.46]
Total (95% CI)	23	10		100.0	0.15 [0.01, 3.46]

Total events: 0 (Urapidil), 1 (Hydralazine)

Test for heterogeneity: not applicable

Test for overall effect z=1.18 p=0.2



Analysis 05.06. Comparison 05 Urapidil versus hydralazine, Outcome 06 Caesarean section

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 05 Urapidil versus hydralazine

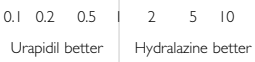
Outcome: 06 Caesarean section

Study	Urapidil n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Germany 1998	7/13	11/13		56.8	0.64 [0.37, 1.11]
South Africa 1997	13/23	6/10		43.2	0.94 [0.51, 1.75]
Total (95% CI)	36	23		100.0	0.77 [0.51, 1.16]

Total events: 20 (Urapidil), 17 (Hydralazine)

Test for heterogeneity chi-square=0.86 df=1 p=0.35 I^2 =0.0%

Test for overall effect z=1.25 p=0.2



Analysis 05.07. Comparison 05 Urapidil versus hydralazine, Outcome 07 Stillbirth

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 05 Urapidil versus hydralazine

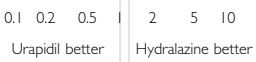
Outcome: 07 Stillbirth

Study	Urapidil n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Germany 1998	0/13	0/13		0.0	Not estimable
Total (95% CI)	13	13		0.0	Not estimable

Total events: 0 (Urapidil), 0 (Hydralazine)

Test for heterogeneity: not applicable

Test for overall effect: not applicable



Analysis 05.08. Comparison 05 Urapidil versus hydralazine, Outcome 08 Neonatal death

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 05 Urapidil versus hydralazine

Outcome: 08 Neonatal death

Study	Urapidil n/N	Hydralazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Germany 1998	0/13	1/13		68.6	0.33 [0.01, 7.50]
South Africa 1997	1/23	0/10		31.4	1.38 [0.06, 31.14]
Total (95% CI)	36	23		100.0	0.66 [0.08, 5.25]

Total events: 1 (Urapidil), 1 (Hydralazine)

Test for heterogeneity chi-square=0.40 df=1 p=0.53 I^2 =0.0%

Test for overall effect z=0.39 p=0.7

Analysis 06.01. Comparison 06 Labetolol versus calcium channel blockers, Outcome 01 Persistent high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 06 Labetolol versus calcium channel blockers

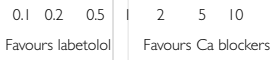
Outcome: 01 Persistent high blood pressure

Study	Labetolol n/N	Calcium ch blockers n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Labetolol versus nicardopine					
Tunisia 2002	11/30	9/30		100.0	1.22 [0.59, 2.51]
Total (95% CI)	30	30		100.0	1.22 [0.59, 2.51]

Total events: 11 (Labetolol), 9 (Calcium ch blockers)

Test for heterogeneity: not applicable

Test for overall effect z=0.55 p=0.6



Analysis 06.02. Comparison 06 Labetolol versus calcium channel blockers, Outcome 02 Hypotension

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 06 Labetolol versus calcium channel blockers

Outcome: 02 Hypotension

Study	Labetolol n/N	Calcium ch blockers n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Labetolol versus nicardopine					
× Tunisia 2002	0/30	0/30		0.0	Not estimable
Total (95% CI)	30	30		0.0	Not estimable
Total events: 0 (Labetolol), 0 (Calcium ch blockers)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 06.03. Comparison 06 Labetolol versus calcium channel blockers, Outcome 03 Side-effects for the woman (specific effects)

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 06 Labetolol versus calcium channel blockers

Outcome: 03 Side-effects for the woman (specific effects)

Study	Labetolol n/N	Calcium ch blockers n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Nausea and/or vomiting					
Tunisia 2002	1/30	1/30		100.0	1.00 [0.07, 15.26]
Subtotal (95% CI)	30	30		100.0	1.00 [0.07, 15.26]
Total events: 1 (Labetolol), 1 (Calcium ch blockers)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.00 p=1					
02 Palpatations					
Tunisia 2002	0/30	3/30		100.0	0.14 [0.01, 2.65]
Subtotal (95% CI)	30	30		100.0	0.14 [0.01, 2.65]
Total events: 0 (Labetolol), 3 (Calcium ch blockers)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.31 p=0.2					

Analysis 07.01. Comparison 07 Labetolol versus methyldopa, Outcome 01 Persistent high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 07 Labetolol versus methyldopa

Outcome: 01 Persistent high blood pressure

Study	Labetolol n/N	Methyldopa n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
England 1982	20/38	15/34		100.0	1.19 [0.74, 1.94]
Total (95% CI)	38	34		100.0	1.19 [0.74, 1.94]
Total events: 20 (Labetolol), 15 (Methyldopa)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.71 p=0.5					

Analysis 07.02. Comparison 07 Labetolol versus methyldopa, Outcome 02 Changed drugs due to side-effects

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 07 Labetolol versus methyldopa

Outcome: 02 Changed drugs due to side-effects

Study	Labetolol n/N	Methyldopa n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
England 1982	4/38	0/34		100.0	8.08 [0.45, 144.73]
Total (95% CI)	38	34		100.0	8.08 [0.45, 144.73]
Total events: 4 (Labetolol), 0 (Methyldopa)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.42 p=0.2					

Analysis 07.03. Comparison 07 Labetolol versus methyldopa, Outcome 03 Caesarean section

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 07 Labetolol versus methyldopa

Outcome: 03 Caesarean section

Study	Labetalol n/N	Methyldopa n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
England 1982	19/38	20/34		100.0	0.85 [0.56, 1.30]
Total (95% CI)	38	34		100.0	0.85 [0.56, 1.30]
Total events: 19 (Labetalol), 20 (Methyldopa)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.75 p=0.5					

Analysis 07.04. Comparison 07 Labetolol versus methyldopa, Outcome 04 Fetal or neonatal death

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 07 Labetolol versus methyldopa

Outcome: 04 Fetal or neonatal death

Study	Labetolol n/N	Methyldopa n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 stillbirth					
× England 1982	0/38	0/34		0.0	Not estimable
Subtotal (95% CI)	38	34		0.0	Not estimable
Total events: 0 (Labetolol), 0 (Methyldopa)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
02 neonatal death					
England 1982	2/38	0/34		100.0	4.49 [0.22, 90.30]
Subtotal (95% CI)	38	34		100.0	4.49 [0.22, 90.30]
Total events: 2 (Labetolol), 0 (Methyldopa)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.98 p=0.3					
03 total stillbirths and neonatal deaths					
England 1982	2/38	0/34		100.0	4.49 [0.22, 90.30]
Subtotal (95% CI)	38	34		100.0	4.49 [0.22, 90.30]
Total events: 2 (Labetolol), 0 (Methyldopa)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.98 p=0.3					

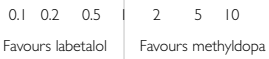
Analysis 07.05. Comparison 07 Labetolol versus methyldopa, Outcome 05 Small-for-gestational age

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 07 Labetolol versus methyldopa

Outcome: 05 Small-for-gestational age

Study	Labetalol n/N	Methyldopa n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
England 1982	13/38	15/34		100.0	0.78 [0.43, 1.39]
Total (95% CI)	38	34		100.0	0.78 [0.43, 1.39]
Total events: 13 (Labetalol), 15 (Methyldopa)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.86 p=0.4					



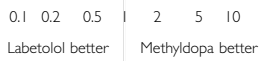
Analysis 07.06. Comparison 07 Labetolol versus methyldopa, Outcome 06 Admission to special care baby unit

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 07 Labetolol versus methyldopa

Outcome: 06 Admission to special care baby unit

Study	Labetolol n/N	Methyldopa n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
England 1982	19/38	16/34		100.0	1.06 [0.66, 1.71]
Total (95% CI)	38	34		100.0	1.06 [0.66, 1.71]
Total events: 19 (Labetolol), 16 (Methyldopa)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.25 p=0.8					



Analysis 08.01. Comparison 08 Labetolol versus diazoxide, Outcome 01 Persistent high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 08 Labetolol versus diazoxide

Outcome: 01 Persistent high blood pressure

Study	Labetolol n/N	Diazoxide n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Australia 1986	3/45	6/45		100.0	0.50 [0.13, 1.88]
Total (95% CI)	45	45		100.0	0.50 [0.13, 1.88]
Total events: 3 (Labetolol), 6 (Diazoxide)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.03 p=0.3					

Analysis 08.02. Comparison 08 Labetolol versus diazoxide, Outcome 02 Low blood pressure, requiring treatment

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 08 Labetolol versus diazoxide

Outcome: 02 Low blood pressure, requiring treatment

Study	Labetolol n/N	Diazoxide n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Australia 1986	0/45	8/45		100.0	0.06 [0.00, 0.99]
Total (95% CI)	45	45		100.0	0.06 [0.00, 0.99]
Total events: 0 (Labetolol), 8 (Diazoxide)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.97 p=0.05					

Analysis 08.03. Comparison 08 Labetolol versus diazoxide, Outcome 03 Caesarean section

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 08 Labetolol versus diazoxide

Outcome: 03 Caesarean section

Study	Labetolol n/N	Diazoxide n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Australia 1986	6/45	14/45		100.0	0.43 [0.18, 1.02]
Total (95% CI)	45	45		100.0	0.43 [0.18, 1.02]
Total events: 6 (Labetolol), 14 (Diazoxide)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.93 p=0.05					

Analysis 08.04. Comparison 08 Labetolol versus diazoxide, Outcome 04 Perinatal deaths

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 08 Labetolol versus diazoxide

Outcome: 04 Perinatal deaths

Study	Labetolol n/N	Diazoxide n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Australia 1986	0/45	3/45		100.0	0.14 [0.01, 2.69]
Total (95% CI)	45	45		100.0	0.14 [0.01, 2.69]
Total events: 0 (Labetolol), 3 (Diazoxide)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.30 p=0.2					

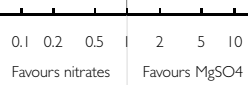
Analysis 09.01. Comparison 09 Nitrates versus magnesium sulphate, Outcome 01 Eclampsia

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 09 Nitrates versus magnesium sulphate

Outcome: 01 Eclampsia

Study	Nitrates n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Isosorbide versus magnesium sulphate					
× Mexico 1998	0/18	0/18		0.0	Not estimable
Total (95% CI)	18	18		0.0	Not estimable
Total events: 0 (Nitrates), 0 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 09.02. Comparison 09 Nitrates versus magnesium sulphate, Outcome 02 Persistent high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 09 Nitrates versus magnesium sulphate

Outcome: 02 Persistent high blood pressure

Study	Nitrates n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Isosorbide versus magnesium sulphate					
Mexico 1998	0/18	3/18		100.0	0.14 [0.01, 2.58]
Total (95% CI)	18	18		100.0	0.14 [0.01, 2.58]
Total events: 0 (Nitrates), 3 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.32 p=0.2					

Analysis 09.03. Comparison 09 Nitrates versus magnesium sulphate, Outcome 03 Caesarean section

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 09 Nitrates versus magnesium sulphate

Outcome: 03 Caesarean section

Study	Nitrates n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 Isosorbide versus magnesium sulphate					
Mexico 1998	3/18	16/18		100.0	0.19 [0.07, 0.53]
Total (95% CI)	18	18		100.0	0.19 [0.07, 0.53]
Total events: 3 (Nitrates), 16 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.14 p=0.002					

Analysis 10.01. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 01 Eclampsia

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 01 Eclampsia

Study	Nimodipine n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	21/819	7/831		71.9	3.04 [1.30, 7.12]
Turkey 1996	0/18	2/15		28.1	0.17 [0.01, 3.26]
Total (95% CI)	837	846		100.0	2.24 [1.06, 4.73]
Total events: 21 (Nimodipine), 9 (Magnesium sulphate)					
Test for heterogeneity chi-square=3.43 df=1 p=0.06 I^2 =70.9%					
Test for overall effect z=2.11 p=0.04					

Analysis 10.02. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 02 Stroke

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 02 Stroke

Study	Calcium ch blockers n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Nimodipine SG 2003	0/819	0/831		0.0	Not estimable
Total (95% CI)	819	831		0.0	Not estimable
Total events: 0 (Calcium ch blockers), 0 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

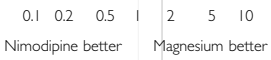
Analysis 10.03. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 03 Persistant high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 03 Persistant high blood pressure

Study	Nimodipine n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	374/819	451/831		100.0	0.84 [0.76, 0.93]
Total (95% CI)	819	831		100.0	0.84 [0.76, 0.93]
Total events: 374 (Nimodipine), 451 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.48 p=0.0005					



Analysis 10.04. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 04 Hypotension

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 04 Hypotension

Study	Nimodipine n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	5/819	7/831		100.0	0.72 [0.23, 2.27]
Total (95% CI)	819	831		100.0	0.72 [0.23, 2.27]
Total events: 5 (Nimodipine), 7 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.55 p=0.6					

Analysis 10.05. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 05 Coagulopathy for the woman

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 05 Coagulopathy for the woman

Study	Nimodipine n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	5/819	3/831		100.0	1.69 [0.41, 7.05]
Total (95% CI)	819	831		100.0	1.69 [0.41, 7.05]
Total events: 5 (Nimodipine), 3 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.72 p=0.5					

Analysis 10.06. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 06 Respiratory difficulty for the woman

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 06 Respiratory difficulty for the woman

Study	Nimodipine n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	3/819	11/831		100.0	0.28 [0.08, 0.99]
Total (95% CI)	819	831		100.0	0.28 [0.08, 0.99]
Total events: 3 (Nimodipine), 11 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.98 p=0.05					

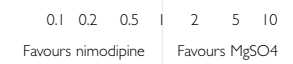
Analysis 10.07. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 07 Placental abruption

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 07 Placental abruption

Study	Nimodipine n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	6/819	8/831		100.0	0.76 [0.27, 2.18]
Total (95% CI)	819	831		100.0	0.76 [0.27, 2.18]
Total events: 6 (Nimodipine), 8 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.51 p=0.6					

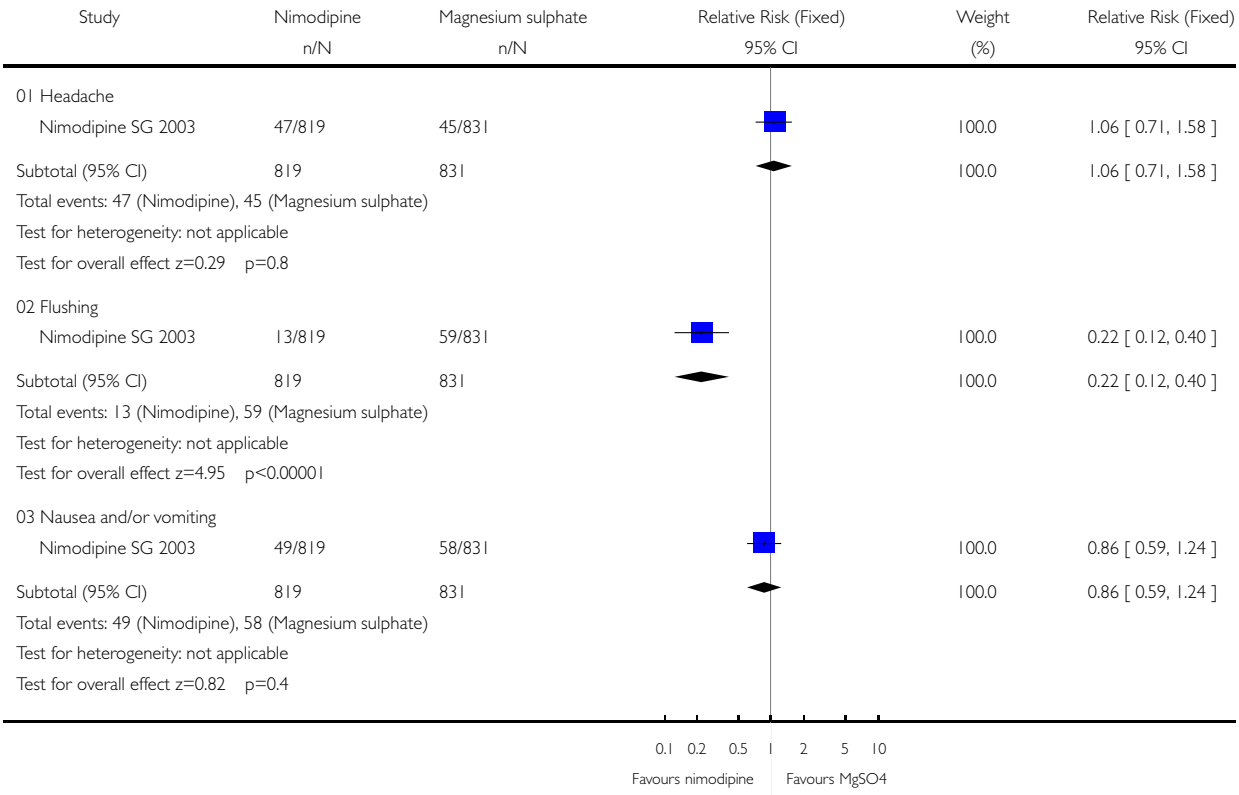


Analysis 10.08. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 08 Side-effects for the woman (specific effects)

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 08 Side-effects for the woman (specific effects)

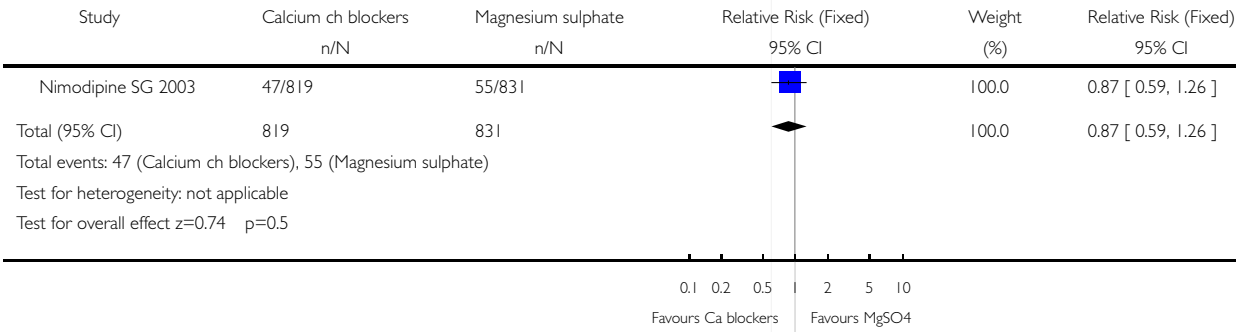


Analysis 10.09. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 09 Oliguria

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 09 Oliguria



Analysis 10.10. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 10 Caesarean section

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 10 Caesarean section

Study	Nimodipine n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	437/819	457/831		98.6	0.97 [0.89, 1.06]
Turkey 1996	7/18	6/15		1.4	0.97 [0.42, 2.27]
Total (95% CI)	837	846		100.0	0.97 [0.89, 1.06]
Total events: 444 (Nimodipine), 463 (Magnesium sulphate)					
Test for heterogeneity chi-square=0.00 df=1 p=1.00 I^2 =0.0%					
Test for overall effect z=0.67 p=0.5					

Analysis 10.11. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 11 Postpartum haemorrhage

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 11 Postpartum haemorrhage

Study	Nimodipine n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	8/819	20/831		100.0	0.41 [0.18, 0.92]
Total (95% CI)	819	831		100.0	0.41 [0.18, 0.92]
Total events: 8 (Nimodipine), 20 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.17 p=0.03					

Analysis 10.12. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 12 Baby intubated at delivery

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 12 Baby intubated at delivery

Study	Nimodipine n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	38/767	54/797		100.0	0.73 [0.49, 1.09]
Total (95% CI)	767	797		100.0	0.73 [0.49, 1.09]
Total events: 38 (Nimodipine), 54 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.52 p=0.1					

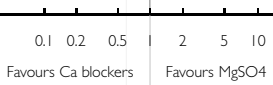
Analysis 10.13. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 13 Respiratory distress syndrome

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 13 Respiratory distress syndrome

Study	Calcium ch blockers n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	43/767	55/797		100.0	0.81 [0.55, 1.20]
Total (95% CI)	767	797		100.0	0.81 [0.55, 1.20]
Total events: 43 (Calcium ch blockers), 55 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.05 p=0.3					



Analysis 10.14. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 14 Low blood pressure for the baby

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 14 Low blood pressure for the baby

Study	Nimodipine n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	6/767	2/797		100.0	3.12 [0.63, 15.40]
Total (95% CI)	767	797		100.0	3.12 [0.63, 15.40]
Total events: 6 (Nimodipine), 2 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.40 p=0.2					

Analysis 10.15. Comparison 10 Nimodipine versus magnesium sulphate, Outcome 15 Hypotonia for the baby

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 10 Nimodipine versus magnesium sulphate

Outcome: 15 Hypotonia for the baby

Study	Nimodipine n/N	Magnesium sulphate n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Nimodipine SG 2003	13/767	24/797		100.0	0.56 [0.29, 1.10]
Total (95% CI)	767	797		100.0	0.56 [0.29, 1.10]
Total events: 13 (Nimodipine), 24 (Magnesium sulphate)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.69 p=0.09					

Analysis 11.01. Comparison 11 Nifedipine versus chlorpromazine, Outcome 01 Eclampsia

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 11 Nifedipine versus chlorpromazine

Outcome: 01 Eclampsia

Study	Nifedipine n/N	Chlorpramazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Mexico 1989	1/30	0/25		100.0	2.52 [0.11, 59.18]
Total (95% CI)	30	25		100.0	2.52 [0.11, 59.18]

Total events: 1 (Nifedipine), 0 (Chlorpramazine)

Test for heterogeneity: not applicable

Test for overall effect z=0.57 p=0.6

Analysis 11.02. Comparison 11 Nifedipine versus chlorpromazine, Outcome 02 Persistent high blood pressure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 11 Nifedipine versus chlorpromazine

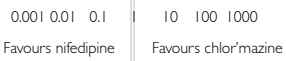
Outcome: 02 Persistent high blood pressure

Study	Nifedipine n/N	Chlorpramazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Mexico 1989	0/30	5/30		100.0	0.09 [0.01, 1.57]
Total (95% CI)	30	30		100.0	0.09 [0.01, 1.57]

Total events: 0 (Nifedipine), 5 (Chlorpramazine)

Test for heterogeneity: not applicable

Test for overall effect z=1.65 p=0.1



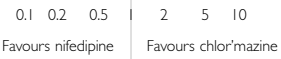
Analysis 11.03. Comparison 11 Nifedipine versus chlorpromazine, Outcome 03 Caesarean section

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 11 Nifedipine versus chlorpromazine

Outcome: 03 Caesarean section

Study	Nifedipine n/N	Chlorpramazine n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Mexico 1989	21/30	22/25		100.0	0.80 [0.60, 1.05]
Total (95% CI)	30	25		100.0	0.80 [0.60, 1.05]
Total events: 21 (Nifedipine), 22 (Chlorpramazine)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.63 p=0.1					



Analysis 12.01. Comparison 12 Nifedipine versus prazosin, Outcome 01 Maternal death

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 01 Maternal death

Study	Nifedipine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2000	0/74	1/71		100.0	0.32 [0.01, 7.73]
Total (95% CI)	74	71		100.0	0.32 [0.01, 7.73]
Total events: 0 (Nifedipine), 1 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.70 p=0.5					

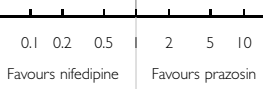
Analysis 12.02. Comparison 12 Nifedipine versus prazosin, Outcome 02 Eclampsia

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 02 Eclampsia

Study	Nifedipine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× South Africa 2000	0/74	0/71		0.0	Not estimable
Total (95% CI)	74	71		0.0	Not estimable
Total events: 0 (Nifedipine), 0 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



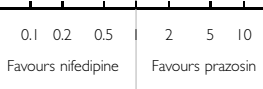
Analysis 12.03. Comparison 12 Nifedipine versus prazosin, Outcome 03 HELLP syndrome

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 03 HELLP syndrome

Study	Nifedipine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2000	6/74	5/71		100.0	1.15 [0.37, 3.60]
Total (95% CI)	74	71		100.0	1.15 [0.37, 3.60]
Total events: 6 (Nifedipine), 5 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.24 p=0.8					



Analysis 12.04. Comparison 12 Nifedipine versus prazosin, Outcome 04 Renal failure

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 04 Renal failure

Study	Nifedipine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2000	1/74	2/71		100.0	0.48 [0.04, 5.17]
Total (95% CI)	74	71		100.0	0.48 [0.04, 5.17]
Total events: 1 (Nifedipine), 2 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.61 p=0.5					

Analysis 12.05. Comparison 12 Nifedipine versus prazosin, Outcome 05 Pulmonary oedema

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 05 Pulmonary oedema

Study	Nifedipine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2000	1/74	5/71		100.0	0.19 [0.02, 1.60]
Total (95% CI)	74	71		100.0	0.19 [0.02, 1.60]
Total events: 1 (Nifedipine), 5 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.52 p=0.1					

Analysis 12.06. Comparison 12 Nifedipine versus prazosin, Outcome 06 Admission to intensive care

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 06 Admission to intensive care

Study	Nifedipine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2000	0/74	1/71		100.0	0.32 [0.01, 7.73]
Total (95% CI)	74	71		100.0	0.32 [0.01, 7.73]
Total events: 0 (Nifedipine), 1 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.70 p=0.5					

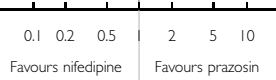
Analysis 12.07. Comparison 12 Nifedipine versus prazosin, Outcome 07 Magnesium sulphate prophylaxis

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 07 Magnesium sulphate prophylaxis

Study	Nifedipine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2000	3/74	4/71		100.0	0.72 [0.17, 3.10]
Total (95% CI)	74	71		100.0	0.72 [0.17, 3.10]
Total events: 3 (Nifedipine), 4 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.44 p=0.7					



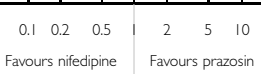
Analysis 12.08. Comparison 12 Nifedipine versus prazosin, Outcome 08 Placental abruption

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 08 Placental abruption

Study	Nifedipine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2000	9/74	9/71		100.0	0.96 [0.40, 2.28]
Total (95% CI)	74	71		100.0	0.96 [0.40, 2.28]
Total events: 9 (Nifedipine), 9 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.09 p=0.9					



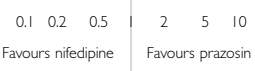
Analysis 12.09. Comparison 12 Nifedipine versus prazosin, Outcome 09 Caesarean section

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 09 Caesarean section

Study	Nifedipine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2000	47/74	50/71		100.0	0.90 [0.72, 1.13]
Total (95% CI)	74	71		100.0	0.90 [0.72, 1.13]
Total events: 47 (Nifedipine), 50 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.88 p=0.4					



Analysis 12.10. Comparison 12 Nifedipine versus prazosin, Outcome 10 Stillbirth

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 10 Stillbirth

Study	Nifedpine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2000	6/75	13/74		100.0	0.46 [0.18, 1.13]
Total (95% CI)	75	74		100.0	0.46 [0.18, 1.13]
Total events: 6 (Nifedpine), 13 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.69 p=0.09					

Analysis 12.11. Comparison 12 Nifedipine versus prazosin, Outcome 11 Admission to special care baby unit

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 11 Admission to special care baby unit

Study	Nifedipine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2000	22/69	25/61		100.0	0.78 [0.49, 1.23]
Total (95% CI)	69	61		100.0	0.78 [0.49, 1.23]
Total events: 22 (Nifedipine), 25 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.07 p=0.3					

Analysis 12.12. Comparison 12 Nifedipine versus prazosin, Outcome 12 Severe respiratory distress syndrome

Review: Drugs for treatment of very high blood pressure during pregnancy

Comparison: 12 Nifedipine versus prazosin

Outcome: 12 Severe respiratory distress syndrome

Study	Nifedipine n/N	Prazosin n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
South Africa 2000	11/69	8/61		100.0	1.22 [0.52, 2.82]
Total (95% CI)	69	61		100.0	1.22 [0.52, 2.82]
Total events: 11 (Nifedipine), 8 (Prazosin)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.45 p=0.6