

DRUGS FOR TREATMENT OF VERY HIGH BLOOD PRESSURE DURING PREGNANCY

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A substantive amendment to this systematic review was last made on 23 August 2002. Cochrane reviews are regularly checked and updated if necessary.

ABSTRACT

Background: Very high blood pressure during pregnancy poses a serious threat to women and their babies. The use of drugs to lower blood pressure will reduce this risk for the women, and possibly also for the baby.

Objective: The objective of this review was to compare different antihypertensive drugs used for treatment of severe hypertension during pregnancy.

Search strategy: We searched the Cochrane Pregnancy and Childbirth Group trials register (April 2002), the Cochrane Controlled Trials Register (The Cochrane Library, Issue 2 2002) and MEDLINE (April 2002).

Selection criteria: Studies were randomised trials. Quasi random designs were excluded. Participants were women with severe hypertension during pregnancy. Women postpartum at trial entry were excluded. Interventions were any comparisons of one antihypertensive agent with another.

Data collection and analysis: Data were extracted independently by two reviewers to assess eligibility and describe the trial characteristics, and by one reviewer for the meta-analyses. Discrepancies were resolved by discussion. There was no blinding of authorship or results. Whenever possible, unpublished data were sought from investigators.

Main results: Twenty trials were included (1637 women) and 19 were excluded. There were ten different comparisons. Hydralazine was the most common drug for others to be evaluated against. Diazoxide, given as 75mg bolus injections, appears to be associated with maternal hypotension requiring treatment, and ketanserin is less effective than hydralazine at reducing blood pressure. There is no other clear evidence that any one of the other antihypertensive agents is better than another for women with severe hypertension during pregnancy.

Reviewers' conclusions: Until better evidence is available, the choice of antihypertensive should depend on the experience and familiarity of an individual clinician with a particular drug, and on what is known about adverse maternal and fetal side-effects. Exceptions are diazoxide and ketanserin, which are probably not good choices.

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 begins to cause concern is usually considered to be around 170mmHg systolic blood pressure or 110mmHg diastolic (Redman 1993). The possible consequences of such high blood pressure for the mother include kidney failure, liver failure and cerebrovascular haemorrhage (stroke). 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 delivery).

Once blood pressure reaches 170mmHg systolic or 110mmHg 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 the delivery will be covered by a separate review.

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 effect 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 2002a). Treatment of mild to moderate hypertension in pregnancy has been reviewed by Abalos

2002. In addition, the role of plasma volume expansion is the subject of another review (Duley 2002b).

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

All randomised trials with adequate concealment of allocation. Quasi random designs were excluded.

Types of participants

Women with severe hypertension (diastolic 105 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.

Types of outcome measures

For the women: blood pressure control, eclampsia, measures of serious maternal morbidity (such as kidney failure, cardiac failure, stroke, abnormalities of the clotting system, liver failure, and respiratory depression), caesarean section, use of health service resources (such as dialysis, ventilation, admission to intensive care, length of stay), and side effects.

For the baby: fetal and neonatal death, measures of serious neonatal morbidity (such as low Apgar scores, intraventricular haemorrhage - bleeding into the brain ventricles), infant and child development (such as cerebral palsy or significant learning disability), and use of health service resources (such as admission to special care nursery, ventilation, length of stay in hospital and special needs in the community).

SEARCH STRATEGY FOR IDENTIFICATION OF STUDIES

See: [Cochrane Pregnancy and Childbirth Group search strategy](#)

This review has drawn on the search strategy developed for the Cochrane Pregnancy and Childbirth Group as a whole. The full list of journals and conference proceedings as well as the search strategies for the electronic databases, which are searched by the Group on behalf of its reviewers, are described in detail in the 'Search strategies for the identification of studies section' within the editorial information about the Cochrane Pregnancy and Childbirth Group. Briefly, the Group searches on a regular basis MEDLINE, the Cochrane Controlled Trials Register and reviews the Contents tables of a further 38 relevant journals received via ZETOC, an electronic current awareness service.

Relevant trials, which are identified through the Group's search strategy, are entered into the Group's Specialised Register of Controlled Trials. Please see Review Group's details for more detailed information. Date of last search: April 2002.

In addition, MEDLINE was searched in April 2002 using the MeSh terms 'pregnancy' and 'hypertension', limited to randomised controlled trials. The Cochrane Controlled Trials Register (The Cochrane Library, Issue 2, 2002) was searched to identify any additional trials, using the following strategy:

- 1. PREGNANCY-TOXEMIAS*: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. ((LABETOLOL or ATENOLOL) or PROPRANOLOL)
- 11. (GTN or (GLYCEROL and TRINITR*))
- 12. (URAPIDIL or PRAZOSIN)
- 13. (((9 or 10) or 11) or 12) or 13)
- 14. (8 and 13)

This search strategy will be repeated annually to update the review.

METHODS OF THE REVIEW

Trials were evaluated independently by the two reviewers to assess eligibility, describe trial characteristics and extract data. Discrepancies were resolved by discussion. There was no blinding of authorship or results. Whenever possible, unpublished data were sought from investigators. Similar outcomes were aggregated whenever possible. For example, the outcome 'persistent hypertension' includes data on need for additional non-trial therapy, need for additional trial therapy or failure to control blood pressure, depending on which was reported.

A quality score for concealment of allocation was assigned to each included trial, using the criteria described in the Cochrane Handbook ([Clarke 2002](#)), with a grade allocated to each on the basis of allocation concealment: A (adequate), B (unclear), or C (clearly inadequate). Where the method of allocation concealment was unclear, authors were contacted to provide further details. Studies with a quasi random design were excluded.

In addition, quality scores for completeness of follow up and 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 Table of Included Studies):

For completeness of follow up:

- (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, and/or 20 per cent or more participants were excluded from the analysis of that outcome.

For blinding of assessment of outcome:

- (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 than 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.

Statistical analyses was performed using the Review Manager ([RevMan 2000](#)) software, with results presented as summary relative risk (RR), risk difference (RD) and number needed to treat (1/RD). Statistical heterogeneity across trial results was evaluated using the chi-squared test as calculated in MetaView. If the results of the trials are obviously different a random effects model was used, and possible explanations for the variation such as study quality and women's characteristics at trial entry explored.

DESCRIPTION OF STUDIES

The women included in this review were largely those with very high blood pressure (diastolic blood pressure 105 mmHg or more) requiring immediate treatment. Two studies also specified proteinuria as an inclusion criterion, and several refer only to 'severe pre-eclampsia' or eclampsia. Most trials specified a minimum gestational age for recruitment. One small trial ([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 women for whom first line therapy with methyldopa had not been successful ([South Africa 2000](#)).

Of the ten comparisons in this review, five compared hydralazine with another agent. Other drugs in these comparisons include nifedipine, labetolol, methyldopa, diazoxide, prostacyclin, ketanserin, urapidil, magnesium sulphate, prazosin and nimodipine. Most

drugs were given either intravenously or intramuscularly except nifedipine and prazosin which were given orally. Dosage varied considerably between studies, in both amount and duration of therapy.

For further details see Table of Included Studies.

METHODOLOGICAL QUALITY

Most of these trials were small, with only three having more than 100 women ([NSG 1998](#); [South Africa 2000](#); [Iran 2002](#)). 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 studies published in languages other than English.

Few of these studies gave adequate information about how or whether the allocation to treatment group was concealed. For most of the studies administration of the drugs was not blinded. Only short term outcomes were reported, but follow up for these was good. There is no information about medium-long term effects on the baby.

RESULTS

This review includes 20 studies, involving 1637 women. Nineteen studies were excluded. The largest study (n = 627) compared nimodipine with magnesium sulphate ([NSG 1998](#)), but most (12/20) recruited less than 50 women.

All drugs included in this review have been shown to reduce blood pressure but there is no evidence that for women with severe hypertension during pregnancy any one agent is better at this than another. The only possible exceptions to this are diazoxide and ketanserin. 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, and an increased risk of caesarean section, when compared with labetalol. Women given ketanserin were more likely to have persistent hypertension than those given hydralazine.

For other reported outcomes the confidence intervals are all very wide, and the differences are not statistically significant.

Few trials reported 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 and scalp tingling;
- for nifedipine: flushing, nausea, vomiting;
- for urapidil nausea and tinnitus.

DISCUSSION

The numbers of women in most of these studies are small, and few outcomes other than control of blood pressure have been reported for many studies. There is also potential for bias in the assessment of blood pressure control, as there was no blinding after trial entry in most of these studies.

It is rather surprising that so 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.

REVIEWERS' CONCLUSIONS

Implications for practice

There is no good evidence that one antihypertensive is better than any of the others for reducing blood pressure. 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. Diazoxide is probably best avoided, however, as although the numbers are small it does seem to be associated with an increased risk of very low blood pressure and of caesarean section when compared to labetalol. Also, ketanserin is less effective in reducing blood pressure than hydralazine.

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. Such studies 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, low blood pressure, side effects, 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 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.

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.

ACKNOWLEDGEMENTS

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POTENTIAL CONFLICT OF INTEREST

None known.

TABLES

Characteristics of included studies

Study	Australia 1986
Methods	Randomly allocated, no further information. CFU - A, blinding - C.
Participants	N = 90. DBP >105mmHg after sedation with either phenobarbitone 200mg or diazepam 10 mg 6 hourly. Delivery planned for soon after treatment.
Interventions	Labetolol: 200mg in 200mls 5% dextrose IV at 0.5mg/kg/hr to a maximum of 3mg/kg/hr, to keep DBP at 85-90mmHg. Continued until 24 hrs after delivery. Diazoxide: 75mg 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 labetolol).
Allocation concealment	B
Study	Brazil 1994
Methods	Sealed envelopes.
Participants	N = 50. DBP >110mmHg after 60 min rest and >28 weeks gestation.
Interventions	Nifedipine: 10mg sl and IV placebo. Hydralazine: 20mg IV and sl placebo.
Outcomes	Women: time to lower blood pressure, side effects (flushing, nausea, palpitations). Baby: stillbirth, neonatal death.
Notes	
Allocation concealment	B
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	N = 74. Women with BP 170/110mmHg, or above, and <36 weeks gestation. Excluded: multiple pregnancy, diabetes, rhesus isoimmunisation.
Interventions	Labetolol: 100mg x 4/dayMethyldopa: 250mg x 4/day.Oral/IV hydralzine in both groups if BP not controlled.
Outcomes	Women: need for other drugs, side effects, caesarean section.Babies: stillbirth, neonatal death, SCBU.
Notes	Interim analysis on an ongoing trial.
Allocation concealment	B
Study	Germany 1998
Methods	Computer generated randomisation list. CFU - A, blinding C.
Participants	N = 26. BP 160/110mmHg after 3 hr bed rest, plus 1 of proteinuria, oedema or hyperreflexia. Gestation 26-38 weeks. No IV antihypertensive before entry.
Interventions	Urapidil: 6.25mg IV repeated after 5 min if BP not decreased. Then 2-4mg/hr until delivery.Hydralazine: IV, mean 0.13 mg/kg/4hrs.
Outcomes	Women: eclampsia, side effects, caesarean section.Baby: stillbirth, neonatal death.
Notes	Both groups of women also received IV magnesium ascorbate (4g load and 1-2g/hr maintenance).
Allocation concealment	C
Study	Iran 2002
Methods	Consecutively numbered sealed envelopes. Randomised in blocks of 4.
Participants	N= 126. BP at least 160/110 mmHg, and criteria for severe PE as defined by American College of Obstetricians and Gynecologists.
Interventions	Nifedipine: 8mg sl, until DBP 90-100 mmHg.Hydralazine: 5-10 mg IV, until DBP 90-100 mmHg.Both: MgSO4, 4 g bolus IV, then 1-2g/hr for 24 hr.

Outcomes	Women: persistent hig BP, further hypertensive crises, adverse effects Baby: Apgar scores.
Notes	
Allocation concealment	D
Study	Mexico 1989
Methods	'Randomised', no further information. 5 women excluded from chlorpromazine group because they received another antihypertensive. CFU - B, blinding C.
Participants	N = 60. Severe PE or eclampsia. Excluded if cardiopathy, diabetes, isoimmunisation, twin pregnancy, or antihypertensive in 48 hr before trial entry.
Interventions	Chlorpromazine: 12.5mg IV and 12.5mg IM. 12.5mg IV repeated every 30 min, to a total of 50mg, until BP controlled or an additional antihypertensive. Nifedipine: 10mg SL, repeated every 30 min to a max of 4 doses until BP controlled or an additional antihypertensive.
Outcomes	Women: eclampsia, additional antihypertensive, caesarean section. Baby: gestation at delivery (mean).
Notes	All women received phenytoin.
Allocation concealment	B
Study	Mexico 1993
Methods	Consecutively numbered sealed opaque envelopes.
Participants	N = 27. Women at 28-42 weeks with severe PE (BP 150mmHg or more, 2/3+ protein), and one or more of epigastric pain, convulsions, headache. No chronic hypertension, or renal or cariac disease.
Interventions	Hydralazine: 5mg IV. Repeated every 20 min if DBP 110mmHg or more, max x 3. If BP not controlled, chlorpromazine 12.5mg IV plus 12.5mg IM x 2. Nifedipine: 10mg SL. Repeated every 20 min if DBP 110mmHg or more, max x 3. If BP not controlled, chlorpromazine 12.5mg IV plus 12.5mg IM x2.
Outcomes	Women: 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
Study	N Ireland 1991
Methods	Sequentially numbered sealed envelopes. CFU - A, blinding - C.
Participants	N = 30. 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: 100mg IV.Hydralazine: 10mg 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	C
Study	NSG 1998
Methods	Randomised, no other information. Multicentre study. CFU - A, blinding - C.
Participants	N = 627. Women with severe pre-eclampsia and no previous therapy.
Interventions	Nimodipine: 60mg orally every 4 hr.MgSO4: IV as per institutional protocol.
Outcomes	Women: eclampsia, additional antihypertensive drug.Baby: none reported.
Notes	Available as an abstract only, interim report of an ongoing study.
Allocation concealment	B
Study	Netherlands 1999
Methods	Open randomised multicentre trial with 4 centres, randomisation by

	telephone call to answering service. CFU - A, blinding - C.
Participants	N = 44. Gestation 26-32 weeks, DBP 110mmHg 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 only if impending eclampsia (8 ketanserin, 11 hydralazine).
Interventions	Ketanserin: 5mg IV bolus then 4mg/hr. Increased every 20 min until target BP. Max 10mg/hr. Further 5mg with every 2mg/hr increment. Hydralazine: 1mg/hr IV, hourly increments of 1 mg/hr until target BP. Max 10mg/hr.
Outcomes	Woman: death, eclampsia, pulmonary oedema, HELLP, DIC, abruption, additional drugs, caesarean section.Baby: death (babies >28 weeks gestation)
Notes	19 women in each group had antenatal steroids.Funding: Janssen-Cilag (manufacture ketanserin).
Allocation concealment	A
Study	South Africa 1987
Methods	Randomly allocated, no other information. CFU - A, blinding - C.
Participants	N = 20. DBP 110mmHg or above, not settled after 2 hrs bed rest and 200mg 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: 200mg in 200ml 5% dextrose at 20mg/hr. Increased every 20 min by 20mg/hr until DBP 90-100mmHg, or maximum dose of 160mg/hr. Then continued for 1 hr.Hydralazine: 25mg in 200ml saline at 3.7mg/hr. Increased every 20 min by 3.7mg/hr until DBP 90-100mmHg, or maximum dose of 15mg/hr. Then continued for 1 hr.
Outcomes	Women: failure of BP control, eclampsia, caesarean section.Baby: death, hypoglycaemia, mean Apgar scores.
Notes	
Allocation concealment	B
Study	South Africa 1989

Methods	Random number table, no further information. CFU - A, blinding - C.
Participants	N = 33. Primigravidae; no hypertension, renal disease, or other medical problems; no antihypertensive therapy; DBP 110mmHg or more for 2 hours; and at least 28 weeks gestation. Not needing immediate delivery and no fetal distress.
Interventions	Nifedipine: 10mg oral. Repeated after 30 minutes if no response. Hydralazine: 6.25mg in 10ml 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	C
Study	South Africa 1992
Methods	Random number tables, no further information. CFU - A, blinding - C.
Participants	N = 47. Admitted to labour ward with DBP >110mmHg, which did not settle after phenobarbitone and bed rest. At least 1+ proteinuria, and above 33 weeks gestation. Excluded if imminent eclampsia or requiring immediate delivery. All had a central venous line.
Interventions	Prostacyclin: 0.5ng/kg/min IV increased at increments of 1.5ng/kg/min to maximum of 10ng/kg/min. Continued for 24 hr after delivery. Hydralazine: 0.5mg/kg.min IV increased every 15 min to a maximum of 1.5mg/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	C
Study	South Africa 1994
Methods	Sealed, numbered, opaque envelopes. Nursing sister not involved in clinical care then made up the allocated solution (4ml). 8 women excluded (9%) as delivered without receiving antihypertensive therapy. CFU - B, blinding - B.

Participants	N = 88. At least 28 weeks of pregnancy, DBP >110mmHg or DBP >100mmHg for 30 minutes.
Interventions	Ketanserin: 500ml crystalloid IV over 15 min, then 10mg ketanserin in 4ml IV. Repeated every 20 min, until DBP = 90mmHg, to a maximum of 4 doses. Hydralazine: 500ml crystalloid IV over 15 min, then 5mg hydralazine in 4ml IV. Repeated every 20 min, until DBP = 90mmHg, to a maximum of 4 doses.
Outcomes	Women: death, treatment failure, delivery for fetal distress, caesarean section. Baby: death.
Notes	Trial stopped by 'monitoring committee', reason not stated.
Allocation concealment	B
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	N = 20. Gestation >28 weeks; DBP >110mmHg after 5 minutes rest, or, 100mmHg or above on 2 occasions 30 minutes apart. Excluded if fetal distress, antihypertensive therapy during previous 12 hours, or epidural anaesthesia.
Interventions	Hydralazine: 5mg in 2ml IV over 2 minutes. Repeated after 20 minutes if BP not below 100mmHg. Ketanserin: 10mg in 2ml IV over 2 minutes. Repeated after 20 minutes if BP not below 100mmHg.
Outcomes	Women: need for second dose of drug, low BP causing fetal distress, caesarean section, eclampsia. Baby: none reported.
Notes	
Allocation concealment	B
Study	South Africa 1996
Methods	Randomised, no further information. CFU - A, blinding - C.
Participants	N = 40. Women with severe hypertension.

Interventions	Isradipine: IV infusion of 0.15mcg/kg/min, increased by 0.0025mcg/kg every 15 min until DBP <95mmHg.Hydralazine: 6.25mg IV over 10 min, repeated once if DBP still >95mmHg.
Outcomes	Women: persistent high BP. Baby: none reported.
Notes	Available as abstract only.
Allocation concealment	B
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	N = 33. MAP >125mmHg 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: 12.5mg IV repeated every 3 min in bolus of 25 mg if MAP >120mmHg. Max dose of 400mg.Hydralazine: 6.25 IV over 15 min, reeated every 30 min to maintain MAP >120mmHg.
Outcomes	Women: hypotension, side effects (headache, palpitations, nausea, tinnitus), caesarean section, treatment failure.Baby: death, Apgar (mean), cord pH (mean).
Notes	
Allocation concealment	A
Study	South Africa 2000
Methods	Consecutive numbered sealed opaque envleopes. 5 women excluded; 2 postpartum, 1 delivered before treatment started, 1 randomised twice, 1 wrongly identified. CFU - B, blinding - C.
Participants	N = 150. Women with severe early onset PE, and BP not controlled by methyl dopa 2g/day. Excluded: planned termination of pregnancy, onset of PE after 34 weeks, postpartum, already on either agent.
Interventions	Prazosin: 1mg x 3/day, to max 21mg/dayNifedipine: 10mg x3/day, to max 60mg/day.If BP still not controlled, crossover.

Outcomes	Women: 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
Study	Turkey 1996
Methods	Randomised, no further information. Drugs identically packaged and infusion rates identical. CFU - A, blinding - A.
Participants	N = 33. Women with severe pre-eclampsia.
Interventions	Nimodipine: 100ml crystalloid, then infusion of 30mg/kg/hr. MgSO4: 6g IV in 100ml crystalloid, then infusion of 2g/hr.
Outcomes	Women: Eclampsia (during therapy only), caesarean section. Baby: None.
Notes	Available as abstract only.
Allocation concealment	B
Study	USA 1987
Methods	Random numbers, 2:1 allocation. No information about concealment of allocation. CFU - A, blinding - C.
Participants	N = 19. Women with hypertension during pregnancy. Also, 41 women with postpartum hypertension, but these are excluded from this review.
Interventions	Labetalol: Either, 20mg IV then 10-50mg every 10 min until DBP 100mmHg or less, or 20mg IV then repeat doses of 20mg, 40mg, 80mg, 80mg every 10 min to a maximum of 300mg or until DBP 100mmHg or less. Hydralazine: 5mg IV every 10 min until DBP 100mmHg or less.
Outcomes	Women: Caesarean section, no others reported separately from the postpartum women. Baby: Apgar scores, respiratory distress syndrome, hypoglycaemia, hypothermia.
Notes	

Allocation concealment	B
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BP = blood pressure; CFU = completeness of follow up; DBP = diastolic blood pressure; DIC = disseminated intravascular coagulation; HELLP = haemolysis, elevated liver enzymes, lowered platelets; Hr = hours; ICU = intensive care unit; IM = intramuscular; IV = intravenous; sl = sublingual; MAP = mean arterial pressure; MgSO₄ = magnesium sulphate; min = minutes; PE = pre-eclampsia; PMH = past medical history; SCBU = special care baby unit; SD = standard deviation; SL = sublingual

Characteristics of excluded studies

Study	Reason for exclusion
Argentina 1986	No data on clinical outcomes. Available as abstract only. "Randomly divided". Comparison of atenolol with methyl dopa (n = 60).
Brazil 1988	No data on clinical outcomes. Double blind comparison of a single dose of oral nifedipine with single bolus IV hydralazine (n = 13).
France 1986	No data on clinical outcomes. Available as abstract only. 'Randomised', no further information. 35 women with DBP>105 after 20 weeks gestation, and in hospital. Comparison of clonidine and labetalol.
Ghana 1995	Quasi random study, allocation by alternate odd and even numbers. Comparison of nifedipine with hydralazine (n = 104).
Iran 1994	Available as abstract only. No clinical outcomes reported, and no information about drug dosages (n = 30). Comparison of nifedipine with hydralazine.
Israel 1991	Not a randomised trial, women allocated to treatment group according to week of the month (n = 54). Comparison of nifedipine with hydralazine.
Israel 1999	Randomised trial but entry at diastolic BP of 90 mmhg and no clinically useful outcomes reported
Jamaica 1999	Quasi random: "selecting numbers blindly from an envelope by assigning odd numbers to hydralazine and even to isradipine" (n = 39).
Japan 2002	Not randomised. Study of 50 women with severe pre-eclampsia grouped according to length of treatment with nicardipine.
Malaysia 1996	Quasi random design, treatment allocation by odd and even numbers on identity cards. 200 women with DBP above 120mmHg and over 28 weeks. Comparison of nifedipine and hydralazine.

Mexico 2000	Comparison of isosorbide with placebo. Normal clinical care after 1 hour. "Assigned randomly". Women with severe PE after 28 weeks with DBP 110mmHg or more after 20 min rest.
New Zealand 1992	No clinical outcomes reported or available from authors (n = 24). Comparison of nifedipine with hydralazine.
Scotland 1983	No clinical outcomes reported (n = 21). Comparison of labetalol with hydralazine.
Singapore 1971	Quasi random design. Women allocated "in strict rotation". Women with BP 180/110 or above, or 160/100 and above with proteinuria. Comparison of protoveratrine with guanethedine with dihydrzinophthalazine (n = 285). Data for a case series of treatment with dihydrzinophthalazine included, not possible to separate.
South Africa 1982	Women with antepartum and postpartum hypertension not reported separately. Comparison of labetalol with hydralazine (n = 12).
South Africa 1993	40 women randomised, and 6 excluded from some of the outcomes. Denominators are not given for the clinical outcomes. Authors contacted, no further data available. Comparison of nifedipine with hydralazine.
South Africa 2002	Some women did not meet eligibility criteria. Dose finding study. Randomised by consecutively numbered sealed envelopes. Computer generated random numbers in blocks of 20. 30 women with DBP 105 mmHg or more, x2 10 min apart, or 100 or more for 30 min. Comparison of 10mg ketanserin every 10 min with every 20 min.
Spain 1988	Available in abstract only. Comparison of hydralazine plus methyl dopa with labetalol. Described as "double blind controlled trial", no other information about concealment of allocation. Numbers allocated to each intervention not reported.
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. 50 women with severe PE, or with chronic hypertension and superimposed PE. Comparison of nifedipine with labetalol.

DBP = diastolic blood pressure; IV = intravenous; min = minutes; PE = pre-eclampsia

Characteristics of ongoing studies

Study	Trial name or title	Participants	Interventions	Outcomes	Starting date	Contact information	Notes
Henne ssy 2002	Diazoxide vs hydralazine for acute treatment of very high BP in pregnancy.	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.	Diazoxide undiluted IV mini-boluses of 15 mg every 2-3 mins versus hydralazine 5 mg IV every 20 mins followed if necessary by an infusion until BP achieves a predetermined level.	Adequate lowering of BP, in 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	2000. Expected close December 2002.	Dr Annemarie Hennessy Department of Renal Medicine, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia. ahennese@renicu.rpa.nsw.gov.au	All women are given simultaneous IV infusion of magnesium sulphate.

BP = blood pressure; hrs = hours; IV = intravenous; mins = minutes; vs = versus

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GRAPHS

Graphs and Tables

To view a graph or table, click on the outcome title of the summary table below.

01 Labetalol versus hydralazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 eclampsia</u>	1	20	Relative Risk (Fixed) 95% CI	Not estimable
<u>02 persistent high blood pressure</u>	1	20	Relative Risk (Fixed) 95% CI	0.50 [0.05, 4.67]
<u>03 caesarean section</u>	3	69	Relative Risk (Random) 95% CI	0.71 [0.40, 1.24]
<u>04 side effects for the woman</u>	1	30	Relative Risk (Fixed) 95% CI	0.75 [0.34, 1.64]
<u>05 fetal or neonatal deaths</u>	3	69	Relative Risk (Fixed) 95% CI	0.50 [0.05, 4.94]
<u>06 Apgar <7 at 5 minutes</u>	1	19	Relative Risk (Fixed) 95% CI	0.10 [0.01, 1.81]
<u>07 respiratory distress syndrome</u>	1	19	Relative Risk (Fixed) 95% CI	0.69 [0.15, 3.12]
<u>08 neonatal hypoglycaemia</u>	2	39	Relative Risk (Fixed) 95% CI	1.14 [0.19, 6.94]

02 Calcium antagonists versus hydralazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 persistent high blood pressure</u>	3	199	Relative Risk (Fixed) 95% CI	0.50 [0.25, 0.98]
<u>02 low blood pressure for the woman</u>	1	33	Relative Risk (Fixed) 95% CI	0.94 [0.06, 13.82]
<u>03 side effects for the woman</u>	2	159	Relative Risk (Fixed) 95% CI	0.94 [0.45, 1.96]

<u>04 side effects for the woman (specific effects)</u>			Relative Risk (Fixed) 95% CI	Subtotals only
<u>05 stillbirth</u>	1	50	Relative Risk (Fixed) 95% CI	0.33 [0.01, 7.81]
<u>06 neonatal death</u>	2	83	Relative Risk (Fixed) 95% CI	2.28 [0.35, 14.78]

03 Prostacyclin versus hydralazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 persistent high blood pressure</u>	1	47	Relative Risk (Fixed) 95% CI	0.23 [0.01, 4.47]
<u>02 caesarean section</u>	1	47	Relative Risk (Fixed) 95% CI	0.74 [0.50, 1.10]
<u>03 side effects for the woman</u>	1	47	Relative Risk (Fixed) 95% CI	1.14 [0.08, 17.11]
<u>04 neonatal death</u>	1	47	Relative Risk (Fixed) 95% CI	1.14 [0.08, 17.11]
<u>05 ventilation of the baby</u>	1	47	Relative Risk (Fixed) 95% CI	0.32 [0.08, 1.40]

04 Ketanserin versus hydralazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 maternal death</u>	2	124	Relative Risk (Fixed) 95% CI	0.32 [0.03, 2.96]
<u>02 eclampsia</u>	2	64	Relative Risk (Fixed) 95% CI	0.60 [0.08, 4.24]
<u>03 persistent high blood pressure</u>	3	144	Relative Risk (Fixed) 95% CI	6.74 [2.49, 18.28]
<u>04 pulmonary oedema</u>	1	44	Relative Risk (Fixed) 95% CI	0.11 [0.01, 1.95]

<u>05 HELLP syndrome</u>	1	44	Relative Risk (Fixed) 95% CI	0.20 [0.05, 0.81]
<u>06 disseminated intravascular coagulation</u>	1	44	Relative Risk (Fixed) 95% CI	3.00 [0.13, 69.87]
<u>07 delivery due to fetal distress</u>	1	80	Relative Risk (Fixed) 95% CI	0.30 [0.03, 2.78]
<u>08 placental abruption</u>	1	44	Relative Risk (Fixed) 95% CI	0.11 [0.01, 1.95]
<u>09 caesarean section</u>	2	64	Relative Risk (Fixed) 95% CI	0.20 [0.03, 1.42]
<u>10 side effects for the women</u>	1	44	Relative Risk (Fixed) 95% CI	0.41 [0.21, 0.79]
<u>11 perinatal mortality (babies born >28 weeks)</u>	1	36	Relative Risk (Fixed) 95% CI	0.16 [0.01, 2.87]

05 Urapidil versus hydralazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 eclampsia</u>	1	26	Relative Risk (Fixed) 95% CI	Not estimable
<u>02 additional antihypertensive</u>	1	33	Relative Risk (Fixed) 95% CI	1.38 [0.06, 31.14]
<u>03 hypotension</u>	1	33	Relative Risk (Fixed) 95% CI	0.22 [0.02, 2.13]
<u>04 side effects for the woman</u>	2	59	Relative Risk (Fixed) 95% CI	0.59 [0.10, 3.58]
<u>05 placental abruption</u>	1	33	Relative Risk (Fixed) 95% CI	0.15 [0.01, 3.46]
<u>06 caesarean section</u>	2	59	Relative Risk (Fixed) 95% CI	0.77 [0.51, 1.16]
<u>07 stillbirth</u>	1	26	Relative Risk (Fixed) 95% CI	Not estimable

<u>08 neonatal death</u>	2	59	Relative Risk (Fixed) 95% CI	0.66 [0.08, 5.25]
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06 Labetolol versus methyldopa

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 use of additional drugs</u>	1	72	Relative Risk (Fixed) 95% CI	1.19 [0.74, 1.94]
<u>02 changed drugs due to side effects</u>	1	72	Relative Risk (Fixed) 95% CI	8.08 [0.45, 144.74]
<u>03 caesarean section</u>	1	72	Relative Risk (Fixed) 95% CI	0.85 [0.56, 1.30]
<u>04 fetal or neonatal death</u>	2	144	Relative Risk (Fixed) 95% CI	4.49 [0.22, 90.30]
<u>05 small for gestational age</u>	1	72	Relative Risk (Fixed) 95% CI	0.78 [0.43, 1.39]
<u>06 admission to special care baby unit</u>	1	72	Relative Risk (Fixed) 95% CI	1.06 [0.66, 1.71]

07 Labetolol versus diazoxide

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 persistent high blood pressure</u>	1	90	Relative Risk (Fixed) 95% CI	0.50 [0.13, 1.88]
<u>02 low blood pressure requiring treatment</u>	1	90	Relative Risk (Fixed) 95% CI	0.06 [0.00, 0.99]
<u>03 caesarean section</u>	1	90	Relative Risk (Fixed) 95% CI	0.43 [0.18, 1.02]
<u>04 perinatal deaths</u>	1	90	Relative Risk (Fixed) 95% CI	0.14 [0.01, 2.69]

09 Nimodipine versus magnesium sulphate

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
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	studies	participants		
<u>01 eclampsia</u>	2	660	Relative Risk (Fixed) 95% CI	1.02 [0.38, 2.72]
<u>02 additional antihypertensive</u>	1	627	Relative Risk (Fixed) 95% CI	0.84 [0.55, 1.29]
<u>03 caesarean section</u>	1	33	Relative Risk (Fixed) 95% CI	0.97 [0.42, 2.27]

10 Nifedipine versus chlorpromazine

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 eclampsia</u>	1	55	Relative Risk (Fixed) 95% CI	2.52 [0.11, 59.18]
<u>02 additional antihypertensive</u>	1	60	Relative Risk (Fixed) 95% CI	0.09 [0.01, 1.57]
<u>03 caesarean section</u>	1	55	Relative Risk (Fixed) 95% CI	0.80 [0.60, 1.05]

11 Nifedipine versus prazosin

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
<u>01 maternal death</u>	1	145	Relative Risk (Fixed) 95% CI	0.32 [0.01, 7.73]
<u>02 eclampsia</u>	1	145	Relative Risk (Fixed) 95% CI	Not estimable
<u>03 HELLP syndrome</u>	1	145	Relative Risk (Fixed) 95% CI	1.15 [0.37, 3.60]
<u>04 renal failure</u>	1	145	Relative Risk (Fixed) 95% CI	0.48 [0.04, 5.17]
<u>05 pulmonary oedema</u>	1	145	Relative Risk (Fixed) 95% CI	0.19 [0.02, 1.60]
<u>06 admission to</u>	1	145	Relative Risk	0.32 [0.01,

<u>intensive care</u>			(Fixed) 95% CI	7.73]
<u>07 magnesium sulphate prophylaxis</u>	1	145	Relative Risk (Fixed) 95% CI	0.72 [0.17, 3.10]
<u>08 placental abruption</u>	1	145	Relative Risk (Fixed) 95% CI	0.96 [0.40, 2.28]
<u>09 caesarean section</u>	1	145	Relative Risk (Fixed) 95% CI	0.90 [0.72, 1.13]
<u>10 stillbirth</u>	1	149	Relative Risk (Fixed) 95% CI	0.46 [0.18, 1.13]
<u>11 admission to special care baby unit</u>	1	130	Relative Risk (Fixed) 95% CI	0.78 [0.49, 1.23]
<u>12 severe respiratory distress syndrome</u>	1	130	Relative Risk (Fixed) 95% CI	1.22 [0.52, 2.82]

COVER SHEET

Drugs for treatment of very high blood pressure during pregnancy

Reviewer(s) Duley L, Henderson-Smart DJ

Contribution of Reviewer(s) Methods for the review were developed by Lelia Duley and David Henderson-Smart. Lelia Duley wrote the text of the review, with discussion and comments from David Henderson-Smart. Data were extracted by Lelia Duley and David Henderson-Smart and then entered by Lelia Duley.

Issue protocol published first 1999 issue 2

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Date of last amendment minor Information not supplied by reviewer

Date of last substantive amendment 23 August 2002

Most recent changes Search updated on 29 April 2002.
New included studies: England 1982, South Africa 2000. Netherlands 1995 now Netherlands 1999 with more outcome data. Brazil 1990 moved from excluded to included, and now Brazil 1994. Germany 1994 moved from excluded to included, and now Germany 1998. New reference for South Africa 1997.

New excluded studies: Singapore 1971, Argentina 1986, Brazil 1988, Ghana 1995, Israel 1999, Jamaica 1999, USA 1999, Mexico 2000.

New trial awaiting assessment: Mexico 1998.

New ongoing trial: Hennessy 2002.

Basic conclusions unchanged.

Date new studies sought but none found Information not supplied by reviewer

Date new studies found but not yet included/excluded Information not supplied by reviewer

Date new studies found and included/excluded 29 April 2002

Date reviewers' conclusions amended 29 April 2002 section

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SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- NSW Centre for Perinatal Health Services Research, University of Sydney AUSTRALIA
- Medical Research Council UK
- Resource Centre for Randomised Trials, Oxford UK

SYNOPSIS

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. The review of trials found that while antihypertensive drugs reduce 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.

KEY WORDS

Female; Humans; Pregnancy; Antihypertensive Agents[adverse effects][*therapeutic use]; Hypertension[*drug therapy]; Pregnancy Complications, Cardiovascular[*drug therapy]; Randomized Controlled Trials