Prevention and treatment of postpartum hypertension (Review)

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[Intervention Review]

Prevention and treatment of postpartum hypertension

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ABSTRACT

Background

Postpartum blood pressure (BP) is highest three to six days after birth when most women have been discharged home. A significant rise in BP may be dangerous (e.g., can lead to stroke), but there is little information about how to prevent or treat postpartum hypertension.

Objectives

To assess the relative benefits and risks of interventions to:

(1) prevent postpartum hypertension, by assessing whether 'routine' postpartum medical therapy is better than placebo/no treatment; and

(2) treat postpartum hypertension, by assessing whether (i) one antihypertensive therapy is better than placebo/no therapy for mild-moderate postpartum hypertension; and (ii) one antihypertensive agent offers advantages over another for mild-moderate or severe postpartum hypertension.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (31 January 2013), bibliographies of retrieved papers, and personal files.

Selection criteria

For women with antenatal hypertension, trials comparing a medical intervention with placebo/no therapy. For women with postpartum hypertension, trials comparing one antihypertensive with either another or placebo/no therapy.

Data collection and analysis

We extracted the data independently and were not blinded to trial characteristics or outcomes. We contacted authors for missing data when possible.

Main results

Nine trials are included.

Prevention: Four trials (358 women) compared furosemide, nifedipine capsules, or L-arginine with placebo/no therapy. For women with antenatal pre-eclampsia, postnatal furosemide is associated with a strong trend towards reduced use of antihypertensive therapy in hospital.

Treatment: For treatment of mild-moderate postpartum hypertension, three trials (189 women) compared timolol, oral hydralazine, or oral nifedipine with methyldopa. Use of additional antihypertensive therapy did not differ between groups (risk ratio (RR) 0.92, 95% confidence interval (CI) 0.20 to 4.20; three trials), but the trials were not consistent in their effects. The drugs were well tolerated.

For treatment of severe postpartum hypertension, two trials (120 women) compared intravenous hydralazine with either sublingual nifedipine or intravenous labetalol. There were no maternal deaths or hypotension. Use of additional antihypertensive therapy did not differ between groups (RR 0.58, 95% CI 0.04 to 9.07; two trials), but the trials were not consistent in their effects.

Authors' conclusions

For women with pre-eclampsia, postnatal furosemide may decrease the need for postnatal antihypertensive therapy in hospital, but more data are needed on substantive outcomes before this practice can be recommended. There are no reliable data to guide management of women who are hypertensive postpartum. Any antihypertensive agent used should be based on a clinician's familiarity with the drug. Future studies should include data on postpartum analgesics, severe maternal hypertension, breastfeeding, hospital length of stay, and maternal satisfaction with care.

PLAIN LANGUAGE SUMMARY

Prevention and treatment of postpartum hypertension

Not enough evidence to know how best to treat women with hypertension after birth.

After birth, it is not uncommon for women to experience high blood pressure (hypertension), but it can have serious consequences. It can lead to stroke and, very rarely, death. It is unclear what causes hypertension after childbirth, or which women may develop the problem, although women with antenatal severe pre-eclampsia appear to be at highest risk. The review of nine trials found no reliable evidence to guide care for these women. Further research is needed, particularly as the problem occurs most commonly three to six days after birth when most women have left hospital.

BACKGROUND

The hypertensive disorders of pregnancy are associated with increased morbidity and mortality. Research has focused on the antenatal complications, for both mother and baby, and the risks and benefits of administering antihypertensive therapy prior to delivery (Abalos 2007; Duley 2002). There is very little information on how best to manage postpartum hypertension, regardless of type or severity, to optimise maternal safety and minimise hospital stay.

The true prevalence of postpartum hypertension is difficult to ascertain, but the importance of monitoring women in the puerperium was highlighted by the Confidential Enquiries into Maternal Deaths in the United Kingdom (Conf Enq 94-96), in which roughly 10% of maternal deaths due to a hypertensive disorder of pregnancy occurred in the postpartum period (Tan 2002). In the 1997 to 1999 triennial report, one of 15 deaths was attributed to severe hypertension that developed only postpartum in a woman with antenatal pre-eclampsia (Conf Enq 97-99). Other complications of severe postpartum hypertension include stroke, and possibly, eclampsia. In a survey of all cases of eclampsia in the United Kingdom, 1992, it was shown that 44% of eclampsia occurs in the postpartum period, usually in the first 48 hours after delivery (Douglas 1994). Women with postpartum hypertension may also

experience longer hospital stays and possibly, heightened anxiety about their recovery.

Blood pressure rises progressively over the first five postnatal days, peaking on days three to six after delivery (Bayliss 2002; Walters 1986). This pattern of blood pressure is thought to result from mobilisation, from the extravascular to the intravascular space, of the six to eight litres of total body water and the 950 mEq of total body sodium accumulated during pregnancy. Excretion of urinary sodium (i.e., natriuresis) has been observed on days three to five postpartum (Davison 1984), and it has been postulated that this may result from an increase in atrial natriuretic peptide (ANP). ANP has roles in natriuresis and inhibition of aldosterone, angiotensin II and vasopressin (Bond 1989) and has been observed to rise during the first week postpartum (Castro 1994).

What causes a postpartum recurrence or de novo (i.e., new) postpartum presentation of hypertension is not known. Perhaps an attenuated increase in ANP plays a role. Five women with de novo postpartum hypertension were seen to have significantly lower ANP levels, compared with 10 normotensive controls (Nagai 1997). Another possibility is a failure to observe the expected postpartum fall in serum angiotensin I, an inactive intermediate of angiotensin II which is a potent vasoconstrictor. This was observed in 10 women with postpartum hypertension (recurrent or de novo) (Mizutani 1993).

There are iatrogenic causes of postpartum hypertension. Bromocriptine, to inhibit lactation, was withdrawn from the American market in 1994, because of numerous case reports of intracerebral haemorrhage and other vasospasm-mediated adverse events (such as myocardial infarction). It is plausible that the administration of non-steroidal anti-inflammatory drugs (NSAIDs) for postpartum analgesia may contribute to the risk of postpartum hypertension by stimulating sodium retention (Makris 2004).

Postpartum hypertension may represent a continuation of an antenatal hypertensive disorder (regardless of type), or the appearance of a new hypertensive disorder after delivery. Although it is recognised that antenatal hypertension may continue into the postpartum period, the incidence with which this occurs and for what duration, have been poorly defined. For clarification, hypertension is defined as a blood pressure of 140/90 mmHg or more. Mild-to-moderate hypertension is usually defined as a blood pressure of 140 to 169/90 to 109 mmHg, and severe hypertension as 170/110 mmHg or more. Hypertension in pregnancy (or the puerperium) is classified as: pre-existing hypertension (defined as that which antedated pregnancy or appeared before 20 weeks' gestation); gestational hypertension without proteinuria (defined as hypertension that appeared at or after 20 weeks, with less than 0.3 grams/day of urinary protein); gestational hypertension with proteinuria (also known as 'pre-eclampsia' or 'toxaemia'); or pre-eclampsia superimposed on pre-existing hypertension. Eclampsia is included in the pre-eclampsia category, and is defined as an otherwise unexplained seizure in a woman with pre-eclampsia.

Prevention of postpartum hypertension for high-risk groups

Women delivered with pre-eclampsia appear to be at increased risk of postpartum hypertension (Tan 2002). This was recognized by JS Henry in 1936, who pointed out that, "... in toxaemic patients, the postpartum fall [in blood pressure] to normal is very variable, but is apt to take longer in eclamptics and in pre-eclamptics" (Henry 1936). In the no treatment arm of a randomised controlled trial comparing furosemide with no treatment, 26% of women with pre-eclampsia were observed to be on antihypertensive therapy at the time of hospital discharge (Ascarelli 1999). An observational study of 67 women with either proteinuric or non-proteinuric gestational hypertension found that 50% of women had a blood pressure greater than 150/100 mmHg on day five postpartum (Walters 1987). In women who develop pre-eclampsia antenatally, postnatal hypertension lasted approximately two weeks (mean ± standard deviation (SD) of 16 ± 9.5 days). Although blood pressure dropped significantly in the first two weeks postpartum, there was substantial variability between women (Bowler 2002; Ferrazzani 1994). Women at increased risk for recurrence of hypertension after delivery were those who delivered preterm, and those multiparous women with higher uric acid levels or blood urea nitrogen (Ferrazzani 1994). In a study of 80 women with pregnancy-induced hypertension, the risk of developing postpartum morbidity increased with higher levels of urinary albumin and urinary immunoglobulin G (IgG), measured in the antepartum and intrapartum periods. In this study, postpartum morbidity was defined as one or more of the following: (1) need for greater than 24 hours of maternal postpartum intensive care or parenteral magnesium sulphate administration; (2) need for postpartum parenteral antihypertensive medication for blood pressure greater than 160/110 mmHg; (3) postpartum blood pressure of greater than 140/90 for more than three days; and/or (4) need for oral antihypertensive medication at the time of hospital discharge (Eden 1986).

Compared with women with pre-eclampsia, fewer women with gestational hypertension appear to have postpartum hypertension. Also, the duration of this hypertension appeared to be shorter (mean ± SD of six days, SD 5.5 days) than in women with pre-eclampsia. Again, the duration was highly variable (Ferrazzani 1994). Multiparous women with higher uric acid and blood urea nitrogen appeared to be at higher risk (Ferrazzani 1994).

It is not known whether or not antihypertensives should be routinely re-instituted postpartum among women with antenatal hypertension in order to prevent postpartum hypertension. No international guidelines give guidance in this regard.

Treatment of postpartum hypertension

The incidence of de novo postpartum hypertension has also been poorly defined. In an observational study of 136 primarily Caucasian women who were normotensive antenatally, 12% had a diastolic blood pressure (dBP) greater than 100 mmHg during the first five postpartum days, with an average rise in blood pressure of 6 mmHg systolic and 4 mmHg diastolic (Walters 1986). In contrast, postpartum hypertension occurred in only 3.5% of 210 Nigerian women who were normotensive during pregnancy. However, excluded were women who were hypertensive within 48 hours of delivery. Of note, is the fact that of the two thirds of women who became hypertensive within six weeks postpartum, 70% did so between days two and seven postpartum (Ojugwu 1993). Long-term follow-up was available for only 35 of the women (17%), most of whom developed gestational hypertension (N = 8) or recurrent isolated postpartum hypertension (N = 17) in subsequent pregnancies. Finally, in a case-control study of women readmitted to hospital with postpartum pre-eclampsia after a normotensive pregnancy (versus controls who were normotensive throughout pregnancy and the postpartum period), a rise in mean arterial pressure of more than 10 mmHg between the intrapartum and postpartum periods was associated with a greater than threefold increased risk of readmission postpartum with severe pre-eclampsia or eclampsia (Atterbury 1996).

For manifest postpartum hypertension, there is general consensus that severe hypertension should be treated (to prevent acute maternal vascular complications such as stroke), but no such consensus exists for mild-moderate postpartum hypertension (whether de novo or not and regardless of type), needs to be treated. The Canadian Hypertension Society recommends treatment for women with severe hypertension or symptoms, and those with target organ damage and moderate gestational hypertension (i.e., dBP greater than 99 mmHg) three days after delivery (Rey 1997). The American and Australasian guidelines acknowledge the postnatal rise in blood pressure and the possibility that antihypertensive medication may need to be increased in women with antenatal (even chronic) hypertension, but they make no specific recommendations about when treatment should be started and what the therapeutic goal should be (Brown 2000; NHBPEPWG 2000).

Despite widespread use of antihypertensives in the postpartum period, there is limited evidence to support their safety for babies of breastfeeding mothers. A review of the available observational literature (37 reports covering 41 different antihypertensives) concluded that the following drugs have minimal milk to maternal plasma ratios to make breastfeeding acceptable: methyldopa, beta-blockers with high protein binding (e.g., oxprenolol), angiotensin converting enzyme inhibitors and some dihydropyridine calcium channel blockers (Beardmore 2002). All of these drugs are used commonly in the postpartum period.

This review focuses on the benefits and risks of antihypertensive therapy for the prevention or treatment of postpartum hypertension. We will not address other therapeutic approaches (e.g., postpartum curettage) (Hunter 1961; Magann 1993; Magann 1994; Robinson 1964) or magnesium sulphate therapy (Livingston 2003; Ehrenberg 2006).

OBJECTIVES

To assess the relative benefits and risks of interventions to prevent postpartum hypertension, by assessing whether or not 'routine' postpartum administration of oral antihypertensive therapy is better than placebo/no treatment.

To assess the relative benefits and risks of treatment of postpartum hypertension by assessing whether or not:

(i) oral antihypertensive therapy is better than placebo/no therapy for mild-moderate postpartum hypertension; and

(ii) one antihypertensive agent offers any advantages over another for either mild-moderate or severe postpartum hypertension.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. Quasi-random designs were excluded.

Types of participants

Women with either:
(i) an antenatal hypertensive disorder of pregnancy; or
(ii) women with de novo postpartum hypertension.
Postpartum hypertension was defined as an elevated blood pressure (140/90 mmHg or more) measured twice at least four hours apart, between delivery and six weeks postpartum.

Types of interventions

For prevention of postpartum hypertension

Comparisons of:
(i) routine postpartum antihypertensive therapy versus placebo/no therapy;
(ii) routine postpartum antihypertensive therapy of one agent versus another.

For treatment of postpartum hypertension

Comparisons of:
(i) oral antihypertensive agents with placebo or no therapy; or
(ii) oral antihypertensive agent(s) versus another.
Any pharmacological therapy that was given to reduce blood pressure was acceptable for this review, and was considered as a source of between-trial heterogeneity in outcome. Also recorded were other aspects of postpartum management, including use of non-steroidal anti-inflammatories (NSAIDs), bromocriptine, and/or ergot alkaloids. Interventions used to treat the syndrome of pre-eclampsia (e.g., endometrial curettage) were not included in the review.

Types of outcome measures

Primary outcomes

Maternal outcomes

Measures that evaluated the effectiveness and safety of antihypertensive therapy for the woman:

- stroke (acute neurological deficit of vascular origin, which lasts more than 48 hours);
- maternal mortality;
- severe hypertension (blood pressure of greater than or equal to 170/110 for four hours or more);
- eclampsia, haemolysis;
- elevated liver enzymes;
- low platelets syndrome;
- the need for additional antihypertensive therapy (according to criteria defined by respective researchers);
- the need to change therapy due to maternal side-effects of antihypertensive therapy;
- maternal hypotension
- duration of postpartum hospital stay (days);
- incidence of readmission to hospital after discharge postpartum;
- measures of maternal anxiety or well-being as defined by respective researchers.

Measures not prespecified were:

- Maternal end-organ failure (any);
- Use of NSAIDs for postpartum analgesia;
- Maternal side effects to antihypertensive medication;
- Severe maternal hypotension.

Secondary outcomes

Breastfeeding and neonatal outcomes

- Proportion of mothers who breastfed their babies and among them, neonatal side-effects such as:

- bradycardia;
- hypotension;
- hypothermia;
- hypoglycaemia, as defined by respective researchers.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (31 January 2013).
The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE;
3. weekly searches of EMBASE;
4. handsearches of 30 journals and the proceedings of major conferences;
5. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE and EMBASE, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.
Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.
For previous versions of this review, we searched PubMed (2002 to 2009) and MEDLINE (1966 to May 2003), EMBASE (1980 to January 2003) using the search strategies listed in Appendix 1 and Appendix 2.

Searching other resources

We searched the bibliographies of retrieved papers and personal files.
We did not apply any language restrictions.

Data collection and analysis

For methods used in previous versions of this review *see* Appendix 3. For this 2013 update, the following methods were used.

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion, or, if required, we consulted a third person.

Data extraction and management

We designed a form to extract data. For eligible studies, at least two review authors (S Sadeghi and LA Magee (LAM), or LAM and P von Dadelszen) extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person. For this update, data were entered into Review Manager (RevMan 2012) software and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We have described for each included study, the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should have produced comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g., random number table; computer random number generator);
- high risk of bias (any non-random process, e.g., odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We have described for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g., telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding (checking for possible performance bias)

We have described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Studies were judged at low risk of bias if they were blinded, or we judged that the lack of blinding could not have affected the results. Blinding was assessed separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding (checking for possible detection bias)

We have described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We planned to assess blinding separately for different outcomes or classes of outcomes.

We assessed the methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We have described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We have stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups; less than 2.5% of women were excluded from the analysis);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; "as treated" analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting bias

We have described for each included study how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the methods as:

- low risk of bias (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review were reported);

- high risk of bias (where not all of the study's pre-specified outcomes were reported; one or more reported primary outcome(s) was(were) not pre-specified; outcomes of interest were reported incompletely and so cannot be used; study failed to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other sources of bias

We described for each included study any important concerns we had about other possible sources of bias.
We assessed whether each study was free of other problems that could put it at risk of bias:

- low risk of other bias;
- high risk of other bias;
- unclear whether there is risk of other bias.

(7) Overall risk of bias

We made explicit judgments about whether studies were at high risk of bias, according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

No trials provided continuous data. In future updates, if continuous data are analysed, we will use the mean difference if outcomes are measured in the same way between trials. We will use the standardised mean difference to combine trials that measure the same outcome, but use different methods.

Unit of analysis issues

Cluster-randomised trials

In future updates, if identified and eligible for inclusion, we will include cluster-randomised trials in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a sensitivity analysis to investigate the effects of the randomisation unit.

Cross-over Trials

Cross-over trials were excluded from this review.

Other unit of analysis issues

None identified.

Dealing with missing data

For included studies, levels of attrition were noted.
For all outcomes, analyses were carried out, as far as possible on an intention-to-treat basis (i.e., we attempted to include all participants randomised to each group in the analyses). The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the T^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if the I^2 was greater than 50% and either the T^2 was greater than zero, or there was a low P value (< 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

There were too few studies included and too few outcomes reported to assess the impact of potential reporting bias on outcomes. In future updates, if more studies are included, we will assess reporting biases.
If there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2012). We used fixed-effect inverse variance meta-analysis for combining data where trials examined the same intervention, and the trials' populations and methods were judged sufficiently similar. Where we suspected clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we used random-effects meta-analyses. The random-effects summary was treated as the average range of possible treatment effects. If the average treatment effect was not clinically meaningful, we did not combine trials.
If we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of T^2 and I^2.

Subgroup analysis and investigation of heterogeneity

If we identified substantial heterogeneity, we investigated it using the following subgroup analyses:

- type of agent used to prevent postpartum hypertension (i.e., furosemide versus an antihypertensive);
- treatment of mild-to-moderate versus severe postpartum hypertension.

The following outcomes were used in subgroup analyses:

- maternal death;
- maternal organ failure;
- severe hypotension;
- antihypertensive use in hospital;
- and antihypertensive use at hospital discharge.

We assessed subgroup differences by interaction tests available within RevMan (RevMan 2012). We reported the results of subgroup analyses quoting the $\chi 2$ statistic and P value, and the interaction test I^2 value.

Sensitivity analysis

We planned to carry out sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, high attrition rates, or both, with poor quality studies being excluded from the analyses in order to assess whether this made any difference to the overall result. Poor quality was defined as studies being at high risk of bias for allocation concealment, or incomplete outcome data, or both.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Included studies

Nine trials were included.
See Characteristics of included studies.

Prevention of postpartum hypertension

Four trials studied (358 women) interventions for prevention of postpartum hypertension in women with antenatal pre-eclampsia (defined as pregnancy-induced hypertension with either proteinuria or adverse features such as haemolysis, elevated liver enzymes, low platelets syndrome). Women with pre-existing hypertension were excluded from one trial and those with chronic kidney disease from another.
Two trials (282 women) compared routine postnatal furosemide therapy (20 to 40 mg orally per day, for five to seven days) with either placebo or no therapy. In one trial (Ascarelli 2005), 20 mEq orally per day of supplemental potassium was administered, and in the other (Matthews 1997), intravenous magnesium sulphate was given if the woman was considered to be at 'high risk' of eclampsia. Neither trial reported mean and standard deviation (SD) of baseline blood pressure, but one trial (Matthews 1997) reported the change in blood pressure (BP) on days one, three and seven after delivery (i.e., -6.5 mmHg (furosemide) versus -3.5 (placebo) on day one, -10.6 (furosemide) versus -9.75 (placebo) on day three, and -11.5 (furosemide) versus -7.8 (placebo) on day seven). Follow-up ranged from day 10 postpartum (Ascarelli 2005) to six weeks postpartum (Matthews 1997).
A third trial (31 women) compared nifedipine capsules (10 mg orally every four hours for 48 hours) with placebo (Barton 1990). Women had mild hypertension at baseline, and at 18 to 24 hours following delivery, mean (±SD) diastolic BP was 93.9 ± 1.6 mmHg (nifedipine) versus 100.2 ± 2.6 (placebo). All women in this trial were on magnesium sulphate. Women were followed until hospital discharge.
A fourth trial (45 women) compared L-arginine (a nitric oxide donor) with placebo. Women had pre-eclampsia antenatally or postnatally and a mean pre-treatment BP of 169 ± 15mmHg systolic and 105 ± 8mmHg diastolic at a mean gestational age of 34.7 ± 4.0 weeks. Women received L-arginine before delivery and for three days postpartum; most women (30/45) were treated only postpartum. Women were followed to day three and day 10 postpartum.
No trials were identified that compared routine postpartum administration of one antihypertensive agent versus another.

Treatment of postpartum hypertension

No trials were identified that compared antihypertensive therapy with placebo/no therapy.

Five trials (480 women) studied treatment of postpartum hypertension by comparing different oral antihypertensive agents.

Women in these trials were hypertensive postpartum, but the nature of the hypertensive disorder was not well described, and included both women who were normotensive ante and intrapartum, and those who had severe antenatal pre-eclampsia. Diastolic BP was moderate to severe in nature. Approximately half of the women delivered their first child in the two trials that reported parity. Women with comorbid conditions were usually excluded, due to pre-existing hypertension (Griffis 1989; Walss Rodriguez 1991), renal disease (Fidler 1992; Walss Rodriguez 1991), hepatic dysfunction (Griffis 1989), need for intensive care (Walss Rodriguez 1991), or diabetes or multiple pregnancy (Fidler 1992).

One trial reported a average gestational age at delivery which was at term [38.6 ± 1.26 (nifedipine sublingual) versus 37.6 ± 2.4 (hydralazine sublingual)] (Walss Rodriguez 1991). Another reported an average gestational age at delivery that was preterm [33.2 ± 4.1 (methyldopa) versus 33.5 ± 4.3 (nifedipine)] (Sayin 2005).

Five trials compared one oral antihypertensive agent with another. In three trials, methyldopa was compared with either timolol (Fidler 1992), hydralazine (Griffis 1989), or nifedipine (oral) (Sayin 2005). In two trials, hydralazine (parenteral) was compared with either nifedipine (sublingual) (Walss Rodriguez 1991) or labetalol (iv) (Vigil-De Gracia 2007). Follow-up appeared to occur until hospital discharge (Griffis 1989; Sayin 2005; Vigil-De Gracia 2007; Walss Rodriguez 1991) or until two to six weeks postpartum (Fidler 1992).

Excluded studies

Twenty trials were excluded based on: applying a surgical intervention (i.e., endometrial curettage), incomplete information about clinical outcomes, failure to report outcomes among women treated only postpartum, or the absence of abstractable data on clinical outcomes. *See* Characteristics of excluded studies.

Risk of bias in included studies

All included trials were small, with a median sample size of 45 women (range 18 to 264). The quality of the trials was poor. No trials reported the potential co-intervention of non-steroidal anti-inflammatory drug (NSAID) use for postnatal analgesia.

See Figure 1 and Figure 2 for summaries of 'Risk of bias' assessment.

Figure 1. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

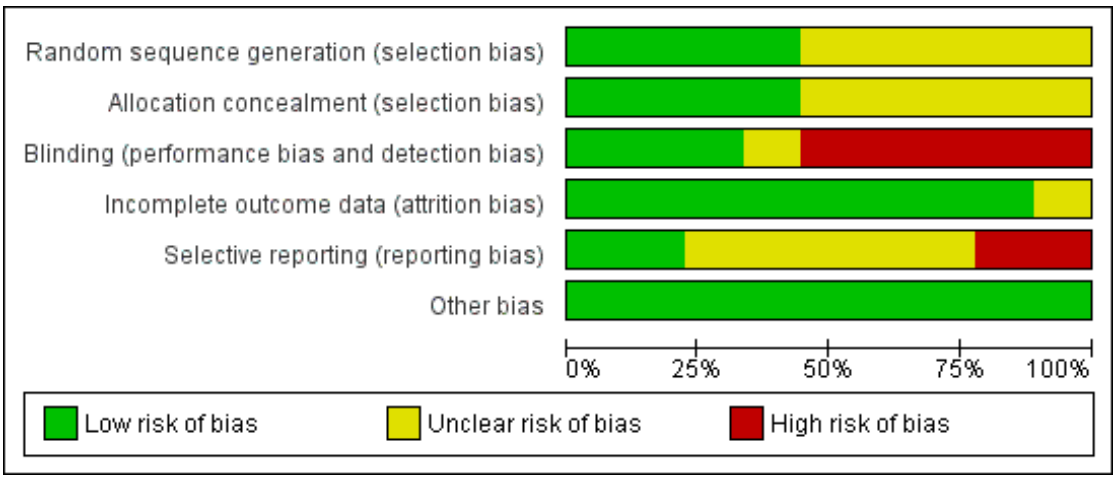
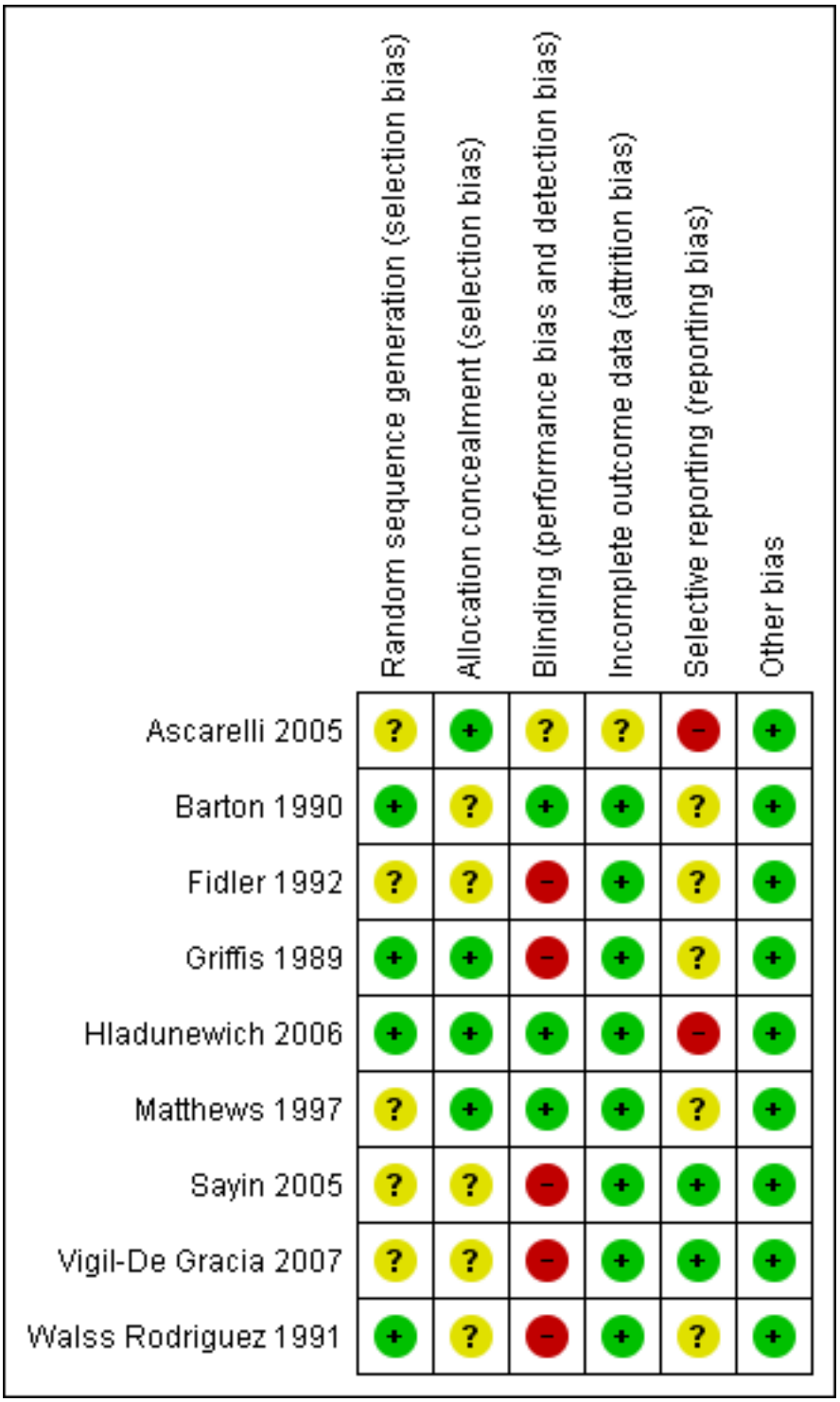


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Four trials described a random component in the sequence generation process. Four trials described adequate concealment of allocation.

Blinding

Three of the nine trials reported outcome assessment blinding and most outcomes included data from only one trial.

Incomplete outcome data

There was adequate follow-up (less than 2.5% loss to follow-up) in all but one trial.

Selective reporting

Only two trials were deemed to be at low risk of bias for selective reporting. The risk of bias was unclear for five of the nine trials; they were published prior to the year 2000 and, as such, did not have published study protocols with which to compare reported outcomes in the manuscripts. One trial did not describe all prespecified outcomes and another did not report all outcomes according to randomised group.

Other potential sources of bias

No other sources of bias were identified.

Effects of interventions

Nine trials are included.

(A) Routine postnatal antihypertensive therapy in women with antenatal pre-eclampsia, in order to prevent postpartum hypertension

Four trials (358 women) compared routine antihypertensive therapy (furosemide, nifedipine capsules, or L-arginine) with an approach that dictated antihypertensive treatment only for severely elevated blood pressure postpartum. There are insufficient data for any conclusions about the possible benefits and harms of these management strategies.

There were no maternal deaths (Analysis 1.1), serious maternal morbidity (Analysis 1.2), or severe maternal hypotension reported (Analysis 1.3) but the data are limited and not consistent with either benefit or risk.

With use of routine postnatal furosemide, there was a strong trend for a decrease in the need for additional antihypertensive therapy (for blood pressure 150 systolic or 100 diastolic, or higher) on the postnatal wards (risk ratio (RR) 0.74, 95% confidence interval (CI) 0.55 to 1.00; one trial, N = 264 women) (Analysis 1.5). The direction of effect was the same for antihypertensive therapy at hospital discharge but the results were not statistically significant (RR 0.81, 95% CI 0.59 to 1.12; two trials, N = 282 women) (Analysis 1.6.1). The mean number of medical attendances during hospitalisation did not differ between the furosemide (14.9 attendances) and control (18.0 attendances) groups in one trial (Matthews 1997); however, statistical comparisons were not possible because standard deviations were not reported. Mean postnatal hospital stay did not appear to differ in one trial (7.3 versus 7.6 days) but SD were not reported (Matthews 1997).

The trial of routine nifedipine capsules reported no significant difference in the occurrence of severe hypertension treatment between groups, but data were not provided (Barton 1990). The trial of L-arginine versus placebo did not find a between-group difference in severe hypertension (or use of antihypertensive therapy on day three postpartum).

None of the 31 women in the nifedipine versus placebo trial changed drugs due to side-effects (Analysis 1.7).

No differences between subgroups were observed (Analysis 1.6).

None of the aforementioned trials reported: whether or not women used NSAIDs for postpartum analgesia, the incidence of adverse drug reactions, or the incidence of breastfeeding.

(B) Antihypertensive therapy for women with postpartum hypertension

No trials were located that compared antihypertensive with placebo or no therapy for mild-to-moderate postpartum hypertension, of any type.

For treatment of mild-moderate postpartum hypertension, three trials (189 women) compared timolol, hydralazine (oral), or nifedipine (oral) with methyldopa. Magnesium sulphate therapy was administered for 12 hours postpartum in one trial (Griffis 1989). There were no maternal deaths (Analysis 2.1). The need for additional antihypertensive therapy did not differ between the groups (average RR 0.92, 95% CI 0.20 to 4.20; three trials, 189 women; heterogeneity: $Tau^2 = 0.75$; $Chi^2 = 2.09$, df = 1 (P = 0.15); $I^2 = 52\%$); however, the trials were more different in their effects than could be expected by chance alone (Analysis 2.3). The need to change drugs due to side-effects was infrequent (Analysis 2.4).

For treatment of severe postpartum hypertension, two trials (120 women) compared intravenous hydralazine with either sublingual nifedipine (Walss Rodriguez 1991) or intravenous labetalol (Vigil-De Gracia 2007). Magnesium sulphate therapy was given for 24 hours postpartum in one trial (Vigil-De Gracia 2007). There were no maternal deaths and no reported maternal hypotension (Vigil-De Gracia 2007) (Analysis 2.1) (Analysis 2.2). The need for

additional antihypertensive therapy did not differ between groups (average RR 0.58, 95% CI 0.04 to 9.07; two trials, 120 women; heterogeneity: Tau² = 2.24; Chi² = 2.21, df = 1 (P = 0.14); I² = 55%), but the trials were not consistent in their effects (Analysis 2.3). The need to change drugs due to side-effects was not reported.

No differences between subgroups were observed (Analysis 2.3).

None of these trials reported whether or not women used NSAIDs for postpartum analgesia.

DISCUSSION

From the few trials that focused on the prevention or management of postpartum hypertension, there are insufficient data for any reliable conclusions to be drawn about the relative benefits and risks of different management strategies.

Prevention of postpartum hypertension

For women with antenatal hypertension, even that of pre-eclampsia, there is a strong trend towards reduced use of antihypertensive therapy in hospital with use of routine postnatal furosemide (with routine potassium supplementation). It is unclear whether there may be other potential benefits (e.g., reduced antihypertensive use at hospital discharge and/or length of maternal hospital stay) or potential harms (e.g., on breastfeeding).

Treatment of postpartum hypertension

For women with manifest postpartum hypertension (whether or not they were hypertensive before delivery), there are no data that inform whether or not mild-to-moderate hypertension should be treated, and if so, whether or not one agent is preferable to another. Certainly, two of the agents studied (timolol and methyldopa) are not in common usage postpartum. Regardless of the approach taken, the currently evaluated antihypertensive therapies appear to be associated with few women changing drugs due to maternal side-effects.

AUTHORS' CONCLUSIONS

Implications for practice

For women with pre-eclampsia, postnatal furosemide may decrease the need for postnatal antihypertensive therapy in hospital, but more data are needed on substantive outcomes before this practice can be recommended. There are no reliable data to guide management of women who are hypertensive postpartum. Any antihypertensive agent used should be based on a clinician's familiarity with the drug. Given that peak postpartum blood pressure occurs on days three to six postpartum, clinicians should be aware that peaks may occur after hospital discharge and, therefore, may be missed unless close follow up is ensured.

Implications for research

Future trials of prevention of postpartum hypertension or treatment of mild-moderate postpartum hypertension should randomise women to an antihypertensive medication versus placebo, before comparing one antihypertensive agent with another. All trials should include information about use of non-steroidal anti-inflammatories after delivery, and examine the following relevant clinical endpoints: severe maternal hypertension, breastfeeding, hospital length of stay, and maternal satisfaction with care.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ascarelli 2005

Methods	Sequentially numbered sealed opaque envelopes. Randomisation method not stated.
Participants	264 postpartum women. Delivered > or equal to 20 weeks. All with the diagnosis of mild or severe pre-eclampsia, or HELLP syndrome, or chronic hypertension with superimposed pre-eclampsia. Excluded women with hypokalaemia, haemodynamic instability, those on diuretics or potassium supplements, and those who did not understand the consent form
Interventions	Furosemide 20 mg po OD x 5 days plus potassium supplements (K-Dur 20 meq/day in 132 women). No therapy in 132 women. IV MgS04 discontinued before onset of trial in both groups, and all women experienced onset of spontaneous diuresis prior to enrolment. Treatment goal: sBP < 150 and/or dBP < 100.
Outcomes	Changes in BP. Need for additional antihypertensive agent during hospitalisation. Need for additional antihypertensive agent at the time of discharge
Notes	Many results are presented by type of hypertensive disorder but randomisation was not stratified for the type of hypertension

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Low risk	Sequentially numbered sealed opaque envelopes.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	For participants, personnel and outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The number of women in the final paper differ from the number in the previously unpublished version, without explanation. There was no explanation for why in each group, one woman who was randomised was not presented in terms of baseline data

Ascarelli 2005 (*Continued*)

		or outcomes
Selective reporting (reporting bias)	High risk	Many results are presented by type of hypertensive disorder but randomisation was not stratified for the type of hypertension. Study protocol not available
Other bias	Low risk	No other bias identified.

Barton 1990

Methods	"Randomized...by sequential assignment from sealed envelopes based on a table of random numbers." Method of randomisation by random number tables.
Participants	31 postpartum women with antepartum diagnosis of pre-eclampsia. sBP > 100 or dBP > 120 or sBP = 160-180 or dBP = 110-120 for > 2 hrs or sBP > 140 or dBP > 90 x 2, > 6 hrs apart. Excluded women with reactions to calcium channel blockers and those requiring supplemental therapy for hypertension other than hydralazine
Interventions	Nifedipine 10 mg po every 4 hrs x 48 hrs (right after delivery) in 16 women. Placebo po Q4H x 48 hrs in 15 women. Both groups received 10 mg of hydralazine IV if sBP > 160 or dBP > 110 every 20 mins until BP <= 150/100. If above failed x 3, then nitroprusside given. All women were given continuous IV MgS04. Treatment goal: BP < or equal to 160/110.
Outcomes	Need for additional antihypertensive therapy. Change in treatment due to maternal side-effects. Significant hypotension. Duration of hospitalisation. MAP. U/O. Urinary specific gravity.
Notes	Author contacted re: doses of hydralazine needed in each group and the duration of hospitalisation for each group

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number tables.
Allocation concealment (selection bias)	Unclear risk	Envelopes not stated to be opaque.

Barton 1990 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Adequate for participants, personnel, and outcome assessors.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Remote publication with no published protocol
Other bias	Low risk	No other bias identified.

Fidler 1992

Methods	"...randomly allocated..". Method of randomisation not stated.
Participants	80 untreated postpartum women. dBP of 95-105 x 2, 24 hrs apart. No antihypertensive treatment for 48 hrs prior to onset of study. Excluded women with diabetes, multiple gestation, and those already receiving antihypertensive therapy
Interventions	Timolol 5 mg po TID in 40 women. Methyldopa 250 mg po TID. In both cases, dose was doubled every 24 hrs x 2 if dBP > 95. If dBP > 95 after 2 attempts at doubling dose, po hydralazine was added
Outcomes	Need for additional antihypertensive therapy. Change in treatment due to maternal side-effects. BP changes.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation not stated.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	High risk	No stated blinding of participants, personnel, or outcome assessment

Fidler 1992 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Remote publication with no published protocol
Other bias	Low risk	No other bias identified.

Griffis 1989

Methods	"..sealed envelope...envelopes contained odd and even numbers generated at random." Randomisation by random number selection.
Participants	26 postpartum women with antepartum or intrapartum hypertension and proteinuria. Postpartum dBP > or equal to 96 x 2. Excluded: women with history of chronic hypertension or hepatic disease and those who had antihypertensive treatment during pregnancy other than what was used for intrapartum PIH
Interventions	Hydralazine 20 mg IM every 6 hrs in 12 women. Methyldopa 250 mg IV every 6 hrs in 12 women. Doses doubled if 2 successive dBP > 110. All women received IV MgS04 at 1.5 g/hr x 12 hrs. Treatment goal: dBP < 110.
Outcomes	Need for additional antihypertensive therapy. Change in treatment due to maternal side-effects. Need for augmentation of dose. Time to diurese. Changes in MAP.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by random number selection.
Allocation concealment (selection bias)	Low risk	Adequate.
Blinding (performance bias and detection bias) All outcomes	High risk	No stated blinding of participants, personnel, or outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data

Griffis 1989 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Remote publication with no published protocol
Other bias	Low risk	No other bias identified.

Hladunewich 2006

Methods	Quality score: AAA Randomisation by computer-generated random number tables with the allocation performed centrally by pharmacy	
Participants	45 women with pre-eclampsia antenatally or postnatally; most patients were treated only postpartum (30/45). Excluded: women with chronic renal disease.	
Interventions	L-arginine (3.5 g po every 6 hr or 10 g IV every 8 hr if unable to take po medication) taken before delivery or within 24 hr postpartum and continued for 3 days postpartum, or placebo taken before delivery or within 24 hr postpartum and continued for 3 days postpartum	
Outcomes	Data on the following clinically important outcomes were obtained from the primary author: severe postpartum hypertension (day 3 postpartum) and use of antihypertensive therapy (day 3 postpartum)	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by computer-generated random number tables.
Allocation concealment (selection bias)	Low risk	Allocation performed centrally by pharmacy.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo used to blind participants and personnel (as well as those assessing outcomes)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	High risk	Published report does not include all expected outcomes
Other bias	Low risk	No other bias identified.

Matthews 1997

Methods	"Randomization was performed by pharmacy." Randomisation method not stated.
Participants	19 postpartum women enrolled at 12-24 hrs postdelivery. Diagnosis of pre-eclampsia. Excluded: women with hepatic or renal impairment or hypovolaemia
Interventions	Furosemide 40 mg po x 7 days in 10 women (2/10 received IV MgS04). Placebo 40 mg po x 7 days in 8 women (3/8 received IV MgS04). Acute control by bolus of IV hydralazine. Treatment goal: not stated.
Outcomes	Need for additional antihypertensive therapy at discharge. Change in treatment due to maternal side-effects. Number of medical attendances: routine and ER visits. Mean length of puerperal hospital stay. Average fall in potassium 48 hrs postdelivery. Oliguria postdelivery. Fall in MAP. Hypertension at postnatal visit.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Low risk	A - Adequate.
Blinding (performance bias and detection bias) All outcomes	Low risk	Placebo used to blind participants and personnel (as well as those assessing outcome)
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Remote publication with no published protocol
Other bias	Low risk	No other bias identified.

Sayin 2005

Methods	Randomisation method not stated in the official translation of this Turkish paper
Participants	83 women with "hypertension" 24 hours after birth. Excluded women with gestational hypertension or superimposed pre-eclampsia
Interventions	Methyldopa 250 mg po TID in 41 women (until sBP was < 150 mmHg and dBP was < 100 mmHg) Nifedipine 10 mg po QID in 42 women (until sBP was < 150 mmHg and dBP was < 100 mmHg) If BP was > 140/90 mmHg, gave metoprolol 100 mg po per day. If BP was "still too high", then a cardiologies was consulted regarding therapy with amlodipine 5 mg po OD or perindopril 4 mg po OD Women were discharged from hospital when sBP was < 140 mmHg and dBP was < 90 mmHg
Outcomes	Number and duration of antihypertensive therapy. Length of hospitalisation.
Notes	No information on adverse effects.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated in the Turkish translation of the paper
Allocation concealment (selection bias)	Unclear risk	"randomly divided into 2 groups."
Blinding (performance bias and detection bias) All outcomes	High risk	No stated blinding of participants, personnel, or outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report appears to contain all expected outcomes
Other bias	Low risk	No other bias identified.

Vigil-De Gracia 2007

Methods	"Randomized." Randomisation method not stated.
Participants	82 women with a hypertensive disorder of pregnancy postpartum sBP >/ 160 mmHg or dBP >/ 110 mmHg.

Vigil-De Gracia 2007 (*Continued*)

	Were at least 24 hours after their last dose of IV antihypertensive therapy antepartum or intrapartum No concurrent antihypertensive therapy. No contraindication to labetalol or hydralazine.
Interventions	Hydralazine 5 mg "slow" IV bolus (every 5 minutes to a maximum of 5 doses) in 42 women Labetalol 20 mg IV (then if BP effect not achieved in 20 minutes, 40 mg IV was given, and then similarly, 80 mg IV every 5 minutes to a maximum of 300 mg, equivalent to 5 doses) in 40 women All women were prescribed bedrest, magnesium sulphate (4 g IV bolus then an infusion of 1 g/hr until 24 hours postpartum), plasma volume expansion (900 mL of Ringer's Lactate with 100 mL of 25% albumin or 1000 mL of Ringer's Lactate, @ 75 mL/hr for 12 hr) Oliguria was treated with 1 or 2 "fluid" boluses of 300-500 mL
Outcomes	BP including hypotension. Number of doses of antihypertensive medication required. Adverse effects.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation method not stated.
Allocation concealment (selection bias)	Unclear risk	"randomized."
Blinding (performance bias and detection bias) All outcomes	High risk	No stated blinding of participants, personnel, or outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Low risk	Published report appears to contain all expected outcomes
Other bias	Low risk	No other bias identified.

Walss Rodriguez 1991

Methods	Randomisation by random number tables.
Participants	38 postpartum women with diagnosis of severe pre-eclampsia and dBP > or equal to 110. Excluded: women with chronic hypertension, renal disease and those in the ICU
Interventions	Hydralazine 40 mg po every 6 hrs, plus nifedipine 10 mg sl if dBP > or equal to 110 in 18 women. No antihypertensive agent but nifedipine 10 mg sl if dBP > or equal to 110 in 10 women Additional antihypertensive agent given if dBP > or equal to 110 persistently. Treatment goal: dBP < 110.
Outcomes	Need for additional antihypertensive therapy. Interval time for nifedipine doses needed.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation by random number tables
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding (performance bias and detection bias) All outcomes	High risk	No stated blinding of participants, personnel, or outcome assessment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data
Selective reporting (reporting bias)	Unclear risk	Remote publication with no published protocol
Other bias	Low risk	No other bias identified.

BP: blood pressure
dBP: diastolic blood pressure
ER: emergency room
HELLP: haemolysis, elevated liver enzyme, low platelet
hrs: hours
ICU: intensive care unit
IM: intramuscular
IV intravenous
MAP: mean arterial pressure
meq: milliequivalent

mins: minutes
OD: dosing once daily
PIH: pregnancy induced hypertension
PO: dosing by mouth
QID: dosing four times daily
Q4H : every 4 hours
sBP: systolic blood pressure
TID: dosing three times daily
U/O: urine output

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adarsh 2006	Postpartum curettage as a therapeutic option has been excluded from this review
Alkan 2006	Postpartum curettage as a therapeutic option has been excluded from this review
Barrilleaux 2003	A trial of dexamethasone for postpartum treatment of the end-organ complications of severe pre-eclampsia (not hypertension)
Belfort 1988	A prospective study; not a RCT.
Ehrenberg 2006	This is a trial of magnesium sulphate for pre-eclampsia and there is a separate review on this topic
Garden 1982	No clinical outcomes reported specifically for postpartum patients
Gomez 2005	Postpartum curettage as a therapeutic option has been excluded from this review
Hennessy 2007	This is an antenatal RCT.
Jia 2007	The intervention (self-prescribed Xiaobai Decoction) was administered to decrease proteinuria, not to affect BP
Keiseb 2002	Prospective randomised single blinded trial studying severe pre-eclampsia/eclampsia related oliguria in the immediate postpartum period. No BP information was provided in the study. There was no response from the authors upon our request for the required additional information
Livingston 2003	This is a trial of magnesium sulphate for pre-eclampsia and there is a separate review on this topic
Mabie 1987	No BP or other maternal outcomes reported within the postpartum group
Magann 1993	Postpartum curettage as a therapeutic option has been excluded from this review
Magann 1994	Postpartum curettage as a therapeutic option has been excluded from this review

(*Continued*)

Mantel 1997	A double-blind RCT studying effects of Dopamine in postpartum preeclamptic women with oliguria. No BP information was provided in the study. There was no response from the authors upon our request for the required additional information
Marsoni 1985	A trial of postpartum hypotension not hypertension.
Montenegro 1985	A double-blind RCT with cross-over with placebo. Number of patients in each treatment arm is unknown. No clinical outcomes reported. There was no response from the authors upon our request for the required additional information
Morrison 1993	Postpartum curettage as a therapeutic option has been excluded from this review
Vermillion 1999	A double-blind RCT. No stratification of postpartum patients therefore, no abstractable data
Weiner 1984	A double-blind RCT with cross-over with placebo. Number of women who crossed over from the ketanserin group is unknown. Number of women who were in the placebo group first and achieved a dBP < 95 is unknown. There was no response from the authors upon our request for the required additional information

BP: blood pressure
dBP: diastolic blood pressure
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Aina-Mumuney 2006

Trial name or title	Hypertonic saline use for volume expansion in postpartum pre-eclampsia. [NCT 00181077]
Methods	Randomised, open label, active control, single group assignment, safety/efficacy trial
Participants	Pre-eclampsia, postpartum. Excluding: maternal age < 18 years, non-English speaking or otherwise unable to give informed consent, serum creatinine of 1.6 mg/dL or higher, medically unstable, serum Na < 130 or > 150 mEq/L, co-morbid conditions that affect renal function
Interventions	2% buffered hypertonic saline infused at the rate of 75 mL/hr or lactated Ringer's solution at 75 mL/hr All women will receive magnesium sulphate.
Outcomes	Primary: fluid input to output ratios. Secondary: laboratory evaluation of inflammatory parameters (platelet count, IL-1, IL-6), liver enzymes, weight

Aina-Mumuney 2006 (*Continued*)

Starting date	June 2003.
Contact information	Abimbola Aina-Mumuney, John Hopkins University.
Notes	Estimated study completion is listed as April 2006, but the information was last updated on May 23, 2006

meq: milliequivalent
Na: sodium

DATA AND ANALYSES

Comparison 1. Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	2	295	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Furosemide versus placebo/no therapy	1	264	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 Routine antihypertensive versus placebo	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Maternal organ failure	1	264	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.1 Furosemide versus placebo/no therapy	1	264	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Severe hypotension	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.1 Routine antihypertensive versus placebo	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Severe hypertension	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.60, 1.39]
4.1 L-arginine vs. placebo	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.60, 1.39]
5 Postnatal antihypertensive use in hospital	1	264	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 1.00]
5.1 Furosemide versus placebo/no therapy	1	264	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.55, 1.00]
6 Postnatal antihypertensive use at hospital DISCHARGE	3	325	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.58, 1.08]
6.1 Furosemide vs. placebo/no therapy	2	282	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.59, 1.12]
6.2 L-arginine vs. placebo	1	43	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.21, 1.94]
7 Medication changed secondary to maternal side-effects	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.1 Routine antihypertensive versus placebo	1	31	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Comparison 2. Oral antihypertensive therapy for treatment of postpartum hypertension

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	2	106	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Antihypertensive agent versus another for mild-moderate postpartum hypertension	2	106	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Maternal hypotension	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

2.1 Antihypertensive agent versus another for severe postpartum hypertension	1	82	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Need for additional antihypertensive therapy	5	309	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.25, 1.96]
3.1 Antihypertensive agent versus another for mild-moderate postpartum hypertension	3	189	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.20, 4.20]
3.2 Antihypertensive agent versus another for severe postpartum hypertension	2	120	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.04, 9.07]
4 Medication changed secondary to maternal side-effects	2	106	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.30]
4.1 Antihypertensive agent versus another for mild-moderate postpartum hypertension	2	106	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.05, 5.30]
4.2 Antihypertensive therapy for severe postpartum hypertension	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 1.1. Comparison 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension, Outcome 1 Maternal death.

Review: Prevention and treatment of postpartum hypertension

Comparison: 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension

Outcome: 1 Maternal death

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Furosemide versus placebo/no therapy				
Ascarelli 2005	0/132	0/132		0.0 [0.0, 0.0]
Subtotal (95% CI)	**132**	**132**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
2 Routine antihypertensive versus placebo				
Barton 1990	0/16	0/15		0.0 [0.0, 0.0]
Subtotal (95% CI)	**16**	**15**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				

(*Continued* . . .)

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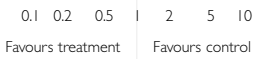
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: Z = 0.0 (P < 0.00001)				
Total (95% CI)	**148**	**147**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				



Analysis 1.2. Comparison 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension, Outcome 2 Maternal organ failure.

Review: Prevention and treatment of postpartum hypertension

Comparison: 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension

Outcome: 2 Maternal organ failure

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Furosemide versus placebo/no therapy				
Ascarelli 2005	0/132	0/132		0.0 [0.0, 0.0]
Total (95% CI)	**132**	**132**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 1.3. Comparison 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension, Outcome 3 Severe hypotension.

Review: Prevention and treatment of postpartum hypertension

Comparison: 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension

Outcome: 3 Severe hypotension

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Routine antihypertensive versus placebo				
Barton 1990	0/16	0/15		0.0 [0.0, 0.0]
Total (95% CI)	**16**	**15**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

Analysis 1.4. Comparison 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension, Outcome 4 Severe hypertension.

Review: Prevention and treatment of postpartum hypertension

Comparison: 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension

Outcome: 4 Severe hypertension

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 L-arginine vs. placebo					
Hladunewich 2006	14/22	16/23		100.0 %	0.91 [0.60, 1.39]
Total (95% CI)	**22**	**23**		**100.0 %**	**0.91 [0.60, 1.39]**
Total events: 14 (Treatment), 16 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.42 (P = 0.67)					
Test for subgroup differences: Not applicable					

Analysis 1.5. Comparison 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension, Outcome 5 Postnatal antihypertensive use in hospital.

Review: Prevention and treatment of postpartum hypertension

Comparison: 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension

Outcome: 5 Postnatal antihypertensive use in hospital

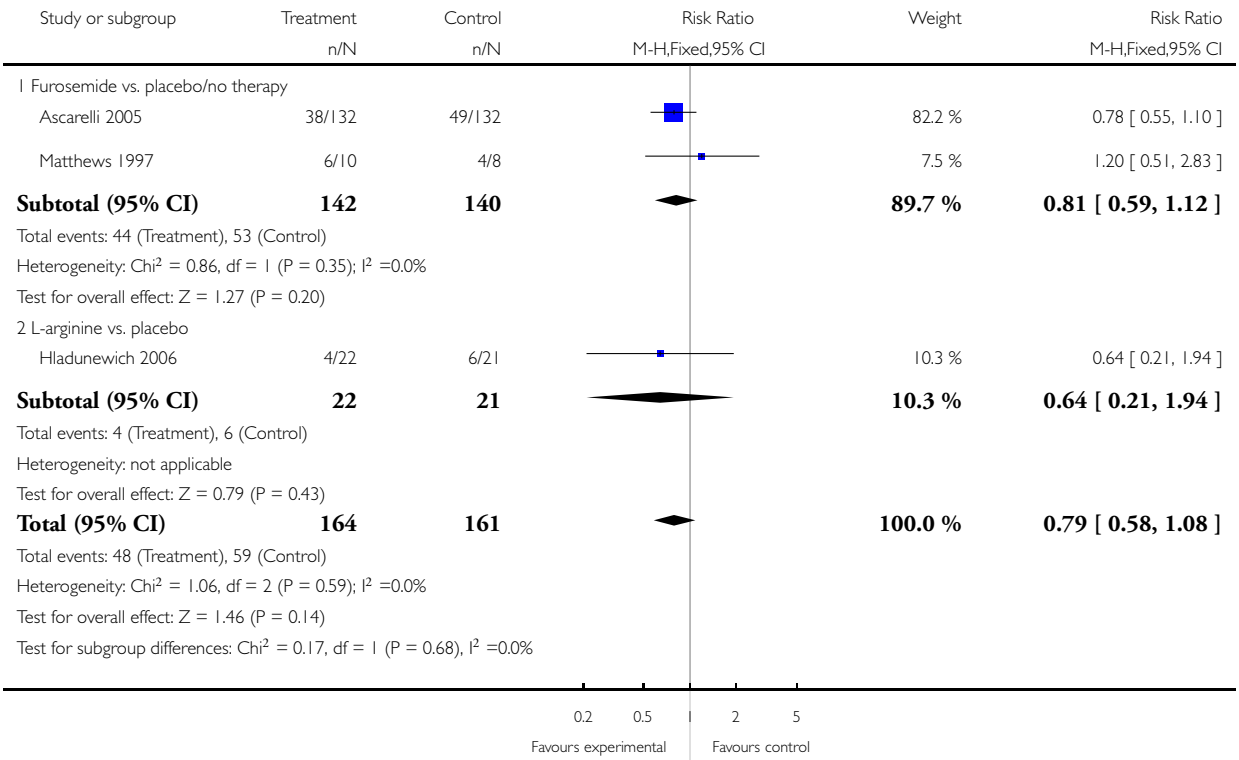
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Furosemide versus placebo/no therapy					
Ascarelli 2005	46/132	62/132		100.0 %	0.74 [0.55, 1.00]
Total (95% CI)	**132**	**132**		**100.0 %**	**0.74 [0.55, 1.00]**
Total events: 46 (Treatment), 62 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.98 (P = 0.048)					
Test for subgroup differences: Not applicable					

Analysis 1.6. Comparison 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension, Outcome 6 Postnatal antihypertensive use at hospital DISCHARGE.

Review: Prevention and treatment of postpartum hypertension

Comparison: 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension

Outcome: 6 Postnatal antihypertensive use at hospital DISCHARGE



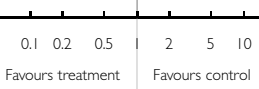
Analysis 1.7. Comparison 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension, Outcome 7 Medication changed secondary to maternal side-effects.

Review: Prevention and treatment of postpartum hypertension

Comparison: 1 Routine postnatal oral antihypertensive therapy for prevention of postpartum hypertension

Outcome: 7 Medication changed secondary to maternal side-effects

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Routine antihypertensive versus placebo				
Barton 1990	0/16	0/15		0.0 [0.0, 0.0]
Total (95% CI)	**16**	**15**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				



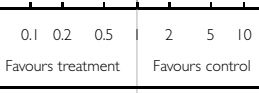
Analysis 2.1. Comparison 2 Oral antihypertensive therapy for treatment of postpartum hypertension, Outcome 1 Maternal death.

Review: Prevention and treatment of postpartum hypertension

Comparison: 2 Oral antihypertensive therapy for treatment of postpartum hypertension

Outcome: 1 Maternal death

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Antihypertensive agent versus another for mild-moderate postpartum hypertension				
Fidler 1992	0/40	0/40		0.0 [0.0, 0.0]
Griffis 1989	0/12	0/14		0.0 [0.0, 0.0]
Total (95% CI)	**52**	**54**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P<0.00001); I^2 =0.0%				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				



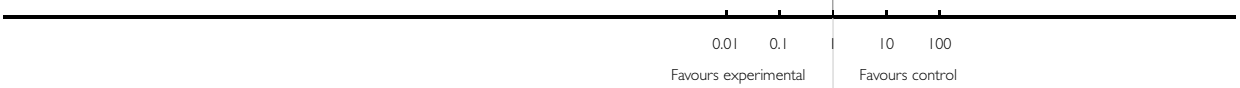
Analysis 2.2. Comparison 2 Oral antihypertensive therapy for treatment of postpartum hypertension, Outcome 2 Maternal hypotension.

Review: Prevention and treatment of postpartum hypertension

Comparison: 2 Oral antihypertensive therapy for treatment of postpartum hypertension

Outcome: 2 Maternal hypotension

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Antihypertensive agent versus another for severe postpartum hypertension				
Vigil-De Gracia 2007	0/40	0/42		0.0 [0.0, 0.0]
Total (95% CI)	**40**	**42**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: Z = 0.0 (P < 0.00001)				
Test for subgroup differences: Chi^2 = 0.0, df = -1 (P = 0.0), I^2 =0.0%				

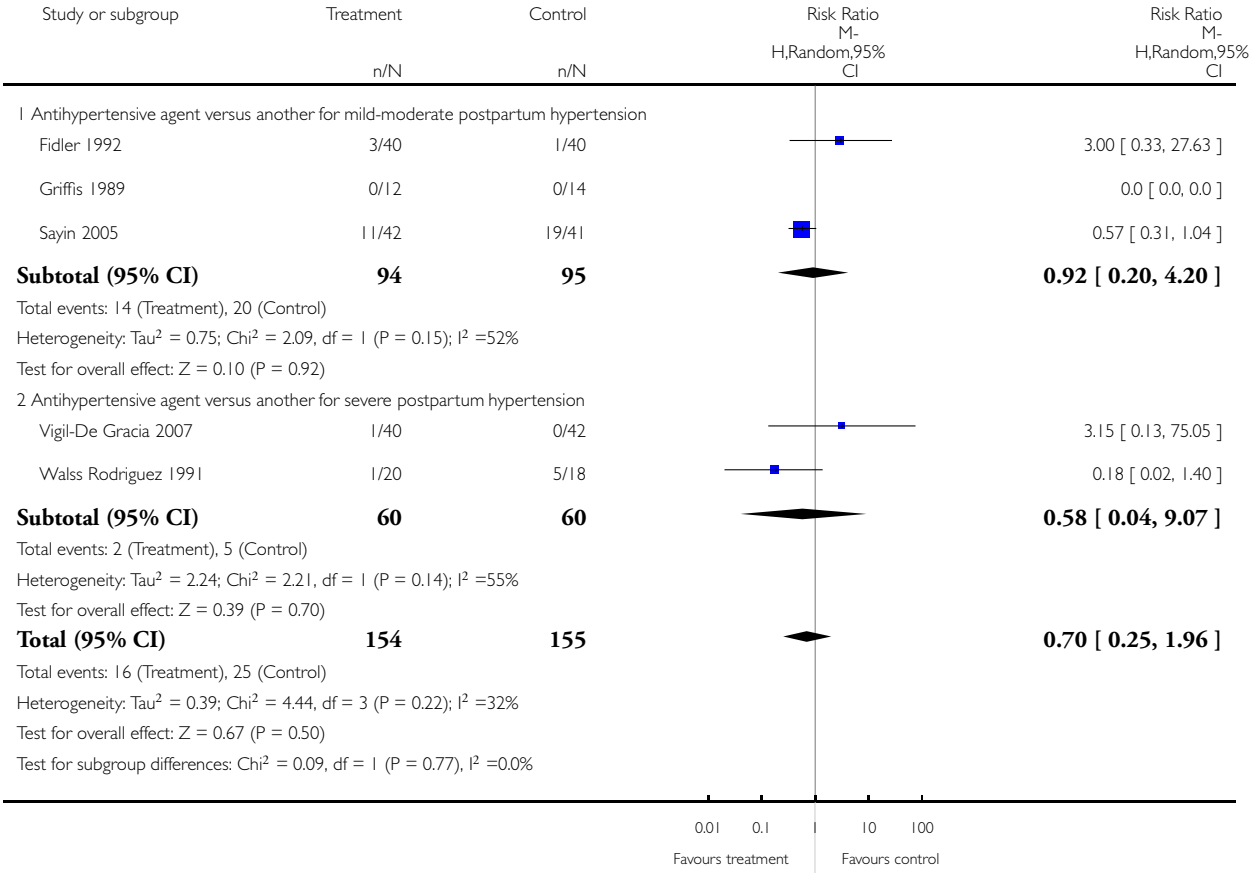


Analysis 2.3. Comparison 2 Oral antihypertensive therapy for treatment of postpartum hypertension, Outcome 3 Need for additional antihypertensive therapy.

Review: Prevention and treatment of postpartum hypertension

Comparison: 2 Oral antihypertensive therapy for treatment of postpartum hypertension

Outcome: 3 Need for additional antihypertensive therapy



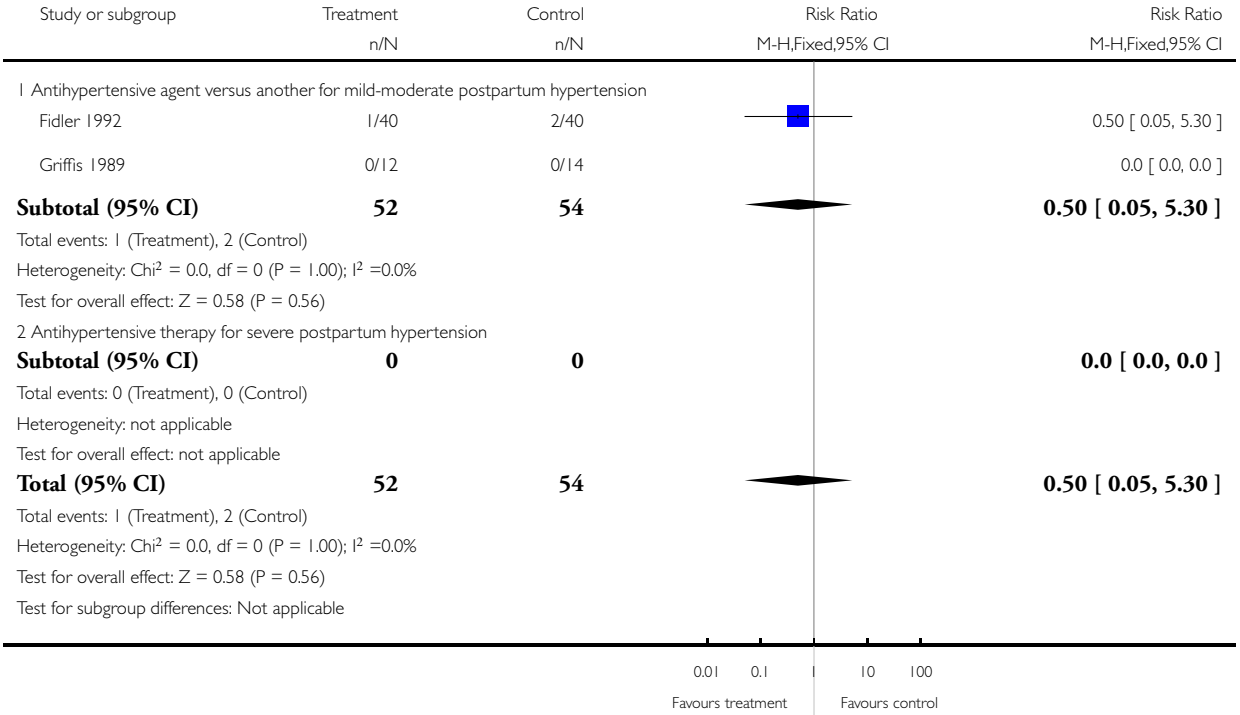
Analysis 2.4. Comparison 2 Oral antihypertensive therapy for treatment of postpartum hypertension, Outcome 4 Medication changed secondary to maternal side-effects.

Review: Prevention and treatment of postpartum hypertension

Comparison: 2 Oral antihypertensive therapy for treatment of postpartum hypertension

Outcome: 4 Medication changed secondary to maternal side-effects

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Antihypertensive agent versus another for mild-moderate postpartum hypertension				
Fidler 1992	1/40	2/40		0.50 [0.05, 5.30]
Griffis 1989	0/12	0/14		0.0 [0.0, 0.0]
Subtotal (95% CI)	**52**	**54**		**0.50 [0.05, 5.30]**
Total events: 1 (Treatment), 2 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.58 (P = 0.56)				
2 Antihypertensive therapy for severe postpartum hypertension				
Subtotal (95% CI)	**0**	**0**		**0.0 [0.0, 0.0]**
Total events: 0 (Treatment), 0 (Control)				
Heterogeneity: not applicable				
Test for overall effect: not applicable				
Total (95% CI)	**52**	**54**		**0.50 [0.05, 5.30]**
Total events: 1 (Treatment), 2 (Control)				
Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%				
Test for overall effect: Z = 0.58 (P = 0.56)				
Test for subgroup differences: Not applicable				



APPENDICES

Appendix 1. Search strategy for PubMed

PubMed (2002-2009) (Search carried out by authors):
(pregnancy complications (MeSH) OR pregnancy (MeSH) AND (hypertension) AND (postpartum OR postnatal OR puerperal OR puerperium)

Appendix 2. Search strategy used in previous version of the review

MEDLINE (1966 to May 2003) and EMBASE (1980 to January 2003) (Search carried out by authors):
("pregnancy complications" OR "pregnancy") AND ("hypertension") AND ("postpartum" OR "postnatal" OR "puerperal" OR "puerperium"

Appendix 3. Methods used in previous versions of this review

Selection of studies

Two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion, or, if required, we consulted a third person.

Data extraction and management

We designed a form to extract data. For eligible studies, at least two review authors (S Sadeghi and LA Magee (LAM), or LAM and P von Dadelszen) extracted the data using the agreed form. We resolved discrepancies through discussion or, if required, we consulted a third person. Data were entered into Review Manager (RevMan 2008) software and checked for accuracy.
When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Sequence generation (checking for possible selection bias)

We have described for each included study, the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should have produced comparable groups.
We assessed the method as:

- adequate (any truly random process, e.g., random number table; computer random number generator);
- inadequate (any non-random process, e.g., odd or even date of birth; hospital or clinic record number); or
- unclear.

(2) Allocation concealment (checking for possible selection bias)

We have described for each included study the method used to conceal the allocation sequence in sufficient detail and determine whether intervention allocation could have been foreseen in advance, or during recruitment, or changed after assignment.
We assessed the methods as:

- adequate (e.g., telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear.

(3) Blinding (checking for possible performance bias)

We have described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Studies were judged at low risk of bias if they were blinded, or we judged that the lack of blinding could not have affected the results. Blinding was assessed separately for different outcomes or classes of outcomes.
We assessed the methods as:

- adequate, inadequate or unclear for participants;
- adequate, inadequate or unclear for personnel;
- adequate, inadequate or unclear for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

We have described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We have stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we re-included missing data in the analyses which we undertook.
We assessed methods as:

- adequate (i.e., less than 2.5% of women were excluded from the analysis);
- inadequate; or
- unclear.

(5) Selective reporting bias

We have described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- adequate (where it was clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review were reported);
- inadequate (where not all of the study's pre-specified outcomes were reported; one or more reported primary outcome(s) was(were) not pre-specified; outcomes of interest were reported incompletely and so cannot be used; study failed to include results of a key outcome that would have been expected to have been reported); or
- unclear.

(6) Other sources of bias

We described for each included study any important concerns we had about other possible sources of bias.
We assessed whether each study was free of other problems that could put it at risk of bias:

- yes;
- no; or
- unclear.

(7) Overall risk of bias

We made explicit judgments about whether studies were at high risk of bias, according to the criteria given in the Handbook (Higgins 2008). With reference to (1) to (6) above, we assessed the likely magnitude and direction of the bias and whether we considered it likely to impact on the findings.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

We had no continuous data.

Dealing with missing data

For included studies, levels of attrition were noted.
For all outcomes, analyses carried out, as far as possible, were on an intention-to-treat basis (i.e., we attempted to include all participants randomised to each group in the analyses). The denominator for each outcome in each trial was the number randomised minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (i.e., I^2 greater than 50%), we explored it by pre-specified subgroup analysis.

Assessment of reporting biases

Assessment of reporting biases

There were too few studies included and too few outcomes reported to assess the impact of potential reporting bias on outcomes.

Data synthesis

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2008). We used fixed-effect inverse variance meta-analysis for combining data where trials examined the same intervention, and the trials' populations and methods were judged sufficiently similar. Where we suspected clinical or methodological heterogeneity between studies sufficient to suggest that treatment effects may differ between trials, we used random-effects meta-analyses.
If substantial heterogeneity was identified in a fixed-effect meta-analysis, this was noted and the analysis repeated using a random-effects method.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses:

- type of agent used to prevent postpartum hypertension (i.e., furosemide versus an antihypertensive);
- treatment of mild to moderate versus severe postpartum hypertension.

The following outcomes were used in the subgroup analyses: maternal death, maternal organ failure, severe hypotension, antihypertensive use in hospital, and antihypertensive use at hospital discharge.
For fixed-effect meta-analyses, we conducted planned subgroup analyses classifying whole trials by interaction tests as described by Deeks 2001. For random-effects meta-analyses, we assessed differences between subgroups by inspection of the subgroups' confidence intervals; non-overlapping confidence intervals indicated a statistically significant difference in treatment effect between the subgroups.

WHAT'S NEW

Last assessed as up-to-date: 12 February 2013.

Date	Event	Description
12 February 2013	New search has been performed	Search updated. Incorporated new data from one trial (Hladunewich 2006), and revised the results and discussion, accordingly. Excluded one trial (Jia 2007). Methods updated.
12 February 2013	New citation required but conclusions have not changed	Incorporated data from one trial.

HISTORY

Protocol first published: Issue 3, 2003

Review first published: Issue 1, 2005

Date	Event	Description
1 June 2009	New search has been performed	Incorporated new data (Ascarelli 2005), included two new studies (Sayin 2005; Vigil-De Gracia 2007), reviewed background, results, and discussion. Excluded six studies (Adarsh 2006; Alkan 2006; Ehrenberg 2006; Gomez 2005; Hennessy 2007; Livingston 2003), added one to Studies awaiting classification (Hladunewich 2006a) and one to Ongoing studies (Aina-Mumuney 2006).
20 September 2008	Amended	Converted to new review format.
4 November 2004	New search has been performed	Search updated on 31 March 2004. We have updated the references in the Background since the protocol was first published

CONTRIBUTIONS OF AUTHORS

For this update, Dr L Magee conducted the updated literature search and data entry. Data entry was double-checked by P von Dadelszen. All review authors revised the review for publication.

DECLARATIONS OF INTEREST

Peter von Dadelszen is a paid consultant to Alere International, and receives grant funding from the Bill & Melinda Gates Foundation and CIHR. These activities are unrelated to this review.

SOURCES OF SUPPORT

Internal sources

- BC Research Institute for Children's and Women's Health, Canada.

Laura Magee has received Establishment Grants from both the MSFHR and the BC Research Institute for Children's and Women's Health.

External sources

- Michael Smith Foundation for Health Research (MSFHR), Canada.

L Magee received salary support from the Michael Smith Foundation for Health Research (MSFHR). She has received Establishment Grants from both the MSFHR and the BC Research Institute for Children's and Women's Health.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Methods for data collection and analysis were updated for the 2013 update. A number of outcomes not prespecified in the protocol have been highlighted.

- Maternal end-organ failure (any).
- Use of non-steroidal anti-inflammatories (NSAIDs) for postpartum analgesia.
- Maternal side-effects to antihypertensive medication.
- Severe maternal hypotension.

INDEX TERMS

Medical Subject Headings (MeSH)

Antihypertensive Agents [*therapeutic use]; Hypertension [*drug therapy; *prevention & control]; Puerperal Disorders [*drug therapy; *prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans