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Oral beta-blockers for mild to moderate hypertension during pregnancy.
Cochrane Database of Systematic Reviews 2003, Issue 3. Art. No.: CD002863.
DOI: [10.1002/14651858.CD002863](https://doi.org/10.1002/14651858.CD002863).

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[Intervention Review]

Oral beta-blockers for mild to moderate hypertension during pregnancy

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Editorial group: Cochrane Pregnancy and Childbirth Group.

Publication status and date: Edited (no change to conclusions), published in Issue 8, 2012.

Citation: Magee L, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD002863. DOI: [10.1002/14651858.CD002863](https://doi.org/10.1002/14651858.CD002863).

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ABSTRACT

Background

Antihypertensives, such as beta-blockers, are used for pregnancy hypertension in the belief these will improve outcome for mother and baby.

Objectives

To assess whether oral beta-blockers are better than placebo, or no beta-blocker, and have advantages over other antihypertensives, for women with mild to moderate pregnancy hypertension.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group trials register (January 2004) and bibliographies of retrieved papers and personal files. We updated this search on 4 July 2012 and added the results to the awaiting classification section of the review.

Selection criteria

Trials comparing beta-blockers with placebo or no therapy, or other antihypertensives, for women with mild to moderate pregnancy hypertension.

Data collection and analysis

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

Main results

Twenty-nine trials (approximately 2500 women) are included. Thirteen trials (1480 women) compared beta-blockers with placebo/no beta blocker. Oral beta-blockers decrease the risk of severe hypertension (relative risk (RR) 0.37, 95% confidence interval (CI) 0.26 to 0.53; 11 trials, N = 1128 women) and the need for additional antihypertensives (RR 0.44, 95% CI 0.31 to 0.62; 7 trials, N = 856 women). There are insufficient data for conclusions about the effect on perinatal mortality or preterm birth. Beta-blockers seem to be associated with an increase in small-for-gestational-age (SGA) infants (RR 1.36, 95% CI 1.02 to 1.82; 12 trials; N = 1346 women). Maternal hospital admission may be decreased, neonatal bradycardia increased and respiratory distress syndrome decreased, but these outcomes are reported in only a small proportion of trials. In 13 trials (854 women), beta-blockers were compared with methyldopa. Beta-blockers appear to be no more effective and probably equally as safe. Single small trials have compared beta-blockers with hydralazine, nifedipine or isradipine. It is unusual for women to change drugs due to side effects.

Authors' conclusions

Improvement in control of maternal blood pressure with use of beta-blockers would be worthwhile only if it were reflected in substantive benefits for mother and/or baby, and none have been clearly demonstrated. The effect of beta-blockers on perinatal outcome is uncertain; the worrying trend to an increase in SGA infants is partly dependent on one small outlying trial. Large randomised trials are needed to determine whether antihypertensive therapy in general (rather than beta-blocker therapy specifically) results in greater benefit than risk, for treatment of mild-moderate pregnancy hypertension. If so, then it would be appropriate to consider which antihypertensive is best, and beta-blockers should be evaluated.

[Note: the seventeen reports in the awaiting classification section of the review may alter the conclusions of the review once assessed.]

PLAIN LANGUAGE SUMMARY

Oral beta-blockers for mild to moderate hypertension during pregnancy

Pregnant women with mild to moderate hypertension taking beta-blockers have reduced blood pressure, but these drugs may have adverse effects on the baby.

While very high blood pressure (hypertension) in pregnancy can damage blood vessel walls and lead to serious complications, small rises in blood pressure may do little harm. The blood pressure level at which treatment should be started in pregnancy is not known. Beta-blocker drugs cause the heart to beat more slowly and less forcefully, reducing pressure on blood vessels. This review of trials found that pregnant women with mild to moderate hypertension who take beta-blockers have lower blood pressure, but the baby may grow more slowly than expected. There is not enough evidence on other effects. Further research is needed.

BACKGROUND

During normal pregnancy, blood pressure falls, reaching its lowest level at about 20 weeks' gestation, and then rises slowly to reach pre-pregnancy levels by term. In up to 10% of pregnancies, blood pressure rises above the accepted norm, usually defined as > 140/90 mm Hg. A large proportion of antenatal care is devoted to the detection and management of hypertensive disorders of pregnancy because, as a group, they are the second major cause of maternal and perinatal serious illness (e.g. stroke or preterm birth, respectively) and/or death in both low to middle income and high income countries (Duley 1992; DH 1998).

Hypertensive disorders of pregnancy is a term used to describe two fundamentally different, but related, conditions (Redman 1989). The first is hypertension that occurs for the first time during the latter half of pregnancy, termed pregnancy-induced hypertension. Pregnancy-induced hypertension may occur in isolation or be associated with multi-organ dysfunction (classically, proteinuria) when it is referred to as pre-eclampsia. The second condition is chronic hypertension that existed before pregnancy or presents in the first 20 weeks of pregnancy. These conditions must be considered separately because they have different implications for mother and baby.

Chronic hypertension affects approximately one in 100 pregnancies. It is associated with an excess of pregnancy complications, accounted for mainly by women who develop superimposed pre-eclampsia. Chronic hypertension is usually due to essential hypertension, but may result from other medical problems such as kidney disease or diabetes mellitus.

Pregnancy-induced hypertension is relatively common, affecting up to one in 10 pregnancies. It is more likely to occur in women with a family history of hypertension or other medical problems, such as obesity or kidney disease. Pre-eclampsia, specifically, also tends to occur in first pregnancies and multiple pregnancies. Pre-eclampsia is a multi-system disorder that can also affect blood clotting, liver function, kidney function, and/or brain function. In addition, the placenta may be affected, leading to poor fetal growth, and possibly preterm birth. In some women, severe hypertension may occur quickly. Aspirin is the only therapy proven to decrease the risk of pre-eclampsia in women at increased risk (Knight 2002), but the magnitude of risk reduction is modest. The only definitive treatment of pre-eclampsia, once established, is delivery of the baby. Even so, pre-eclampsia may still worsen (or develop for the first time) in the immediate postpartum period; there is usually a full recovery.

Marked elevations of blood pressure, to levels at or above 170 mm Hg systolic and/or 110 mm Hg diastolic, may damage maternal blood vessels and possibly increase the risk of partial separation of the placenta from the womb (placental abruption). This is the case regardless of whether this high blood pressure is due to chronic hypertension, isolated pregnancy-induced hypertension, or pre-eclampsia. There is general agreement that such women should receive antihypertensive therapy, that will lower the blood pressure and, hence, may prevent some of the consequences of severe hypertension. This issue is covered by a separate review (Duley 2002). When the blood pressure is less markedly elevated, to levels below 170/110 mm Hg, there is little risk of such direct damage, and there is no agreement as to whether or not antihypertensive therapy is of benefit to either the woman or the child (Collins 1989).

One international working group has advocated treatment of a diastolic blood pressure greater than 105 mm Hg (NHB 2000), whereas others recommend treatment of a diastolic BP of 90 to 95 mm Hg (Rey 1997; Brown 2000). The possible risks and benefits of various approaches are not known.

Antihypertensive agents are often given to lower maternal blood pressure in the hope that this will delay progression of the disease and so prolong the pregnancy (Redman 1993); this hypothesis is unproven, however. There are potential benefits, for both mother (such as fewer hospital visits and less time in hospital) and baby (such as better survival and fewer problems after birth), but there are also potential risks. Firstly, it has been suggested that beta-blockers may themselves be associated with intrauterine growth restriction (Scotland 1990). Secondly, many of the commonly used agents (e.g. methyldopa) may cause drowsiness and dizziness, as well as other less common problems (e.g. abnormal liver tests). Thirdly, it has been argued that antihypertensive treatment removes an accessible marker for pre-eclampsia, and that normal blood pressures may give false reassurance. Finally, there is very little information about the long-term safety for the child after antihypertensive exposure during pregnancy. A woman should not be advised to take drugs during pregnancy unless we can provide reasonable reassurance that they are both effective and safe.

In summary, while most clinicians would agree that severe hypertension should be treated to prevent maternal vascular damage, antihypertensive treatment for mild to moderate hypertension during pregnancy remains controversial. At these levels of blood pressure, there is no direct risk to the mother, so treatment is only likely to be worthwhile if it delays or prevents progression of pre-eclampsia and/or is associated with substantive benefit(s) for the baby (Laupacis 1988).

Whilst a wide variety of antihypertensive agents have been used during pregnancy, this review summarises only the data on a commonly used class of agents, beta-blockers. The interested reader is referred to another review of all oral antihypertensive agents for treatment of mild to moderate hypertension (Abalos 2002).

OBJECTIVES

To assess whether oral beta-blockers are, overall, better than placebo or no therapy for women with mild to moderate hypertension during pregnancy.

If beta-blockers are effective, to assess whether oral beta-blockers have any advantages over other antihypertensive agents for women with mild to moderate hypertension during pregnancy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials. Quasi-random designs were excluded.

Types of participants

Women with mild to moderate hypertension during pregnancy, however defined.

Types of interventions

Comparisons of (i) oral beta-blockers (including labetalol) with placebo or no therapy, or (ii) oral beta-blockers (including labetalol) with other antihypertensive drug therapy. We excluded single dose studies or studies that compared beta-blockers with beta-blockers.

Types of outcome measures

For the women: measures that evaluated the effectiveness and safety of antihypertensive therapy, including stroke, maternal mortality, severe hypertension, proteinuria at delivery (as a surrogate marker for pre-eclampsia), eclampsia, the need for additional antihypertensive therapy, admission to hospital before delivery, placental abruption, caesarean section, and the need to change therapy due to maternal side effects.

For the baby: perinatal mortality, small-for-gestational-age infants (SGA; defined as either less than the third, fifth or 10th percentiles when birth weight was corrected for gestational age), preterm birth (less than 37 completed weeks' gestation), admission to a special care baby unit (SCBU) or a neonatal intensive care unit (NICU), neonatal morbidity (such as bradycardia, hypotension, hypothermia, and hypoglycaemia), low Apgar scores (less than seven at five minutes), respiratory distress syndrome (RDS), and measures of long-term health and development such as cerebral palsy, and IQ less than one standard deviation below the mean. Preterm delivery and SGA infants are reported for all fetuses, whereas neonatal and pediatric health problems are reported for all live births.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group trials register (January 2004). We updated this search on 4 July 2012 and added the results to [Studies awaiting classification](#).

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.

Searching other resources

In addition, we searched bibliographies of retrieved papers and personal files.

We did not apply any language restrictions.

Data collection and analysis

We extracted trial characteristics and outcome data independently and were not blinded to the results or other parts of the reports. We only included data from graphs if we both agreed on the estimate. When needed, we requested further (missing) information from the authors.

We rated methodological quality according to whether the participants could guess what the next allocated treatment would be. We defined concealment of allocation as:

- (A) 'adequate' if the method was described in enough detail to be reasonably confident that the allocation was blinded (e.g. randomisation by telephone, or by consecutively numbered sealed opaque envelopes);
- (B) 'unclear' if the method of randomisation was not described in enough detail to give reasonable reassurance that the allocation was blinded ;
- (C) 'inadequate' if methods were quasi-randomised and the potential for bias was unacceptably high.

We rated outcome assessment blinding as:

- (A) double-blind;
- (B) single-blind;
- (C) not blinded.

We rated completeness of follow up (for each outcome) according to the proportion of participants who were excluded from the analysis of that outcome, as follows:

- (A) less than 2.5% of women;
- (B) 2.5 to 9.9%;
- (C) 10 to 19.9%.

If 20% or more participants were excluded, then we excluded the data for that outcome from the analysis.

We used the Cochrane Review Manager software ([RevMan 2000](#)) to enter data and to perform the analyses. A statistically significant treatment effect was reflected by a relative risk (RR) for which the 95% confidence interval did not include 1.0; a RR greater than 1.0 reflected more events among the treatment (i.e. beta-blocker) groups and a RR less than 1.0 reflected more events among control groups. Significant between-trial heterogeneity was explained descriptively according to trial quality, the women enrolled, interventions administered, and/or outcome definitions/assessment. For the beta-blocker versus other antihypertensive comparisons, the analysis was stratified by type of other antihypertensive, as the latter was considered a priori to be a potential source of between-trial heterogeneity in outcome.

RESULTS

Description of studies

Characteristics of participants were poorly described in most reports. In the majority, it was not possible to tell whether participants had isolated hypertension or pre-eclampsia. In two trials, antihypertensive therapy was started early in the second

trimester (USA 1987a; Scotland 1990); otherwise, therapy was started late in the second trimester or in the third trimester. Eleven trials compared oral beta-blockers with placebo (seven trials) or no therapy, for women enrolled in the late second trimester or third trimester. Eighteen trials compared beta-blockers with other antihypertensive therapy for women in the third trimester.

Labetalol was the most commonly used beta-blocker (11 trials); other drugs used were metoprolol (four trials), pindolol (four trials), atenolol (four trials), oxprenolol (three trials), propranolol (two trials), acebutolol (one trial) and mepindolol (two trials). Two trials had two beta-blocker treatment arms (Israel 1995; France 1988a), which accounts for the fact that 31 beta-blockers are listed for only 29 trials.

When oral beta-blockers were compared with other drugs, methyldopa was most commonly used (13 trials); other comparative drugs were hydralazine (three trials), nicardipine (one trial), and isradipine (one trial).

Trials were excluded based on failure to report data according to the randomised group (unless this information was available directly from authors), examination of endpoints not relevant to the overview (e.g. Doppler velocimetry), single dose studies remote from term (as the drug could not be expected to be on board at delivery and impact on neonatal health), and direct comparison of beta-blocker with beta-blocker.

Risk of bias in included studies

Twenty-nine trials with approximately 2500 women are included in this review. The trials themselves were all small with a median [range] sample size of 60 [20, 200]. The quality of these trials was poor. Concealment of treatment allocation was 'adequate' in only five (17%) reports and 'unclear' in most others; two trials with clearly inadequate methods (Italy 1990; Kuwait 1995) were excluded from the analysis. Double blinding (of physicians and patients) for outcome assessment was reported to have occurred in seven trials (24%). For maternal and pregnancy outcomes, follow up of greater than 90% was achieved for all outcomes in 20 trials (69%); long-term follow up was very limited, as the duration of follow up was rarely more than a few days after delivery.

Effects of interventions

Twenty-nine trials, involving approximately 2500 women, are included in this review. (Seventeen reports from an updated search in July 2012 have been added to [Studies awaiting classification](#).)

A. Beta-blockers versus placebo or no beta-blocker

Thirteen trials (1480 women) compared beta-blockers with placebo/no beta blocker. Oral beta-blockers substantially reduced the incidence of severe hypertension (relative risk (RR) 0.37, 95% confidence interval (CI) 0.26 to 0.53; 1 trial, N = 1128 women) and the need for additional antihypertensive drugs (RR 0.44, 95% CI 0.31 to 0.62; 7 trials, N = 856 women). This did not appear to be reflected in any overall effect on proteinuria (RR 0.86, 95% CI 0.68 to 1.08; 11 trials, N = 1340 women) or caesarean section (RR 0.95, 95% CI 0.80 to 1.12; 12 trials, N = 1392 women) although a moderate increase or decrease in either has not been excluded. The number of admissions to hospital before delivery was also reduced (RR 0.77, 95% CI 0.64 to 0.93; 3 trials, N = 291 women), but this result should be interpreted with caution as only three trials reported this

outcome and there is considerable potential for bias. Many trials did not report side effects per se, but beta-blockers seem to be well tolerated by women, as very few on active treatment changed their drug due to side effects. There are insufficient data for any reliable conclusions about other maternal outcomes. Maternal stroke, renal failure, and disseminated intravascular coagulation (DIC) were not reported by any of the trials, and few mentioned maternal death, eclampsia, or HELLP syndrome.

There are insufficient data for any conclusions about the possible effects of beta-blockers on perinatal mortality. There were 10 deaths in each arm, and the confidence intervals include everything from a halving to over a doubling in perinatal deaths. The effect on the incidence of small-for-gestational-age infants is difficult to determine. For the twelve trials reporting this outcome, the summary RR is 1.36, 95% CI 1.02 to 1.82 (12 trials, N = 1346 women). Although the result of one small trial appears to be different, the 95% CI is wide and overlaps with those of all of the other trials. This trial (Scotland 1990) randomised 33 women with chronic hypertension to atenolol versus placebo early in pregnancy (as in USA 1987a), and had two post-randomisation exclusions from the control group for severe hypertension. Also, if this trial is removed from the analysis, the effect size is essentially unchanged, although the confidence interval just crosses statistical significance (RR 1.30, 95% CI 0.97 to 1.74; 11 trials, N = 1317 women). Beta-blockers appear to increase the risk of neonatal bradycardia based on data from three trials that reported this outcome (RR 1.93, 95% CI 1.05 to 3.53; 3 trials, N = 416 women), but there is considerable heterogeneity that could not be explained. Beta-blockers may decrease the risk of respiratory distress syndrome (RR 0.29, 95% CI 0.12 to 0.67; 4 trials, N = 567 women) based on data from the four trials that reported this outcome, although there is no apparent influence on the incidence of preterm birth (RR 1.00, 95% CI 0.76 to 1.30; 8 trials, N = 962 women). No study reported on prolonged stay in a special care baby unit (SCBU) (e.g. more than 7 days). The data available on follow up beyond the perinatal period are limited to those from one trial (Scotland 1983) which found no difference in the rates of cerebral palsy or low IQ at one year of age.

It should be noted that few maternal (i.e. severe hypertension, proteinuria at delivery, caesarean section) or perinatal (i.e. mortality) outcomes were reported by the majority of included trials. Therefore, given the potential for bias, data on inadequately reported outcomes should be interpreted with caution.

B. Beta-blockers versus other antihypertensive agents

Thirteen trials (854 women) compared beta-blockers with methyldopa. There are no clear maternal or perinatal advantages or disadvantages associated with oral beta-blockers, when compared with methyldopa. However, the confidence intervals are all wide and no maternal or perinatal outcomes were reported by the majority of included trials. Therefore, given the potential for bias, data on outcomes should be interpreted with caution.

Single trials have compared beta-blockers with hydralazine, nicardipine, or isradipine. These were too small for any reliable conclusions to be drawn.

When beta-blockers were compared with any other antihypertensive drug, beta-blockers were associated with a lower risk of small-for-gestational-age infants, and this effect was borderline for statistical significance (RR 0.69, 95% CI 0.48 to 0.99; 7

trials, N = 485 women). There was insufficient evidence for any firm conclusions about the effects on any other outcomes.

DISCUSSION

Not surprisingly, when prescribed for mild to moderate hypertension in pregnancy and compared with placebo/no therapy, oral beta-blockers decrease the incidence of severe hypertension and the need for additional antihypertensive therapy. These effects would only be worthwhile if they were reflected in other more substantive benefits (such as a decrease in pre-eclampsia or eclampsia for the mother, and/or a decrease in preterm birth and its complications for the baby), or if they reduced the need for hospital admission; no such benefits have yet been clearly demonstrated. Specifically, better control of blood pressure does not seem to influence the progression to pre-eclampsia or the risk of caesarean section, although these data are compatible with the true effect being anything from moderate benefit to a small increase in risk. Data on other outcomes are insufficient for any reliable conclusions to be made.

There are insufficient data for any conclusions about the effect on perinatal mortality. When compared with placebo/no therapy, beta-blockers are associated with an increase in small-for-gestational-age infants. This result is partly dependent on one small trial ([Scotland 1990](#)), which may be exaggerating the real effect. Although this trial was of poor quality, other potential explanations include a specific effect of atenolol ([Easterling 1999](#); [Lydakis 1999](#)) or the fact that the drug was started early in pregnancy. In addition, a recent meta-regression analysis of all trials of antihypertensive medication for mild to moderate pregnancy hypertension found an association between treatment-induced fall in mean arterial pressure (by administration of any antihypertensive agent) and an increased risk of small for gestational infants ([von Dadelszen 2000](#)). This would suggest that if the effect of beta-blockers on fetal growth were real, it might not be specific to beta-blockers.

Beta-blockers appear to be associated with an excess of neonatal bradycardia. This may reflect reporting bias but, even if real, this may be a pharmacological effect of beta-blockers rather than a clinically important one, given that the one trial ([Scotland 1983](#)) which found a significant increase in bradycardia did so by performing continuous monitoring of neonatal heart rate. No affected newborn required treatment. Finally, beta-blockers appear to decrease the risk of respiratory distress syndrome although, again, there was potential for bias as few studies reported the outcome. Also, the apparent effect on respiratory distress was not associated with any change in preterm birth, and the incidence was high given that babies were born at or near term. In view of the selective reporting, it remains unclear whether this reflects some direct effect of beta-blockers on the fetal lung.

When compared with methyldopa, there are insufficient data for any reliable conclusions. There is even less information about how beta-blockers compare with other agents. Even when all trials comparing beta-blockers with alternative antihypertensive drugs are taken together, there is insufficient evidence for any firm conclusions about the comparative effects, although it is possible that the risk of a small-for-gestational-age infant may be less with beta-blocker therapy than with an alternative drug.

The low frequency with which women need to change drugs suggests that if antihypertensive therapy is considered to be necessary, then the choice of agent should be based on the clinician's personal experience and/or maternal and/or perinatal considerations.

AUTHORS' CONCLUSIONS

Implications for practice

Beta blockers, along with other antihypertensive drugs ([Abalos 2002](#)), reduce the risk of severe hypertension, and the need for additional drugs. Overall, however, it is unclear whether they do more good than harm. Beta-blockers, when compared with placebo or no antihypertensive therapy, seem to be associated with an increase in the risk of small-for-gestational-age infants, but the size of this effect is unclear. When compared with other antihypertensive agents, beta-blockers seem to be associated with a comparative decrease in small-for-gestational-age infants, although this effect is borderline for statistical significance. The impact of beta-blockers (and antihypertensive therapy in general) on intrauterine fetal growth is important to clarify, as even a relatively modest increase in risk could have considerable clinical importance, given that being small for gestational age is associated with an increased risk of perinatal morbidity, neurodevelopmental abnormalities, and possibly, cardiovascular disease in later life. If the clinician feels that antihypertensive therapy is indicated for a woman with mild to moderate hypertension during pregnancy, beta-blockers should be considered as candidate agents. The possible exception to this is atenolol, which it would seem sensible to avoid.

Implications for research

Large, randomised placebo-controlled trials are required to determine whether, overall, antihypertensive therapy (with any agent) is preferable to no treatment of mild to moderate hypertension during pregnancy. Beta-blockers should be considered as relevant drugs to evaluate. Outcomes should include measures of clinical effectiveness (for both the mother and child), importance to women and use of health service resources. These would include pre-eclampsia, health-related quality of life, perinatal and infant mortality, admission to special care baby unit for more than 7 days, preterm birth, small for gestational age, and measures of major disability in the short- and long-term (e.g. cerebral palsy). If treatment is beneficial overall, it would then be appropriate to conduct trials of one antihypertensive drug compared with another.

[Note: the seventeen reports in the awaiting classification section of the review may alter the conclusions of the review once assessed.]

ACKNOWLEDGEMENTS

Dr Magee received an Establishment Grant from the BC Research Institute for Children's and Women's Health, and also receives salary support from BC Women's Hospital Foundation.

As part of the pre-publication editorial process, this review has been commented on by three peers (an editor and two referees who are external to the editorial team), one or more members of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

REFERENCES

References to studies included in this review

Argentina 1988 {published data only}

Casavilla F, Vega HR. Prospective and randomized study on mepindolol and alpha-methyldopa efficacy in arterial hypertension (AH) treatment during pregnancy.. World Congress of Gynecology and Obstetrics; 1988 October 23-28; Brazil, 1988:182. Brazil, 1988:182.

Australia 1983 {published data only}

Livingstone I, Craswell PW, Bevan EB. Propranolol in pregnancy. Three year prospective study. *Clinical and Experimental Hypertension* 1983;**B2**:341-50.

Australia 1985 {published data only}

Gallery EDM, Hunyor SN, Saunders DM, Gyory AZ. A randomized trial of oxyprenolol and alpha-methyldopa in the therapy of hypertension in pregnancy.. Proceedings of the 1st Congress of the International Society of Hypertension in Pregnancy;1978 September 27-29; Dublin, Ireland, 1978;88. Dublin, 1978:88.

* Gallery EDM, Ross MR, Gyory AZ. Antihypertensive treatment in pregnancy: analysis of different responses to oxprenolol and methyldopa. *BMJ* 1985;**291**:563-6.

Gallery EDM, Saunders DM, Hunyor SN, Gyory AZ. Randomized comparison of methyldopa and oxprenolol for treatment of hypertension in pregnancy. *BMJ* 1979;**1**:1591-4.

Brazil 1998 {published data only}

Kahhale S, Alves EA, Takiuti NH, Zugaib M. Efficacy and safety of isradipina and atenolol in hypertensive disorders in pregnancy. *Hypertension in Pregnancy* 2000;**19**(1):98.

England 1978 {published data only}

* Redman CWG. A controlled trial of the treatment of hypertension in pregnancy: labetalol compared with methyldopa. In: Riley AJ, Symonds EM editor(s). The Investigation of labetalol in the management of hypertension in pregnancy. International Congress Series 591. Amsterdam: Excerpta Medica, 1978:101-10.

Redman CWG. Controlled trials of treatment of hypertension during pregnancy.. Proceedings of the 8th International Congress of Nephrology; 1981; Athens, Greece, 1981:523-4. Athens, 1981:523-4.

England 1980 {published data only}

* Lamming GD, Broughton Pipkin F, Symonds EM. Comparison of the alpha and beta blocking drug, labetalol, and methyldopa in the treatment of moderate and severe pregnancy-induced hypertension. *Clinical and Experimental Hypertension* 1980;**2**:865-95.

Lamming GD, Symonds EM. Use of labetalol and methyldopa in pregnancy-induced hypertension. *British Journal of Clinical Pharmacology* 1979;**8**:217S-22S.

Lamming, GD, Symonds, EM. Comparison of the alpha and beta blocking drug labetalol and aldomet in the treatment

of pregnancy induced hypertension.. Proceedings of the 2nd Congress of the International Society for the Study of Hypertension in Pregnancy; 1980 December 1-4; Cairo, Egypt, 1980:9. Egypt, 1980:9.

England 1983 {published data only}

* Fidler J, Smith V, Fayers P, De Swiet M. Randomised controlled comparative study of methyldopa and oxprenolol in treatment of hypertension in pregnancy. *BMJ* 1983;**286**:1927-30.

Fidler J, Smith V, Fayers P, De Swiet M. Randomised controlled comparative study of methyldopa and oxprenolol in treatment of hypertension in pregnancy. *Obstetrical and Gynecological Survey* 1983;**286**:202-5.

England 1984 {published data only}

Thorley KJ. Atenolol: side effects in the newborn infant. *BMJ* 1982;**285**:1116.

Thorley KJ. Randomised trial of atenolol and methyl dopa in pregnancy related hypertension.. 4th World Congress of the International Society for the Study of Hypertension in Pregnancy; 1984 June 18-21; Amsterdam, The Netherlands, 1984:53. Amsterdam, 1984:53.

* Thorley KJ. Randomised trial of atenolol and methyldopa in pregnancy related hypertension. *Clinical and Experimental Hypertension* 1984;**B3**:168.

England 1989 {published data only}

Pickles CJ, Broughton Pipkin F, Symonds EM. A randomised placebo controlled trial of labetalol in the treatment of mild to moderate pregnancy induced hypertension. *British Journal of Obstetrics and Gynaecology* 1992;**99**:964-8.

* Pickles CJ, Symonds EM, Broughton Pipkin F. The fetal outcome in a randomized double-blind controlled trial of labetalol versus placebo in pregnancy-induced hypertension. *British Journal of Obstetrics and Gynaecology* 1989;**96**:38-43.

Pickles CJ, Symonds EM, Broughton Pipkin F. The fetal outcome of early intervention therapy in pregnancy induced hypertension. A randomised, double-blind controlled trial of labetalol vs placebo.. Proceedings of the 6th International Congress, International Society for the Study of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada, 1988:107. Montreal, 1988:107.

France 1988a {published data only}

Lardoux H, Blazquez G, Leperlier E, Gerard J. Randomized and comparative study of methyldopa acebutolol and labetalol for the treatment of moderate hypertension during pregnancy [Essai ouvert, comparatif, avec tirage au sort pour le traitement de l'HTA gravidique moderee: methyldopa, acebutolol, labetalol]. *Archives des Maladies du Coeur* 1988;**81**:137-40.

France 1988b {published data only}

Plouin PF, Breart G, Maillard F, Papiernik E, Relier JP, le Groupe d'Etude Labetol-Methyldopa. Maternal effects and perinatal safety of labetalol in the treatment of hypertension

in pregnancy. Comparison with methyldopa in a randomized cooperative trial [Effets maternels et securite perinatale du labetalol dans le traitement des hypertension de la grossesse. Comparaison a la methyldopa par un essai cooperatif randomise]. *Archives des Maladies du Coeur* 1987;**80**:952-5.

* Plouin PF, Breart G, Maillard F, Papiernik E, Relier JP, the Labetalol Methyldopa Study Group. Comparison of antihypertensive efficacy and perinatal safety of labetalol and methyldopa in the treatment of hypertension in pregnancy: a randomized controlled trial. *British Journal of Obstetrics and Gynaecology* 1988;**95**:868-76.

France 1994 {published data only}

* Jannet D, Carbonne B, Sebban E, Milliez J. Nicardipine versus metoprolol in the treatment of hypertension during pregnancy: a randomized comparative trial. *Obstetrics & Gynecology* 1994;**84**:354-9.

Jannet D, Carbonne B, Sebban E, Milliez J. Nicardipine vs metoprolol in the treatment of hypertension during pregnancy: a randomized comparative trial. *International Journal of Gynecology & Obstetrics* 1995;**49**:225.

Fr Caribbean 1990 {published data only}

Plouin PF, Breart C, Llado J, Dalle M, Keller ME, Goujon H, et al. A randomized comparison of early with conservative use of antihypertensive drugs in the management of pregnancy-induced hypertension. *British Journal of Obstetrics and Gynaecology* 1990;**97**:134-41.

Hong Kong 1990 {published data only}

Li CY, Lao TT, Yu KM, Wong SP, Leung CF. The effect of labetalol on mild pre-eclampsia.. Proceedings of 7th World Congress of Hypertension in Pregnancy; 1990; Perugia, Italy, 1990:191. Perugia, 1990:191.

India 1992 {published data only}

Oumachigui A, Verghese M, Balachander J. A comparative evaluation of metoprolol and methyldopa in the management of pregnancy induced hypertension. *Indian Heart Journal* 1992;**44**:39-41.

Israel 1986a {published data only}

* Ellenbogen A, Jaschevatzy O, Davidson A, Anderman S, Grunstein S. Management of pregnancy-induced hypertension with pindolol - comparative study with methyldopa. *International Journal of Gynecology & Obstetrics* 1986;**24**:3-7.

Jaschevatzy OE, Davidson A, Ellenbogen A, Anderman S, Grunstein S. Comparative study of pindolol and methyl dopa and transplacental cross of pindolol in PIH.. Proceedings of the 5th World Congress of Hypertension in Pregnancy; 1986 July 7-10; Nottingham, UK, 1986:137. 1986, 1986:137.

Israel 1986b {published data only}

Rosenfeld J, Bott-Kanner G, Boner G, Nissenkorn A, Friedman S, Ovadia J, et al. Treatment of hypertension during pregnancy with hydralazine monotherapy or with combined therapy with hydralazine and pindolol. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1986;**22**:197-204.

Israel 1992a {published data only}

Bott-Kanner G, Hirsch M, Friedman S, Boner G, Ovadia J, Merlob P, et al. Antihypertensive therapy in the management of hypertension in pregnancy - a clinical double-blind study of pindolol. *Clinical and Experimental Hypertension* 1992;**B11**:207-20.

Israel 1995 {published data only}

Paran E, Holzberg G, Mazor M, Zmora E, Insler V. Beta-adrenergic blocking agents in the treatment of pregnancy-induced hypertension. *International Journal of Clinical Pharmacology and Therapeutics* 1995;**33**:119-23.

Scotland 1982 {published data only}

Cameron AD, Walker JJ, Bonduelle M, Calder AA. A randomised trial of the antihypertensive agent, labetalol, against bed rest in pregnancy hypertension. *Archives of Gynecology* 1985;**237 Suppl 1**:295.

* Walker J. Intrauterine growth retardation and maternal labetalol treatment in a random allocation controlled study [MD thesis]. Scotland: University of Glasgow, 1992:141-55.

Walker JJ, Crooks A, Erwin L, Calder AA. Labetalol in pregnancy-induced hypertension: fetal and maternal effects. In: Reilly A, Symonds EM editor(s). International Congress Series 591. Excerpta Medica, 1982:148-60.

Scotland 1983 {published data only}

Reynolds B, Butters L, Evans J, Adams T, Rubin PC. First year of life after the use of atenolol in pregnancy associated hypertension. *Archives of Disease in Childhood* 1984;**59**:1061-3.

Rubin PC, Butters L, Clark D, Sumner D, Belfield A, Pledger D, et al. Obstetric aspects of the use in regnancy-associated hypertension of the beta-adrenoceptor antagonist atenolol. *American Journal of Obstetrics and Gynecology* 1984;**150**:389-92.

* Rubin PC, Butters L, Clark DM, Reynolds B, Sumner DJ, Steedman D, et al. Placebo-controlled trial of atenolol in treatment of pregnancy-associated hypertension. *Lancet* 1983;**1**:431-4.

Rubin PC, Butters L, Reynolds B, Low RAL. Atenolol in the management of pregnancy associated hypertension: obstetric and paediatric aspects. *Clinical and Experimental Hypertension* 1984;**133**:154.

Rubin PC, Butters L, Reynolds B, Low RAL. Atenolol in the management of pregnancy associated hypertension: obstetric and paediatric aspects.. 4th World Congress of the International Society for the Study of Hypertension in Pregnancy; 1984 June 18-21; Amsterdam, The Netherlands, 1984:41. Amsterdam, 1984:41.

Scotland 1990 {published data only}

Butters L, Kennedy S, Rubin PC. Atenolol in essential hypertension during pregnancy. *BMJ* 1990;**301**:587-9.

Scotland 1992 {published data only}

* Cruickshank DJ, Campbell D, Robertson AA, MacGillivray I. Intra-uterine growth retardation and maternal labetalol

treatment in a random allocation controlled study. *Journal of Obstetrics and Gynaecology* 1992;**12**:223-7.

Cruickshank DJ, Campbell DM. Atenolol in essential hypertension during pregnancy. *BMJ* 1990;**301**:1103.

Cruickshank DJ, Robertson AA, Campbell DM, MacGillivray I. Does labetalol influence the development of proteinuria in pregnancy hypertension? A randomised controlled study. *European Journal of Obstetrics, Gynecology and Reproductive Biology* 1992;**45**:47-51.

Cruickshank DJ, Robertson AA, Campbell DM, MacGillivray I. Maternal obstetric outcome measures in a randomised controlled study of labetalol in the treatment of hypertension in pregnancy. *Clinical and Experimental Hypertension* 1991;**B10**:333-44.

Sweden 1984 {published and unpublished data}

Bjorksten B, Finnstrom O, Wichman K. Intrauterine exposure to the beta-adrenergic receptor-blocking agent metoprolol and allergy. *International Archives of Allergy and Immunology* 1988;**87**:59-62.

Finnstrom O, Ezitis J, Ryden G, Wichman K. Neonatal effect of beta-blocking drugs in pregnancy. *Acta Obstetrica et Gynecologica Scandinavica Supplement* 1984;**118**:91-3.

Ryden G, Karlberg BE, Wichman K. Metoprolol in the treatment of hypertension in pregnancy - effect on the mother and foetus.. Proceedings of the 4th World Congress of the International Society for the study of Hypertension in Pregnancy; 1984 June 18-21; Amsterdam, The Netherlands, 1984:38. Amsterdam, 1984:38.

Wichman K. Metoprolol in the treatment of mild to moderate hypertension in pregnancy - effects on fetal heart activity. *Clinical and Experimental Hypertension* 1986;**5**(2):195-202.

Wichman K, Ezitis J, Finnstrom O, Ryden G. Metoprolol in the treatment of hypertension in pregnancy - effect on the newborn baby. *Clinical and Experimental Hypertension* 1984;**B3**:153.

Wichman K, Ezitis J, Finnstrom O, Ryden G. Metoprolol in the treatment of hypertension in pregnancy - effects on the newborn baby.. 4th World Congress of the International Society for the study of Hypertension in Pregnancy; 1984 June 18-21; Amsterdam, The Netherlands, 1984:40. Amsterdam, 1984:40.

Wichman K, Karlberg E, Ryden G. Metoprolol in the treatment of mild to moderate hypertension in pregnancy - effects on the mother. *Clinical and Experimental Hypertension* 1985;**B4**:141-56.

* Wichman K, Ryden G, Karlberg BE. A placebo controlled trial of metoprolol in the treatment of hypertension in pregnancy. *Scandinavian Journal of Clinical and Laboratory Investigation* 1984;**169**:90-5.

Sweden 1985 {published data only}

Hogstedt S, Lindberg B, Lindberg S, Ludviksson K, Sandstrom B. Effect of metoprolol on fetal heart rate patterns during pregnancy and delivery.. Proceedings of the 4th World Congress of the International Society for the Study of Hypertension in

Pregnancy; 1984 18-21 June; Amsterdam, The Netherlands, 1984:39. Amsterdam, 1984:39.

Hogstedt S, Lindberg B, Lindeberg S, Ludviksson K, Sandstrom B. Effect of metoprolol on fetal heart rate patterns during pregnancy and delivery. *Clinical and Experimental Hypertension* 1984;**B3**:152.

* Hogstedt S, Lindeberg S, Axelsson O, Lindmark G, Rane A, Sandstrom B, et al. A prospective controlled trial of metoprolol-hydralazine treatment in hypertension during pregnancy. *Acta Obstetrica et Gynecologica Scandinavica* 1985;**64**:505-10.

Sweden 1993a {published data only}

Hjertberg R, Belfrage P, Faxelius G, Lagercrantz H. Neonatal outcome in infants <1500g, a randomized study of labetalol vs dihydralazine-treated hypertensive pregnant women.. Proceedings of the 7th World Congress of Hypertension in Pregnancy; 1990; Perugia, Italy, 1990:361. Perugia, 1990:361.

* Hjertberg R, Faxelius G, Lagercrantz H. Neonatal adaptation in hypertensive pregnancy - a study of labetalol vs hydralazine treatment. *Journal of Perinatal Medicine* 1993;**21**:69-75.

Hjertberg R, Faxelius G, Lagercrantz H. Neonatal adaptation in hypertensive pregnancy - a study of labetalol vs hydralazine treatment.. Proceedings of the 14th European Congress of Perinatal Medicine; 1994; Helsinki, Finland, 1994:18. Helsinki, 1994:18.

USA 1987 {published data only}

Sibai BM, Gonzalez AR, Mabie WC, Moretti M. A comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term. *Obstetrics and Gynecology* 1987;**70**:323-7.

USA 1990a {published data only}

Sibai BM. The need of hypertensive drugs in management of mild to moderate pregnant hypertension.. Proceedings of 7th World Congress of Hypertension in Pregnancy; 1990; Perugia, Italy, 1990:133. Perugia, 1990:133.

* Sibai BM, Mabie WC, Shamsa F, Villar MA, Anderson GD. A comparison of no medication versus methyl dopa or labetalol in chronic hypertension during pregnancy. *American Journal of Obstetrics and Gynecology* 1990;**162**:960-7.

Venezuela 1988 {published data only}

Faneite A. PJ, González de Chirivella X, Salazar de Dugarte G, Tuimala R, Hartikainen SAL. Evaluation of antihypertensive agents in pregnancy: prospective, randomized study of mepindolol and alpha methyl dopa [Evaluacion de antihipertensivos en embarazadas: mepindolol y alfa metildopa: estudio prospectivo y randomizado]. *Revista de Obstetricia y Ginecologia de Venezuela* 1988;**48**:139-43.

References to studies excluded from this review

Argentina 1986 {published data only}

Voto L, Lapidus A, Neira J, Margulies M. Atenolol vs alpha methyl dopa in the treatment of hypertension in pregnancy.. 5th International Congress for the International Society for

the study of Hypertension in Pregnancy; 1986 July 7-10; Nottingham, UK, 1986:138. Nottingham, 1986:138.

Argentina 1994 {published data only}

Fabregues G, Sure P, Knaudt S, Gonzalez Pena J, Esper R. The use of atenolol to prevent preeclampsia and superimposed preeclampsia. *International Journal of Gynecology and Obstetrics* 1994;**46**:95.

Belgium 1988 {published data only}

Loquet Ph, Buytaert Ph, Renier M. The influence of pindolol and atenolol on serial feto-placental blood flow measurements in non-proteinuric hypertension in pregnancy.. Proceedings of the 6th International Congress, International Society for the Study of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada, 1988:111. Montreal, 1988:111.

Canada 1988 {published data only}

Davidson A, Ellenbogen A, Jaschevatzky O, Attias Y, Anderman S, Grunstein S. Randomized comparison of pindolol and atenolol for treatment of hypertension during pregnancy.. Proceedings of the 6th International Congress, International Society for the Study of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada, 1988:99. Montreal, 1988:99.

England 1986 {published data only}

Pickles, CJ, Symonds, EM, Brinkman, CR. Effects of labetalol (L) vs placebo (P) on arterial pressure (AP) and forearm venous distensibility (FVD) in women with pregnancy induced hypertension (PIH).. Proceedings of the 5th International Congress for the International Society for the Study of Hypertension in Pregnancy; 1986 July 7-10; Nottingham, England, 1986:92. Nottingham, 1986:92.

Finland 1984 {published data only}

Tuimala RJ, Hartikainen-Sorri AL. Treatment of hypertension during pregnancy by beta blocking agents.. 4th World Congress of the International Society for the Study of Hypertension in Pregnancy; 1984 June 18-21; Amsterdam, The Netherlands, 1984:52. Amsterdam, 1984:52.

Finland 1995 {published data only}

Rasanen J, Jouppila P. Uterine and fetal hemodynamics and fetal cardiac function after atenolol and pindolol infusion. A randomized study. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1995;**62**:195-201.

Finland 1999 {published data only}

Laivuori HM, Laakso M, Tikkanen MJ, Cacciatore B, Ylikorkala RO, Kaaja RJ. Short-term metabolic effects of isradipine and metoprolol in pre-eclampsia. *Journal of Hypertension* 1999;**17**:1189-94.

France 1986 {published data only}

Fievet P, El Esper N, Gueroult JF, Gueroult JC, Fournier A. Comparative study of clonidine and labetalol in severe hypertension induced by pregnancy.. Proceedings of the 5th World Congress of Hypertension in Pregnancy; 1986 July 7-10; Nottingham, 1986:136. Nottingham, 1986:136.

France 1988c {published data only}

Blazquez, Lardoux H, Leperlier E. Randomized and comparative study of methyl dopa (MD), acebu-tolol (ACE) and labetalol for the treatment of moderate hypertension during pregnancy (HDP).. Proceedings of the 6th International Congress, International Society for the Study of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada, 1988:100. Montreal, 1988:100.

France 1988d {published data only}

Renier M, Loquet P, Buytaert P. The influence of pindolol and atenolol on serial feto-placental blood flow measurements in non-proteinuric hypertension in pregnancy.. Proceedings of the 11th European Congress of Perinatal Medicine; 1988; Rome, Italy, 1988. Rome, 1988.

France 1988e {published data only}

Madonna O, M'Pio I, Labeeuw M, Pozet N, Zech P. Evaluation of renal function in pregnant hypertensives under treatment. A comparison between methyl dopa, pindolol and atenolol.. Proceedings of the 6th International Congress, International Society for the Study of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada, 1988:260. Montreal, 1988:260.

France 1989 {published data only}

Mintz P, Ciraru-Vigneron N, Ravina JH, Pruna A, Bonnin P, Beaufile M. Comparison of the effects of nifedipine and atenolol in the treatment of uncomplicated gestational hypertension [Comparaison des effets de la nifedipine et de l'atenolol dans le traitement de l'hypertension arterielle gravidique non compliquee]. *Therapie* 1989;**44**:461.

France 1990a {published data only}

Ciraru-Vigneron N, Pruna A, Mintz P, Bonnin P, Lefevre V, et al. Comparison of nifedipine and atenolol in treatment of moderate pregnancy hypertension.. Proceedings of the 7th World Congress of Hypertension in Pregnancy; 1990; Perugia, Italy, 1990:340. Perugia, 1990:340.

France 1990b {published data only}

Bonnin Ph, Mintz Ph, Kedra AW, Pruna A, Ciraru-Vigneron N, Savin E, et al. Effects of nifedipine and atenolol on the fetal-maternal circulation in moderate hypertension in pregnancy [Effets de la nifedipine et de l'atenolol sur les circulations foeto:maternelles en cas d'hypertension arterielle gravidique moderee]. *Therapie* 1990;**45**:525.

France 1992 {published data only}

Ciraru-Vigneron N, Pruna A, Akposso K, Bonnin Ph, Kedra W, Mintaz Ph, et al. Comparison of the effects of nifedipine and atenolol in uncomplicated gestational hypertension [Comparaison des effets de la nifedipine et de l'atenolol dans le traitement de l'hypertension arterielle gravidique non compliquee]. *Therapie* 1992;**47**:221.

Hong Kong 1993 {published data only}

Yuen FT, Mo YP, Yin LC, Terence L. A double-blind randomised placebo controlled trial of labetalol in the treatment of mild pregnancy induced hypertension.. Proceedings of 2nd International Scientific Meeting of the Royal College of

Obstetricians and Gynaecologists; 1993; Hong Kong, Singapore, 1993. Hong Kong, Singapore, 1993.

Ingemarsson 1991 {unpublished data only}

Ingemarsson I. Trial to assess the effects of atenolol or pindolol in pregnancy on pregnancy-induced hypertension. Personal communication February 1991.

Israel 1988 {published data only}

Paran E, Maisner I, Holzberg G, Mazor M, Zmora E, Biale Y, et al. Beta-blocker treatment of PIH correlated with uteroplacental blood flow measurement.. Proceedings of the 6th International Congress, International Society for the Study of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada, 1988:109. Montreal, 1988:109.

Israel 1992b {published data only}

Meizner I, Paran E, Katz M, Holcberg G, Insler V. Flow velocity analysis of umbilical and uterine artery flow in pre-eclampsia treated with propranolol or pindolol. *Journal of Clinical Ultrasound* 1992;**20**:115-9.

Israel 1994 {published data only}

Bar J, Hirsch M, Friedman S, Fuchs J, Ovadia J, Bott-Kanner G. The effect of beta-adrenergic blocker pindolol on platelet function in chronic hypertensive pregnancies.. Proceedings of the 9th International Congress, International Society for the Study of Hypertension in Pregnancy; 1994; Sydney, Australia, 1994:155. Sydney, 1994:155.

Italy 1986 {published data only}

Martinelli P, Ferrara LA, Pasanisi F, Arpaia F, Paladini D, Mancini M, et al. Nifedipine and atenolol in the treatment of pregnancy associated hypertension.. Proceedings of the 5th International Congress for the International Society for the study of Hypertension in Pregnancy; 1986 7-10 July; Nottingham, England, 1986:128. Nottingham, 1986:128.

Italy 1988 {published data only}

Orlandi C, Marlettini MG, Cassani A, Crippa S. Antihypertensive therapy in pregnancy.. Proceedings of the 11th European Congress of Perinatal Medicine; 1988; Rome, Italy, 1988:271. Rome, 1988:271.

Italy 1990 {published data only}

Marlettini MG, Crippa S, Morselli-Labate AM, Contarini A, Orlandi C. Randomized comparison of calcium antagonists and beta-blockers in the treatment of pregnancy-induced hypertension. *Current Therapeutic Research* 1990;**45**:684-94.

Kuwait 1995 {published data only}

El-Qarmalawi AM, Morsy AH, Al-Fadly A, Obeid A, Hashem M. Labetalol vs methyldopa in the treatment of pregnancy-induced hypertension. *International Journal of Gynecology & Obstetrics* 1995;**49**:125-30.

Lule 1992 {unpublished data only}

Lule J. Aspirin and methyldopa for moderate hypertension in pregnancy. Personal communication June 6 1992.

N Ireland 1986 {published data only}

Harper A, Murnaghan GA, Erskine L, Ritchie JK. Response of fetal umbilical artery time velocity waveforms to antihypertensive drugs.. Proceedings of the British Congress of Obstetrics and Gynaecology; 1986; UK, 1986:33. 1986:33.

N Ireland 1991 {published data only}

Harper A, Murnaghan GA. Maternal and fetal haemodynamics in hypertensive pregnancies during maternal treatment with intravenous hydralazine or labetalol. *British Journal of Obstetrics and Gynecology* 1991;**98**:453-9.

Pello 1988 {unpublished data only}

Pello L. Multicentre trial of treatment of hypertension in pregnancy. Personal communication October 18 1988.

Scotland 1983a {published data only}

Lang GD, Lowe GDO, Walker JJ, Forbes CD, Calder AA. Increased blood viscosity in pre-eclampsia: effect of treatment with labetalol. *Thrombosis and Haemostasis* 1983;**50**(1):156.

Singapore 1998 {published data only}

Yin KH, Koh SC, Malcus P, SvenMontan S, Biswas A, Arulkumaran S. Preeclampsia: haemostatic status and the short-term effects of methyldopa and isradipine therapy. *Journal of Obstetrics and Gynaecology Research* 1998;**24**:231-8.

Spain 1988 {published data only}

Torres Pons PJ, Roca M, Codina C, Cobo E, Cararach V, Gonzalez-Merlo J. Labetalol in the treatment of mild hypertension in pregnancy. A double blind controlled trial.. 6th International Congress, International Society for the Study of Hypertension in Pregnancy; 1988 May 22-26; Montreal, Quebec, Canada, 1988:102. Montreal, 1988:102.

Sweden 1986a {unpublished data only}

Wichman K. Metoprolol in the treatment of mild to moderate hypertension in pregnancy - effects on the newborn baby. Personal communication November 19 1986.

Sweden 1986b {unpublished data only}

Wichman K. Metoprolol in the treatment of mild to moderate hypertension in pregnancy - two-year follow-up study of the infants. Personal communication November 19 1986.

Sweden 1990 {published data only}

Montan S, Ingemarsson I, Marsal K, Sjoberg NO. Negative influence of atenolol compared with pindolol on fetal hemodynamics in pregnancies with hypertension - a controlled study.. Proceedings of the 7th World Congress of Hypertension in Pregnancy; 1990; Perugia, Italy, 1990:192. Perugia, 1990:192.

Sweden 1992 {published data only}

Montan S, Ingemarsson I, Marsal K, Sjoberg NO. Randomised controlled trial of atenolol and pindolol in human pregnancy: effects on fetal haemodynamics. *BMJ* 1992;**304**:946-9.

Sweden 1993b {published data only}

Hjertberg R, Faxelius G, Belfrage P. Comparison of outcome of labetalol or hydralazine therapy during hypertension in

pregnancy in very low birth weight infants. *Acta Obstetrica et Gynecologica Scandinavica* 1993;**72**:611-5.

USA 1981 {published data only}

Welt SI, Dorminy JH, Jelovsek FR, Crenshaw MC, Gall SA. The effect of prophylactic management and therapeutics on hypertensive disease in pregnancy: preliminary studies. *Obstetrics and Gynecology* 1981;**57**:557-65.

USA 1987a {unpublished data only}

Welt SI. The use of prophylactic antihypertensive therapy in chronic hypertension in pregnancy. Personal communication October 27 1987.

USA 1990b {unpublished data only}

Weiner CP. Trial to evaluate oral hypotensive agents in early onset preeclampsia. Personal communication November 1990.

Wales 1991 {published data only}

Blake S, MacDonald D. The prevention of the maternal manifestations of pre-eclampsia by intensive antihypertensive treatment. *British Journal of Obstetrics and Gynaecology* 1991;**98**:244-8.

References to studies awaiting assessment

Alves 1998 {published data only}

Alves EA. Estudo prospectivo comparativo da isradipina e atenolol no tratamento de gestantes hipertensas [Prospective, comparative study of isradipine and atenolol for the treatment of hypertensive pregnant women] [thesis]. Sao Paulo: University of Sao Paulo, 1998.

August 2005 {published data only}

August P. Treatment targets for chronic hypertension in pregnancy. <http://clinicaltrials.gov/ct2/show/record/NCT00194974> (accessed 3 June 2012) 2005.

Centeno 2007 {published data only}

Centeno DMW, Urbina JCP, De Las Salas M, Fuenmayor AJ. Effect of carvedilol in the treatment of hypertension in pregnant women. XLIV ERA-EDTA Congress; 2007 June 21-24; Barcelona, Spain. 2007:Poster no: FP078.

Darcie 2004 {published data only}

Darcie S, Leone CR, Calil VMLT, Prescinotti EP, Kahhale S, Zugaib M. Glycemia in newborns of hypertensive mothers according to maternal treatment. *Revista do Hospital das Clinicas* 2004;**59**(5):244-50.

Freire 1988 {published data only}

Freire FS, Franca LA, Callou MRA, Oliveira JEA, Filho JB. Comparative study with pindolol and methildopa in pregnant women with chronic hypertension. *Jornal Brasileiro de Ginecologia* 1988;**98**(3):157-60.

Gallery 1984 {published data only}

Gallery EDM, Gyory AZ. Antihypertensive therapy in pregnancy [abstract]. *Kidney International* 1984;**26**(2):232.

Gonzalez 1997 {published data only}

Gonzalez JC, Andolcetti R. Labetalol vs alpha methyldopa in the treatment of hypertension in pregnancy [Labetalol vs alfa metildopa en el tratamiento de la hipertension arterial asociada con el embarazo]. *Boletin Medico de Postgrado* 1997;**13**(1):3-8.

Hameed 2008 {published data only}

Hameed AB. A comparison of compliance between clonidine patch and methyldopa for the treatment of chronic hypertension in pregnancy. *ClinicalTrials.gov* (<http://clinicaltrials.gov/>) (accessed 20 February 2008). NCT00329511 2008.

Leone 2003 {published data only}

Leone CR, Calil VMLT, Darcie S, Prescinotti EP, Kahhale S, Zugaib M. Growth of newborn of the mothers with hypertension during the first year of life: influence of therapeutics in pregnancy. *Revista Paulista de Pediatria* 2003;**21**(1):19-26.

Lindeberg 1985 {published data only}

Lindeberg S, Axelsson O, Lindberg BS, Lindmark G, Ludviksson K, Sandstrom B. Effect of metoprolol in combination with hydralazine on fetal heart rate patterns during hypertensive pregnancy and delivery. *Clinical & Experimental Hypertension - Part B, Hypertension in Pregnancy* 1985;**4**(1):87-94.

Osvaldo 2012 {published data only}

Osvaldo A, Reyes T. Hydralazine vs. Labetalol for the management of hypertensive crisis in patients with hypertensive disorders of pregnancy. a randomized controlled trial. <http://clinicaltrials.gov/ct2/show/record/NCT01538875> (accessed 3 July 2012).

Pandey 2011 {published data only}

Pandey K, Gupta N, Gupta R, Gupta S. Comparing obstetric outcome using labetalol/methyldopa in pregnancy induced hypertension. 54th All India Congress of Obstetrics and Gynaecology; 2011 January 5-9; Hyderabad, Andhra Pradesh, India. 2011:46.

Paran 1988 {published data only}

Paran E, Baile Y, Holzberg G, Masor M, Zmora E, Insler V. Treatment of hypertension in pregnancy: different regime, different outcome. 6th International Congress of the International Society for the Study of Hypertension in Pregnancy; 1988 May 22-26, Montreal, Quebec, Canada. 1988:105.

Rubin 1983 {published data only}

Rubin PC, Butters L, Low RA, Clark DC, Reid JL. Atenolol in the management of hypertension during pregnancy. *Drugs* 1983;**25**:212-4.

Voto 1985 {published data only}

Voto LS, Lapidus AM, Neira J, Magulies M. Treatment of hypertension in pregnancy: atenolol versus alpha-methyldopa [Tratamiento de la hipertension en el embarazo: atenolol versus alfa metildopa]. *Obstetricia y Ginecologia Latino-Americanas* 1985;**43**(9-10):335-41.

Voto 1990 {published data only}

Voto LS, Quiroga CA, Lapidus AM, Catuzzi P, Uranga IF, Margulies M. Effectiveness of antihypertensive drugs in the treatment of hypertension in pregnancy. *Clinical and Experimental Hypertension - Part B Hypertension in Pregnancy* 1990;**9**(3):339-48.

Warren 2004 {published data only}

Warren J, Lacoursiere Y, Varner M, Silver R, Anthony J, Belfort M. First interim report on the labetalol versus magnesium sulfate for the prevention of eclampsia trial (LAMPET) [abstract]. *Hypertension in Pregnancy* 2004;**23**(Suppl 1):9.

Additional references

Abalos 2002

Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy (Cochrane Review). *The Cochrane Library* 2002, Issue 1.

Brown 2000

Brown MA, Hague WM, Higgins J, Lowe S, McCowan L, Oats J, et al. The detection, investigation and management of hypertension in pregnancy: executive summary. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 2000;**40**(2):133-8.

Collins 1989

Collins R, Wallenburg HCS. Pharmacological prevention and treatment of hypertensive disorders in pregnancy. In: Chalmers I, Enkin M, Keirse MJNC editor(s). *Effective Care in Pregnancy and Childbirth*. Oxford: Oxford University Press, 1989:512-33.

DH 1998

Department of Health, Welsh Office, Scottish Home and Health Department, Department of Health and Social Security, Northern Ireland. Report on Confidential Inquiries into Maternal Deaths in the United Kingdom 1994-96. London: HMSO, 1998.

Duley 1992

Duley L. Maternal mortality and hypertensive disorders of pregnancy in Africa, Asia, Latin America and the Caribbean. *British Journal of Obstetrics and Gynaecology* 1992;**99**:547-53.

Duley 2002

Duley L, Henderson-Smart DJ. Drugs for rapid treatment of very high blood pressure during pregnancy (Cochrane Review). *The Cochrane Library* 2002, Issue 1.

Easterling 1999

Easterling TR, Brateng D, Schmucker B, Brown Z, Millard SP. Prevention of preeclampsia: a randomized trial of atenolol in hyperdynamic patients before onset of hypertension. *Obstetrics & Gynecology* 1999;**93**:725-33.

Knight 2002

Knight M, Duley L, Henderson-Smart DJ, King JF. Antiplatelet agents for preventing and treating pre-eclampsia (Cochrane Review). *The Cochrane Library* 2002, Issue 1.

Laupacis 1988

Laupacis A, Sackett DL, Roberts RS. As assessment of clinically useful measures of the consequences of treatment. *New England Journal of Medicine* 1988;**318**:1728-33.

Lydakis 1999

Lydakis C, Lip GYH, Beevers M, Beevers DG. Atenolol and fetal growth in pregnancies complicated by hypertension. *American Journal of Hypertension* 1999;**12**:541-7.

NHB 2000

National High Blood Pressure Education Program Working Group. Report on High Blood Pressure in Pregnancy. *American Journal of Obstetrics and Gynecology* 2000;**183**:S1-22.

Redman 1989

Redman CWG. Hypertension in pregnancy. In: Turnbull AC, Chamberlain GVP editor(s). *Textbook of obstetrics*. London: Churchill Livingstone, 1989:515-41.

Redman 1993

Redman CW. Management of severe, early pre-eclampsia: is conservative management justified?. *European Journal of Obstetrics & Gynecology and Reproductive Biology* 1993;**51**:175-80.

RevMan 2000 [Computer program]

The Cochrane Collaboration. Review Manager (RevMan) [Computer program]. Version 4.1 for Windows. Oxford, England: The Cochrane Collaboration, 2000.

Rey 1997

Rey E, LeLorier J, Burgess E, Lange IR, Leduc L. Report of the Canadian Hypertension Society Consensus Conference: 3. Pharmacologic treatment of hypertensive disorders in pregnancy. *Canadian Medical Association Journal* 1997;**157**:1245-54.

von Dadelszen 2000

von Dadelszen P, Ornstein MP, Bull SB, Logan AG, Koren G, Magee LA. Fall in mean arterial pressure and fetal growth restriction in pregnancy hypertension: a meta-analysis. *Lancet* 2000;**355**:87-92.

References to other published versions of this review

CDSR 2003

Magee LA, Duley L. Oral beta-blockers for mild to moderate hypertension during pregnancy (Cochrane Review). *The Cochrane Library* 2003, Issue 2.

Collins 1995a

Collins R, Duley L. Beta-blockers vs methyldopa in the treatment of pre-eclampsia. [revised 21 March 1994] In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) *Pregnancy and Childbirth Module*. In: *The Cochrane Pregnancy and Childbirth Database* [database on disk and CDROM]. The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

Collins 1995b

Collins R, Duley L. Beta-blockers in the treatment of pre-eclampsia. [revised 21 April 1994] In: Enkin MW, Keirse MJNC, Renfrew MJ, Neilson JP, Crowther C (eds.) Pregnancy and Childbirth Module. In: The Cochrane Pregnancy and Childbirth

Database [database on disk and CDROM]. The Cochrane Collaboration; Issue 2, Oxford: Update Software; 1995.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies *[ordered by study ID]*
Argentina 1988

Methods	Quality score: BCA. "...randomised..." is the only information given. Randomisation method not stated.
Participants	36 women; > 14 weeks; BP 140/90 to 170/110.
Interventions	Mepindolol at increasing weekly doses (from 5-10 mg OD); methyldopa at increasing weekly doses (from 500-2000 mg OD); treatment goal was an "...optimal response..."; ancillary therapy not specified.
Outcomes	Additional antihypertensive therapy, caesarean section, changed drugs due to maternal side effects, perinatal mortality, SGA infants (not defined).
Notes	Available only as an abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Australia 1983

Methods	Quality score: BCA. "...randomly allocated..." Randomisation method not stated.
Participants	28 women, from routine antenatal clinic. BP > 140/90 mmHg x 2, 24 hours apart. Excluded 'severe' hypertension, impaired renal function.
Interventions	Propranolol 30-160 mg daily vs methyldopa 500-1000 mg daily in divided doses. Treatment goal not stated.
Outcomes	Severe hypertension, proteinuria (not defined), additional antihypertensive therapy, changed drugs due to maternal side effects, caesarean section, Hb, Hct, BUN, creat, uric acid, maternal heart rate, perinatal mortality, prematurity, neonatal jaundice, neonatal bradycardia, neonatal hypoglycaemia.
Notes	

Risk of bias
Oral beta-blockers for mild to moderate hypertension during pregnancy (Review)

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Australia 1983 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Australia 1985

Methods	Quality score: BCA. "...allocated by a series of random numbers..." Randomisation method: random number table.
Participants	183 women, from antenatal clinics. dBP > or equal to 90 mmHg x 2, 24 hours apart, or dBP > or equal to 95 mmHg x 2, 12 hr apart, or dBP > or equal to 100 mmHg x 2, 8 hr apart.
Interventions	Oxprenolol 40 mg po BID (max 640 mg daily) vs methyldopa 250 mg po BID (max 3000 mg daily); treatment goal dBP < or equal to 80 mm Hg; ancillary therapy: hydralazine 12.5 mg po BID (max 300 mg daily); elective delivery at 37-41 weeks.
Outcomes	Severe hypertension, proteinuria ('heavy and increasing requiring delivery'), additional antihypertensive therapy, caesarean section, perinatal mortality, admission to SCBU, RDS, days in SCBU.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Brazil 1998

Methods	Quality score: BCA. "...prospective randomized, controlled trial..."
Participants	94 women; no details of inclusion criteria provided; stated that they were treating "...hypertensive disorders of pregnancy".
Interventions	Atenolol 50 mg po BID vs isradipine slow-release 5 mg po BID; no max doses stated.
Outcomes	SGA infants (not defined).
Notes	Available only as an abstract.

Risk of bias

Bias	Authors' judgement	Support for judgement
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Brazil 1998 (Continued)

Allocation concealment (selection bias)	Unclear risk	B - Unclear
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England 1978

Methods	Quality score: B CA. "...randomly allocated...". 2 women still pregnant at time of interim report (therefore, no data on 1 from treatment, and 1 from control group). Randomisation method not stated.
Participants	74 women with singleton pregnancy; dBP > or equal to 170/100 mmHg x 2; < or equal to 36 weeks' gestation; excluded insulin dependent diabetes mellitus, rhesus isoimmunisation.
Interventions	Labetalol 100 mg po QID (max 1200 mg daily) vs methyldopa 250 mg po QID (up to 4000 mg daily); treatment goal ~140/90 mmHg; ancillary treatment: hydralazine (dose not stated).
Outcomes	Severe hypertension, proteinuria ('greater than trace'), additional antihypertensive therapy, changed drugs due to maternal side effects, caesarean section, perinatal mortality, SGA infants (< 10th centile), intubated, umbilical cord pH.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

England 1980

Methods	Quality score: BC A or C (depending on the outcome). "...allocated to treatment....using a random number table..." Randomisation method was random number table. 2 withdrawals (from control group due to uncontrolled hypertension); analysis was intention-to-treat; incomplete data for neonatal jaundice, neurodevelopmental follow up.
Participants	26 women; mean arterial BP > or equal to 103.3 mmHg x 24 hr; < 38 weeks' gestation; normal BP < 16 weeks' gestation; excluded chronic hypertension, contraindication to beta-blockers.
Interventions	Labetalol 400 mg daily (max 800 mg daily) vs methyldopa 750 mg daily (max 1500 mg daily); treatment goal BP < 140/85 mmHg; ancillary therapy: iv labetalol then oral hydralazine if needed.

England 1980 (Continued)

Outcomes	Severe hypertension, proteinuria (not defined), additional antihypertensive therapy, caesarean section, length of maternal hospital stay (in days), perinatal mortality, neonatal jaundice, length of stay in SCBU (in days).
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

England 1983

Methods	Quality score: B CA. "...allocated at random..." 4 withdrawals (2 in each group, 1 for miscarriage and 1 lost to follow up); not ITT analysis. Randomisation method not stated.
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Participants	100 women booked for delivery at London teaching hospital; dBP > or equal to 95 mmHg x 2, 24 hr apart, dBP > 105 mmHg; singleton; exclusions not stated.
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Interventions	Oxprenolol 80 mg po BID (max 640 mg daily) vs methyldopa 250 mg po TID (max 3000 mg daily); treatment goal d < 95 mmHg; ancillary therapy: hydralazine 25 mg po TID (max 300 mg daily); hospital admission for d > 110 mm Hg, proteinuria, obstetric reasons.
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Outcomes	Proteinuria ('greater than trace'), additional antihypertensive therapy, admission to hospital prior to delivery, caesarean section, uric acid, maternal days in hospital (median), perinatal mortality.
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

England 1984

Methods	Quality score: BCA. "...randomised trial..." stated in title of abstract. Randomisation method not stated.
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Participants	60 women, with hypertension in pregnancy; 18-36 weeks' gestation.
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Interventions	Atenolol 100 mg po OD vs methyldopa 250 mg po TID; treatment goal not stated.
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Oral beta-blockers for mild to moderate hypertension during pregnancy (Review)

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England 1984 (Continued)

Outcomes	Severe hypertension, proteinuria (not defined), perinatal mortality, SGA infants (< 10th centile), neonatal hypoglycaemia.
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Notes	Available only as an abstract.
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Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

England 1989

Methods	Quality score: AAB. Randomisation centralised (through pharmacy). 8 withdrawals (6 from treatment, 2 from control groups); not ITT analysis. Randomisation method: list of random numbers.
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Participants	152 women, from antenatal wards of 5 hospitals; sBP 140-160/90-105 mmHg x 2, 24 hr apart; no proteinuria; 20-38 weeks' gestation.
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Interventions	Labetalol 'one tablet' po TID (maximum 6 tablets daily) vs placebo one tablet po TID; treatment goal: 'control'; ancillary therapy: 'another antihypertensive'.
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Outcomes	Severe hypertension, proteinuria (not defined), additional antihypertensive therapy, changed drugs due to maternal side effects, caesarean section, perinatal mortality, prematurity, SGA infants (< 5th and < 10th; < 10th used in this review), admission to SCBU, neonatal jaundice, neonatal bradycardia, neonatal hypoglycaemia, RDS.
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Notes	
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Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Fr Caribbean 1990

Methods	Quality score: AAA. Sealed envelopes prepared centrally, contained second sealed envelope with allocation. Only 1 post-randomisation withdrawal in placebo group; not ITT analysis. Randomisation method not stated.
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Participants	155 women, from antenatal clinic; singleton pregnancy; dBP < 85 mmHg before 20 weeks, but > 84 mmHg x 2 after 20 weeks; 20-36 weeks' gestation;
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Oral beta-blockers for mild to moderate hypertension during pregnancy (Review)

Fr Caribbean 1990 (Continued)

excluded medical disorders: insulin dependent diabetes mellitus, congestive heart failure, asthma, heart block, pre-pregnancy hypertension, antihypertensive treatment during pregnancy.

Interventions	Oxprenolol 80 mg po BID (max 320 mg daily) vs placebo ("identical"); treatment goal d < 86 mmHg; ancillary treatment with dihydralazine 50-100 po as required to meet treatment goal; withdrawn for 'major intolerance', d > 105 mmHg x 2 despite hydralazine, max dosage of medications, proteinuria; after withdrawal, women were given active treatment (if they'd been on placebo) or methyldopa (if they'd been on active treatment).
Outcomes	Maternal death, eclampsia, severe hypertension, proteinuria (> 1+ or 0.25 g/L), additional antihypertensive therapy, changed drugs due to maternal side effects, admission to hospital before delivery, abruption, caesarean section, perinatal mortality, prematurity, SGA infants (not defined as information from Cochrane Centre; < 10th centile was mentioned in manuscript), low Apgars, RDS.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

France 1988a

Methods	Quality score: BCA. Allocated in "...random order...". Randomisation method not stated; blocked.
Participants	42 women; dBP > 90 mm Hg; 7-36 weeks' gestation; exclusions not stated.
Interventions	3 treatment groups: (i) labetalol 200 mg BID (max 1200 mg daily), (ii) acebutolol 200 mg BID (max 1200 mg daily), (iii) methyldopa 500 mg po BID (max 1500 mg daily); treatment goal not stated; ancillary therapy: acebutolol po for labetalol group, labetalol (?po) for acebutolol group, hydralazine iv for methyldopa group.
Outcomes	Proteinuria ("pre-eclampsia"), additional antihypertensive therapy, perinatal mortality, neonatal hypoglycaemia.
Notes	In this review, the labetalol and acebutolol groups (together) were compared with methyldopa.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

France 1988b

Methods	Quality score: BCC. "...assigned at random..." 12 withdrawals (5 from treatment, 7 from controls); not ITT analysis. Randomisation method not stated.
Participants	176 women, from antenatal clinics; dBP > 89 mm Hg x 2 -12-34 weeks' gestation; singletons; excluded previous antihypertensive treatment in this pregnancy, diabetes mellitus, depression, con- traindication to beta-blockers.
Interventions	Labetalol 200 mg po BID (maximum 1200 mg daily) vs methyldopa 250 mg po BID (max 1500 mg daily); treatment goal dBP < or equal to 85 mmHg; ancillary therapy: hydralazine 50 mg po daily (max 100 mg daily); withdrawal for d > 105 mmHg or use of other medications; admission to hospital for d > 105 mmHg, pre-eclampsia, obstetric problems.
Outcomes	proteinuria (> 2+ or 0.5 g/L), additional antihypertensive therapy, changed drugs due to maternal side effects, admission to hospital prior to delivery, caesarean section, perinatal mortality, prematurity, SGA infants (< 5th centile), admission to SCBU, low Apgars.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

France 1994

Methods	Quality score: BCA. used serially numbered, sealed envelopes, but they were not stated to be opaque. Randomisation method adequate (computer-generated list of random numbers).
Participants	100 women, from antenatal clinic; mild to moderate hypertension, BP > or equal to 140/90 mm Hg x 2; singleton pregnancy; > or equal to 20 weeks' gestation; excluded previous antihypertensive therapy.
Interventions	Metoprolol slow release 200 mg po OD vs nifedipine 20 mg po TID (+ 'conventional therapy'); ancillary therapy: hydralazine 25 mg po TID, started for BP > 160/110 mmHg in addition to the patient being admitted to hospital.
Outcomes	Severe hypertension, proteinuria (not defined), maternal HELLP, additional antihypertensive therapy, changed drugs due to side effects, caesarean section, umbilical Doppler, perinatal mortality, admission to SCBU.
Notes	

Risk of bias

France 1994 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Hong Kong 1990

Methods	Quality score: BAB. "...prospective randomized double-blind control study..." 3 withdrawals (2 from treatment, 1 from control group) for birth weight and SGA infants. Randomisation method not stated.	
Participants	41 women, nulliparous; pre-eclampsia (BP > or equal to 140/90 mmHg x 2, in 24 hours); excluded women who were not 'previously healthy'.	
Interventions	Labetalol 200 mg po TID vs placebo ('identical'); treatment goal < 165/105 mmHg; ancillary therapy not stated.	
Outcomes	Severe hypertension, additional antihypertensive therapy, SGA infants (< 10th centile).	
Notes	Available only as an abstract.	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

India 1992

Methods	Quality score: BCA. "...randomly allocated..." Randomisation method not stated.	
Participants	30 women; pregnancy-induced hypertension; BP > 140/90 mmHg x 2, 6 hr apart; 24-37 weeks' gestation; excluded history of urinary tract infection, heart disease, secondary hypertension.	
Interventions	Metoprolol 25 mg po BID (max 300 mg daily) vs methyldopa 250 mg po TID (max 2000 mg daily); treatment goal dBP < 85 mmHg; also used furosemide for severe peripheral edema.	
Outcomes	Perinatal mortality, prematurity.	
Notes		

Risk of bias

India 1992 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Israel 1986a

Methods	Quality score: BCA. "...randomly allocated" Randomisation method not stated.	
Participants	32 women, from high risk obstetrics unit; dBP > or equal to 95 mmHg, x 2, 6 hr apart; "pregnancy-induced hypertension"; 27-33 weeks' gestation; singletons; excluded essential hypertension, chronic renal disease.	
Interventions	Pindolol 15 mg po daily vs methyldopa (max 2000 mg daily); no other dosage info; treatment goal BP < 160/110 mmHg; ancillary therapy: hydralazine and/or MgSO4 (doses not given).	
Outcomes	Eclampsia, proteinuria (> 2+ or 0.5 g/L), additional antihypertensive therapy, changed drugs due to side effects, maternal heart rate, perinatal mortality.	
Notes		

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Israel 1986b

Methods	Quality score: BCC. "...randomly allocated" 2 cross-overs (2 women with side effects in the hydralazine alone group crossed over into the pindolol/hydralazine group and were reported as if they had been randomised to this group from the start). Randomisation method not stated.	
Participants	44 women, referrals to high risk clinic for pregnancy hypertension; sBP > 150 or dBP > 90 mmHg; < or equal to 36 weeks' gestation; excluded for insulin dependent diabetes, obstructive lung disease, contraindications to pindolol or hydralazine.	
Interventions	Pindolol + hydralazine 5/25 mg po BID (max 15/200 daily) vs hydralazine alone 25 mg po BID (max 200 mg daily); treatment goal dBP < 90 mm Hg; hospitalisation at 37 weeks, or if complications occurred;	

Oral beta-blockers for mild to moderate hypertension during pregnancy (Review)

Israel 1986b (Continued)

withdrawn and given "other" treatment if treatment goal not met.

Outcomes	Severe hypertension, proteinuria (sudden increase AND > 1 gm per 24 hours), changed drugs due to side effects, caesarean section, perinatal mortality, prematurity, SGA infants (< 250 on Usher's curve), neonatal hypoglycaemia, neonatal hypothermia, low Apgars.
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Israel 1992a

Methods	Quality score: AAA. Centralised randomisation through pharmacy. Randomisation method not stated.
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Participants	60 women, from medical clinics (for hypertension and renal disease); dBP 85-99 mmHg x 2, 12 hours apart; < 35 weeks' gestation; singletons; excluded previous antihypertensive treatment in this pregnancy, insulin dependent diabetes mellitus, contraindication to beta-blocker.
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Interventions	Pindolol 5 mg po BID (max 20 mg daily) vs placebo one tablet po BID; treatment goal not stated; withdrawn if dBP 100-109 mmHg x 2, or dBP > or equal to 110 mmHg; after withdrawal, women were given additional therapy with hydralazine (pindolol group), or pindolol (placebo group).
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Outcomes	Severe hypertension, proteinuria (> 2+ or 0.5 g/L), additional antihypertensive therapy, changed treatment due to maternal side effects, caesarean section, maternal stay in hospital before delivery (in days), perinatal mortality.
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Israel 1995

Methods	Quality score: BCA. "...randomly allocated..." Randomisation method not stated.
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Participants	51 women;
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Oral beta-blockers for mild to moderate hypertension during pregnancy (Review)

Israel 1995 (Continued)

sBP 140-160 mmHg, dBP 95-110 mmHg;
28-32 weeks' gestation;
excluded > 2+proteinuria, 'other disease'.

Interventions	3 treatment groups: i) pindolol (5-15 mg po daily) + hydralazine (60-200 mg po daily) po, ii) propranolol (40-120 mg po daily) + hydralazine (60-200 mg po daily), and iii) hydralazine alone (60-200 mg po daily) - doses were "gradually increased" to achieve treatment goal; treatment goal: BP < 140/90 mmHg.
Outcomes	Eclampsia, caesarean section, 'serious' maternal side effects, perinatal mortality, prematurity, SGA infants (< 10th centile).
Notes	In this review, the pindolol + hydralazine and propranolol + hydralazine groups (total) were compared with hydralazine alone.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Scotland 1982

Methods	Quality score: BCA. "...randomised into treatment and non-treatment..." Used envelopes, but did not state that they were opaque. Randomisation method not stated (i.e. "...randomized into treatment and non-treatment...").
Participants	126 women; women with either chronic hypertension or pregnancy-induced hypertension; dBP > 95 but < 109 mmHg.
Interventions	Labetalol 100 mg po BID (max 1200 mg daily) vs no treatment; treatment goal not stated; additional antihypertensive therapy was hydralazine 25 mg po TID (max 200 mg daily).
Outcomes	Severe hypertension, proteinuria (not defined; from correspondence with authors), caesarean section, abortion, perinatal mortality, SGA infants (not defined).
Notes	Data for all outcomes except perinatal mortality were obtained from author by UK Cochrane Centre.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Scotland 1983

Methods	Quality score: BA A or B (depending on the outcome). "...allocated in a double-blind and randomised manner..."
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Scotland 1983 (Continued)

Most endpoints reported for all patients (exceptions: admission to hospital prior to delivery which includes data on 71%; neurodevelopmental outcomes which included data on 92%).
Randomisation method not stated.

Participants	120 women, admitted for bedrest because of pregnancy-induced hypertension in last trimester; sBP 140-170 mmHg; dBP 90-110 mmHg on 2 occasions, 24 hr apart. Excluded women with "usual" contraindications to beta-blockers.
Interventions	Atenolol 100 mg po OD (max 200 mg daily) vs placebo 1 tablet po OD. Treatment goal: dBP < 90 mmHg; withdrawn for sBP > 170 or dBP > 110 mmHg x 2 occasions, side effects of therapy or noncompliance with treatment; ancillary treatment was decided upon by the patient's own obstetrician.
Outcomes	Severe hypertension, proteinuria (> 0.5 g/24 hours), additional antihypertensive therapy, changed treatment due to maternal side effects, admission to hospital prior to delivery, caesarean section, perinatal mortality, SGA infants (< 10th centile), neonatal bradycardia (measured by continuous monitoring of neonatal HR), neonatal hypoglycaemia, RDS, cerebral palsy, IQ < 1 SD below mean, pediatric weight at 12 months.
Notes	The fact that continuous monitoring of neonatal heart rate was used to detect neonatal bradycardia, and that no neonate with bradycardia required treatment, implies that the beta-blocker associated increase in bradycardia may not be clinically significant; important data on long-term outcomes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Scotland 1990

Methods	Quality score: BAB. "randomised." 4 withdrawals [1 treatment (patient changed her mind); 3 controls (2 severe hypertension, 1 breathlessness)]; not ITT analysis. Randomisation method not stated.
Participants	33 women, from obstetric medical clinics at 2 hospitals; BP 140-170/90-110 mmHg x 2, 24 hr apart; 12-24 weeks; excluded "usual" contraindications to beta-blockers.
Interventions	Atenolol 50 mg po OD (max 200 mg daily) vs placebo (character not stated); Treatment goal <140/90 mmHg.
Outcomes	Severe hypertension, changed treatment due to side effects, perinatal mortality, SGA infants (< 5th centile, data obtained from author by UK Cochrane Centre).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
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Scotland 1990 (Continued)

Allocation concealment (selection bias)	Unclear risk	B - Unclear
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Scotland 1992

Methods	Quality score: ACA. Used sealed opaque envelopes. Randomisation method not stated; stratified by parity (primip/multip).
Participants	114 women, from antenatal clinics; dBP > 90 mmHg x 24 hours; no proteinuria by 24 hr collection; 24-39 weeks' gestation; singleton pregnancy; excluded diabetes mellitus, contraindication to beta-blockers, antenatal antihypertensive treatment, 'psychoneurosis'.
Interventions	Labetalol 100 mg po BID (max 1200 mg daily) vs no treatment; treatment goal dBP < 90 mmHg, or dBP decrease by 5 mmHg.
Outcomes	Proteinuria (> 1+ or 0.25 g/L), changed drugs due to side effects, caesarean section, length of maternal hospital stay (in days), perinatal mortality, prematurity, SGA infants (< 5th centile), admission to SCBU, length of neonatal/infant stay in hospital (in days).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Sweden 1984

Methods	Quality score: AAA. Telephone randomisation (confirmed by communication with author).
Participants	52 women, from antenatal clinics; BP > or equal to 140/90 mmHg, or an increase of > or equal to 30/15 mmHg x 2 within 24 hours; < 37 weeks' gestation; singletons; excluded for severe hypertension > 170/110 mmHg, symptomatic, fetal distress, Rh disease, 'diabetes mellitus', contraindication to beta-blockers, 'social or psychological handicaps'.
Interventions	Metoprolol 50 mg po BID (max 200 mg daily) vs placebo 1 tablet po BID; treatment goal < 140/90 mmHg; ancillary therapy with hydralazine 25-50 mg po BID; withdrawn if BP > or equal to 160/100 mmHg on maximum treatment, or BP 170/110 mmHg, symptomatic, proteinuria, fetal distress.

Sweden 1984 (Continued)

Outcomes	Severe hypertension, proteinuria (pre-eclampsia defined as hypertension, proteinuria, and hyperuricemia), changed drugs due to maternal side effects, admission to hospital prior to delivery, abruption, caesarean section, perinatal mortality, low Apgars, umbilical cord pH.
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Sweden 1985

Methods	Quality score: BC A or B (depending on the outcome). Women were "...randomly allocated...". 7 withdrawals (4 treatment, 3 controls), depending on outcome; not ITT analysis. Randomisation method not stated.
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Participants	168 women, from public antenatal wards in 3 counties; dBP > or equal to 90 mmHg after admission for 24 hours; < 37 weeks' gestation; no proteinuria (< 0.3 g/L in 24 hour collection); singleton pregnancy; excluded dBP > 110 mmHg, medical conditions (see list in paper).
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Interventions	Metoprolol/hydralazine 50/25 mg po BID (max 200/150 mg daily) vs no treatment; treatment goal dBP < 90 mmHg; withdrawal for dBP > or equal to 110 mmHg on maximum treatment, induction of labour; discharged if dBP < 100 mmHg.
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Outcomes	Severe hypertension, proteinuria (> 1+ or 0.25 g/L), changed drugs due to maternal side effects, abruption, caesarean section, perinatal mortality, prematurity, SGA infants (not defined), neonatal bradycardia, neonatal hypoglycaemia, low Apgars, RDS.
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Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Sweden 1993a

Methods	Quality score: BCA. "...allocated at random..." Randomisation method not stated.
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Participants	20 women; dBP > or equal to 100 mmHg.
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Oral beta-blockers for mild to moderate hypertension during pregnancy (Review)

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Sweden 1993a (Continued)

Interventions	Labetalol po 300 mg daily (max 1200 mg daily) vs hydralazine 25 mg po TID (max 400 mg daily); treatment goal dBp 90-100 mmHg; ancillary therapy: iv therapy using the same drug (to which women were randomised).
Outcomes	Severe hypertension, additional antihypertensive therapy, caesarean section, perinatal mortality, SGA infants (2 SD below the mean), neonatal bradycardia, neonatal hypotension, neonatal hypoglycaemia, low Apgars, RDS, cord pH (< 7.20, median value).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

USA 1987

Methods	Quality score: BCB. Sealed envelopes were used, but they were not stated to be opaque. 14 withdrawals (8 from treatment and 6 from control) not in ITT analysis. Randomisation method: computer-generated list of random numbers.
Participants	200 women, from maternity wards after hospitalisation for 24 hr; mild pre-eclampsia: BP 140-160/90-110 mmHg AND > 0.3 g/L proteinuria AND uric acid > 4.6 mg/dL; 26-35 weeks' gestation; excluded "...associated medical and obstetrical complications...", other antihypertensive medication.
Interventions	Labetalol 300 mg daily (increased every few days to max of 2400 mg daily) vs hospitalisation alone; no other detail about dosing; treatment goal < 140/90 mmHg.
Outcomes	Severe hypertension, proteinuria ('increasing' proteinuria as all women had pre-eclampsia at entry), abruption, caesarean section, maternal renal function, perinatal mortality, SGA infants (< 10th centile), admission to SCBU, umbilical cord pH < 7.20.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

USA 1990a

Methods	Quality score: BCC. Allocation blinding not discussed. 24 withdrawals (14 from treatment, 10 from controls); not ITT analysis. Randomisation method adequate (computer-generated list of random numbers).
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USA 1990a (Continued)

Participants	200 women, from antenatal ward; 6-13 weeks' gestation; chronic hypertension before pregnancy; excluded "associated medical complications".
Interventions	Labetalol 300 mg daily (max 2400 mg daily) vs no treatment; treatment goal < 140/90 mmHg; ancillary therapy: hydralazine (max 300 mg daily).
Outcomes	Proteinuria (pre-eclampsia, defined as hypertension, proteinuria, and hyperuricemia), additional antihypertensive therapy, abruption, caesarean section, congestive heart failure, serum creatinine, uric acid, perinatal mortality, prematurity, SGA infants (not defined as data in review are from Cochrane centre; not < 2500 g which is given in the paper), neonatal hypoglycaemia, low Apgars.
Notes	The labetalol vs no therapy arms were used (instead of labetalol vs methyldopa given interest in first knowing whether any treatment is beneficial).

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

Venezuela 1988

Methods	Quality score BCA. Randomisation method: random number tables. Blinding not mentioned.
Participants	31 women; GA > 14 wk, chronic or pregnancy-induced hypertension, BP 140-169/90-109 mmHg (x 2 after 5 min rest); excluded women with contraindication to beta-blocker, Rh disease, haemorrhagic disorder.
Interventions	Mepindolol 5 mg po OD (increased weekly to max of 10 mg po OD) vs methyldopa 250 mg po BID (increased weekly to max of 1 g/d).
Outcomes	Stillbirth, preterm birth, birthweight < or equal to 2500 g, one minute Apgar < 7.
Notes	Spanish language.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Unclear risk	B - Unclear

BID: dosing twice daily
 BP: blood pressure
 BUN: blood urea nitrogen
 Creat: creatinine
 dBp: diastolic blood pressure
 Hb: hemoglobin

Hct: hematocrit

HELLP: syndrome of Haemolysis, Elevated Liver enzymes and Low Platelets

hr: hour/hours

HR: heart rate

IQ: intelligence quotient

ITT: intention to treat

iv: intravenous

max: maximum

OD: dosing once daily

po: oral dosing

QID: dosing four times daily

Quality score: first score: ALLOCATION BLINDING (A/B/C), second score: OUTCOME ASSESSMENT BLINDING (A/B/C), third score: COMPLETENESS OF FOLLOW-UP (A/B/C); Please see Methods of Review for definitions.

RDS: respiratory distress syndrome

sBP: systolic blood pressure

SCBU: special care baby unit, equivalent to a neonatal intensive care unit in North America

SD: standard deviation

SGA: small for gestational age at birth

TID: dosing three times daily

vs: versus

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

Study	Reason for exclusion
Argentina 1986	May be a RCT. No data are abstractable as the number of women per treatment arm is not known.
Argentina 1994	Not clearly randomised, "187 women were included in the study and divided into two groups". Available as abstract only.
Belgium 1988	RCT but beta-blocker versus beta-blocker comparison which is not informative for this review.
Canada 1988	RCT but beta-blocker versus beta-blocker comparison (not informative for this review).
England 1986	Appears to be a RCT but no clinical outcomes of interest are reported.
Finland 1984	Not clearly randomised. Also a beta-blocker versus beta-blocker comparison which is not informative for this review.
Finland 1995	Beta-blocker versus beta-blocker comparison which is not informative. Enrolled some women with severe pre-eclampsia. IV administration. Drug infusion to delivery interval was not stated; therefore, it is not clear that the drug was in the maternal circulation at the time of delivery, and could therefore, impact on neonatal outcomes.
Finland 1999	Double blind "randomised" controlled trial BUT the lost to follow up rate was approximately 30% for all outcomes.
France 1986	No clinical outcomes reported. Available as abstract only. Comparison of labetalol versus clonidine, 35 women with dBP > 105 mmHg and hospitalised.
France 1988c	Cannot abstract data because the number of women per treatment group is not known.
France 1988d	Not clearly randomised.
France 1988e	RCT but no abstractable data on clinical outcomes are reported.

Study	Reason for exclusion
France 1989	RCT but no abstractable data are reported in the abstract.
France 1990a	RCT but no abstractable data are reported in the abstract.
France 1990b	Apparently a RCT but no abstractable data are reported.
France 1992	RCT but no abstractable data are reported in the abstract.
Hong Kong 1993	RCT but no abstractable data are reported.
Ingemarsson 1991	RCT by title but no other data available.
Israel 1988	RCT but no clinical outcomes of interest were reported.
Israel 1992b	Beta-blocker versus beta-blocker comparison. Also, endpoints were not clinical, but rather, were surrogate markers (i.e. utero-placental blood flow).
Israel 1994	RCT but no clinical outcomes reported.
Italy 1986	'Group A' appears to have been randomised to atenolol or slow-release nifedipine, but the results are not reported by randomised group. Data are presented only for 'group A' versus a 'control group' designated as 'group B'.
Italy 1988	Not clearly randomised.
Italy 1990	Clearly inadequate method of randomisation (i.e. alternate).
Kuwait 1995	Clearly inadequate method of randomisation (i.e. allocation in sequence).
Lule 1992	Not clearly randomised.
N Ireland 1986	Not clearly randomised.
N Ireland 1991	Women with severe pre-eclampsia and IV agents administered.
Pello 1988	Trial abandoned.
Scotland 1983a	Not a randomised trial, women appear to have been matched. Comparison of labetalol with bed rest alone, 18 women with pre-eclampsia.
Singapore 1998	RCT but there are no data available on clinical outcomes of interest.
Spain 1988	RCT but no abstractable data are available as the number of women per treatment arm is not reported.
Sweden 1986a	Not clearly randomised.
Sweden 1986b	Not clearly randomised.
Sweden 1990	RCT but beta-blocker versus beta-blocker comparison which is not informative for this review.
Sweden 1992	Beta-blocker versus beta-blocker comparison. Wrong endpoints.
Sweden 1993b	RCT but results are not presented according to randomised group.

Study	Reason for exclusion
	Could be an overlapping trial with Sweden 1993 but insufficient data are presented to be sure of this.
USA 1981	Cannot extract data by treatment arm.
USA 1987a	Not clearly a randomised controlled trial.
USA 1990b	RCT but no other information available.
Wales 1991	RCT of aggressive versus less aggressive control of BP with methyldopa, diuretic and/or atenolol versus usually no medication. However, outcomes are not reported by randomised group.

BP: blood pressure

dBP: diastolic blood pressure

IV: intravenous

RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Beta-blocker versus placebo/no beta-blocker

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal death	2	206	Risk Ratio (M-H, Fixed, 95% CI)	2.92 [0.12, 70.68]
2 Eclampsia	3	391	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Severe hypertension	11	1128	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.26, 0.53]
4 Proteinuria at delivery	11	1340	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.68, 1.08]
5 Additional antihypertensive drugs	7	856	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.31, 0.62]
6 Changed drugs due to maternal side effects	11	1059	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.79, 3.72]
7 Admission to hospital prior to delivery	3	291	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.64, 0.93]
8 Placental abruption	6	862	Risk Ratio (M-H, Fixed, 95% CI)	2.01 [0.61, 6.64]
9 Caesarean section	12	1392	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.12]
10 Perinatal mortality	13	1429	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.46, 2.22]
11 Preterm delivery	8	962	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.76, 1.30]
12 Small-for-gestational-age infants	12	1346	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [1.02, 1.82]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Admission to special care baby unit	4	600	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.76, 1.24]
14 Neonatal jaundice	2	226	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.24, 1.28]
15 Neonatal bradycardia	3	416	Risk Ratio (M-H, Fixed, 95% CI)	1.93 [1.05, 3.53]
16 Neonatal hypoglycaemia	5	635	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.44, 1.49]
17 Neonatal hypothermia	1	44	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.15, 2.02]
18 Apgar score less than 7 at 5 minutes	6	702	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.38, 1.52]
19 Respiratory distress syndrome	4	567	Risk Ratio (M-H, Fixed, 95% CI)	0.29 [0.12, 0.67]
20 Cerebral palsy at 1 year	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.01]
21 IQ less than one standard deviation below mean	1	110	Risk Ratio (M-H, Fixed, 95% CI)	0.14 [0.01, 2.70]

Analysis 1.1. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 1 Maternal death.

Analysis 1.2. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 2 Eclampsia.

Analysis 1.3. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 3 Severe hypertension.

Analysis 1.4. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 4 Proteinuria at delivery.

Analysis 1.5. Comparison 1 Beta-blocker versus placebo/ no beta-blocker, Outcome 5 Additional antihypertensive drugs.

Analysis 1.6. Comparison 1 Beta-blocker versus placebo/no beta- blocker, Outcome 6 Changed drugs due to maternal side effects.

Analysis 1.7. Comparison 1 Beta-blocker versus placebo/no beta- blocker, Outcome 7 Admission to hospital prior to delivery.

Analysis 1.8. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 8 Placental abruption.

Analysis 1.9. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 9 Caesarean section.

Analysis 1.10. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 10 Perinatal mortality.

Analysis 1.11. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 11 Preterm delivery.

**Analysis 1.12. Comparison 1 Beta-blocker versus placebo/
no beta-blocker, Outcome 12 Small-for-gestational-age infants.**

**Analysis 1.13. Comparison 1 Beta-blocker versus placebo/
no beta-blocker, Outcome 13 Admission to special care baby unit.**

Analysis 1.14. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 14 Neonatal jaundice.

Analysis 1.15. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 15 Neonatal bradycardia.

Analysis 1.16. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 16 Neonatal hypoglycaemia.

Analysis 1.17. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 17 Neonatal hypothermia.

Analysis 1.18. Comparison 1 Beta-blocker versus placebo/ no beta-blocker, Outcome 18 Apgar score less than 7 at 5 minutes.

Analysis 1.19. Comparison 1 Beta-blocker versus placebo/ no beta-blocker, Outcome 19 Respiratory distress syndrome.

Analysis 1.20. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 20 Cerebral palsy at 1 year.

Analysis 1.21. Comparison 1 Beta-blocker versus placebo/no beta-blocker, Outcome 21 IQ less than one standard deviation below mean.

Comparison 2. Beta-blocker versus other antihypertensive therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Eclampsia	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.1 Beta-blocker versus methyl-dopa	1	32	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Severe hypertension	6	417	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.86, 1.92]
2.1 Beta-blocker versus methyl-dopa	4	297	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.39, 1.61]
2.2 Beta-blocker versus hydralazine	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.96, 2.41]
2.3 Beta-blocker versus calcium channel blocker	1	100	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.96, 4.80]
3 Proteinuria	10	842	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.80, 1.41]
3.1 Beta-blocker versus methyl-dopa	9	742	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.74, 1.32]
3.3 Beta-blocker versus calcium channel blocker	1	100	Risk Ratio (M-H, Fixed, 95% CI)	2.67 [0.75, 9.47]
4 Additional antihypertensive drugs	11	838	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.88, 1.33]
4.1 Beta-blocker versus methyl-dopa	9	718	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.23]
4.2 Beta-blocker versus hydralazine	1	20	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.96, 2.41]
4.3 Beta-blocker versus calcium channel blocker	1	100	Risk Ratio (M-H, Fixed, 95% CI)	2.14 [0.96, 4.80]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 Changed drugs due to maternal side effects	5	410	Risk Ratio (M-H, Fixed, 95% CI)	5.48 [0.67, 44.77]
5.1 Beta-blocker versus methyl-dopa	4	310	Risk Ratio (M-H, Fixed, 95% CI)	5.48 [0.67, 44.77]
5.3 Beta-blocker versus calcium channel blocker	1	100	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Admission to hospital prior to delivery	2	272	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.81, 1.17]
6.1 Beta-blocker versus methyl-dopa	2	272	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.81, 1.17]
7 Caesarean section	11	774	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.84, 1.21]
7.1 Beta-blocker versus methyl-dopa	9	654	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.78, 1.17]
7.2 Beta-blocker versus hydralazine	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.38, 1.52]
7.3 Beta-blocker versus calcium channel blocker	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.91, 2.71]
8 Perinatal mortality	14	958	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.30, 1.26]
8.1 Beta-blocker versus methyl-dopa	12	838	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.28, 1.31]
8.2 Beta-blocker versus hydralazine	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.4 [0.02, 8.78]
8.3 Beta-blocker versus calcium channel blocker	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.55]
9 Preterm delivery	4	264	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.52, 1.24]
9.1 Beta-blocker versus methyl-dopa	4	264	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.52, 1.24]
10 Small-for-gestational-age infants	7	485	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.48, 0.99]
10.1 Beta-blocker versus methyl-dopa	5	371	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.50, 1.16]
10.2 Beta-blocker versus hydralazine	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.17, 1.24]
10.3 Beta-blocker versus calcium channel blocker	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.20, 1.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11 Admission to special care baby unit	4	528	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.75, 1.29]
11.1 Beta-blocker versus methyl-dopa	3	428	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.72, 1.26]
11.3 Beta-blocker versus calcium channel blocker	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.5 [0.45, 4.99]
12 Neonatal jaundice	2	47	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.65, 2.68]
12.1 Beta-blocker versus methyl-dopa	2	47	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.65, 2.68]
13 Neonatal bradycardia	2	48	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.1 Beta-blocker versus methyl-dopa	1	28	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13.2 Beta-blocker versus hydralazine	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14 Neonatal hypotension	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.2 Beta-blocker versus hydralazine	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Neonatal hypoglycaemia	4	169	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.48, 2.32]
15.1 Beta-blocker versus methyl-dopa	3	149	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.48, 2.32]
15.2 Beta-blocker versus hydralazine	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Apgar score less than 7 at 5 minutes	2	192	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.63, 4.99]
16.1 Beta-blocker versus methyl-dopa	1	172	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [0.63, 4.99]
16.2 Beta-blocker versus hydralazine	1	20	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Respiratory distress syndrome	2	202	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.16, 2.37]
17.1 Beta-blocker versus methyl-dopa	1	182	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.03, 2.01]
17.2 Beta-blocker versus hydralazine	1	20	Risk Ratio (M-H, Fixed, 95% CI)	2.44 [0.26, 22.80]

Analysis 2.1. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 1 Eclampsia.

Analysis 2.2. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 2 Severe hypertension.

Analysis 2.3. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 3 Proteinuria.

Analysis 2.4. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 4 Additional antihypertensive drugs.

Analysis 2.5. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 5 Changed drugs due to maternal side effects.

Analysis 2.6. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 6 Admission to hospital prior to delivery.

Analysis 2.7. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 7 Caesarean section.

Analysis 2.8. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 8 Perinatal mortality.

Analysis 2.9. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 9 Preterm delivery.

Analysis 2.10. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 10 Small-for-gestational-age infants.

Analysis 2.11. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 11 Admission to special care baby unit.

Analysis 2.12. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 12 Neonatal jaundice.

Analysis 2.13. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 13 Neonatal bradycardia.

Analysis 2.14. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 14 Neonatal hypotension.

Study or subgroup	beta-blocker n/N	other drugs n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.14.2 Beta-blocker versus hydralazine					
Sweden 1993a	0/9	0/11			Not estimable
Subtotal (95% CI)	9	11			Not estimable
Total events: 0 (beta-blocker), 0 (other drugs)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	9	11			Not estimable
Total events: 0 (beta-blocker), 0 (other drugs)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

beta-blockers better 0.1 0.2 0.5 1 2 5 10 other drugs better

Analysis 2.15. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 15 Neonatal hypoglycaemia.

Study or subgroup	beta-blocker n/N	other drugs n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.15.1 Beta-blocker versus methyldopa					
France 1988a	11/41	5/20		69.14%	1.07[0.43,2.67]
Australia 1983	2/14	0/14		5.14%	5[0.26,95.61]
England 1984	0/30	2/30		25.72%	0.2[0.01,4]
Subtotal (95% CI)	85	64		100%	1.05[0.48,2.32]
Total events: 13 (beta-blocker), 7 (other drugs)					
Heterogeneity: Tau ² =0; Chi ² =2.25, df=2(P=0.32); I ² =11.27%					
Test for overall effect: Z=0.12(P=0.9)					
2.15.2 Beta-blocker versus hydralazine					
Sweden 1993a	0/9	0/11			Not estimable
Subtotal (95% CI)	9	11			Not estimable
Total events: 0 (beta-blocker), 0 (other drugs)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	94	75		100%	1.05[0.48,2.32]
Total events: 13 (beta-blocker), 7 (other drugs)					
Heterogeneity: Tau ² =0; Chi ² =2.25, df=2(P=0.32); I ² =11.27%					
Test for overall effect: Z=0.12(P=0.9)					
Test for subgroup differences: Not applicable					

beta-blockers better 0.1 0.2 0.5 1 2 5 10 other drugs better

Analysis 2.16. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 16 Apgar score less than 7 at 5 minutes.

Analysis 2.17. Comparison 2 Beta-blocker versus other antihypertensive therapy, Outcome 17 Respiratory distress syndrome.

WHAT'S NEW

Date	Event	Description
4 July 2012	Amended	Search updated. Seventeen reports added to Studies awaiting classification .

HISTORY

Protocol first published: Issue 4, 2000

Review first published: Issue 4, 2000

Date	Event	Description
20 September 2008	Amended	Converted to new review format.
30 January 2004	New search has been performed	There are no new trials included in this update.
6 March 2003	New citation required and conclusions have changed	<p>Substantive amendment</p> <p>This update includes two new trials. For transparency, the text now indicates, for each relative risk, the number of trials and the number of women that contributed to that outcome.</p> <p>The results are largely unchanged, in that it is still unclear whether treatment of mild to moderate pregnancy hypertension, with oral beta-blockers, results in greater benefit than risk versus no treatment. The only difference in the results is that when beta-blockers are now compared with any other antihypertensive drug, beta-blockers are associated with a lower risk of small-for-gestational-age infants, although this effect is borderline for statistical significance.</p>

CONTRIBUTIONS OF AUTHORS

Dr Magee was responsible for updating the literature search. She drafted and amended the revised review, including the statistical analyses. Both reviewers contributed to deciding which studies to include, and both did data extraction. Dr Magee entered all the data into RevMan. Dr Duley checked the data entry, and revised drafts of the review.

DECLARATIONS OF INTEREST

Dr Magee has received a speaker's fee from Shire Inc, the manufacturer of labetalol.

SOURCES OF SUPPORT

Internal sources

- The Hospital for Sick Children Research Foundation, Canada.
- BC Women's Hospital Foundation, Canada.

External sources

- The Royal College of Physicians and Surgeons of Canada, Canada.
- Physicians' Services Incorporated, Ontario, Canada.
- Medical Research Council, UK.

- Department for International Development, UK.
- BC Research Institute for Children's and Women's Health, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Adrenergic beta-Antagonists [administration & dosage] [*therapeutic use]; Antihypertensive Agents [administration & dosage] [*therapeutic use]; Hypertension [*drug therapy]; Pregnancy Complications, Cardiovascular [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Female; Humans; Pregnancy