National Institute for Health and Care Excellence

FINAL

Hypertension in pregnancy

[E] Evidence review for postnatal management of hypertension

NICE guideline NG133

Evidence review

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This evidence review was developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Contents

Review question: What is the optimal management of hypertension for women during the postnatal period?

Introduction

Hypertension in the postnatal period affects several groups of women, including those with chronic hypertension, gestational hypertension and pre-eclampsia. Hypertension may also present for the first time in the postnatal period. Regardless of the different underlying causes and clinical presentations, treatment of hypertension is broadly similar.

There is limited information about the use of antihypertensive drugs in the postnatal period, particularly in women who choose to breastfeed, and some antihypertensive drugs are contraindicated or must be used with caution by women who are breastfeeding. The choice of medication should therefore be discussed with women requiring antihypertensive drugs so that women can make informed choices. Encouraging and supporting breastfeeding is a key priority for maternity care providers.

The aim of this review is to identify the efficacy and safety of different antihypertensives for the management of hypertension in the postnatal period.

Summary of the protocol

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Postnatal women who require antihypertensive treatment up to 6 weeks after delivery
Intervention	• Beta blockers / mixed alpha-beta blockers • Centrally acting α2-adrenoceptor agonists • Calcium channel blockers • Angiotensin receptor blockers • Angiotensin converting enzyme (ACE) inhibitors • Diuretics • Vasodilators
Comparison	• Other antihypertensive agents • Placebo • No treatment

Outcome	**Critical outcomes:**
	• Outcomes for women
	  ○ Blood pressure (BP) control
	• Outcomes for babies
	  ○ Neonatal complications:
	  - Hypoglycaemia
	  - Hypothermia (temperature control)
	  - Blood pressure (hypotension)
	  - Bradycardia
	• Drug levels in breast milk
	Important outcomes:
	• Outcomes for women
	  ○ Maternal breastfeeding (initiation and any breastfeeding at primary discharge)

	• Outcomes for babies ○ Admission of baby into neonatal unit (NNU)

ACE: angiotensin-converting-enzyme; BP: blood pressure; NNU: neonatal unit

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual 2014. Methods specific to this review question are described in the review protocol in appendix A.

Declaration of interests were recorded according to NICE's 2018 conflicts of interest policy (see Register of interests).

Clinical evidence

Nine randomised controlled trials (RCTs) and 9 observational studies (comparative cross-sectional studies and non-comparative case series) were included in this review. Participants consisted of women in the postpartum period experiencing hypertension (both with antenatal hypertension and women with *de novo* postpartum hypertension). One of the included studies also involved prenatal women (<40% participants) and 1 study included women who were treated with atenolol for cardiomyopathy or arrhythmia, rather than hypertension (<20% participants). Evidence was found for all types of interventions, except for angiotensin receptor blockers. In terms of outcomes, there was no evidence for maternal breast feeding (initiation or any breastfeeding at primary discharge) or neonatal hypothermia.

The identified trials were not suitable for meta-analysis (due to heterogeneity in the conduct of studies and reporting of outcomes), therefore comparisons from individual studies have been reported.

Included studies

Eighteen studies (n=921) were included in the review (Ascarelli 2005, Barton 1990, Darcie 2004, Eyal 2010, Fidler 1982, Jarreau 2000, Kulas 1984, Liedholm 1981, Livingstone 1983, Mabie 1987, Michael 1979, Matsumura 2014, Naito 2015, Noronha-Neto 2017, Sharma 2017, Sioufi 1984,Thorley 1983, Vigil-de Gracia 2007).

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2 provides a brief summary of the included studies

Table 2: Summary of included studies

Study	Participants/Diagnosis (and definition)	Intervention	Control	Outcomes
Ascarelli 2005 USA	N=264 postpartum women with mild preeclampsia, severe preeclampsia or chronic	Furosemide 20 mg OD x 5 days + potassium supplements,	No diuretic medication	Mean sBP on the second postpartum day

Study	Participants/Diagnosis (and definition)	Intervention	Control	Outcomes
RCT	hypertension with superimposed preeclampsia *Definitions for HDOP not reported*	initiated after the spontaneous onset of diuresis Women with intermittent or persistent sBP/dBP (≥150/100 mmHg x 2 times) received antihypertensive medication (type not specified)	Women with intermittent or persistent sBP/dBP (≥150/100 mmHg x 2 times) received antihypertensive medication (type not specified)	
Barton 1990 USA RCT	N=31 women with antepartum diagnosis of severe preeclampsia. *sBP> 180 mmHg or dBP> 120 mmHg on one occasion; or sBP of 160-180 mmHg or dBP > 90mmHg on 2 occasions > 6 hours apart plus one of the following systemic features: proteinuria, oliguria, pulmonary oedema, seizure or abnormal blood results (raised ALT or low platelet count).*	Nifedipine 10 mg PO every 4 hours x 2 days + 10 mg IV hydralazine for those with sBP/dBP >160/110 mmHg every 20 minutes up to 3 times until sBP/dBP ≤150/100 mmHg. Those not reaching the target BP were excluded from the study.	Placebo 10 mg PO every 4 hours x 2 days (presented in identical packaging as the nifedipine) + 10 mg IV hydralazine for those with sBP/dBp >160/110 mmHg every 20 minutes up to 3 times until sBP/dBP ≤150/100 mmHg. Those not reaching the target BP were excluded from the study.	Mean arterial pressure
Darcie 2004 Brazil RCT	N=93 women with arterial hypertension *dBP ≥ 90 mmHg* (three arm trial with two different interventions)	Intervention group 1: Isradipine 5 mg PO BID + low sodium diet Intervention group 2: Atenolol 50 mg PO BID + low sodium diet	Low sodium diet	Neonatal hypoglycaemia during the 1st, 3rd, 6th, 12th and 24th hours of life *(considered to be blood glycaemia values < 40 mg/dL)*
Eyal 2010 Non-comparative case series USA	N=28 lactating women with hypertension. Note than an additional 4 women were taking atenolol for hypertrophic cardiomyopathy and arrhythmia. *Definition for hypertension was not provided*	Atenolol doses ranged between 25 to 200 mg/day. Total daily dose was administered every 12 hours.	N/A	Daily excretion of atenolol in breast milk (µg), according to maternal dose

Study	Participants/Diagnosis (and definition)	Intervention	Control	Outcomes
Fidler 1982 RCT UK	N=80 untreated women with postpartum hypertension *dBP between 95 and 105 mmHg on 2 occasions, 24 h apart*	Timolol 5mg PO x 3 times/day If target dBP (≤95 mmHg) was not achieved within 24 h of starting the treatment, the dosage was doubled, and doubled again if necessary every 24 h). Those not reaching the target BP were deemed a treatment failure and oral hydralazine was added.	Methyldopa 250mg PO x 3 times/day If target dBP (≤95 mmHg) was not achieved within 24 h of starting the treatment, the dosage was doubled, and doubled again if necessary every 24 h). Those not reaching the target BP were deemed a treatment failure and oral hydralazine was added.	Mean sBP and dBP difference from day 1 to 9 and total number achieving target dBP according to the treatment dosage
Jarreau 2000 Non-comparative case series France	N=11 women with gestation hypertension, pre-eclampsia or essential hypertension prior pregnancy *Definitions for HDOP not reported*	Nicardipine. n= 4 received the standard oral tablet form (40-80 mg/24 h,). n=6 received the slow release form (100-150 mg/ 24h). n=1 received it intravenously (120 mg/24h)	N/A	Mean concentrations of nicardipine in breast milk according to the type of administration
Kulas 1984 Cross-sectional study Sweden	N=7 women with hypertension during pregnancy *Definition not reported*	Atenolol (100 mg)	Metoprolol (100 mg)	Mean concentration of the medications in breast milk (nmol/l)
Liedholm 1981 Case-control study Sweden	N=10 women with pregnancy induced hypertension *Definition not reported*	Atenolol; 50 mg or 100 mg BID	Metoprolol; 50 mg BID on day 1, 100 mg BID on days 2 and 3 and 4	Estimated total dose of medications in 75ml breast milk
Livingstone 1983 RCT	N=28 women with pregnancy induced hypertension	Propranolol; dosages not reported	Methyldopa; dosages not reported	Mean change in arterial pressure during treatment.

Study	Participants/Diagnosis (and definition)	Intervention	Control	Outcomes
Australia	*sBP ≥ 140mmHg and dBP ≥ 90mmHg on 2 consecutive readings at least 24 hours apart*			Number of new-borns who developed hypoglycaemia; number of new-borns who developed bradycardia
Mabie 1987 RCT USA	N=60 postnatal women with preeclampsia, chronic hypertension with or without superimposed preeclampsia *dBP ≥ 110 mmHg*	Hydralazine 5 mg IV every 10 minutes until the dBP< 100 mmHg	Labetalol 20 mg IV. For N= 10 women, dosages were increased between 10 to 50 mg every 10 minutes until dBP< 100 mmHg. For n=30 women, 20 mg extra were given every 10 minutes to a maximum cumulative dosage of 300 mg or until the dBP < 100 mmHg	Mean arterial pressure Time (minutes) to maximal decrease in blood pressure
Matsumura 2014 Non-comparative case series Japan	N=18 women with severe preeclampsia *BP>160/110 mmHg and > 0.3g proteinuria in a 24 hour period*	Nicardipine was started at a dose of 0.5mg/hr and increased by 0.5 mg/hr until maternal BP was <160/110mmHg	N/A	Nicardipine concentrations in breast milk and admission to neonatal unit
Michael 1979 Non-comparative case series Australia	N=25 women with blood pressure ≥ 150/105 mmHg	Labetalol 100mg PO x 3 times/day. Dose was increased in intervals until adequate control of BP (target dBP ≤ 90 mmHg)	N/A	Mean concentration of the medication in breast milk (ng/ml, day 3 postpartum) Neonatal hypotension *(no definition was provided)*
Naito 2015 Non-comparative case series Japan	N=31 women with pregnancy induced hypertension *Definition not reported*	Amlodipine 5 mg PO BID	N/A	Median of the pre-dose milk concentrations of amlodipine at day 10 after starting the medication

Study	Participants/Diagnosis (and definition)	Intervention	Control	Outcomes
Noronha Neto 2017 RCT Brazil	N=88 women with HDOP and very high blood pressure *HDOP were defined according to the National High Blood Pressure Education Program (2000) criteria and very high blood pressure was defined as sBP ≥ 180 mmHg or dBP ≥ 110 mmHg*	Clonidine 0.1mg PO as required to treat episodes of very high BP (maximum 6 doses per day)	Captopril 25 mg PO as required to treat episodes of very high BP (maximum 6 doses per day)	Mean number of very high blood pressure episodes/day Mean number of days until blood pressure control Percentage reduction in sBP and dBP Mean blood pressure per hospitalisation day
Sharma 2017 RCT USA	N=50 women with persistent postpartum hypertension *sBP ≥ 150 mmHg or dBP ≥ 100 mmHg*	Nifedipine was started at 30 mg PO and increased up to 90 mg daily Additional treatments to achieve BP control or for seizure propyhylaxis could be used at the discretion of the medical team (including concomitant IV antihypertensives or magnesium sulfate).	Labetalol was started at 200mg PO BID and increased up to 800mg PO BID Additional treatments to achieve BP control or for seizure propyhylaxis could be used at the discretion of the medical team (including concomitant IV antihypertensives or magnesium sulfate).	Mean hours elapsed to control blood pressure Blood pressure control post discharge
Sioufi 1984 Non-comparative case series France	N=32 women; breast milk samples obtained from n=9 women *Definition not reported*	Trasipressol (80mg oxprenolol hydrochloride and 25mg of dihydralazine sulphate) x 3 times/day	N/A	Mean concentration of the medication in breast milk (nmol/l, day 3 to 6 postpartum) Neonatal hypoglycaemia during first 24 hours *(glucose ≤ 1.6 mmol/l)*
Thorley 1983 Cross-sectional study	N=10 women with hypertension *Definition not reported*	Atenolol 100 mg PO OD	Propranolol 40 mg PO BID	Mean concentration of the medications in breast milk (ng/ml-1, at defined times post-dose)

Study	Participants/Diagnosis (and definition)	Intervention	Control	Outcomes
UK				
Vigil- de Gracia 2007 RCT Panama	N=82 women with severe hypertension *sBP > 160 mmHg or dBP > 110 mmHg*	Hydralazine IV 5 mg every 20 minutes to a maximum of 5 dosages Women with persistent severe hypertension (dBP/sBP ≥ 140/90 with proteinuria with other symptoms such as headache, oliguria, haemolysis, etc.) received other antihypertensive treatments	Labetalol IV 20 mg followed by 40 mg if not effective within 20 minutes, followed by 80 mg every 20 minutes to a maximum dose of 300 mg. Women with persistent severe hypertension (dBP/sBP ≥ 140/90 with proteinuria with other symptoms such as headache, oliguria, haemolysis, etc.) received other antihypertensive treatments	Total number of women with severe, persistent hypertension post-treatment

ALT: alanine aminotransferase; BID: twice a day; BP: blood pressure; Dbp: diastolic blood pressure; h: hours; HDOP: Hypertensive disorders of pregnancy; IV: intravenous; MAP: mean arterial pressure; N: total number of participants; N/A: not applicable; OD: once daily; PO: oral administration; RCT: randomised controlled trial; sBP: systolic blood pressure.

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

See appendix F for GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1. Beta blockers / mixed alpha-beta blockers versus centrally acting α2-adrenoceptor agonists

Critical outcomes

Outcomes for women

Blood pressure control

- One randomised controlled trial (n=79) provided low to very low quality evidence to show that those who received timolol experienced a clinically important reduction in blood pressure on day 1 (systolic and diastolic), day 3 (systolic only), and day 4 (diastolic only) of treatment as compared to those who received methyldopa. In contrast, those who received methyldopa experienced a clinically important reduction in blood pressure on day 7 (systolic and diastolic) and 8 (diastolic) of treatment as compared to those who received timolol. No clinically important differences in blood pressure control were noted at any other time points.
- One randomised controlled trial (n=80) provided low to very low quality evidence to show no clinically important difference in the number of women who achieved blood pressure control (diastolic ≤95 mmHg) between those who received timolol or methyldopa by day 1 (starting dose), day 2 (starting dose/first dose escalation) or day 3 (starting dose/first or second dose escalation). This same randomised controlled trial provided very low quality evidence to show no clinically important difference in the number of women in whom treatment did not control blood pressure (after four days of escalating treatment) between those who received methyldopa and timolol.
- One randomised controlled trial (n=28) provided very low quality evidence to show that there were no clinically important differences in mean arterial blood pressure measurements during treatment between those who received propranolol and methyldopa.

Outcomes for babies

Neonatal complications

- One randomised controlled trial (n=28) provided moderate to very low quality evidence to show no differences in neonatal complications (hypoglycaemia and bradycardia) for the new-borns of mothers who received methyldopa or propranolol.

Comparison 2. Beta blockers versus beta blockers.

Comparison 2.1 Atenolol versus metoprolol

Critical outcomes

Drug levels in breast milk

- One observational study (n=7) provided very low quality evidence to show that the mean (standard deviation, SD) concentrations of atenolol in breast milk at 0 hours after the dose was administered were of 1386.66 (555.81) nmol/l in the left breast and of 1750 (809.03) nmol/l in the right breast. Milk concentrations of metoprolol in the left and right breast at 0 hours after the dose was administered were not reported.
- One observational study (n=7) provided very low quality evidence to show that the mean (SD) concentrations of atenolol in breast milk at 4 hours after the dose was administered were of 5532.50 (1752.68) nmol/l in the left breast and of 3990 (1841.77) nmol/l in the

right breast. Milk concentrations of metoprolol in the left breast were of 271.66 (18.03) nmol/l and 320 (2.82) in the right breast.

- One observational study (n=7) provided very low quality evidence to show that the mean (SD) concentrations of atenolol in breast milk at 8 hours after the dose was administered were of 4107.50 (932.28) nmol/l in the left breast and of 3720 (113.13) nmol/l in the right breast. Milk concentrations of metoprolol in the left breast were of 82 (49.78) nmol/l and 84 (15.62) in the right breast.
- One observational study (n=10) provided very low quality evidence to show that the maximum concentration of atenolol recorded in breast milk was 6.35 µmol and the maximum concentration of metoprolol recorded in breast milk was 2.58 µmol. There was an estimated intake of 0.13mg of atenolol and 0.05 mg of metoprolol for 75 ml of milk.

Comparison 2.2 Atenolol versus propranolol

Critical outcomes

Drug levels in breast milk

- One observational study (n=10) provided very low quality evidence to show that the mean (SD) concentrations of atenolol in breast milk 2 hours after it was administered were 630 (271) ng ml^{-1}. Mean (SD) concentrations of propranolol 2 hours after it was administered were 27 (11) ng ml^{-1}. There was an estimated intake of 0.3 mg of atenolol and 0.01 mg of propranolol for 500 ml of milk/day.

Comparison 3. Beta blockers/mixed alpha-beta blockers versus placebo

Critical outcomes

Outcomes for babies

Neonatal complications

- One randomised controlled trial (n=46) provided low quality evidence to show there may be a clinically important increase in the number of infants experiencing hypoglycaemia during the first hour of life for women treated with atenolol, as compared to placebo, but there was some uncertainty around the effect. No clinically important difference in the occurrence of hypoglycaemia was demonstrated at other time points (3rd hour, 6th hour, 12th hour and 24th hour, very low quality evidence)

Comparison 4. Centrally acting α2-adrenoceptor agonists versus ACE inhibitors

Critical outcomes

Outcomes for women

Blood pressure control

- One randomised controlled trial (n=88) provided very low quality evidence to show no clinically important difference in the number of episodes of very high blood pressure per day, the percentage reduction of sBP/dBP or the number of days until blood pressure was controlled in women who received captopril as compared to those who received clonidine.
- One randomised controlled trial (n=88) provided low to very low quality evidence to show that those who received clonidine experienced a clinically important reduction in systolic blood pressure on day 3 of treatment as compared to those who received captopril. No differences were observed between treatment arms for diastolic blood pressure. No

differences were observed in systolic or diastolic blood pressure on days 1, 2 and 4 between those who received clonidine or captopril.

Comparison 5. Calcium channel blockers versus placebo/ low sodium diet

Critical outcomes

Outcomes for women

Blood pressure control

- One randomised controlled trial (n=31) provided moderate quality evidence to show that those who received nifedipine experienced a clinically important reduction in mean arterial blood pressure (18 to 24 hours after delivery) than those who received placebo.

Outcomes for babies

Neonatal complications

- One randomised controlled trial (n=50) provided very low quality evidence to show no clinically important difference in the number of hypoglycaemic events experienced by the babies of women who received isradipine as compared to placebo at the following time points: 1st hour, 3rd hour, 6th hours, 12th hour and 24th hour of life.

Comparison 6. Calcium channel blockers versus beta blockers

Critical outcomes

Outcomes for women

Blood pressure control

- One randomised controlled trial (n=50) provided low quality evidence to show no clinically important difference in the time taken to achieve control of blood pressure (defined as ≤160/105 mmHg for at least 12 hours) between those who received nifedipine and labetalol.
- One randomised controlled trial (n=50) provided low to very low quality evidence to show no clinically important differences in systolic or diastolic blood pressure between those who received nifedipine or labetalol at 72 hours, 1 to 2 weeks and 4 to 6 weeks of treatment.
- One randomised controlled trial (n=50) provided very low quality evidence to show no clinically important difference in the need for additional anti-hypertensive medication (intravenous or oral) between those who received nifedipine and labetalol.

Outcomes for babies

Neonatal complications

- One randomised controlled trial (n=70) provided very low quality evidence to show no clinically important difference in the number of hypoglycaemic events between the new-borns of women randomised to isradipine or atenolol at the following time points: 1st hour, 3rd hour, 6th hour, 12th hour and 24th hour.

Comparison 7. Diuretics versus placebo/no intervention

Critical outcomes

Outcomes for women

Blood pressure control

- One randomised controlled trial (n=264) provided very low quality evidence to show that those who received furosemide had a clinically important reduction in blood pressure on day 2 postpartum as compared to those who did not receive diuretic medication.

Comparison 8. Vasodilators versus beta blockers / mixed alpha-beta blockers

Critical outcomes

Outcomes for women

Blood pressure control

- One randomised controlled trial (n=60) provided low quality evidence to show that those who received IV hydralazine had a clinically important reduction in mean arterial blood pressure as compared to those who received IV labetalol.
- One randomised controlled trial (n=82) provided very low quality evidence to show no clinically important difference in the number of women with severe persistent hypertension (defined as 160/110 mmHg) between those who received IV labetalol and IV hydralazine.
- One randomised controlled trial (n=60) provided very low quality evidence to show a clinically important reduction in the time taken to achieve maximal decrease in blood pressure in those who received IV labetalol as compared to those who received IV hydralazine.

Beta-blockers (non-comparative studies)

Critical outcomes

Drug levels in breast milk

- One non-comparative observational study (n= 3 to 16) provided very low quality evidence to show that the mean (SD) daily excretion of atenolol in breast milk at 2-4 weeks postpartum and a dosage of 25 mg/day was 227µg± 80; at a dosage of 50mg/day was 350µg ± 167; at a dosage of 100mg/day was 429µg ± 126, and at a dosage of 200mg/day was 350µg ± 524.
- One non-comparative observational study (n=4 to 11) provided very low quality evidence to show that the mean concentrations of labetalol in breast milk at a daily of dose of 330 mg was 29 ng/l; at a daily dose of 400 mg was 27 ng/l; at a daily dose of 600 mg was 39 ng/l; at a daily dose of 700 mg was 46 ng/l; at a daily dose of 800 mg was 43 ng/l, and at a daily dose of 1200 mg was 600 ng/l. This same study showed that 3.27% of new-borns presented with hypotension.
- One non-comparative observational study (n=9) provided very low quality evidence to show that the mean (SD) nmol/l concentrations of oxprenolol in breast milk at a daily dose of 80 mg was 387 nmol/l ± 426. This same study showed that 6.25% new-borns presented with hypoglycaemia.

Calcium channel blockers (non-comparative studies)

Critical outcomes

Drug levels in breast milk

- One non-comparative observational study (n=1 to 6) provided very low quality evidence to show that the mean (SD) maximum milk concentration of nicardipine at a dosage of 20 mg during 3 days was 5.67 (3.20) ng/ml, at a dose of 50 mg during 2 days was 6.41 (3.48) ng/ml, and with IV nicardipine was 18.8 ng/ml.
- One non-comparative observational study (n=17-21) provided very low quality evidence to show that the mean (SD) of milk concentrations of nicardipine was 6.89 ± 8.28 ng/ml. This same study provided very low quality evidence to show that 67% of the children whose mothers received nicardipine were admitted to the neonatal unit.
- One non-comparative observational study (n=31) provided very low quality evidence to show that the median pre-dose (trough) breast milk concentrations of amlopidine was 11.5ng/mL IQR= 9.84-18 ng/mL. This same study estimated that the daily dose of amlopidine in the infant breast milk was 4.17 µg/kg (IQR, 3.05-6.32 µg/kg)

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The maternal outcome of blood pressure control was considered to be a critical outcome by the committee, as the consequences of not controlling blood pressure are very serious and could include stroke in the mother. In mothers who breastfeed while taking antihypertensives, the outcomes for babies were also considered to be critical, and the committee agreed that neonatal complications (hypoglycaemia, hypothermia, hypotension and bradycardia) may occur in babies who ingest antihypertensive medication from their mother's breast milk. Neonatal hypoglycaemia was reported in several studies, and hypotension in one study, but other neonatal complications, such as hypothermia; blood pressure or bradycardia were not reported in any of the studies. In lieu of outcome data on neonatal complications, the committee were interested in the outcome of studies which measured drug levels in breast milk, as these would be important to guide decision-making because a drug that is not excreted in breast milk could not lead to neonatal complications.

The committee agreed that breastfeeding (including initiation or any breastfeeding at primary discharge) was an important outcome as mothers should, wherever possible, receive medication in the postnatal period which allows them to breastfeed. However, this outcome was not reported in any of the studies.

Admission to a neonatal unit was an outcome that may indicate serious adverse effects in the baby, but this outcome was not reported in any of the studies.

The quality of the evidence

For the randomised controlled studies, the quality of the evidence for this review was assessed using GRADE. Both the maternal and baby outcomes were of moderate to very low quality evidence. The main reasons for downgrading were imprecision, i.e. the trials had a low number of women/babies included, and therefore our confidence around the estimate for each of the outcomes decreased. Trials were also downgraded because of high to very high risk of bias; mainly due to not reporting how the randomisation was performed or concealed, or because women, investigators and assessors were aware of treatment allocation. In addition, one trial included indirect evidence (a minority of prenatal women in a sample of postnatal women). This trial was downgraded for indirectness.

For the comparative cross-sectional studies the quality of the evidence was assessed using the Newcastle-Ottawa scale and the evidence on drug levels in breast milk was all of very low quality. Overall, the studies did not control for confounding factors, therefore it was not possible to establish whether a given outcome was due to the effects of the intervention or other factors (such as gestational age, co-occurring conditions in the baby or the mother). In addition, some of the information was obtained from medical records. This is subject to bias because we cannot be certain that all information has been obtained in the same way and following the same process in every woman. Another factor is that most of these studies did not report the definition of hypertension, therefore we could expect substantial differences in terms of symptomology and severity of the condition.

For the non-comparative studies the quality of the evidence was assessed using the Institute of Health Economics (IHE) quality appraisal checklist and the evidence on drug levels in breast milk was all of very low quality. These studies included very low numbers of participants, and there were many factors that were not well established in the studies, such as the eligibility criteria, the follow-up time or the conflicts of interest of the authors. One study also included a small number of women who were treated with anti-hypertensive agents for conditions other than hypertension (hypertrophic cardiomyopathy and arrhythmia).

Benefits and harms

The committee agreed that their priority in making these recommendations was to ensure good control of the mother's blood pressure in the postnatal period. This was because it would reduce the likelihood of adverse effects of high blood pressure in the mother, which could include organ damage and stroke. The committee agreed that the recommendations should not compromise women who could not breastfeed, or chose not to breastfeed. However, many women may start breastfeeding and then stop early, or those who did not start in the immediate postnatal period may start slightly later, therefore the recommendations should be applicable wherever possible to all women in the postnatal period.

There was some evidence for the effectiveness of atenolol, clonidine, nifedipine, furosemide, labetalol and hydralazine at controlling blood pressure in this population, but the evidence was not conclusive enough to recommend one medicine over another. There was also evidence of medicines not routinely used or available in England (such as timolol), therefore the committee did not consider these for inclusion in the recommendations.

The passage of drugs into breast-milk and the effects on the baby were also considered by the committee. It was noted that there was evidence that atenolol, metoprolol, propranolol, labetalol, oxprenolol, nicardipineand amlodipine were found in breast milk, but there was very little evidence available on the effects in babies, and the data on drug levels in breast milk that were available were very difficult to interpret. It is not known, for example, what levels in breast milk will lead to neonatal complications such as hypoglycaemia. In clinical practice, babies of mothers taking beta-blockers have their blood glucose tested in some (but not all) maternity units, and if found to be hypoglycaemic would be given additional feeds and extra support.

The committee agreed that treatment of hypertension in the postnatal period should reflect the best evidence-based practice applicable to the general adult population, but revised to take into account the fact that these women may wish to breastfeed, and therefore should include medicines with the greatest evidence for safety in breastfeeding. The committee therefore referred to the NICE guideline on Hypertension in adults: diagnosis and management. There is the additional advantage of basing recommendations on this guideline, as women who need to remain on antihypertensive treatment in the longer term will not require further switching (which would potentially expose them to sub-optimal blood pressure control, as well as inconvenience).

The NICE guideline on hypertension in adults recommends angiotensin-converting enzyme inhibitors (ACEI) as first line in people under 55. No evidence was available from the review on the effectiveness of ACEIs or on the levels of ACEIs detected in breast milk or on potential harms to the baby. However, the committee were aware that captopril and enalapril had been recommended in the previous guideline and had been used widely in clinical practice in breast-feeding mothers, but that as enalapril was a once-daily treatment they agreed that this was the preferred option.

In women of black African or Caribbean family origin, the NICE guideline recommends a calcium channel blocker (CCB) as first line treatment. As there was evidence for the effectiveness of nifedipine in the postnatal population the committee selected that as the drug of first choice, although amlodipine was an alternative in women who had previously received this. There was some evidence regarding the levels of nicardipine seen in breast milk but the committee agreed that nicardipine was not widely used and there was limited clinical experience of its use in breast feeding and so they did not recommend its use. There was some evidence from the review that CCBs were found in breast milk but did not lead to neonatal hypoglycaemia.

As second-line therapy, the NICE guideline recommends a combination of an ACEI and CCB, therefore this was also recommended for women in the postnatal period. As there was some evidence for the effectiveness of atenolol and labetaolol in the postnatal population one of these was recommended if the combination of nifedipine and enalapril was not effective or not tolerated. Labetalol requires administration three times daily, which reduces adherence, and the committee agreed that, once daily atenolol may be the preferred beta-blocker to use in the postnatal period. The previous version of this guideline also considered the use of metoprolol during the postnatal period. However, the committee agreed that this was now rarely used in clinical practice and as there was no specific evidence to show that efficacy or adverse effects were improved with metoprolol, they decided to simplify the guidance to recommend atenolol or labetaolol as the beta-blockers of choice. Similarly, there was some evidence on oxprenolol and propranolol levels in breast milk, but the committee agreed that neither of these drugs were used in routine practice in the UK, they had no clinical experience relating to their use in pregnancy or breast-feeding, there was no evidence of clinical benefit compared to atenolol or labetalol, and so they did not recommend them.

The committee were aware of concerns that beta-blockers may increase the risk of neonatal hypoglycaemia, but there was uncertainty around the effect in the evidence regarding this. The committee were also aware that the transfer of antihypertensive agents into breast milk could lead to low blood pressure in babies, and that additional monitoring may be necessary, and made a recommendation relating to this based on their clinical experience.

Diuretics and angiotensin II receptor blockers (ARB) are also recommended for the treatment of hypertension in the general population but the committee were aware from their own clinical experience and knowledge that these medicines were not the most suitable medicines for use in mothers who may wish to breast-feed: diuretics are thought to decrease the production of breast milk and ARBs should not be used as an alternative to ACEI, as the latter have a much more well known safety profile.

Overall, the committee discussed the risks and benefits of using antihypertensive therapy in mothers with hypertension in the postnatal period and agreed that although there was limited evidence available, there was very little evidence of harm to babies, that it was important to control the mother's blood pressure, and that the benefits of breastfeeding outweighed the risks to the baby from any ingestion of antihypertensive medication from the breast milk.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee agreed that as all the medications they were recommending were widely available as generics there would not be any changes to the costs of treating women with hypertension in the postnatal period as a result of these recommendations. Furthermore, the recommendations reflect current practice and so no substantial resource impact is anticipated.

Other factors the committee took into account

Due to the paucity of the evidence, the committee also referred to other sources to assist them: these included the Summary of Product Characteristics for the medicines they were considering, which may provide some advice from manufacturers on whether use in breast-feeding mothers is recommended. The committee also consulted a Specialist Pharmacy Services database created by the NHS which provides advice on the safety of drugs for breastfeeding mothers, and a previous systematic review of the excretion of antihypertensive medication into human breast milk (Beardmore, 2002).

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Appendices

Appendix A – Review protocol

Table 3: Review protocol

Field (based on PRISMA-P)	Content
Key area in the scope	Assessment and management of women with pre-existing hypertension during their pregnancy and the postnatal period.
Draft review question from the previous guideline	How should women, who were hypertensive during pregnancy who wish to breastfeed be managed in the postnatal period?
Actual review question	What is the optimal management of hypertension for women during the postnatal period?
Type of review question	Intervention
Objective of the review	To determine the clinical effectiveness of anti-hypertensives, and the safety of drugs in breast-feeding
Eligibility criteria – population/disease/condition/issue/domain	Postnatal women who require antihypertensive treatment up to 6 weeks
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Single or combination therapy with any of the following: • Beta blockers / mixed alpha-beta blockers • Centrally acting α2-Adrenoceptor Agonists • Calcium channel blockers • Angiotensin receptor blockers • ACE inhibitors • Diuretics • Vasodilators

Field (based on PRISMA-P)	Content
Eligibility criteria – comparator(s)/control or reference (gold) standard	• One intervention compared to another • One combination of eligible interventions compared to another combination • Placebo • No treatment

Outcomes and prioritisation	**Critical outcomes:**
	• Outcomes for women
	  ○ Blood pressure (BP) control
	• Outcomes for babies
	  ○ Neonatal complications:
	  - Hypoglycaemia
	  - Hypothermia (temperature control)
	  - Blood pressure (hypotension)
	  - Bradycardia
	• Drug levels in breast milk
	
	Important outcomes:
	• Outcomes for women
	  ○ Maternal breastfeeding (initiation and any breastfeeding at primary discharge)
	• Outcomes for babies
	  ○ Admission of baby into neonatal unit (NNU)

Eligibility criteria – study design	Only published full text papers in English language • Systematic reviews of RCTs • RCTs • Cohort studies if not evidence from RCTs is found

Field (based on PRISMA-P)	Content
	• Case-control studies if not evidence from cohort studies is found • if no data from comparative studies is identified, larger (n ≥ 10) non-comparative studies will be included to assess safety aspects of drugs in breast feeding Conference abstracts of RCTs will only be considered if no evidence is available from full published RCTs and are recent (i.e., in the last 2 years-authors will be contacted for further information). Small studies (<30 participants) will not be considered if larger data from RCTs is found.
Exclusion criteria	• Up to 6 weeks post-partum (as looking at short-term outcomes) • Women with hypertension and diabetes • The infants of women who have had hypertensive disorders during pregnancy (only the fetus until birth will be covered)
Proposed stratified, sensitivity/sub-group analysis, or meta-regression	**Stratify according to the following types of antihypertensive drugs:** Beta blockers / mixed alpha-beta blockers • Labetalol • Atenolol • Metoprolol Centrally acting α2-Adrenoceptor Agonists • Methyldopa Calcium channel blockers • Nicardipine • Nifedipine • Amlodipine Angiotensin receptor blockers • Losartan • Valsartan ACE inhibitors

Field (based on PRISMA-P)	Content
	• Enalapril • Captopril Vasodilators • Hydralazine Diuretics • Furosemide Stratify according to gestational hypertension/chronic hypertension/pre-eclampsia Subgroup analysis will be performed for women who plan to breast feed their infants, if relevant data are identified.
Selection process – duplicate screening/selection/analysis	Duplicate screening/selection/analysis will not be undertaken for this review as this question was not prioritised for it. Included and excluded studies will be cross checked with the committee and with published systematic reviews when available.
Data management (software)	If pairwise meta-analyses are undertaken, they will be performed using Cochrane Review Manager (RevMan5). 'GRADE' will be used to assess the quality of evidence for each outcome. Microsoft Word will be used for data extraction and quality assessment/critical appraisal STAR will be used bibliographies/citations, text mining, and study sifting, data extraction and quality assessment/critical appraisal.
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA and Embase.

Field (based on PRISMA-P)	Content
	Limits (e.g. date, study design): All study designs. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. See appendix B for full strategies.
Identify if an update	This is an update. Studies meeting the current protocol criteria and previously included in the 2010 guideline (CG107) will be included in this update.
Author contacts	Developer: National Guideline Alliance NGA-enquiries@RCOG.org.uk
Highlight if amendment to previous protocol	Items added in this protocol: • As part of the interventions: beta blockers/ mixed alpha-beta blockers, centrally acting α2-Adrenoceptor Agonists, angiotensin receptor blockers, ACE inhibitors • As part of the outcomes: blood pressure, maternal breastfeeding. Items deleted from the previous protocol: • As part of the interventions: antihypertensives, anticonvulsants, vasodilators, fluid balance, thromboprophylaxis (heparin, LMWH, anticoagulants, compression stockings). • As part of the outcomes (for the mother): prolonged treatment, renal function, breastfeeding. • As part of the outcomes (from the baby): jaundice and feeding difficulties • As part of the comparisons: watchful waiting The population is the same as in the 2010 protocol for this review question.
Search strategy – for one database	For details please see appendix B of the full guideline
Data collection process – forms/duplicate	Studies included in the previous guideline (CG107) that meet the inclusion criteria of this protocol will be re-extracted in a standardised evidence table and published as appendix D (clinical evidence tables) or H (economic evidence tables) of the full guideline.

Field (based on PRISMA-P)	Content
Data items – define all variables to be collected	For clinical evidence tables (appendix D), the following data items will be collected: full reference, study ID, type of study, objective country/ies where the study was carried out, inclusion criteria, exclusion criteria, methods, results and limitations.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • Systematic review and Meta-analyses – ROBIS • Cochrane risk of bias tool for randomised studies • Newcastle-Ottowa scale for cohort studies • Newcastle-Ottowa scale for case-control studies • Institute of Health Economics checklist for Case Series For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager/ STATA. Minimum important differences Default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes, unless more appropriate values are identified by the guideline committee or in the literature.

Field (based on PRISMA-P)	Content
	Double sifting, data extraction and methodological quality assessment: Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual quality assessment and data extraction will not be performed. How the evidence included in the previous guideline will be incorporated with the new evidence Studies meeting the current protocol criteria and previously included in the 2010 guideline (CG107) will be included in this update. The methods for quantitative analysis –combining studies and exploring (in)consistency- will be the same as for the new evidence (see above).
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review in the full guideline.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the National Guideline Alliance and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from the National Guideline Alliance undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds the National Guideline Alliance to develop guidelines for the NHS in England.

Field (based on PRISMA-P)	Content
PROSPERO registration number	Not registered with PROSPERO

Appendix B – Literature search strategies

Review question search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 19/12/17

#	Searches
1	HYPERTENSION, PREGNANCY-INDUCED/
2	PREGNANCY/ and HYPERTENSION/
3	PRE-ECLAMPSIA/
4	ECLAMPSIA/
5	HELLP SYNDROME/
6	*PREGNANCY COMPLICATIONS, CARDIOVASCULAR/
7	((pregnan$ or gestation$) adj5 hypertensi$).ti.
8	((pregnan$ or gestation$) adj3 hypertensi$).ab. /freq=2
9	preeclamp$.ti,ab.
10	eclamp$.ti,ab.
11	HELLP.ti,ab.
12	tox?emi$.ti,ab.
13	or/1-12
14	exp ANTIHYPERTENSIVE AGENTS/
15	(antihypertensive? or anti-hypertensive?).ti,ab.
16	(Acebutolol or Adrenomedullin or Alprenolol or Amlodipine or Atenolol or Bendroflumethiazide or Bepridilor Betaxolol or Bethanidine or Bimatoprost or Bisoprolol or Bretylium Tosylate or Brimonidine Tartrate or Bupranolol or Captoprilor Carteolol or Celiprolol or Chlorisondamine or Chlorothiazide or Chlorthalidone or Cilazapril or Clonidine or Cromakalim or Cyclopenthiazide or Debrisoquin or Diazoxide or Dihydralazine or Dihydroalprenolol or Diltiazem or Doxazosin or Enalapril or Enalaprilat or Epoprostenol or Felodipine or Fenoldopam or Fosinopril or Guanabenz or Guanethidine or Guanfacine or Hexamethonium or Hydralazine or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Indoramin or Isradipine or Kallidin or Ketanserin or Labetalol or Lisinopril or Losartan or Mecamylamine or Methyldopa or Metipranolol or Metolazone or Metoprolol or Mibefradil or Minoxidil or Muzolimine or Nadolol or Nebivolol or Nicardipine or Nicorandil or Nimodipine or Nisoldipine or Nitrendipine or Nitroprusside or Olmesartan Medoxomil or Oxprenolol or Pargyline or Pempidine or Penbutolol or Pentolinium Tartrate or Perindopril or Phenoxybenzamine or Phentolamine or Pinacidil or Pindolol or Piperoxan or Polythiazide or Prazosin or Propranolol or Protoveratrine? or Ramipril or Reserpine or Teprotide or Ticrynafen or Timolol or Todralazine or Tolazoline or Travoprost or Trichlormethiazide or Trimethaphan or Valsartan or Veratrum Alkaloid? or Vincamine or Xipamide).mp.
17	exp ADRENERGIC BETA-ANTAGONISTS/
18	(adrenergic adj3 beta adj3 antagonist?).ti,ab.
19	(beta adj3 blocker?).ti,ab.
20	(mixed adj3 blocker?).ti,ab.
21	(Alprenolol or (Brimonidine Tartrate adj2 Timolol Maleate) or Bunolol or Bupranolol or Carteolol or Dihydroalprenolol or Iodocyanopindolol or Labetalol or Levobunolol or Metipranolol or Nadolol or Oxprenolol or Penbutolol or Pindolol or Propranolol or Sotalol or Timolol or Acebutolol or Atenolol or Betaxolol or Bisoprolol or Celiprolol or Metoprolol or Practolol or Butoxamine).mp.
22	exp ADRENERGIC ALPHA-2 RECEPTOR AGONISTS/
23	((adrenergic or Adrenoceptor?) adj3 (alpha 2 or alpha2) adj3 agonist?).ti,ab.
24	(Brimonidine Tartrate or Clonidine or Dexmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine).mp.
25	exp CALCIUM CHANNEL BLOCKERS/
26	(calcium channel adj3 (blocker? or antagonist?)).ti,ab.
27	(Amlodipine or Amrinone or Bencyclane or Bepridil or Cinnarizine or Conotoxin? or Diltiazem or Felodipine or Fendiline or Flunarizine or Gallopamil or Isradipine or Lidoflazine or Magnesium Sulfate or Mibefradil or Nicardipine or Nifedipine or Nimodipine or Nisoldipine or Nitrendipine or Perhexiline or Pregabalin or Prenylamine or Risedronate Sodium or Tiapamil Hydrochloride or Verapamil or omega-Agatoxin IVA or omega-Conotoxin?).mp.
28	exp ANGIOTENSIN RECEPTOR ANTAGONISTS/
29	(angiotensin adj3 receptor adj3 (antagonist? or blocker?)).ti,ab.
30	(1-Sarcosine-8-Isoleucine Angiotensin II or Losartan or Olmesartan Medoxomil or Saralasin or Valsartan).mp.
31	exp ANGIOTENSIN-CONVERTING ENZYME INHIBITORS/
32	(angiotensin converting enzyme adj3 (antagonist? or inhibitor?)).ti,ab.
33	(ACE adj3 (antagonist? or inhibitor?)).ti,ab.

#	Searches
34	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide).mp.
35	FUROSEMIDE/
36	furosemide.mp.
37	or/14-36
38	PERIPARTUM PERIOD/
39	POSTPARTUM PERIOD/
40	POSTNATAL CARE/
41	(Peripart$ or Peri-part$ or Postpart$ or Post-part$ or Postnatal$ or Post-natal$ or Puerper$).ti,ab.
42	((follow$ or post$) adj1 (birth$ or deliver$)).ti,ab.
43	or/38-42
44	exp BREAST FEEDING/
45	breastfe$.ti,ab.
46	(breast adj3 (fed$ or feed$)).ti,ab.
47	(breast$ adj3 (pump$ or express$ or collect$)).ti,ab.
48	MILK, HUMAN/
49	breastmilk.ti,ab.
50	((breast or human) adj3 milk).ti,ab.
51	LACTATION/
52	lactat$.ti,ab.
53	(milk adj3 (eject$ or express$)).ti,ab.
54	or/44-53
55	exp *ANTIHYPERTENSIVE AGENTS/ae [Adverse Effects]
56	exp *ANTIHYPERTENSIVE AGENTS/tu [Therapeutic Use]
57	exp *ADRENERGIC BETA-ANTAGONISTS/ae [Adverse Effects]
58	exp *ADRENERGIC BETA-ANTAGONISTS/tu [Therapeutic Use]
59	exp *ADRENERGIC ALPHA-2 RECEPTOR AGONISTS/ae [Adverse Effects]
60	exp *ADRENERGIC ALPHA-2 RECEPTOR AGONISTS/tu [Therapeutic Use]
61	exp *CALCIUM CHANNEL BLOCKERS/ae [Adverse Effects]
62	exp *CALCIUM CHANNEL BLOCKERS/tu [Therapeutic Use]
63	exp *ANGIOTENSIN RECEPTOR ANTAGONISTS/ae [Adverse Effects]
64	exp *ANGIOTENSIN RECEPTOR ANTAGONISTS/tu [Therapeutic Use]
65	exp *ANGIOTENSIN-CONVERTING ENZYME INHIBITORS/ae [Adverse Effects]
66	exp *ANGIOTENSIN-CONVERTING ENZYME INHIBITORS/tu [Therapeutic Use]
67	*FUROSEMIDE/ae [Adverse Effects]
68	*FUROSEMIDE/tu [Therapeutic Use]
69	or/55-68
70	exp *HYPERTENSION, PREGNANCY-INDUCED/dt [Drug Therapy]
71	exp *HYPERTENSION, PREGNANCY-INDUCED/pc [Prevention & Control]
72	exp *HYPERTENSION, PREGNANCY-INDUCED/th [Therapy]
73	or/70-72
74	POSTNATAL CARE/mt [Methods]
75	13 and 37 and 43
76	13 and 37 and 54
77	43 and 69
78	43 and 73
79	13 and 74
80	or/75-79
81	limit 80 to english language
82	LETTER/
83	EDITORIAL/
84	NEWS/
85	exp HISTORICAL ARTICLE/
86	ANECDOTES AS TOPIC/
87	COMMENT/
88	CASE REPORT/
89	(letter or comment*).ti.
90	or/82-89
91	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
92	90 not 91
93	ANIMALS/ not HUMANS/
94	exp ANIMALS, LABORATORY/
95	exp ANIMAL EXPERIMENTATION/
96	exp MODELS, ANIMAL/

#	Searches
97	exp RODENTIA/
98	(rat or rats or mouse or mice).ti.
99	or/92-98
100	81 not 99

Database: Embase; and Embase Classic

Date of last search: 19/12/17

#	Searches
1	MATERNAL HYPERTENSION/
2	PREGNANCY/ and HYPERTENSION/
3	exp "ECLAMPSIA AND PREECLAMPSIA"/
4	HELLP SYNDROME/
5	((pregnan$ or gestation$) adj5 hypertensi$).ti.
6	((pregnan$ or gestation$) adj3 hypertensi$).ab. /freq=2
7	preeclamp$.ti,ab.
8	eclamp$.ti,ab.
9	HELLP.ti,ab.
10	tox?emi$.ti,ab.
11	or/1-10
12	exp ANTIHYPERTENSIVE AGENT/
13	(antihypertensive? or anti-hypertensive?).ti,ab.
14	(Acebutolol or Adrenomedullin or Alprenolol or Amlodipine or Atenolol or Bendroflumethiazide or Bepridilor Betaxolol or Bethanidine or Bimatoprost or Bisoprolol or Bretylium Tosylate or Brimonidine Tartrate or Bupranolol or Captoprilor Carteolol or Celiprolol or Chlorisondamine or Chlorothiazide or Chlorthalidone or Cilazapril or Clonidine or Cromakalim or Cyclopenthiazide or Debrisoquin or Diazoxide or Dihydralazine or Dihydroalprenolol or Diltiazem or Doxazosin or Enalapril or Enalaprilat or Epoprostenol or Felodipine or Fenoldopam or Fosinopril or Guanabenz or Guanethidine or Guanfacine or Hexamethonium or Hydralazine or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Indoramin or Isradipine or Kallidin or Ketanserin or Labetalol or Lisinopril or Losartan or Mecamylamine or Methyldopa or Metipranolol or Metolazone or Metoprolol or Mibefradil or Minoxidil or Muzolimine or Nadolol or Nebivolol or Nicardipine or Nicorandil or Nimodipine or Nisoldipine or Nitrendipine or Nitroprusside or Olmesartan Medoxomil or Oxprenolol or Pargyline or Pempidine or Penbutolol or Pentolinium Tartrate or Perindopril or Phenoxybenzamine or Phentolamine or Pinacidil or Pindolol or Piperoxan or Polythiazide or Prazosin or Propranolol or Protoveratrine? or Ramipril or Reserpine or Teprotide or Ticrynafen or Timolol or Todralazine or Tolazoline or Travoprost or Trichlormethiazide or Trimethaphan or Valsartan or Veratrum Alkaloid? or Vincamine or Xipamide).mp.
15	exp BETA ADRENERGIC RECEPTOR BLOCKING AGENT/
16	(adrenergic adj3 beta adj3 antagonist?).ti,ab.
17	(beta adj3 blocker?).ti,ab.
18	(mixed adj3 blocker?).ti,ab.
19	(Alprenolol or (Brimonidine Tartrate adj2 Timolol Maleate) or Bunolol or Bupranolol or Carteolol or Dihydroalprenolol or Iodocyanopindolol or Labetalol or Levobunolol or Metipranolol or Nadolol or Oxprenolol or Penbutolol or Pindolol or Propranolol or Sotalol or Timolol or Acebutolol or Atenolol or Betaxolol or Bisoprolol or Celiprolol or Metoprolol or Practolol or Butoxamine).mp.
20	exp ALPHA 2 ADRENERGIC RECEPTOR STIMULATING AGENT/
21	((adrenergic or Adrenoceptor?) adj3 (alpha 2 or alpha2) adj3 agonist?).ti,ab.
22	(Brimonidine Tartrate or Clonidine or Dexmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine).mp.
23	exp CALCIUM CHANNEL BLOCKING AGENT/
24	(calcium channel adj3 (blocker? or antagonist?)).ti,ab.
25	(Amlodipine or Amrinone or Bencyclane or Bepridil or Cinnarizine or Conotoxin? or Diltiazem or Felodipine or Fendiline or Flunarizine or Gallopamil or Isradipine or Lidoflazine or Magnesium Sulfate or Mibefradil or Nicardipine or Nifedipine or Nimodipine or Nisoldipine or Nitrendipine or Perhexiline or Pregabalin or Prenylamine or Risedronate Sodium or Tiapamil Hydrochloride or Verapamil or omega-Agatoxin IVA or omega-Conotoxin?).mp.
26	exp ANGIOTENSIN RECEPTOR ANTAGONIST/
27	(angiotensin adj3 receptor adj3 (antagonist? or blocker?)).ti,ab.
28	(1-Sarcosine-8-Isoleucine Angiotensin II or Losartan or Olmesartan Medoxomil or Saralasin or Valsartan).mp.
29	exp DIPEPTIDYL CARBOXYPEPTIDASE INHIBITOR/
30	(angiotensin converting enzyme adj3 (antagonist? or inhibitor?)).ti,ab.
31	(ACE adj3 (antagonist? or inhibitor?)).ti,ab.
32	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide).mp.
33	FUROSEMIDE/

#	Searches
34	furosemide.mp.
35	or/12-34
36	PERINATAL PERIOD/
37	*PUERPERIUM/
38	POSTNATAL CARE/
39	(Peripart$ or Peri-part$ or Postpart$ or Post-part$ or Postnatal$ or Post-natal$ or Puerper$).ti.
40	(Peripart$ or Peri-part$ or Postpart$ or Post-part$ or Postnatal$ or Post-natal$ or Puerper$).ab. /freq=2
41	((follow$ or post$) adj1 (birth$ or deliver$)).ti,ab.
42	or/36-41
43	((hypertensi$ or preeclamp$ or eclamp$ or HELLP or tox?emi$) adj5 (Peripart$ or Peri-part$ or Postpart$ or Post-part$ or Postnatal$ or Post-natal$ or Puerper$)).ti,ab.
44	exp *BREAST FEEDING/
45	breastfe$.ti,ab.
46	(breast adj3 (fed$ or feed$)).ti,ab.
47	(breast$ adj3 (pump$ or express$ or collect$)).ti,ab.
48	*BREAST MILK/
49	breastmilk.ti,ab.
50	((breast or human) adj3 milk).ti,ab.
51	*LACTATION/
52	lactat$.ti,ab.
53	(milk adj3 (eject$ or express$)).ti,ab.
54	or/44-53
55	exp *ANTIHYPERTENSIVE AGENT/ae [Adverse Drug Reaction]
56	exp *ANTIHYPERTENSIVE AGENT/dt [Drug Therapy]
57	exp *BETA ADRENERGIC RECEPTOR BLOCKING AGENT/ae [Adverse Drug Reaction]
58	exp *BETA ADRENERGIC RECEPTOR BLOCKING AGENT/dt [Drug Therapy]
59	exp *ALPHA 2 ADRENERGIC RECEPTOR STIMULATING AGENT/ae [Adverse Drug Reaction]
60	exp *ALPHA 2 ADRENERGIC RECEPTOR STIMULATING AGENT/dt [Drug Therapy]
61	exp *CALCIUM CHANNEL BLOCKING AGENT/ae [Adverse Drug Reaction]
62	exp *CALCIUM CHANNEL BLOCKING AGENT/dt [Drug Therapy]
63	exp *ANGIOTENSIN RECEPTOR ANTAGONIST/ae [Adverse Drug Reaction]
64	exp *ANGIOTENSIN RECEPTOR ANTAGONIST/dt [Drug Therapy]
65	exp *DIPEPTIDYL CARBOXYPEPTIDASE INHIBITOR/ae [Adverse Drug Reaction]
66	exp *DIPEPTIDYL CARBOXYPEPTIDASE INHIBITOR/dt [Drug Therapy]
67	*FUROSEMIDE/ae [Adverse Drug Reaction]
68	*FUROSEMIDE/dt [Drug Therapy]
69	or/55-68
70	*MATERNAL HYPERTENSION/dm [Disease Management]
71	*MATERNAL HYPERTENSION/dt [Drug Therapy]
72	*MATERNAL HYPERTENSION/pc [Prevention]
73	*MATERNAL HYPERTENSION/th [Therapy]
74	exp *"ECLAMPSIA AND PREECLAMPSIA"/dm [Disease Management]
75	exp *"ECLAMPSIA AND PREECLAMPSIA"/dt [Drug Therapy]
76	exp *"ECLAMPSIA AND PREECLAMPSIA"/pc [Prevention]
77	exp *"ECLAMPSIA AND PREECLAMPSIA"/th [Therapy]
78	*HELLP SYNDROME/dm [Disease Management]
79	*HELLP SYNDROME/dt [Drug Therapy]
80	*HELLP SYNDROME/pc [Prevention]
81	*HELLP SYNDROME/th [Therapy]
82	or/70-81
83	11 and 35 and 42
84	35 and 43
85	11 and 35 and 54
86	42 and 69
87	42 and 82
88	or/83-87
89	limit 88 to english language
90	letter.pt. or LETTER/
91	note.pt.
92	editorial.pt.
93	CASE REPORT/ or CASE STUDY/
94	(letter or comment*).ti.
95	or/90-94

#	Searches
96	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
97	95 not 96
98	ANIMAL/ not HUMAN/
99	NONHUMAN/
100	exp ANIMAL EXPERIMENT/
101	exp EXPERIMENTAL ANIMAL/
102	ANIMAL MODEL/
103	exp RODENT/
104	(rat or rats or mouse or mice).ti.
105	or/97-104
106	89 not 105

Databases: Cochrane Central Register of Controlled Trials; Cochrane Database of Systematic Reviews; Database of Abstracts of Reviews of Effects; and Health Technology Assessment

Date of last search: 19/12/17

#	Searches
1	MeSH descriptor: [HYPERTENSION, PREGNANCY-INDUCED] this term only
2	MeSH descriptor: [PREGNANCY] this term only
3	MeSH descriptor: [HYPERTENSION] this term only
4	#2 and #3
5	MeSH descriptor: [PRE-ECLAMPSIA] this term only
6	MeSH descriptor: [ECLAMPSIA] this term only
7	MeSH descriptor: [HELLP SYNDROME] this term only
8	MeSH descriptor: [PREGNANCY COMPLICATIONS, CARDIOVASCULAR] this term only
9	((pregnan* or gestation*) near/5 hypertensi*).ti.
10	preeclamp*.ti,ab.
11	eclamp*.ti,ab.
12	HELLP.ti,ab.
13	tox?emi*.ti,ab.
14	#1 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
15	MeSH descriptor: [ANTIHYPERTENSIVE AGENTS] explode all trees
16	(antihypertensive? or anti-hypertensive?).ti,ab.
17	(Acebutolol or Adrenomedullin or Alprenolol or Amlodipine or Atenolol or Bendroflumethiazide or Bepridilor Betaxolol or Bethanidine or Bimatoprost or Bisoprolol or Bretylium Tosylate or Brimonidine Tartrate or Bupranolol or Captoprilor Carteolol or Celiprolol or Chlorisondamine or Chlorothiazide or Chlorthalidone or Cilazapril or Clonidine or Cromakalim or Cyclopenthiazide or Debrisoquin or Diazoxide or Dihydralazine or Dihydroalprenolol or Diltiazem or Doxazosin or Enalapril or Enalaprilat or Epoprostenol or Felodipine or Fenoldopam or Fosinopril or Guanabenz or Guanethidine or Guanfacine or Hexamethonium or Hydralazine or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Indoramin or Isradipine or Kallidin or Ketanserin or Labetalol or Lisinopril or Losartan or Mecamylamine or Methyldopa or Metipranolol or Metolazone or Metoprolol or Mibefradil or Minoxidil or Muzolimine or Nadolol or Nebivolol or Nicardipine or Nicorandil or Nimodipine or Nisoldipine or Nitrendipine or Nitroprusside or Olmesartan Medoxomil or Oxprenolol or Pargyline or Pempidine or Penbutolol or Pentolinium Tartrate or Perindopril or Phenoxybenzamine or Phentolamine or Pinacidil or Pindolol or Piperoxan or Polythiazide or Prazosin or Propranolol or Protoveratrine? or Ramipril or Reserpine or Teprotide or Ticrynafen or Timolol or Todralazine or Tolazoline or Travoprost or Trichlormethiazide or Trimethaphan or Valsartan or Veratrum Alkaloid? or Vincamine or Xipamide).ti,ab.
18	MeSH descriptor: [ADRENERGIC BETA-ANTAGONISTS] explode all trees
19	(adrenergic near/3 beta near/3 antagonist?).ti,ab.
20	(beta near/3 blocker?).ti,ab.
21	(mixed near/3 blocker?).ti,ab.
22	(Alprenolol or (Brimonidine Tartrate near/2 Timolol Maleate) or Bunolol or Bupranolol or Carteolol or Dihydroalprenolol or Iodocyanopindolol or Labetalol or Levobunolol or Metipranolol or Nadolol or Oxprenolol or Penbutolol or Pindolol or Propranolol or Sotalol or Timolol or Acebutolol or Atenolol or Betaxolol or Bisoprolol or Celiprolol or Metoprolol or Practolol or Butoxamine).ti,ab.
23	MeSH descriptor: [ADRENERGIC ALPHA-2 RECEPTOR AGONISTS] explode all trees
24	((adrenergic or Adrenoceptor?) near/3 (alpha 2 or alpha2) near/3 agonist?).ti,ab.
25	(Brimonidine Tartrate or Clonidine or Dexmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine).ti,ab.
26	MeSH descriptor: [CALCIUM CHANNEL BLOCKERS] explode all trees

#	Searches
27	(calcium channel near/3 (blocker? or antagonist?)).ti,ab.
28	(Amlodipine or Amrinone or Bencyclane or Bepridil or Cinnarizine or Conotoxin? or Diltiazem or Felodipine or Fendiline or Flunarizine or Gallopamil or Isradipine or Lidoflazine or Magnesium Sulfate or Mibefradil or Nicardipine or Nifedipine or Nimodipine or Nisoldipine or Nitrendipine or Perhexiline or Pregabalin or Prenylamine or Risedronate Sodium or Tiapamil Hydrochloride or Verapamil or omega-Agatoxin IVA or omega-Conotoxin?).ti,ab.
29	MeSH descriptor: [ANGIOTENSIN RECEPTOR ANTAGONISTS] explode all trees
30	(angiotensin near/3 receptor near/3 (antagonist? or blocker?)).ti,ab.
31	(1-Sarcosine-8-Isoleucine Angiotensin II or Losartan or Olmesartan Medoxomil or Saralasin or Valsartan).ti,ab.
32	MeSH descriptor: [ANGIOTENSIN-CONVERTING ENZYME INHIBITORS] explode all trees
33	(angiotensin converting enzyme near/3 (antagonist? or inhibitor?)).ti,ab.
34	(ACE near/3 (antagonist? or inhibitor?)).ti,ab.
35	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide).ti,ab.
36	MeSH descriptor: [FUROSEMIDE] this term only
37	furosemide.ti,ab.
38	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
39	MeSH descriptor: [PERIPARTUM PERIOD] this term only
40	MeSH descriptor: [POSTPARTUM PERIOD] this term only
41	MeSH descriptor: [POSTNATAL CARE] this term only
42	(Peripart* or Peri-part* or Postpart* or Post-part* or Postnatal* or Post-natal* or Puerper*) .ti,ab.
43	((follow* or post*) near/1 (birth* or deliver*)) .ti,ab.
44	#39 or #40 or #41 or #42 or #43
45	MeSH descriptor: [BREAST FEEDING] explode all trees
46	breastfe*.ti,ab.
47	(breast near/3 (fed* or feed*)).ti,ab.
48	(breast* near/3 (pump* or express* or collect*)).ti,ab.
49	MeSH descriptor: [MILK, HUMAN] this term only
50	breastmilk.ti,ab.
51	((breast or human) near/3 milk).ti,ab.
52	MeSH descriptor: [LACTATION] this term only
53	lactat*.ti,ab.
54	(milk near/3 (eject* or express*)).ti,ab.
55	#45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54
56	MeSH descriptor: [ANTIHYPERTENSIVE AGENTS] explode all trees and with qualifier(s): [Adverse effects - AE]
57	MeSH descriptor: [ANTIHYPERTENSIVE AGENTS] explode all trees and with qualifier(s): [Therapeutic use - TU]
58	MeSH descriptor: [ADRENERGIC BETA-ANTAGONISTS] explode all trees and with qualifier(s): [Adverse effects - AE]
59	MeSH descriptor: [ADRENERGIC BETA-ANTAGONISTS] explode all trees and with qualifier(s): [Therapeutic use - TU]
60	MeSH descriptor: [ADRENERGIC ALPHA-2 RECEPTOR AGONISTS] explode all trees and with qualifier(s): [Adverse effects - AE]
61	MeSH descriptor: [ADRENERGIC ALPHA-2 RECEPTOR AGONISTS] explode all trees and with qualifier(s): [Therapeutic use - TU]
62	MeSH descriptor: [CALCIUM CHANNEL BLOCKERS] explode all trees and with qualifier(s): [Adverse effects - AE]
63	MeSH descriptor: [CALCIUM CHANNEL BLOCKERS] explode all trees and with qualifier(s): [Therapeutic use - TU]
64	MeSH descriptor: [ANGIOTENSIN RECEPTOR ANTAGONISTS] explode all trees and with qualifier(s): [Adverse effects - AE]
65	MeSH descriptor: [ANGIOTENSIN RECEPTOR ANTAGONISTS] explode all trees and with qualifier(s): [Therapeutic use - TU]
66	MeSH descriptor: [ANGIOTENSIN-CONVERTING ENZYME INHIBITORS] explode all trees and with qualifier(s): [Adverse effects - AE]
67	MeSH descriptor: [ANGIOTENSIN-CONVERTING ENZYME INHIBITORS] explode all trees and with qualifier(s): [Therapeutic use - TU]
68	MeSH descriptor: [FUROSEMIDE] this term only and with qualifier(s): [Adverse effects - AE]
69	MeSH descriptor: [FUROSEMIDE] this term only and with qualifier(s): [Therapeutic use - TU]
70	#56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69
71	MeSH descriptor: [HYPERTENSION, PREGNANCY-INDUCED] explode all trees and with qualifier(s): [Drug therapy - DT]
72	MeSH descriptor: [HYPERTENSION, PREGNANCY-INDUCED] explode all trees and with qualifier(s): [Prevention & control - PC]
73	MeSH descriptor: [HYPERTENSION, PREGNANCY-INDUCED] explode all trees and with qualifier(s): [Therapy - TH]
74	#71 or #72 or #73
75	MeSH descriptor: [POSTNATAL CARE] explode all trees and with qualifier(s): [Methods - MT]
76	#14 and #38 and #44
77	#14 and #38 and #55
78	#44 and #70
79	#44 and #74

#	Searches
80	#14 and #75
81	#76 or #77 or #78 or #79 or #80

Health economics search strategies

Databases: Medline; Medline EPub Ahead of Print; and Medline In-Process & Other Non-Indexed Citations

Date of last search: 19/12/17

#	Searches
1	ECONOMICS/
2	VALUE OF LIFE/
3	exp "COSTS AND COST ANALYSIS"/
4	exp ECONOMICS, HOSPITAL/
5	exp ECONOMICS, MEDICAL/
6	exp RESOURCE ALLOCATION/
7	ECONOMICS, NURSING/
8	ECONOMICS, PHARMACEUTICAL/
9	exp "FEES AND CHARGES"/
10	exp BUDGETS/
11	budget*.ti,ab.
12	cost*.ti,ab.
13	(economic* or pharmaco?economic*).ti,ab.
14	(price* or pricing*).ti,ab.
15	(financ* or fee or fees or expenditure* or saving*).ti,ab.
16	(value adj2 (money or monetary)).ti,ab.
17	resourc* allocat*.ti,ab.
18	(fund or funds or funding* or funded).ti,ab.
19	(ration or rations or rationing* or rationed).ti,ab.
20	ec.fs.
21	or/1-20
22	HYPERTENSION, PREGNANCY-INDUCED/
23	PREGNANCY/ and HYPERTENSION/
24	PRE-ECLAMPSIA/
25	ECLAMPSIA/
26	HELLP SYNDROME/
27	*PREGNANCY COMPLICATIONS, CARDIOVASCULAR/
28	((pregnan$ or gestation$) adj5 hypertensi$).ti.
29	((pregnan$ or gestation$) adj3 hypertensi$).ab. /freq=2
30	preeclamp$.ti,ab.
31	eclamp$.ti,ab.
32	HELLP.ti,ab.
33	tox?emi$.ti,ab.
34	or/22-33
35	exp ANTIHYPERTENSIVE AGENTS/
36	(antihypertensive? or anti-hypertensive?).ti,ab.
37	(Acebutolol or Adrenomedullin or Alprenolol or Amlodipine or Atenolol or Bendroflumethiazide or Bepridilor Betaxolol or Bethanidine or Bimatoprost or Bisoprolol or Bretylium Tosylate or Brimonidine Tartrate or Bupranolol or Captoprilor Carteolol or Celiprolol or Chlorisondamine or Chlorothiazide or Chlorthalidone or Cilazapril or Clonidine or Cromakalim or Cyclopenthiazide or Debrisoquin or Diazoxide or Dihydralazine or Dihydroalprenolol or Diltiazem or Doxazosin or Enalapril or Enalaprilat or Epoprostenol or Felodipine or Fenoldopam or Fosinopril or Guanabenz or Guanethidine or Guanfacine or Hexamethonium or Hydralazine or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Indoramin or Isradipine or Kallidin or Ketanserin or Labetalol or Lisinopril or Losartan or Mecamylamine or Methyldopa or Metipranolol or Metolazone or Metoprolol or Mibefradil or Minoxidil or Muzolimine or Nadolol or Nebivolol or Nicardipine or Nicorandil or Nimodipine or Nisoldipine or Nitrendipine or Nitroprusside or Olmesartan Medoxomil or Oxprenolol or Pargyline or Pempidine or Penbutolol or Pentolinium Tartrate or Perindopril or Phenoxybenzamine or Phentolamine or Pinacidil or Pindolol or Piperoxan or Polythiazide or Prazosin or Propranolol or Protoveratrine? or Ramipril or Reserpine or Teprotide or Ticrynafen or Timolol or Todralazine or

#	Searches
	Tolazoline or Travoprost or Trichlormethiazide or Trimethaphan or Valsartan or Veratrum Alkaloid? or Vincamine or Xipamide).mp.
38	exp ADRENERGIC BETA-ANTAGONISTS/
39	(adrenergic adj3 beta adj3 antagonist?).ti,ab.
40	(beta adj3 blocker?).ti,ab.
41	(mixed adj3 blocker?).ti,ab.
42	(Alprenolol or (Brimonidine Tartrate adj2 Timolol Maleate) or Bunolol or Bupranolol or Carteolol or Dihydroalprenolol or Iodocyanopindolol or Labetalol or Levobunolol or Metipranolol or Nadolol or Oxprenolol or Penbutolol or Pindolol or Propranolol or Sotalol or Timolol or Acebutolol or Atenolol or Betaxolol or Bisoprolol or Celiprolol or Metoprolol or Practolol or Butoxamine).mp.
43	exp ADRENERGIC ALPHA-2 RECEPTOR AGONISTS/
44	((adrenergic or Adrenoceptor?) adj3 (alpha 2 or alpha2) adj3 agonist?).ti,ab.
45	(Brimonidine Tartrate or Clonidine or Dexmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine).mp.
46	exp CALCIUM CHANNEL BLOCKERS/
47	(calcium channel adj3 (blocker? or antagonist?)).ti,ab.
48	(Amlodipine or Amrinone or Bencyclane or Bepridil or Cinnarizine or Conotoxin? or Diltiazem or Felodipine or Fendiline or Flunarizine or Gallopamil or Isradipine or Lidoflazine or Magnesium Sulfate or Mibefradil or Nicardipine or Nifedipine or Nimodipine or Nisoldipine or Nitrendipine or Perhexiline or Pregabalin or Prenylamine or Risedronate Sodium or Tiapamil Hydrochloride or Verapamil or omega-Agatoxin IVA or omega-Conotoxin?).mp.
49	exp ANGIOTENSIN RECEPTOR ANTAGONISTS/
50	(angiotensin adj3 receptor adj3 (antagonist? or blocker?)).ti,ab.
51	(1-Sarcosine-8-Isoleucine Angiotensin II or Losartan or Olmesartan Medoxomil or Saralasin or Valsartan).mp.
52	exp ANGIOTENSIN-CONVERTING ENZYME INHIBITORS/
53	(angiotensin converting enzyme adj3 (antagonist? or inhibitor?)).ti,ab.
54	(ACE adj3 (antagonist? or inhibitor?)).ti,ab.
55	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide).mp.
56	FUROSEMIDE/
57	furosemide.mp.
58	or/35-57
59	PERIPARTUM PERIOD/
60	POSTPARTUM PERIOD/
61	POSTNATAL CARE/
62	(Peripart$ or Peri-part$ or Postpart$ or Post-part$ or Postnatal$ or Post-natal$ or Puerper$).ti,ab.
63	((follow$ or post$) adj1 (birth$ or deliver$)).ti,ab.
64	or/59-63
65	exp BREAST FEEDING/
66	breastfe$.ti,ab.
67	(breast adj3 (fed$ or feed$)).ti,ab.
68	(breast$ adj3 (pump$ or express$ or collect$)).ti,ab.
69	MILK, HUMAN/
70	breastmilk.ti,ab.
71	((breast or human) adj3 milk).ti,ab.
72	LACTATION/
73	lactat$.ti,ab.
74	(milk adj3 (eject$ or express$)).ti,ab.
75	or/65-74
76	exp *ANTIHYPERTENSIVE AGENTS/ae [Adverse Effects]
77	exp *ANTIHYPERTENSIVE AGENTS/tu [Therapeutic Use]
78	exp *ADRENERGIC BETA-ANTAGONISTS/ae [Adverse Effects]
79	exp *ADRENERGIC BETA-ANTAGONISTS/tu [Therapeutic Use]
80	exp *ADRENERGIC ALPHA-2 RECEPTOR AGONISTS/ae [Adverse Effects]
81	exp *ADRENERGIC ALPHA-2 RECEPTOR AGONISTS/tu [Therapeutic Use]
82	exp *CALCIUM CHANNEL BLOCKERS/ae [Adverse Effects]
83	exp *CALCIUM CHANNEL BLOCKERS/tu [Therapeutic Use]
84	exp *ANGIOTENSIN RECEPTOR ANTAGONISTS/ae [Adverse Effects]
85	exp *ANGIOTENSIN RECEPTOR ANTAGONISTS/tu [Therapeutic Use]
86	exp *ANGIOTENSIN-CONVERTING ENZYME INHIBITORS/ae [Adverse Effects]
87	exp *ANGIOTENSIN-CONVERTING ENZYME INHIBITORS/tu [Therapeutic Use]
88	*FUROSEMIDE/ae [Adverse Effects]
89	*FUROSEMIDE/tu [Therapeutic Use]
90	or/76-89
91	exp *HYPERTENSION, PREGNANCY-INDUCED/dt [Drug Therapy]

#	Searches
92	exp *HYPERTENSION, PREGNANCY-INDUCED/pc [Prevention & Control]
93	exp *HYPERTENSION, PREGNANCY-INDUCED/th [Therapy]
94	or/91-93
95	POSTNATAL CARE/mt [Methods]
96	34 and 58 and 64
97	34 and 58 and 75
98	64 and 90
99	64 and 94
100	34 and 95
101	or/96-100
102	limit 101 to english language
103	LETTER/
104	EDITORIAL/
105	NEWS/
106	exp HISTORICAL ARTICLE/
107	ANECDOTES AS TOPIC/
108	COMMENT/
109	CASE REPORT/
110	(letter or comment*).ti.
111	or/103-110
112	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
113	111 not 112
114	ANIMALS/ not HUMANS/
115	exp ANIMALS, LABORATORY/
116	exp ANIMAL EXPERIMENTATION/
117	exp MODELS, ANIMAL/
118	exp RODENTIA/
119	(rat or rats or mouse or mice).ti.
120	or/113-119
121	102 not 120
122	21 and 121

Databases: Embase; and Embase Classic

Date of last search: 19/12/17

#	Searches
1	HEALTH ECONOMICS/
2	exp ECONOMIC EVALUATION/
3	exp HEALTH CARE COST/
4	exp FEE/
5	BUDGET/
6	FUNDING/
7	RESOURCE ALLOCATION/
8	budget*.ti,ab.
9	cost*.ti,ab.
10	(economic* or pharmaco?economic*).ti,ab.
11	(price* or pricing*).ti,ab.
12	(financ* or fee or fees or expenditure* or saving*).ti,ab.
13	(value adj2 (money or monetary)).ti,ab.
14	resourc* allocat*.ti,ab.
15	(fund or funds or funding* or funded).ti,ab.
16	(ration or rations or rationing* or rationed).ti,ab.
17	or/1-16
18	MATERNAL HYPERTENSION/
19	PREGNANCY/ and HYPERTENSION/
20	exp "ECLAMPSIA AND PREECLAMPSIA"/
21	HELLP SYNDROME/
22	((pregnan$ or gestation$) adj5 hypertensi$).ti.
23	((pregnan$ or gestation$) adj3 hypertensi$).ab. /freq=2

#	Searches
24	preeclamp$.ti,ab.
25	eclamp$.ti,ab.
26	HELLP.ti,ab.
27	tox?emi$.ti,ab.
28	or/18-27
29	exp ANTIHYPERTENSIVE AGENT/
30	(antihypertensive? or anti-hypertensive?).ti,ab.
31	(Acebutolol or Adrenomedullin or Alprenolol or Amlodipine or Atenolol or Bendroflumethiazide or Bepridilor Betaxolol or Bethanidine or Bimatoprost or Bisoprolol or Bretylium Tosylate or Brimonidine Tartrate or Bupranolol or Captoprilor Carteolol or Celiprolol or Chlorisondamine or Chlorothiazide or Chlorthalidone or Cilazapril or Clonidine or Cromakalim or Cyclopenthiazide or Debrisoquin or Diazoxide or Dihydralazine or Dihydroalprenolol or Diltiazem or Doxazosin or Enalapril or Enalaprilat or Epoprostenol or Felodipine or Fenoldopam or Fosinopril or Guanabenz or Guanethidine or Guanfacine or Hexamethonium or Hydralazine or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Indoramin or Isradipine or Kallidin or Ketanserin or Labetalol or Lisinopril or Losartan or Mecamylamine or Methyldopa or Metipranolol or Metolazone or Metoprolol or Mibefradil or Minoxidil or Muzolimine or Nadolol or Nebivolol or Nicardipine or Nicorandil or Nimodipine or Nisoldipine or Nitrendipine or Nitroprusside or Olmesartan Medoxomil or Oxprenolol or Pargyline or Pempidine or Penbutolol or Pentolinium Tartrate or Perindopril or Phenoxybenzamine or Phentolamine or Pinacidil or Pindolol or Piperoxan or Polythiazide or Prazosin or Propranolol or Protoveratrine? or Ramipril or Reserpine or Teprotide or Ticrynafen or Timolol or Todralazine or Tolazoline or Travoprost or Trichlormethiazide or Trimethaphan or Valsartan or Veratrum Alkaloid? or Vincamine or Xipamide).mp.
32	exp BETA ADRENERGIC RECEPTOR BLOCKING AGENT/
33	(adrenergic adj3 beta adj3 antagonist?).ti,ab.
34	(beta adj3 blocker?).ti,ab.
35	(mixed adj3 blocker?).ti,ab.
36	(Alprenolol or (Brimonidine Tartrate adj2 Timolol Maleate) or Bunolol or Bupranolol or Carteolol or Dihydroalprenolol or Iodocyanopindolol or Labetalol or Levobunolol or Metipranolol or Nadolol or Oxprenolol or Penbutolol or Pindolol or Propranolol or Sotalol or Timolol or Acebutolol or Atenolol or Betaxolol or Bisoprolol or Celiprolol or Metoprolol or Practolol or Butoxamine).mp.
37	exp ALPHA 2 ADRENERGIC RECEPTOR STIMULATING AGENT/
38	((adrenergic or Adrenoceptor?) adj3 (alpha 2 or alpha2) adj3 agonist?).ti,ab.
39	(Brimonidine Tartrate or Clonidine or Dexmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine).mp.
40	exp CALCIUM CHANNEL BLOCKING AGENT/
41	(calcium channel adj3 (blocker? or antagonist?)).ti,ab.
42	(Amlodipine or Amrinone or Bencyclane or Bepridil or Cinnarizine or Conotoxin? or Diltiazem or Felodipine or Fendiline or Flunarizine or Gallopamil or Isradipine or Lidoflazine or Magnesium Sulfate or Mibefradil or Nicardipine or Nifedipine or Nimodipine or Nisoldipine or Nitrendipine or Perhexiline or Pregabalin or Prenylamine or Risedronate Sodium or Tiapamil Hydrochloride or Verapamil or omega-Agatoxin IVA or omega-Conotoxin?).mp.
43	exp ANGIOTENSIN RECEPTOR ANTAGONIST/
44	(angiotensin adj3 receptor adj3 (antagonist? or blocker?)).ti,ab.
45	(1-Sarcosine-8-Isoleucine Angiotensin II or Losartan or Olmesartan Medoxomil or Saralasin or Valsartan).mp.
46	exp DIPEPTIDYL CARBOXYPEPTIDASE INHIBITOR/
47	(angiotensin converting enzyme adj3 (antagonist? or inhibitor?)).ti,ab.
48	(ACE adj3 (antagonist? or inhibitor?)).ti,ab.
49	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide).mp.
50	FUROSEMIDE/
51	furosemide.mp.
52	or/29-51
53	PERINATAL PERIOD/
54	*PUERPERIUM/
55	POSTNATAL CARE/
56	(Peripart$ or Peri-part$ or Postpart$ or Post-part$ or Postnatal$ or Post-natal$ or Puerper$).ti.
57	(Peripart$ or Peri-part$ or Postpart$ or Post-part$ or Postnatal$ or Post-natal$ or Puerper$).ab. /freq=2
58	((follow$ or post$) adj1 (birth$ or deliver$)).ti,ab.
59	or/53-58
60	((hypertensi$ or preeclamp$ or eclamp$ or HELLP or tox?emi$) adj5 (Peripart$ or Peri-part$ or Postpart$ or Post-part$ or Postnatal$ or Post-natal$ or Puerper$)).ti,ab.
61	exp *BREAST FEEDING/
62	breastfe$.ti,ab.
63	(breast adj3 (fed$ or feed$)).ti,ab.
64	(breast$ adj3 (pump$ or express$ or collect$)).ti,ab.
65	*BREAST MILK/
66	breastmilk.ti,ab.

#	Searches
67	((breast or human) adj3 milk).ti,ab.
68	*LACTATION/
69	lactat$.ti,ab.
70	(milk adj3 (eject$ or express$)).ti,ab.
71	or/61-70
72	exp *ANTIHYPERTENSIVE AGENT/ae [Adverse Drug Reaction]
73	exp *ANTIHYPERTENSIVE AGENT/dt [Drug Therapy]
74	exp *BETA ADRENERGIC RECEPTOR BLOCKING AGENT/ae [Adverse Drug Reaction]
75	exp *BETA ADRENERGIC RECEPTOR BLOCKING AGENT/dt [Drug Therapy]
76	exp *ALPHA 2 ADRENERGIC RECEPTOR STIMULATING AGENT/ae [Adverse Drug Reaction]
77	exp *ALPHA 2 ADRENERGIC RECEPTOR STIMULATING AGENT/dt [Drug Therapy]
78	exp *CALCIUM CHANNEL BLOCKING AGENT/ae [Adverse Drug Reaction]
79	exp *CALCIUM CHANNEL BLOCKING AGENT/dt [Drug Therapy]
80	exp *ANGIOTENSIN RECEPTOR ANTAGONIST/ae [Adverse Drug Reaction]
81	exp *ANGIOTENSIN RECEPTOR ANTAGONIST/dt [Drug Therapy]
82	exp *DIPEPTIDYL CARBOXYPEPTIDASE INHIBITOR/ae [Adverse Drug Reaction]
83	exp *DIPEPTIDYL CARBOXYPEPTIDASE INHIBITOR/dt [Drug Therapy]
84	*FUROSEMIDE/ae [Adverse Drug Reaction]
85	*FUROSEMIDE/dt [Drug Therapy]
86	or/72-85
87	*MATERNAL HYPERTENSION/dm [Disease Management]
88	*MATERNAL HYPERTENSION/dt [Drug Therapy]
89	*MATERNAL HYPERTENSION/pc [Prevention]
90	*MATERNAL HYPERTENSION/th [Therapy]
91	exp *"ECLAMPSIA AND PREECLAMPSIA"/dm [Disease Management]
92	exp *"ECLAMPSIA AND PREECLAMPSIA"/dt [Drug Therapy]
93	exp *"ECLAMPSIA AND PREECLAMPSIA"/pc [Prevention]
94	exp *"ECLAMPSIA AND PREECLAMPSIA"/th [Therapy]
95	*HELLP SYNDROME/dm [Disease Management]
96	*HELLP SYNDROME/dt [Drug Therapy]
97	*HELLP SYNDROME/pc [Prevention]
98	*HELLP SYNDROME/th [Therapy]
99	or/87-98
100	28 and 52 and 59
101	52 and 60
102	28 and 52 and 71
103	59 and 86
104	59 and 99
105	or/100-104
106	limit 105 to english language
107	letter.pt. or LETTER/
108	note.pt.
109	editorial.pt.
110	CASE REPORT/ or CASE STUDY/
111	(letter or comment*).ti.
112	or/107-111
113	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
114	112 not 113
115	ANIMAL/ not HUMAN/
116	NONHUMAN/
117	exp ANIMAL EXPERIMENT/
118	exp EXPERIMENTAL ANIMAL/
119	ANIMAL MODEL/
120	exp RODENT/
121	(rat or rats or mouse or mice).ti.
122	or/114-121
123	106 not 122
124	17 and 123

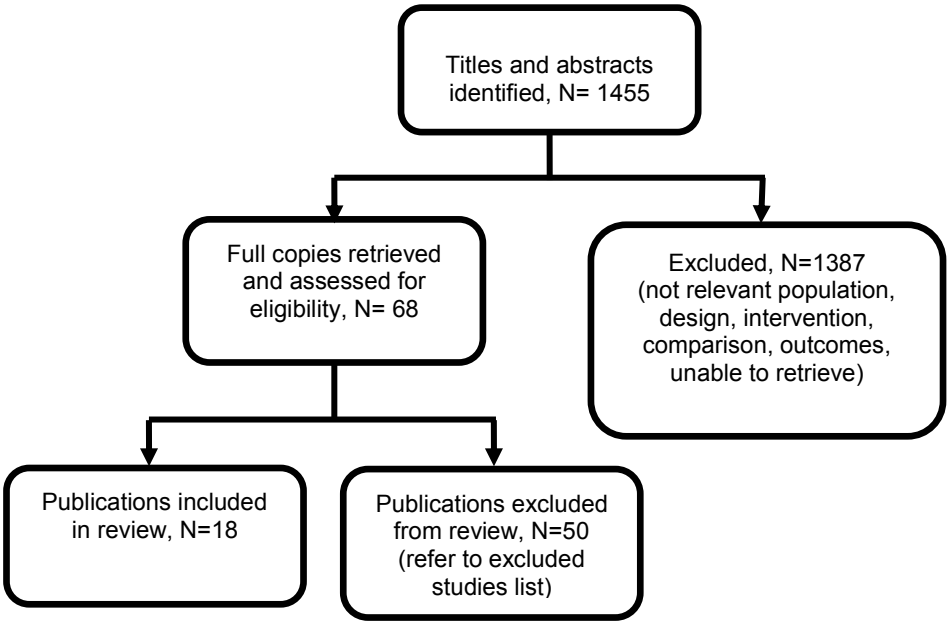
Databases: Cochrane Central Register of Controlled Trials; Health Technology Assessment; and NHS Economic Evaluation Database

Date of last search: 19/12/17

#	Searches
1	MeSH descriptor: [HYPERTENSION, PREGNANCY-INDUCED] this term only
2	MeSH descriptor: [PREGNANCY] this term only
3	MeSH descriptor: [HYPERTENSION] this term only
4	#2 and #3
5	MeSH descriptor: [PRE-ECLAMPSIA] this term only
6	MeSH descriptor: [ECLAMPSIA] this term only
7	MeSH descriptor: [HELLP SYNDROME] this term only
8	MeSH descriptor: [PREGNANCY COMPLICATIONS, CARDIOVASCULAR] this term only
9	((pregnan* or gestation*) near/5 hypertensi*).ti.
10	preeclamp*.ti,ab.
11	eclamp*.ti,ab.
12	HELLP.ti,ab.
13	tox?emi*.ti,ab.
14	#1 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
15	MeSH descriptor: [ANTIHYPERTENSIVE AGENTS] explode all trees
16	(antihypertensive? or anti-hypertensive?).ti,ab.
17	(Acebutolol or Adrenomedullin or Alprenolol or Amlodipine or Atenolol or Bendroflumethiazide or Bepridilor Betaxolol or Bethanidine or Bimatoprost or Bisoprolol or Bretylium Tosylate or Brimonidine Tartrate or Bupranolol or Captoprilor Carteolol or Celiprolol or Chlorisondamine or Chlorothiazide or Chlorthalidone or Cilazapril or Clonidine or Cromakalim or Cyclopenthiazide or Debrisoquin or Diazoxide or Dihydralazine or Dihydroalprenolol or Diltiazem or Doxazosin or Enalapril or Enalaprilat or Epoprostenol or Felodipine or Fenoldopam or Fosinopril or Guanabenz or Guanethidine or Guanfacine or Hexamethonium or Hydralazine or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Indoramin or Isradipine or Kallidin or Ketanserin or Labetalol or Lisinopril or Losartan or Mecamylamine or Methyldopa or Metipranolol or Metolazone or Metoprolol or Mibefradil or Minoxidil or Muzolimine or Nadolol or Nebivolol or Nicardipine or Nicorandil or Nimodipine or Nisoldipine or Nitrendipine or Nitroprusside or Olmesartan Medoxomil or Oxprenolol or Pargyline or Pempidine or Penbutolol or Pentolinium Tartrate or Perindopril or Phenoxybenzamine or Phentolamine or Pinacidil or Pindolol or Piperoxan or Polythiazide or Prazosin or Propranolol or Protoveratrine? or Ramipril or Reserpine or Teprotide or Ticrynafen or Timolol or Todralazine or Tolazoline or Travoprost or Trichlormethiazide or Trimethaphan or Valsartan or Veratrum Alkaloid? or Vincamine or Xipamide).ti,ab.
18	MeSH descriptor: [ADRENERGIC BETA-ANTAGONISTS] explode all trees
19	(adrenergic near/3 beta near/3 antagonist?).ti,ab.
20	(beta near/3 blocker?).ti,ab.
21	(mixed near/3 blocker?).ti,ab.
22	(Alprenolol or (Brimonidine Tartrate near/2 Timolol Maleate) or Bunolol or Bupranolol or Carteolol or Dihydroalprenolol or Iodocyanopindolol or Labetalol or Levobunolol or Metipranolol or Nadolol or Oxprenolol or Penbutolol or Pindolol or Propranolol or Sotalol or Timolol or Acebutolol or Atenolol or Betaxolol or Bisoprolol or Celiprolol or Metoprolol or Practolol or Butoxamine).ti,ab.
23	MeSH descriptor: [ADRENERGIC ALPHA-2 RECEPTOR AGONISTS] explode all trees
24	((adrenergic or Adrenoceptor?) near/3 (alpha 2 or alpha2) near/3 agonist?).ti,ab.
25	(Brimonidine Tartrate or Clonidine or Dexmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine).ti,ab.
26	MeSH descriptor: [CALCIUM CHANNEL BLOCKERS] explode all trees
27	(calcium channel near/3 (blocker? or antagonist?)).ti,ab.
28	(Amlodipine or Amrinone or Bencyclane or Bepridil or Cinnarizine or Conotoxin? or Diltiazem or Felodipine or Fendiline or Flunarizine or Gallopamil or Isradipine or Lidoflazine or Magnesium Sulfate or Mibefradil or Nicardipine or Nifedipine or Nimodipine or Nisoldipine or Nitrendipine or Perhexiline or Pregabalin or Prenylamine or Risedronate Sodium or Tiapamil Hydrochloride or Verapamil or omega-Agatoxin IVA or omega-Conotoxin?).ti,ab.
29	MeSH descriptor: [ANGIOTENSIN RECEPTOR ANTAGONISTS] explode all trees
30	(angiotensin near/3 receptor near/3 (antagonist? or blocker?)).ti,ab.
31	(1-Sarcosine-8-Isoleucine Angiotensin II or Losartan or Olmesartan Medoxomil or Saralasin or Valsartan).ti,ab.
32	MeSH descriptor: [ANGIOTENSIN-CONVERTING ENZYME INHIBITORS] explode all trees
33	(angiotensin converting enzyme near/3 (antagonist? or inhibitor?)).ti,ab.
34	(ACE near/3 (antagonist? or inhibitor?)).ti,ab.
35	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide).ti,ab.
36	MeSH descriptor: [FUROSEMIDE] this term only
37	furosemide.ti,ab.

#	Searches
38	#15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37
39	MeSH descriptor: [PERIPARTUM PERIOD] this term only
40	MeSH descriptor: [POSTPARTUM PERIOD] this term only
41	MeSH descriptor: [POSTNATAL CARE] this term only
42	(Peripart* or Peri-part* or Postpart* or Post-part* or Postnatal* or Post-natal* or Puerper*) .ti,ab.
43	((follow* or post*) near/1 (birth* or deliver*)) .ti,ab.
44	#39 or #40 or #41 or #42 or #43
45	MeSH descriptor: [BREAST FEEDING] explode all trees
46	breastfe*.ti,ab.
47	(breast near/3 (fed* or feed*)).ti,ab.
48	(breast* near/3 (pump* or express* or collect*)).ti,ab.
49	MeSH descriptor: [MILK, HUMAN] this term only
50	breastmilk.ti,ab.
51	((breast or human) near/3 milk).ti,ab.
52	MeSH descriptor: [LACTATION] this term only
53	lactat*.ti,ab.
54	(milk near/3 (eject* or express*)).ti,ab.
55	#45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54
56	MeSH descriptor: [ANTIHYPERTENSIVE AGENTS] explode all trees and with qualifier(s): [Adverse effects - AE]
57	MeSH descriptor: [ANTIHYPERTENSIVE AGENTS] explode all trees and with qualifier(s): [Therapeutic use - TU]
58	MeSH descriptor: [ADRENERGIC BETA-ANTAGONISTS] explode all trees and with qualifier(s): [Adverse effects - AE]
59	MeSH descriptor: [ADRENERGIC BETA-ANTAGONISTS] explode all trees and with qualifier(s): [Therapeutic use - TU]
60	MeSH descriptor: [ADRENERGIC ALPHA-2 RECEPTOR AGONISTS] explode all trees and with qualifier(s): [Adverse effects - AE]
61	MeSH descriptor: [ADRENERGIC ALPHA-2 RECEPTOR AGONISTS] explode all trees and with qualifier(s): [Therapeutic use - TU]
62	MeSH descriptor: [CALCIUM CHANNEL BLOCKERS] explode all trees and with qualifier(s): [Adverse effects - AE]
63	MeSH descriptor: [CALCIUM CHANNEL BLOCKERS] explode all trees and with qualifier(s): [Therapeutic use - TU]
64	MeSH descriptor: [ANGIOTENSIN RECEPTOR ANTAGONISTS] explode all trees and with qualifier(s): [Adverse effects - AE]
65	MeSH descriptor: [ANGIOTENSIN RECEPTOR ANTAGONISTS] explode all trees and with qualifier(s): [Therapeutic use - TU]
66	MeSH descriptor: [ANGIOTENSIN-CONVERTING ENZYME INHIBITORS] explode all trees and with qualifier(s): [Adverse effects - AE]
67	MeSH descriptor: [ANGIOTENSIN-CONVERTING ENZYME INHIBITORS] explode all trees and with qualifier(s): [Therapeutic use - TU]
68	MeSH descriptor: [FUROSEMIDE] this term only and with qualifier(s): [Adverse effects - AE]
69	MeSH descriptor: [FUROSEMIDE] this term only and with qualifier(s): [Therapeutic use - TU]
70	#56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69
71	MeSH descriptor: [HYPERTENSION, PREGNANCY-INDUCED] explode all trees and with qualifier(s): [Drug therapy - DT]
72	MeSH descriptor: [HYPERTENSION, PREGNANCY-INDUCED] explode all trees and with qualifier(s): [Prevention & control - PC]
73	MeSH descriptor: [HYPERTENSION, PREGNANCY-INDUCED] explode all trees and with qualifier(s): [Therapy - TH]
74	#71 or #72 or #73
75	MeSH descriptor: [POSTNATAL CARE] explode all trees and with qualifier(s): [Methods - MT]
76	#14 and #38 and #44
77	#14 and #38 and #55
78	#44 and #70
79	#44 and #74
80	#14 and #75
81	#76 or #77 or #78 or #79 or #80

Appendix C – Clinical evidence study selection



Appendix D – Clinical evidence tables

Table 4: Clinical evidance tables

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Full citation

Ascarelli, M. H., Johnson, V., McCreary, H., Cushman, J., May, W. L., Martin Jr, J. N., Postpartum preeclampsia management with furosemide: A randomized clinical trial, Obstetrics and Gynecology, 105, 29-33, 2005

Ref Id

742703

Country/ies where the</td>
<td>Sample size

N=264 postpartum women; n= 132 women randomised to furosemide and n= 132 randomised to no diuretic medication

Characteristics

64% experienced mild preeclampsia; 26.5% experienced severe preeclampsia and 9.5% experienced chronic hypertension with superimposed preeclampsia (definitions for these were not reported)
<table>
<tr><td></td><td>Furosemide</td><td>Control</td></tr>
<tr><td>Age - mean years (SD)</td><td>22.8 (6.1)</td><td>22.9 (6)</td></tr>
<tr><td>Weight mean lb (SD)</td><td>199(54)</td><td>206 (53)</td></tr>
<tr><td>African-American origin</td><td>74.4</td><td>74.2</td></tr>
</table>
</td>
<td>Interventions

Furosemide (20mg/d) together with an oral potassium supplement (20 mEq/d) for a total of 5 consecutive days during hospitalization and after discharge, initiated after the onset of spontaneous diuresis.
Patients in the control group did not receive any medication.
Both groups received antihypertensive medication (type not specified) for women experiencing inter</td>
<td>Details

Treatment was begun at the time that intravenous magnesium was discontinued before the onset of the trial in both groups, and all women presented with spontaneous diuresis at enrolment.
Treatment goal: sBP < 150 and/or dBP < 100</td>
<td>Results

Mean systolic BP in the second postpartum day for those who received furosemide = 142 ± 13 mm Hg
Mean systolic BP in the second postpartum day for those who did not receive any intervention = 153 ± 19 mm Hg, p<.004</td>
<td>Limitations

Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

Random sequence generation: unclear risk (randomisation method not reported)
Allocation concealment: low risk ("sequentially numbered opaque study envelopes")
Blinding of participants and personnel: unclear risk (no details reported)
Blinding of outcome assessment: unclear risk (no details reported)</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
study was carried out USA **Study type** RCT **Aim of the study** To assess the efficacy of furosemide as compared with no intervention on blood pressure control in postpartum women with hypertension **Study dates** July 1997 to March 1998 **Source of funding** Not reported	C-section delivery | 35.6 | 37.4 **Inclusion criteria** Gestational age at delivery >20 weeks; with mild/ severe preeclampsia, HELLP syndrome, or chronic hypertension with superimposed preeclampsia. **Exclusion criteria** Women with comorbidities, such as hypokalaemia, haemodynamic instability, those on diuretics/ potassium supplements	mittent or persistent sBP/dBP (≥150/100 mmHg x 2 times). The total number of women who received antihypertensive medication during hospitalisation were 36 (27%) in the furosemide group and 17 (12.8%) in the non -diuretic medication group.			Blinding (performance bias and detection bias): unclear risk (see above details) Incomplete outcome data: unclear risk (no registered protocol) Selective reporting: high risk (blood pressure was reported by type of hypertensive disorder rather than by treatment group and only this information is reported by treatment group at one time point)

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>Full citation

Barton, J. R., Hiett, A. K., Conover, W. B., The use of nifedipine during the postpartum period in patients with severe preeclampsia, American Journal of Obstetrics and Gynecology, 162, 788-92, 1990

Ref Id

755828

Country/ies where the study was carried out

USA

Study type</td>
<td>Sample size

N=31 postpartum women, n= 16 randomised to receive nifedipine and n=15 randomised to receive placebo

Characteristics
<table>
<tr><td></td><td>Nifedipine</td><td>Placebo</td></tr>
<tr><td>Age</td><td>24</td><td>26.3</td></tr>
<tr><td>GA</td><td>30.3</td><td>32.9</td></tr>
<tr><td>Vaginal delivery</td><td>9</td><td>8</td></tr>
<tr><td>C-section</td><td>7</td><td>7</td></tr>
</table>
Inclusion criteria

Severe preeclampsia as defined by one of the following:
• sBP > 180 mm Hg/ dBP > 120 mm Hg on one occasion
• sBP ranging between 160-180 mm Hg or dBP > 90 mm Hg on 2 occasions more than 6 hours apart despite bed rest + one of the following:</td>
<td>Interventions

Nifedipine 10 mg po every 4 hours x 2 days
Placebo 10 mg po every 4 hours x 2 days (placebo was presented in identical packaging as the nifedipine)

The medication was withheld if the women's BP was ≤120/70 mm Hg and was administered again as soon as the BP reached a level above these values
Both groups received hydralazine 10 mg IV until BP ≤160/110 mm Hg. This was repeated every 20' until the BP</td>
<td>Details

All women remained in the ward 48 hours postpartum, and during this time BP and pulse were assessed every hour by automated monitors. 24-h urine and creatinine collections were submitted at 24 and 48 hours postpartum. Oral intake was no permitted during the study.</td>
<td>Results

Raw data was not reported for the different time points, however "there were no significant differences between the two groups in sBP and dBP". During the 18- to 24- hour interval after delivery, the mean arterial blood pressure was 93.9 ± 1.6 mm Hg in the nifedipine group and 100.2 ± 2.6 mm Hg in the placebo group.</td>
<td>Limitations

Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

Random sequence generation: Low risk (random number tables)

Allocation concealment: Unclear risk (unclear whether the enveloped used were opaque)

Blinding of participants and personnel: low risk (participants and personnel were blinded)

Blinding of outcome assessment: low risk (assessors were blinded to treatment allocation)</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT **Aim of the study** To assess the effect of nifedipine on postpartum women with preeclampsia **Study dates** May 1988-May 1989 **Source of funding** Not reported	○ proteinuria > 5 gm in 24h or ≥ 3 as measured by a urine dipstick on 2 occasions at least 2 hours apart with no previous history of renal disease. ○ urine output < 500 ml in 24 hr or < 80 ml in any 4-hour period despite a 250 ml fluid change. ○ pulmonary oedema without evidence of fluid overload. ○ alanine aminotransferase > 100 IU/L ○ platelet count < 75000 cells/mm^3 ○ seizure with no prior history of seizure disorder **Exclusion criteria** Previous use of calcium channel blocker during pregnancy, allergy to calcium channel blockers, requirement of other antihypertensive treatments other than hydralazine	was ≤ 150/100 mm Hg.			Blinding (performance bias and detection bias): low risk (see above details) Incomplete outcome data: unclear risk (no information on drop outs) Selective reporting: high risk (mean arterial blood pressure was represented with a graph, but not raw data was reported)
Full citation Darcie, S., Leone, C. R., Calil, V. M., Prescinotti, E. P., Kahhale, S., Zugaib, M.,	**Sample size** N=93 new-borns; n= 37 of women randomised to the isradipine + low sodium diet ; n=33 randomised to the atenolol + low sodium diet and n=13 randomised to low sodium diet only	**Interventions** Atenolol (50 mg twice a day) + low sodium diet; Isradipine (5 mg twice a day) + low	**Details** Glycaemia was determined in the new-born through blood tests in the 1st, 3rd, 6th, 12th	**Results** Hypoglycaemia events in each of the groups	**Limitations** Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Glycemia in newborns of hypertensive mothers according to maternal treatment, Revista do Hospital das Clinicas; Faculdade de Medicina Da Universidade de Sao Paulo, 59, 244-50, 2004

Ref Id

659094

Country/ies where the study was carried out

Brazil

Study type

RCT</td>
<td>Characteristics
<table>
<tr><th></th><th>Isradipine (n=39)</th><th>Atenolol (n=40)</th><th>Control (n=14)</th></tr>
<tr><td>Gestational age mean weeks ± SD (days)</td><td>37±13.2</td><td>37±15.2</td><td>38±13.6</td></tr>
<tr><td>Weight mean kg ± SD</td><td>2.91 ±0.7</td><td>2.63 ± 0.6</td><td>2.97±0.6</td></tr>
<tr><td>Gender Female -n (%)</td><td>18 (46.2)</td><td>18 (45)</td><td>7 (50)</td></tr>
</table>
Inclusion criteria

Newborns of women with arterial hypertension (diastolic BP- Korotkoff phase 4 ≥ 90mmHg, measured in the left arm); the diagnosis was a specific hypertensive disease of pregnancy or chronic arterial hypertension and superimposed specific hypertensive disease of pregnancy; women should have been taking the same medication for at least 2 weeks before delivery; the newborn was from a singleton pregnancy.

Exclusion criteria</td>
<td>sodium diet and low sodium diet</td>
<td>and 24th hours postpartum. Methods used were the glucose oxidase and the Dextrotix Glucometer in the same time intervals as the blood tests. The new-borns could be breastfed, and in cases where this was not possible, formula was given after the 6 hours postpartum (no details regarding the total number of new-borns who were breastfed/formula fed) Hypoglycaemia was considered to be blood glycaemia</td>
<td>
<table>
<tr><th></th><th>Isradipine</th><th>Atenolol</th><th>Control</th></tr>
<tr><td>1st hour</td><td>15</td><td>17</td><td>2</td></tr>
<tr><td>3rd hour</td><td>8</td><td>10</td><td>1</td></tr>
<tr><td>6th hour</td><td>5</td><td>8</td><td>1</td></tr>
<tr><td>12th hour</td><td>3</td><td>6</td><td>2</td></tr>
<tr><td>24th hour</td><td>5</td><td>3</td><td>1</td></tr>
</table>
</td>
<td>Random sequence generation: Unclear risk (no details reported if any form of random sequence generation was used)

Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used)

Blinding of participants and personnel: Unclear risk (no details reported)

Blinding of outcome assessment: Unclear risk (no details reported)

Blinding (performance bias and detection bias): Unclear risk (no details reported)</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the glycaemic levels in new-borns of mothers receiving isradipine, atenolol or low sodium diet **Study dates** 01/06/1994 to 19/03/1997 **Source of funding** Not reported	Women with previous fetal loss; women with other pathologies (such as hemopathy, cardiopathy, diabetes or pneumopathy); women were taking other drugs that could interfere with the metabolism of carbohydrates in the newborn		values less than 40mg/dL		Incomplete outcome data: Unclear risk (no drop out data has been reported) Selective reporting: Unclear risk (study protocol not registered)
Full citation Eyal, S., Kim, J. D., Anderson, G. D., Buchanan, M. L., Brateng, D. A., Carr, D., Woodrum, D.	**Sample size** N = 32 women **Characteristics**	**Interventions** Total daily atenolol dose was divided in half and administered every 12 hours. Tablets were provided by the investigators for	**Details** Breast milk collections were performed at 2-hour intervals (2-4 weeks postpartum) or 3-hour intervals	**Results** **Daily excretion of atenolol in breast milk (µg), according to maternal dose** At 2-4 weeks post-partum (n = 32), mean ± SD (range) 25mg/day: 227 ± 80 (138 - 345, n = 8)	**Limitations** Quality appraisal using the Institute of Health Economics checklist for Case Series Clear objectives: yes Prospective: yes Multicentre: no

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>E., Easterling, T. R., Hebert, M. F., Atenolol pharmacokinetics and excretion in breast milk during the first 6 to 8 months postpartum, Journal of Clinical Pharmacology, 50, 1301-1309, 2010

Ref Id

755916

Country/ies where the study was carried out

USA

Study type
Non-comparative case series</td>
<td>
<table>
<tr><th></th><th>2-4 weeks postpartum (n = 32)</th><th>3-4 months postpartum (n = 22)</th><th>6-8 months postpartum (n = 17)</th></tr>
<tr><td>Weight, kg (mean ± SD)</td><td>93.3 ± 26.1</td><td>88.6 ± 24.9</td><td>86.1 ± 24.8</td></tr>
<tr><td>Age, y (mean ± SD)</td><td>32.3 ± 6.5</td><td></td><td></td></tr>
<tr><td>Reason for atenolol use</td><td></td><td></td><td></td></tr>
<tr><td>Hypertension</td><td>n = 28</td><td></td><td></td></tr>
<tr><td>Hypertrophic cardiomyopathy</td><td>n = 2</td><td></td><td></td></tr>
<tr><td>Arrythmia</td><td>n = 2</td><td></td><td></td></tr>
<tr><td>Serum creatinine, mg/dL (mean ± SD)</td><td>0.8 ± 0.1</td><td>0.7 ± 0.1</td><td>0.7 ± 0.1</td></tr>
</table>
</td>
<td>the 3 days prior to each study day, and pill counts were conducted. Subjects fasted for 6 hours prior to study drug administration until 1 hour post-dosing. Caffeine containing foods and beverages were avoided for 24 hours prior to each study day, and throughout sampling.</td>
<td>(3-4 months and 6-8 months) using a breast pump, over the 12 hour study period. Breasts were completely emptied of milk during each collection (to allow total milk volume to be determined) and breast feeding was not allowed on study days. A small breast milk aliquot was saved for determination of atenolol concentration, and the remaining milk was returned to the mother for feeding her infant.</td>
<td>50mg/day: 350 ± 167 (56 - 630, n = 16)
100mg/day: 429 ± 126 (307 - 596, n = 4)
200mg/day: 350 ± 524 (30 - 955, n = 3)

<u>At 3-4 months post-partum (n = 21), mean ± SD (range)</u>
25mg/day: 198 ± 72 (72 - 294, n = 9)
50mg/day: 265 ± 175 (11 - 462, n = 8)
100mg/day: 413 ± 530 (11 - 1191, n = 4)

<u>At 6-8 months post-partum (n = 16), mean ± SD (range)</u>
25mg/day: 168 ± 71 (83 - 273, n = 8)
50mg/day: 267 ± 116 (18 - 345, n = 7)
100mg/day: 259 (n = 1)

Atenolol plasma concentrations in all 3-4 month-old study infants (n = 15) were below the limit of assay quantification (10ng/mL). Samples were collected approximately 9 hours after the maternal dose.</td>
<td>Consecutive recruitment: unclear
Characteristics described: yes
Eligibility criteria defined: yes
Did patients enter the study at a similar point in the disease: yes, postpartum samples collected
Intervention clearly described: yes
Additional interventions clearly described: N/A
Relevant outcomes established a priori: yes
Outcome assessor blinding: no
(no report of blinding, all women taking study drug)
Appropriate methods for outcome assessment: yes
Outcome measures before and after intervention: N/A
Statistical analysis appropriate: yes
(mean values and</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine the time course for atenolol pharmacokinetics in lactating women, assess drug levels in breast milk and infant plasma levels. **Study dates** January 2005 to February 2008. **Source of funding** Not reported.	<table><tr><td>Creatinine clearance, mL/min (mean ± SD)</td><td>140.1 ± 35.4</td><td>146.6 ± 40.2</td><td>158.9 ± 48.2</td></tr><tr><td>Atenolol dose/day, n (%)</td><td></td><td></td><td></td></tr><tr><td>25mg</td><td>8 (25%)</td><td>9 (41%)</td><td>8 (47.1 %)</td></tr><tr><td>50mg</td><td>17 (53.1%)</td><td>9 (41%)</td><td>8 (47.1%)</td></tr><tr><td>100mg</td><td>4 (12.5%)</td><td>4 (18%)</td><td>1 (5.8%)</td></tr><tr><td>200mg</td><td>3 (9.4%)</td><td>0</td><td>0</td></tr></table>SD, standard deviation **Inclusion criteria** Women treated with atenolol for therapeutic reasons, aged 18 to 50 years, intention to breast feed their infant for 6 months or more, on a stable atenolol dose for 3 days prior to each study day.		Atenolol breast milk concentration was determined by a standard high-performance liquid chromatography assay.		standard deviation reported in addition to range) Follow up duration sufficient: yes (samples collected over three different time periods) Losses to follow up reported: yes (significant loss to follow up, but clearly reported for all time points) Estimates of random variability provided: no Adverse events reported: no Conclusions supported by results: yes Competing interests/support reported: no **Other information** Note that population did include 4 women who were treated with atenolol for

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td>Exclusion criteria
Haematocrit less than 28%.</td><td></td><td></td><td></td><td>cardiomyopathy or arrhythmia, rather than hypertension.</td></tr>
<tr><td>Full citation

Fidler, J., Smith, V., De Swiet, M., A randomized study comparing timolol and methyldopa in hospital treatment of puerperal hypertension, British Journal of Obstetrics and Gynaecology, 89, 1031-4, 1982

Ref Id

755921

Country/ies where the</td><td>Sample size

N=80 postpartum women with dBP between 95 and 105 mmHg, n=40 randomised to timolol and n=40 randomised to methyldopa

Characteristics
<table><tr><td></td><td>Timolol</td><td>Methyldopa</td></tr><tr><td>Mean age (SD)</td><td>29.7 (1)</td><td>27.8 (0.9)</td></tr><tr><td>sBP at entry (mean mmHg, SD)</td><td>143.8 (1.7)</td><td>147.6 (1.9)</td></tr><tr><td>dBP at entry (mean mmHg, SD)</td><td>99.8 (0.88)</td><td>101.3 (0.87)</td></tr><tr><td>Primiparous (N)</td><td>18</td><td>17</td></tr><tr><td>Multiparous (N)</td><td>22</td><td>23</td></tr><tr><td>Days since delivery before</td><td>4.4 ± 0.5</td><td>4.4 ± 0.7</td></tr></table></td><td>Interventions

Timolol 5mg po x 3 times/day
Methyldopa 250mg po x 3 times/day
Treatment goal: dBP ≤95 mm Hg
If treatment goal was not achieved within 24 h of starting the treatment, the dosage was doubled and doubled again every 24 h). Those not reaching the goal BP were deemed a treatment failure and oral hydralazine was added.</td><td>Details

If target BP was not reached within 24 hours after the start of the treatment, the dosage was doubled, and doubled again if the treatment goal was not reached. If the treatment goal was not reached after the treatment was increased twice, hydralazine was added.</td><td>Results

Mean ± SD (N) sBP measured from day 1 to 9
<table><tr><td></td><td>Timolol</td><td>Methyldopa</td></tr><tr><td>Day 1</td><td>133.5 ±1.9 (39)</td><td>138 ± 1.9 (40)</td></tr><tr><td>Day 2</td><td>132.7 ±2.3 (33)</td><td>133.4 ±1.9 (35)</td></tr><tr><td>Day 3</td><td>130.5 ±3.1 (27)</td><td>132.1 ±2.3 (28)</td></tr><tr><td>Day 4</td><td>129.7 ±2.2 (21)</td><td>130.2±2.9 (25)</td></tr><tr><td>Day 5</td><td>132.2 ±4.3 (13)</td><td>130.3 ±3.7 (22)</td></tr><tr><td>Day 6</td><td>130.2 ±4.8 (10)</td><td>129.5 ±4.5 (13)</td></tr><tr><td>Day 7</td><td>130.8 ± 6.1 (6)</td><td>116.8 ±2.9 (8)</td></tr><tr><td>Day 8</td><td>130 ±8.2 (4)</td><td>126.8 ±3.3 (8)</td></tr><tr><td>Day 9</td><td>120 (1)</td><td>132 (1)</td></tr></table>
Mean ± SD (N) dBP measured from day 1 to 9</td><td>Limitations

<u>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias</u>

Random sequence generation: Unclear risk (randomisation details were not provided)

Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used)

Blinding of participants and personnel: Unclear</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>study was carried out

UK

Study type

RCT

Aim of the study

To compare the effectiveness of methyldopa and timolol for controlling blood pressure

Study dates

Not reported

Source of funding

Merck, Sharp and Dohme and Ciba Laboratories</td>
<td>
<table>
<tr><td>intervention (± SEM)</td><td></td><td></td></tr>
</table>

Inclusion criteria

Presenting with hypertension (defined as dBP between 95 and 105 mmHg on two occasions, 24 hours apart), not having taken any other hypertensive drug 48 hours before the study

Exclusion criteria

"Other complications of pregnancy: multiple pregnancy, diabetes, renal disease, taking other hypertensive drugs"
</td>
<td></td>
<td></td>
<td>
<table>
<tr><td></td><td>Timolol</td><td>Methyldopa</td></tr>
<tr><td>Day 1</td><td>88.7 ±1.6 (39)</td><td>93.8±1.4 (40)</td></tr>
<tr><td>Day 2</td><td>87.9±1.6 (33)</td><td>88.4 ± 1.4 (35)</td></tr>
<tr><td>Day 3</td><td>85.2±2.2 (27)</td><td>85.9 ±1.6 (28)</td></tr>
<tr><td>Day 4</td><td>82 ± 2.2 (21)</td><td>85.8 ± 1.9 (25)</td></tr>
<tr><td>Day 5</td><td>86.5 ±2.8 (13)</td><td>85.6 ±2.4 (22)</td></tr>
<tr><td>Day 6</td><td>82.7 ±3.8 (10)</td><td>85.3 ± 3.2 (13)</td></tr>
<tr><td>Day 7</td><td>86.3 ±4 (6)</td><td>76.6 ±3.3 (8)</td></tr>
<tr><td>Day 8</td><td>86 ±2.5 (4)</td><td>79.4 ± 2.5 (8)</td></tr>
<tr><td>Day 9</td><td>70 (1)</td><td>88 (1)</td></tr>
</table>

Number of women achieving target blood pressure (≤95 mm Hg) according to the treatment dosage
<table>
<tr><td>Methyldopa (mg)</td><td>N (%)</td></tr>
<tr><td>750</td><td>23 (57.5)</td></tr>
<tr><td>1500</td><td>16 (40)</td></tr>
<tr><td>3000</td><td>0</td></tr>
<tr><td>Treatment failure</td><td>1 (2.5)</td></tr>
</table>
</td>
<td>risk (no details were reported)

Blinding of outcome assessment: Unclear risk (no details were reported)

Blinding (performance bias and detection bias): Unclear risk (no details were reported)

Incomplete outcome data: low risk

Selective reporting: unclear risk

Other bias: high risk (trial funded by a pharmaceutical company)</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Timolol (mg) | N (%) 15 | 30 (75) 30 | 5 (12.5) 60 | 2 (5) Treatment failure | 3 (7.5)	
Full citation Jarreau, P. H., Le Beller, C., Guillonneau, M., Jacqz-Aigrain, E., Excretion of nicardipine in human milk, Paediatric and Perinatal Drug Therapy, 4, 28-30, 2000 **Ref Id** 742840 **Country/ies where the study was carried out** France	**Sample size** N=11 women **Characteristics** 5 women presented with gestational hypertension, 3 women had pre-eclampsia, and 3 had essential hypertension prior pregnancy; age was 34 ±7 years; n= 6 had C-section and n=5 had a spontaneous delivery. Clinical examination at birth was normal for all infants **Inclusion criteria** Not reported **Exclusion criteria** Not reported	**Interventions** Nicardipine. N= 4 received the standard oral tablet form (40-80 mg/ 24 h, n=4). N=6 received the slow release form (100-150 mg/ 24h). N= 1 received it intravenously (120 mg/ 24h).	**Details** Milk was collected with a breast pump for 24 hours. 4 ± 2 milk samples were obtained per patient 4 to 14 days after delibery. Total milk volumes were measured and aliquots were kept for the determination of Nicardipine concentrations. Three hours after dosing, milk samples were collected. Nicardipine	**Results** Breast milk levels of nicardipine by type of administration Standard dosage (in 4 women [20mg x 3 days]) Maximum milk concentration (mean [SD] ng/ml)= 5.67 (3.20) Maximum dose ingested by the infant (mean [SD] ng/kg/day)= 851.25 (480.05) Maximum dose ingested by the infant (mean [SD] as a percentage of the weight-adjusted maternal daily dose)= 0.09 (0.04) Slow release dose (in 6 women [50mg x 2 days])	**Limitations** Quality appraisal using the Institute of Health Economics checklist for Case Series Clear objectives: yes Prospective: yes Multicentre: no Consecutive recruitment: unclear Characteristics described: yes Eligibility criteria defined: no Did patients enter the study at a similar point in the disease: yes, postpartum samples collected Intervention clearly described: yes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Non-comparative case series **Aim of the study** To assess the levels of nicardipine in breast milk **Study dates** Not reported **Source of funding** Not reported			concentrations in plasma and milk were measured by gas chromatography-mass spectrometry. The sensitivity limit was 5ng/ml and recovery from the plasma was 92.5 ± 5.3 % (n=6)	Maximum milk concentration (mean [SD] ng/ml)= 6.41 (3.48) Maximum dose ingested by the infant (mean [SD] ng/kg/day)= 931.33 (523.19) Maximum dose ingested by the infant (mean [SD] as a percentage of the weight-adjusted maternal daily dose)= 0.05 (0.03) <u>IV (in 1 woman [120 IV])</u> Maximum milk concentration (ng/ml)= 18.8 Maximum dose ingested by the infant (ng/kg/day)= 2823 Maximum dose ingested by the infant (as a percentage of the weight-adjusted maternal daily dose)= 0.14	Additional interventions clearly described: N/A Relevant outcomes established *a priori*: yes Outcome assessor blinding: no (no report of blinding, all women taking study drug) Appropriate methods for outcome assessment: yes Outcome measures before and after intervention: N/A Statistical analysis appropriate: yes (results given in absolute amounts per kg and day) Follow up duration sufficient: unclear if sufficient (breast milk samples were collected during 24 hours) Losses to follow up reported: N/A Estimates of random variability provided: no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Adverse events reported: no Conclusions supported by results: yes Competing interests/support reported: no
Full citation Kulas, J., Lunell, N. O., Rosing, U., Steen, B., Rane, A., Atenolol and metoprolol. A comparison of their excretion into human breast milk, Acta Obstetricia et Gynecologica Scandinavica - Supplement, 118, 65-9, 1984 **Ref Id**	**Sample size** N=7 women, n=4 women in the atenolol group and n=3 women in the metoprolol group **Characteristics** Not reported **Inclusion criteria** Not reported **Exclusion criteria** Not reported	**Interventions** Atenolol (100 mg) and metropolol (100 mg)	**Details** Women received the same dose of atenolol and metoprolol as during pregnancy, no other drugs were given. The milk was collected from the left breast with a pumping machine at 10 different time points during 8 hours. Milk concentrations were measured in nmol/l	**Results** <u>Mean (SD) atenolol concentrations in the left breast at 0,4 and 8 hours</u> At 0 hours : 1386.66 (555.81) nmol/l At 4 hours: 5532.5 (1752.68) nmol/l At 8 hours: 4107.5 (932.28) nmol/l <u>Mean (SD) metropolol concentrations in the left breast at 0,4 and 8 hours</u> At 0 hours : NR At 4 hours: 271.66 (18.03) nmol/l At 8 hours: 82 (49.78) nmol/l	**Limitations** <u>Study limitation assessed with the Newcastle-Ottowa scale for case-control studies</u> <u>Selection</u> Is the case definition adequate?: c)no description (definition for ´hypertension during pregnancy´ was not reported) Representativeness of the cases: c) potential for selection biases Selection of controls: hospital controls

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
659148 **Country/ies where the study was carried out** Sweden **Study type** Cross-sectional **Aim of the study** To assess the milk concentrations of atenolol and metoprolol in lactating women **Study dates** Not reported **Source of funding**				<u>Mean (SD) atenolol concentrations in the right breast at 0,4 and 8 hours</u> At 0 hours : 1750 (809.03) nmol/l At 4 hours: 3990 (1841.77) nmol/l At 8 hours: 3720 (113.13) nmol/l <u>Mean (SD) metropolol concentrations in the right breast at 0,4 and 8 hours</u> At 0 hours : NR nmol/l At 4 hours: 320 (2.82) nmol/l At 8 hours: 84 (15.62) nmol/l	Description of controls: no description of sources <u>Comparability</u> Comparability of the cases and controls on the basis of the design or analysis: no confounding factors were controlled for <u>Exposure</u> 1.Ascertainment of exposure: written self-report or medical record only 2. Same method of ascertainment for cases and controls: yes* 3. non response rate: rate difference and no designation

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Karolinska Institutet, Hassle AB and ICI Pharma					
Full citation Liedholm, H., Melander, A., Bitzen, P. O., Helm, G., Lonnerholm, G., Mattiasson, I., Nilsson, B., Wahlin-Boll, E., Accumulation of atenolol and metoprolol in human breast milk, Eur J Clin Pharmacol, 20, 229-31, 1981 **Ref Id** 767024 **Country/ies where the study was carried out**	**Sample size** N=10 lactating women; n=7 received atenolol and n=3 were healthy volunteers receiving metoprolol **Characteristics** Not reported **Inclusion criteria** Not reported **Exclusion criteria** Not reported	**Interventions** Atenolol 50 mg (n=2) or 100 mg (n=5) once daily or metoprolol 50 mg BID on day 1; 100 mg BID on days 2, 3, and 4.	**Details** Breast milk was obtained with a breast pump, collected in tubes and stored at -20ºC until analysed. In the women who received atenolol, blood and milk samples were obtained on 3 to 7 occasions subsequent to intake of the daily dose of atenolol. Women who received metoprolol (controls) were analysed 4 to 6 months after ceasing breastfeeding.	**Results** Maximum concentration of atenolol recorded: 6.35 µmol/L Maximum concentration of metoprolol recorded: 2.58 µmol/L Estimated intake of 0.13mg of atenolol and 0.05 mg of metoprolol for 75 ml of milk. No adverse outcomes on new-borns were studied	**Limitations** Study limitation assessed with the Newcastle-Ottowa scale for case-control studies Selection Is the case definition adequate?: c)no description (definition for ´hypertension during pregnancy´ was not reported) Representativeness of the cases: c) potential for selection biases Selection of controls: hospital controls Description of controls: no description of sources

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Sweden **Study type** Case-control **Aim of the study** To assess the breast milk levels of atenolol in nursing mothers **Study dates** Not reported **Source of funding** Swedish medical Research Council			0, 3, 6, 9 and 12 samples were obtained.		Comparability Comparability of the cases and controls on the basis of the design or analysis: no confounding factors were controlled for <u>Exposure</u> 1.Ascertainment of exposure: written self-report or medical record only 2. Same method of ascertainment for cases and controls: no 3. non response rate: rate difference and no designation
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Livingstone,I., Craswell,P.W., Bevan,E.B., Smith,M.T.,	N=28 women postpartum; n=14 received propranolol and n=14 received methyldopa Characteristics	Initial dosages of propranolol and methyldopa were not reported. The	Women were randomly assigned to the methyldopa or	Mean (SD) arterial pressure before and during treatment Before / During	<u>Methodological limitations assessed using the Cochrane collaboration's tool</u>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Eadie,M.J., Propranolol in pregnancy three year prospective study, Clinical and Experimental Hypertension - Part B, Hypertension in Pregnancy, 2, 341-350, 1983 **Ref Id** 195658 **Country/ies where the study was carried out** Australia **Study type** RCT **Aim of the study**	Not reported Inclusion criteria Postpartum women with hypertension (defined as 140/90 mmHg or above) on 2 consecutive readings 24 hours apart Exclusion criteria Women with impaired renal function	dose of propranolol needed to reach adequate BP was between 30 and 160 mg/day. The dose of methyldopa ranged between 0.5 and 1 g daily.	propranolol group and were assessed. New-borns' vital signs were monitored during 48 hours postpartum.	<table><tr><td>Propranolol</td><td>114.8 (7)</td><td>93.6 (9.5)</td></tr><tr><td>Methyldopa</td><td>111.3 (6.8)</td><td>95.2 (7)</td></tr></table>Number of new-borns with hypoglycaemia Propranolol group=2/14 Methyldopa group=0/14 Number of new-borns with bradycardia Propranolol group=0/14 Methyldopa group=0/14	<u>for assessing risk of bias</u> Random sequence generation: Unclear risk (no details reported) Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used) Blinding of participants and personnel: Unclear risk (no details reported) Blinding of outcome assessment: Unclear risk (no details reported) Blinding (performance bias and detection bias): Unclear risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To assess the effectiveness of propranolol and methyldopa for controlling blood pressure in postpartum women **Study dates** Not reported **Source of funding** Not reported					Incomplete outcome data: Unclear risk Selective reporting: Unclear risk **Other information** Patients with only mild to moderate pregnancy associated hypertension were admitted into the study. Length of the intervention was not reported.
Full citation Mabie,W.C., Gonzalez,A.R., Sibai,B.M., Amon,E., A comparative trial of labetalol and hydralazine in the acute management of severe	**Sample size** N=60 women. N=40 were randomised to the labetalol group and n=20 were randomised to the hydralazine group Characteristics | | Labetalol | Hydralazine | | Age | 23.7 ±6.9 | 22.9±7 |	**Interventions** Labetalol 20 mg IV. For N= 10 women, dosages were increased between 10 to 50 mg every 10' until dBP< 100 mmHg. For n=30 women, 20 mg extra were given every 10' to a	**Details** A mercury sphygmomanometer was used to measure blood pressure, with the first and fifth Korotkoff sounds. N=12 women had radial arterial	**Results** Mean change in MAP before and after treatment Labetalol group: -25.5 ± 11.2 Hydralazine: -33.3 ± 13.2 Time (minutes) to maximal decrease in blood pressure Labetalol: 55.1±33.1 Hydralazine: 75.8 ± 30.6 Mean total dosage needed to reach BP goal Labetalol:140 ± 5.9 mg	**Limitations** Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias Random sequence generation: Low risk (Randomisation was performed through a

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
hypertension complicating pregnancy, Obstetrics and Gynecology, 70, 328-333, 1987 **Ref Id** 195683 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To assess the effectiveness of labetalol as compared to hydralazine in controlling hypertension in pregnancy **Study dates**	<table><tr><td>Ethnic origin (black)</td><td>32/40</td><td>16/20</td></tr><tr><td>Antenatal</td><td>13/40</td><td>6/20</td></tr></table> In the antenatal group, 5 women were stabilised before induction or C-section, 8 were in the latent phase, and 6 were in the active phase of labour when the medication was given Inclusion criteria Women with preeclampsia, chronic hypertension with or without superimposed preeclampsia with dBP ≥110 mmHg dBP ; no concurrent antihypertensive treatment Exclusion criteria Not reported	maximum cumulative dosage of 300 mg/ or until the dBP< 100 mmHg. Hydralazine 5 mg IV every 10' until the dBP< 100 mmHg.	caterers placed for continuous blood pressure monitoring. All the patients with caterers had a severe disease, usually requiring a C-section. Both antenatal and postpartum women were receiving magnesium sulphate infusions at 1-3g/hour, adjusted to maintain serum concentrations in the range of 4.8-8.4 mg/dL. In the antenatal group, n=5 women were being stabilised befor e induction of C-section, n=8 were in the latent phase	Hydralazine: 14 ± 5.9 mg	series of random numbers) Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used) Blinding of participants and personnel: Unclear risk (no details were specified) Blinding of outcome assessment: Unclear risk (no details were specified) Blinding (performance bias and detection bias): unclear risk (see above details) Incomplete outcome data: low risk Selective reporting: unclear risk (protocol does not appear to

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>Not reported

Source of funding
Not reported</td><td></td><td></td><td>and n=6 were in the active phase of labour when the medication was given.
BP was measured after taking the medication and at 5, 10, 15, 20, 30, 45, 60, 90 and 120 minutes thereafter.</td><td></td><td>have been registered)</td></tr>
<tr><td>Full citation

Matsumura, Hideyoshi, Takagi, Kenjiro, Seki, Hiroyuki, Ono, Yoshihisa, Ichinose, Shunichiro, Masuko, Hiroko, Fukatsu, Mayumi,</td><td>Sample size
N = 18 women

Characteristics<table><tr><th>Characteristics (n = 18)</th><th></th></tr><tr><td>Maternal age, years, mean (range)</td><td>35 (25 - 42)</td></tr><tr><td>Primiparous</td><td>9/18 (50%)</td></tr></table></td><td>Interventions
Intravenous nicardipine infusion was started at a dose of 0.5mg/hr and increased by 0.5mg/hr until maternal systolic BP was <160mmHg and diastolic pressure was <110mmHg. The maximum</td><td>Details
Breast milk was obtained on postpartum days 2 to 7, whilst the mother was still on nicardipine infusion.
Nicardipine concentrations in plasma and breast milk were</td><td>Results
Nicardipine concentration in breast milk (n = 17) ranged from 2.26 to 37.55 ng/ml (mean ± SD 6.89 ± 8.28 ng/ml; median 4.68 ng/ml).
14/21 infants were admitted to the neonatal unit (67%)</td><td>Limitations
<u>Quality appraisal using the Institute of Health Economics checklist for Case Series</u>
Clear objectives: yes
Prospective: yes
Multicentre: no
Consecutive recruitment: unclear
Characteristics described: yes</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Miyashita, Aiji, Mera, Ayako, Placental transfer of intravenous nicardipine and disposition into breast milk during the control of hypertension in women with pre-eclampsia, Hypertension in Pregnancy, 33, 93-101, 2014 **Ref Id** 742909 **Country/ies where the study was carried out** Japan **Study type** Non-comparative case series.	<table><tr><td>Multiple pregnancy</td><td>3/18 (17.6%)</td></tr><tr><td>GA at start of nicardipine IV, mean (range)</td><td>32+3 weeks (27+6 to 35+3)</td></tr><tr><td>Systolic BP, mean (range)</td><td>166.2 mmHg (154 - 190)</td></tr><tr><td>Diastolic BP, mean (range)</td><td>100.5 mmHg (90 - 110)</td></tr><tr><td>GA at delivery, mean (range)</td><td>34+4 weeks (27+6 to 36+4)</td></tr></table> **Inclusion criteria** Women admitted to hospital for the management of severe preeclampsia (BP > 160/110 mmHg and >0.3g proteinuria in a 24 hour period, after 20 weeks gestation) and treated with intravenous nicardipine. **Exclusion criteria**	allowed dose was 80mg/day.	determined using a validated method of high performance liquid chromatography-tandem mass spectrometry. The lower limit of quantification was 0.1ng/ml.		Eligibility criteria defined: yes Did patients enter the study at a similar point in the disease: yes Intervention clearly described: yes Additional interventions clearly described: N/A Relevant outcomes established *a priori*: yes Outcome assessor blinding: no (no report of blinding) Appropriate methods for outcome assessment: yes Outcome measures before and after intervention: N/A Statistical analysis appropriate: yes (mean, SD and median levels reported) Follow up duration sufficient: unclear (milk levels taken on day two to seven, unclear if this

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To investigate the transfer of nicardipine into breast milk. **Study dates** 29 June 2011 until 1 October 2012. **Source of funding** Not reported.	Delivery prior to 22 weeks gestation, or at another institution. Fetus with life threatening severe anomaly or condition. Life threatening complications in the mother, or positive screen for hepatitis B or C or HIV.				represents steady state) Losses to follow up reported: no (reported as 17 sample of breast milk, although 18 women included in the study, and methods imply serial sample of milk were collected on days 2 until 7 postpartum) Estimates of random variability provided: no Adverse events reported: yes Conclusions supported by results: yes Competing interests/support reported: no
Full citation Michael, C. A., Use of labetalol in the treatment of severe hypertension	**Sample size** N = 25 women Characteristics Number of participants: 25	**Interventions** All participants were treated with a starting dose of 100mg labetalol orally three times per day. The	**Details** Breast milk samples were acquired three days post-partum, to ascertain the	**Results** Breast milk labetalol concentration on day 3 postpartum	**Limitations** Quality appraisal using the Institute of Health Economics checklist for Case Series

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>during pregnancy, British Journal of Clinical Pharmacology, 8, 211S-215S, 1979
Ref Id 392206
Country/ies where the study was carried out
Australia
Study type
Non-comparative c ase series.

Aim of the study
To evaluate the effectiveness of labetalol in patients with severe hypertensive disease in pregnancy.

Study dates
Not reported.</td>
<td>
<table>
<tr><td>Primigravidae</td><td>19</td></tr>
<tr><td>Age distribution</td><td>16 - 40 years</td></tr>
<tr><td>Multiple pregnancy</td><td>3</td></tr>
<tr><td>BP range (mmHg)</td><td>150/105 to 210/130</td></tr>
<tr><td>Proteinuria</td><td>18</td></tr>
<tr><td>Underlying renal disease</td><td>4*</td></tr>
<tr><td>Diabetes</td><td>1</td></tr>
</table>
* including n = 1 patient with diabetes

Inclusion criteria
Pregnant women with a BP of ≥ 150/105 mmHg, with or without proteinuria, where the fetus was immature, and where it was desirable and safe to prolong pregnancy.

Exclusion criteria
None reported.
</td>
<td>dose was increased at half-weekly intervals until adequate control of blood pressure was achieved (target diastolic BP of ≤90mmHg).</td>
<td>concentration of labetalol. No details were reported on the assay used. Levels were reported according to the maternal labetalol dose.</td>
<td>
<table>
<tr><th>Maternal labetalol dose (total daily dose, mg)</th><th>Number of women</th><th>Mean breast milk concentration (ng/ml)</th></tr>
<tr><td>330</td><td>4</td><td>29</td></tr>
<tr><td>400</td><td>11</td><td>27</td></tr>
<tr><td>600</td><td>6</td><td>39</td></tr>
<tr><td>700</td><td>2</td><td>46</td></tr>
<tr><td>800</td><td>1</td><td>43</td></tr>
<tr><td>1200</td><td>1</td><td>600</td></tr>
</table>
Neonatal hypotension (no definition provided)
Number of infants with hypotension: 1/27*
* note that the only infant with hypotension was delivered at 28 weeks by Caesarean section, and died on day 6 from "pulmonary consolidation"
</td>
<td>Clear objectives: yes

Prospective: yes

Multicentre: no

Consecutive recruitment: unclear

Characteristics described: yes

Eligibility criteria defined: partial (exclusion criteria not stated)

Did patients enter the study at a similar point in the disease: Unclear (gestational age not described)

Intervention clearly described: yes

Additional interventions clearly described: N/A

Relevant outcomes established a priori: yes</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Labetalol was provided by Allen and Hanburys (Australia).					Outcome assessor blinding: no (no report of blinding, single author) Appropriate methods for outcome assessment: unclear (no description of assay used for breast milk levels) Outcome measures before and after intervention: N/A Statistical analysis appropriate: unclear (mean values reported, no information on underlying distribution and small study) Follow up duration sufficient: unclear (milk levels taken on day three, unclear if this represents steady state)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					Losses to follow up reported: yes (no loss to follow up) Estimates of random variability provided: no Adverse events reported: yes Conclusions supported by results: yes Competing interests/support reported: yes
Full citation Naito, Takafumi, Kubono, Naoko, Deguchi, Shuhei, Sugihara, Masahisa, Itoh, Hiroaki, Kanayama, Naohiro, Kawakami, Junichi,	**Sample size** N=31 with pregnancy-induced hypertension (definition NR) **Characteristics** | | Median (IQR) | | --- | --- | | Age | 35 (31-37) | | Body weight post-delivery | 61.4 (53.9-66.4) | | sBP pre-treatment | 152 (146-162) | | dBP pre-treatment | 94 (89-100) |	**Interventions** Amlodipine 5 mg PO BID.	**Details** The study was conducted in a University Hospital. Milk sampling was performed at day 10 (IQR8-10) after starting the medication. The daily dose of amlodipine ingested by	**Results** Median of the predose milk concentrations 11.5ng/mL (IQR, 9.84-18.0 ng/mL) Daily dose of amlodipine in the infant via breast milk 4.17 μg/kg (IQR, 3.05-6.32 μg/kg). Plasma concentrations of amlodipine 15.5 ng/mL	**Limitations** Quality appraisal using the Institute of Health Economics checklist for Case Series Clear objectives: yes Prospective: yes Multicentre: no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Amlodipine passage into breast milk in lactating women with pregnancy-induced hypertension and its estimation of infant risk for breastfeeding, Journal of human lactation : official journal of International Lactation Consultant Association, 31, 301-6, 2015 **Ref Id** 742931 **Country/ies where the study was carried out** Japan	<table><tr><td>New-born birth weigh</td><td>2170 (1904-2635)</td></tr><tr><td>Serum albumin, g/L</td><td>26 (23-28)</td></tr></table> **Inclusion criteria** Not reported **Exclusion criteria** Women being co-treated with a macrolide antibiotic or rifampin; on hemodyalisis or peritoneal dialysis; women who had hepatopathy (total bilirubin > 2mg/dL).		new-borns was calculated by multiplying the amlodipine concentration in milk intake by the infant.		Consecutive recruitment: unclear Characteristics described: yes Eligibility criteria defined: partial (inclusion criteria not stated; definition of pregnancy-induced hypertension not stated) Did patients enter the study at a similar point in the disease: yes Intervention clearly described: yes Additional interventions clearly described: N/A Relevant outcomes established a priori: yes Outcome assessor blinding: no (no report of blinding)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Non-comparative case series **Aim of the study** To assess the concentrations of amlodipine in breast milk in women with pregnancy-induced hypertension and to estimate the risk on breastfeeding new-borns **Study dates** Not reported **Source of funding** JSPS KAKENHI					Appropriate methods for outcome assessment: yes Outcome measures before and after intervention: N/A Statistical analysis appropriate: yes Follow up duration sufficient: unclear (milk levels taken on day 10, unclear if this represents steady state) Losses to follow up reported: yes (no loss to follow up) Estimates of random variability provided: no Adverse events reported: no Conclusions supported by results: yes

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>Competing interests/support reported: yes</td></tr>
<tr><td>Full citation

Noronha Neto, C., Maia, S. S. B., Katz, L., Coutinho, I. C., Souza, A. R., Amorim, M. M., Clonidine versus captopril for severe postpartum hypertension: A randomized controlled trial, PLoS ONE, 12, e0168124, 2017
Ref Id 742947
Country/ies where the study was carried out
Brazil</td><td>Sample size

N = 88 postpartum women; n = 45 randomised to receive captopril; n = 43 randomised to receive clonidine

Characteristics
<table>
<tr><th></th><th>Clonidine n = 43</th><th>Captopril n = 45</th></tr>
<tr><td>Age (years), mean (SD)</td><td>28.9 (6.7)</td><td>28.8 (6.7)</td></tr>
<tr><td>Number of pregnancies, median (IQR)</td><td>2.0 (1.0 - 3.5)</td><td>2.0 (1.0 to 3.0)</td></tr>
<tr><td>Parity, median (IQR)</td><td>2.0 (1.0 to 2.0)</td><td>2.0 (1.0 to 3.5)</td></tr>
<tr><td>Gestational age (weeks), mean (SD)</td><td>34.1 (4.0)</td><td>35.0 (3.4)</td></tr>
<tr><td>Type of hypertensive disorder, number (%)</td><td></td><td></td></tr>
</table></td><td>Interventions

Women were randomised to receive either captopril (25 mg) or clonidine (0.1mg), to be administered whenever the woman suffered a very high blood pressure episode. Participants could receive a maximum of six doses per day of either drug (equating to 150mg/day of captopril, or 0.6mg/day clonidine). If the dose required exceeded the maximum daily dose then</td><td>Details

All participants included in the study were identified and admitted to the hospital's obstetric intensive care unit following delivery. All were given magnesium sulphate intravenously to prevent or control eclampsia, in accordance with local practice (a loading dose of 6g IV followed by 1-2g per hour IV for 24 hours). During</td><td>Results

Number of very high blood pressure episodes/day, mean (SD)
defined as systolic BP ≥ 180mmHg and/or diastolic BP ≥ 110mmHg
Clonidine (n = 43): 2.1 (2.1)
Captopril (n = 45): 3.5 (4.7)

Number of days until blood pressure control, mean (SD)
Clonidine: 4.1 (2.5)
Captopril: 3.5 (2.0)

Percentage reduction in systolic BP, mean (SD)
Clonidine: 14.0% (8.6)
Captopril: 10.8% (8.8)

Percentage reduction in diastolic BP, mean (SD)
Clonidine: 15.6% (9.7)
Captopril: 14.9% (9.1)</td><td>Limitations

<u>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias</u>

Random sequence generation: low risk (computer generated random numbers)

Allocation concealment: low risk (identical boxes prepared for study drug, numbered sequentially in accordance with the randomisation list)

Blinding of participants and personnel: low risk (investigators,</td></tr>
</table>

Study details	Participants			Interventions	Methods	Outcomes and Results			Comments
Study type RCT **Aim of the study** To determine the effectiveness of clonidine compared to captopril for treating severe postpartum hypertension **Study dates** November 2012 to June 2013. **Source of funding** Article reports that "The authors received no specific funding for this work".	Severe preeclampsia	27 (62.8)	31 (68.9)	another anti-hypertensive drug (nifedipine or hydralazine) was selected to treat further episodes. Sodium nitroprusside was used for women who continued to have very high blood pressure episodes even after other antihypertensive drugs were used.	use of magnesium sulphate, blood pressure was measured every two hours for the first 24 hours, then every six hours. Following confirmation of the first episode of very high blood pressure, the women was provided with information about the study. All women provided informed consent to participate. Randomisation was carried out according to a list prepared by a statistician, using the Random Allocation software	Mean blood pressure per hospitalisation day			participants and statistician reported to be blinded to group allocation) Blinding of outcome assessment: low risk (investigators blinded to group allocation) Blinding (performance bias and detection bias): low risk (see above details) Incomplete outcome data: low risk (outcome data missing for 2 participants only, due to inadvertent additional administration of a study drug to treat hypertension) Selective reporting: unclear risk (a published protocol was registered, but the primary outcome measure was altered
	Imminent eclampsia	4 (9.3)	6 (13.3)				Clonidine n = 43	Captopril n = 45	
	Superimposed preeclampsia	15 (34.8)	9 (20.0)			1st day			
	Eclampsia	3 (6.9)	3 (6.6)			Systolic BP (mmHg), mean (SD)	155.5 (14.6)	154.4 (16.2)	
	HELLP syndrome	8 (18.6)	11 (24.4)			Diastolic BP (mmHg), mean (SD)	99.7 (9.5)	97.1 (11.9)	
	Blood pressure at admission					2nd day			
	Systolic BP (mmHg), mean (SD)	156.7 (16.7)	161.2 (21.6)			Systolic BP (mmHg), mean (SD)	153.2 (12.2)	156.4 (14.4)	
	Diastolic BP (mmHg), mean (SD)	102.6 (12.0)	102.6 (16.1)			Diastolic BP (mmHg), mean (SD)	98.3 (8.6)	101.2 (12.4)	
	The National High Blood Pressure Education Program (2000) criteria were used to diagnose severe preeclampsia, superimposed preeclampsia and eclampsia. Inclusion criteria Postpartum women with a diagnosis of hypertensive disorders of pregnancy with very high blood pressure episodes†, and					3rd day			
						Systolic BP	151.9 (11.8)	158.1 (13.6)	

Study details	Participants	Interventions	Methods	Outcomes and Results			Comments
	requiring magnesium sulfate to prevent or treat eclampsia. † A very high blood pressure episode was defined as systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥110 mmHg Exclusion criteria Women with heart conditions, smokers, users of illicit drugs that could interfere with maternal haemodynamics, those with contraindications to the use of captopril (acute or chronic renal disease, chronic liver disease and hypersensitivity to the drug) contraindications to clonidine (sinus node disease, chronic liver disease and hypersensitivity to the drug), women unable to take oral medication and those who had used captopril or clonidine prior to admission.		program (Isphahan, Iran). Participants, investigators and statistician were blinded to the allocation. Sample size was calculated using the OpenEpi software program (Centers for Disease Control and Prevention, GA, USA). A pilot study was conducted with an initial sample of 30 postpartum women (15 in each group). The mean number of very high blood pressure episodes during hospitalisation in the obstetric	(mmHg), mean (SD)			between publication of the protocol and collection of outcome data)
				Diastolic BP (mmHg), mean (SD)	99.3 (9.0)	100.6 (8.6)	
				4th day			
				Systolic BP (mmHg), mean (SD)	151.3 (13.3)	154.3 (13.8)	
				Diastolic BP (mmHg), mean (SD)	98.9 (9.1)	100.2 (10.0)	

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td>ICU (2.8 ± 2.0 in the clonidine group; 6.2 ± 6.2 in the captopril group) was used to calculate sample size. For a power of 90% and a 95% confidence level (2 sided t-test), 78 patients were required.</td><td></td><td></td></tr>
<tr><td>Full citation

Sharma, Kj, Greene, N, Kilpatrick, Sj, Oral labetalol compared to oral nifedipine for postpartum hypertension: a randomized controlled trial, Hypertension in pregnancy, 36, 44-47, 2017

Ref Id</td><td>Sample size

N=50, n=25 women randomised to the labetalol group and n=25 women randomised to the nifedipine group

Characteristics<table><tr><td></td><td>Labetalol</td><td>Nifedipine</td></tr><tr><td>Maternal age</td><td>34</td><td>33.3</td></tr><tr><td>Twin pregnancy</td><td>3 (12%)</td><td>2 (8%)</td></tr><tr><td>Primiparous</td><td>9 (36%)</td><td>9 (36%)</td></tr></table></td><td>Interventions

Labetalol was started at 200mg PO BID and increased up to 800mg PO BID as needed to control blood pressure, nidefipine as started at 30 mg PO daily then increased up to 90mg PO daily as needed to control blood pressure,</td><td>Details

Participants were randomised using a computerised random number generator, group allocations were kept in a sealed, opaque envelope. Neither women nor the medical team were blinded to the</td><td>Results

Mean hours (SD) to control blood pressure
Labetalol = 37.6 (32.5)
Nifedipine= 38.2 (27.6)
Required additional oral agent for control blood pressure
Labetalol 3/25
Nifedipine 2/25
Required additional IV medication for control blood pressure
Labetalol 6/25
Nifedipine 9/25
Blood pressure control post-discharge - mean mmHG (SD)</td><td>Limitations

<u>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias</u>

Random sequence generation: Low risk (randomisation was performed using a computerised random number generator)

Allocation concealment: Low</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
755792 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To assess the efficacy of labetalol as compared to nifedipine for blood pressure control in postpartum women **Study dates** June 2014 to June 2015 **Source of funding**	Multiparous 3 (12%) 4 (16%) Gestational diabetes 2(8%) 3 (12%) **Inclusion criteria** Women who delivered at ≥ 32 weeks gestational age with persistent postpartum hypertension (sustained blood pressure ≥ 150/100 mmHg) requiring an oral antihypertensive agent. These women could present wit gestational hypertension, preeclapsia, or chronic hypertension, but should have never been previously medicated for a hypertensive disorder. **Exclusion criteria** Those with heart block; heart rate < 60 or > 120 beats per minute, contraindication to nifedipine or labetalol, significant renal disease (creatinine > 1.5 mg/dL), heart failure, or moderate/severe asthma.	If maximum dose of a given medication was reached without achieving blood pressure control, it was at the discretion of the treating medical team to use additional treatments to achieve blood pressure control - this could be concomitant IV antihypertensive medication or magnesium sulphate for seizure prophylaxis.	assigned treatment. 3 (12%) in the labetalol group and 2(8%) in the nifedipine group required additional oral agent to control blood pressure and 6 (24%) and 9 (36%) required additional IV medication for control of blood pressure	Systolic / Diastolic 72 h / 72 h Labetalol 140 (15) 89(4) Nifedipine 141 (27) 87 (13) 1-2 w / 1 - 2 w Labetalol 129 (15) 80 (10) Nidedipine 124 (10) 81 (6) 4-6 w / 4 -6 w Labetalol 119 (9) 76 (10) Nifedipine 127 (14) 80 (8)	risk (group assignments were kept inside sequentially numbers, sealed opaque envelopes) Blinding of participants and personnel: High risk ("neither patients nor their providers were blinded to the assigned study drug") Blinding of outcome assessment: high risk (open label) Blinding (performance bias and detection bias): high risk (see above details) Incomplete outcome data: low risk (ITT analysis, all drops outs clearly accounted for) Selective reporting: low risk (all pre-specified outcomes

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported					have been reported, protocol was registered)
Full citation Sioufi, A., Hillion, D., Lumbroso, P., Wainer, R., Olivier-Martin, M., Schoeller, J. P., Colussi, D., Leroux, F., Mangoni, P., Oxprenolol placental transfer, plasma concentrations in newborns and passage into breast milk, British Journal of Clinical Pharmacology, 18, 453-6, 1984 **Ref Id** 659223	**Sample size** N = 32 pregnant women Breast milk samples obtained in n = 9 women Characteristics Not reported fully. Participants aged between 18 and 34 years. n = 20 with type I hypertension n = 3 with type II hypertension n = 2 with type III hypertension n = 7 with type IV hypertension **Inclusion criteria** Pregnant women undergoing treatment with oxprenolol. **Exclusion criteria** Not reported.	**Interventions** All women were treated with Trasipressol (80mg oxprenolol hydrochloride and 25mg of dihydralazine sulphate) three times per day.	**Details** Maternal milk was collected between days three and six postpartum. Samples were stored at -20°C until analysis. Oxprenolol concentrations were determined by chromatography according to a method described for assays in plasma. The limit of quantitation was 33nmol/l.	**Results** Oxprenolol concentration in milk (n = 9 samples) Range 0 to 1342 nmol/l (mean ± SD: 387 nmol/l ± 426) Neonatal hypoglycaemia during first 24 hours (glucose ≤ 1.6 mmol/l) Number of infants with hypoglycaemia: 5/32* *denominator presumed to be 32 infants, but not clearly reported	**Limitations** Quality appraisal using the Institute of Health Economics checklist for Case Series Clear objectives: yes Prospective: yes Multicentre: no Consecutive recruitment: unclear Characteristics described: partial Eligibility criteria defined: partial (exclusion criteria not stated) Did patients enter the study at a similar point in the disease:

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out France **Study type** Non-comparative case series. **Aim of the study** To obtain some information about the placental transfer of oxprenolol and its passage into breast milk of hypertensive women. **Study dates** Not reported.					Unclear (gestational age not described) Intervention clearly described: yes Additional interventions clearly described: N/A Relevant outcomes established a priori: yes Outcome assessor blinding: no (no report of blinding) Appropriate methods for outcome assessment: yes (details provided regarding assay used and accuracy data) Outcome measures before and after intervention: N/A Statistical analysis appropriate: yes (range and mean values reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported.					Follow up duration sufficient: unclear (milk levels taken on day three to six, unclear if this represents steady state) Losses to follow up reported: no (n = 32 participants, but only n = 9 breast milk samples. No information provided on this discrepancy) Estimates of random variability provided: no Adverse events reported: yes Conclusions supported by results: yes Competing interests/support reported: no

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Thorley, K. J., McAinsh, J., Levels of the beta-blockers atenolol and propranolol in the breast milk of women treated for hypertension in pregnancy, Biopharmaceutics & drug disposition, 4, 299-301, 1983 **Ref Id** 743049 **Country/ies where the study was carried out** UK **Study type** Cross sectional	**Sample size** N= 10 women, n=5 receiving atenolol and n=5 receiving propranolol **Characteristics** Not reported **Inclusion criteria** Not reported **Exclusion criteria** Not reported	**Interventions** Atenolol 100 mg po x 1 per day Propranolol 40 mg po x 2 per day	**Details** Samples of breast milk were obtained 2 hours after the morning dose. Atenolol concentrations were measured by the "gas-liquid chromatographic method of Scales and Copsey" and samples of propranolol were measured by the "gas-liquid chromatographic method of McAinsh"	**Results** The mean (SD) of the pH of the milk was 7.54 (0.19) <u>Milk concentrations of atenolol 2 hours after dose. Mean (SD)</u> 2 hours after dose: 630 (271) ng ml-1 <u>Milk concentrations of propranolol 2 hours after dose. Mean (SD)</u> 2 hours after dose: 27 (11) ng ml-1 Estimated intake of 0.3 mg of atenolol and 0.01 mg of propranolol for 500 ml of milk/ day. No adverse events on new-borns were studied	**Limitations** <u>Study limitation assessed with the Newcastle-Ottowa scale for case-control studies</u> Selection Is the case definition adequate?: c)no description (definition for ´hypertension during pregnancy´ was not reported) Representativeness of the cases: c) potential for selection biases Selection of controls: hospital controls Description of controls: no description of sources <u>Comparability</u> Comparability of the cases and controls on the basis of the

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the levels of atenolol and propranolol in the breast milk of women treated for hypertension during the puerperium **Study dates** Not reported **Source of funding** Not reported					design or analysis: no confounding factors were controlled for <u>Exposure</u> 1.Ascertainment of exposure: written self report or medical record only 2. Same method of ascertainment for cases and controls: yes* 3. non response rate: rate difference and no designation
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**
Vigil-De Gracia, P., Ruiz, E., Lopez, J. C., De Jaramillo, I. A., Vega-	N= 82, n=42 randomised to hydralazine and n= 40 randomised to labetalol Characteristics	Hydralazine IV 5 mg every 20 minutes to a maximum of 5 dosages.	BP was measured using standard mercury sphygmomanometers with	Total number of women with severe persistent hypertension post-treatment Hydralazine group= 0/42 Labetalol group= 1/40	<u>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias</u>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Maleck, J. C., Pinzon, J., Management of severe hypertension in the postpartum period with intravenous hydralazine or labetalol: A randomized clinical trial, Hypertension in Pregnancy, 26, 163-171, 2007 **Ref Id** 742803 **Country/ies where the study was carried out** Panama **Study type** RCT	<table><tr><td></td><td>Hydralazine</td><td>Labetalol</td></tr><tr><td>Age (years)</td><td>29.9 ± 5.9</td><td>31.3 ± 5.5</td></tr><tr><td>Severe preeclampsia * n (%)</td><td>26 (61.9)</td><td>25 (62.5)</td></tr><tr><td>Gestational hypertension * n (%)</td><td>8 (19)</td><td>3 (7.5)</td></tr><tr><td>Superimposed preeclampsia *</td><td>6 (14.2)</td><td>8 (20)</td></tr><tr><td>Chronic hypertension *</td><td>2 (4.7)</td><td>4 (10)</td></tr><tr><td>SBP mm Hg (mean)</td><td>162 ± 9.4</td><td>165 ± 8</td></tr><tr><td>DBP mm Hg (mean)</td><td>104 ± 9</td><td>102 ± 9</td></tr><tr><td>MBP mm Hg (mean)</td><td>123 ± 6.4</td><td>123 ±6.6</td></tr></table>*severe preeclampsia was defined as BP ≥ 140 Hg or dBP ≥ 90 mm Hg and proteinuria defined as urinary excretion of 0.3 g protein in a 24 hour - urine specimen with one of the following: headache, visual disturbances, epigastric pain, oliguria,	Labetalol IV 20 mg, followed by 40 mg if not effective within 20 minutes, followed by 80 mg every 20 minutes if not effective to a maximum dose of 300 mg. Treatment goal: dBP< 110 mm Hg and sBP < 160 mm Hg	cuffs. The 1st (for systolic) and 5th (for diastolic) Korotkoff sounds were recorded.		Random sequence generation: unclear risk (randomisation method not reported) Allocation concealment: Unclear risk (no details reported if any form of allocation concealment was used) Blinding of participants and personnel: High risk ("the study was not blinded") Blinding of outcome assessors: High risk ("the study was not blinded") Blinding (performance bias and detection bias): high risk (see above details) Incomplete outcome data: low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the efficacy of IV hydralazine and IV labetalol for controlling blood pressure in postpartum women **Study dates** Not reported **Source of funding** Not reported	HELLP, pulmonary edema.. For gestational hypertension, the diagnosis included hypertension with urinary excretion < 0.3 g protein in a 24-hour urine specimen. Chronic hypertension was defined as one of the following: 1) hypertension that is present before pregnancy sBP ≥ 140 mm Hg or dBP ≥ 90 mm Hg 2) BP elevations of at least 140/90 mm Hg before the 20th week GA without previous history of known hypertension. **Inclusion criteria** Systolic BP ≥ 160 mm Hg or diastolic BP ≥ 160/110 mm Hg; to have received the treatment more than 24 hours before the start of the study; not on other antihypertensive medications; no contraindications to labetalol or hydralazine. **Exclusion criteria** Not reported				Selective reporting: low risk

Appendix E – Forest plots

Not applicable for this review question.

Appendix F – GRADE tables

Table 5: Clinical evidence profile. Comparison 1: beta blockers / mixed alpha-beta blockers versus centrally acting α2-adrenoceptor agonists

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Timolol	Methyldopa	Relative (95% CI)	Absolute		
Systolic blood pressure - Day 1 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	40	-	MD 4.5 lower (5.34 to 3.66 lower)	LOW	CRITICAL
Diastolic blood pressure - Day 1 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	39	40	-	MD 5.1 lower (5.76 to 4.44 lower)	LOW	CRITICAL
Systolic blood pressure - Day 2 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	33	35	-	MD 0.7 lower (1.71 lower to 0.31 higher)	VERY LOW	CRITICAL
Diastolic blood pressure - Day 2 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	33	35	-	MD 0.5 lower (1.22 lower to 0.22 higher)	VERY LOW	CRITICAL
Systolic blood pressure - Day 3 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	27	28	-	MD 1.6 lower (3.05 to 0.15 lower)	VERY LOW	CRITICAL
Diastolic blood pressure - Day 3 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	27	28	-	MD 0.7 lower (1.72 lower to 0.32 higher)	VERY LOW	CRITICAL
Systolic blood pressure - Day 4 (Better indicated by lower values)												

Quality assessment							Number of patients		Effect		Quality	Importance
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	21	25	-	MD 0.5 lower (1.98 lower to 0.98 higher)	VERY LOW	CRITICAL
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Timolol**	**Methyldopa**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Diastolic blood pressure - Day 4 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	21	25	-	MD 3.8 lower (5 to 2.6 lower)	LOW	CRITICAL
Systolic blood pressure - Day 5 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	13	22	-	MD 1.9 higher (0.9 lower to 4.7 higher)	VERY LOW	CRITICAL
Diastolic blood pressure - Day 5 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[5]	none	13	22	-	MD 0.9 higher (0.92 lower to 2.72 higher)	VERY LOW	CRITICAL
Systolic blood pressure - Day 6 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	10	13	-	MD 0.7 higher (3.15 lower to 4.55 higher)	VERY LOW	CRITICAL
Diastolic blood pressure - Day 6 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	10	13	-	MD 2.6 lower (5.53 lower to 0.33 higher)	VERY LOW	CRITICAL
Systolic blood pressure - Day 7 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6	8	-	MD 14 higher (8.72 to 19.28 higher)	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Diastolic blood pressure - Day 7 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6	8	-	MD 9.7 higher (5.77 to 13.63 higher)	LOW	CRITICAL
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other cosiderations**	**Timolol**	**Methyldopa**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Systolic blood pressure - Day 8 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	4	8	-	MD 3.2 higher (5.15 lower to 11.55 higher)	VERY LOW	CRITICAL
Diastolic blood pressure - Day 8 (Better indicated by lower values)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	4	8	-	MD 6.6 higher (3.6 to 9.6 higher)	LOW	CRITICAL
Women with blood pressure controlled[a] by day 1 (starting dose)												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	30/40 (75%)	23/40 (57.5%)	RR 1.30 (0.95 to 1.8)	172 more per 1000 (from 29 fewer to 460 more)	VERY LOW	CRITICAL
Women with blood pressure controlled[a] by day 2 (starting dose/first dose escalation)[a]												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	35/40 (87.5%)	39/40 (97.5%)	RR 0.90 (0.79 to 1.02)	98 fewer per 1000 (from 205 fewer to 19 more)	VERY LOW	CRITICAL
Women with blood pressure controlled[a] by day 3 (starting dose/first or second dose escalation)												

Quality assessment							Number of patients		Effect		Quality	Importance
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious	none	37/40 (92.5%)	39/40 (97.5%)	RR 0.95 (0.86 to 1.05)	49 fewer per 1000 (from 136 fewer to 49 more)	LOW	CRITICAL
Women in whom treatment did not control blood pressure												
1 (Fidler 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[8]	none	3/40 (7.5%)	1/40 (2.5%)	RR 3.00 (0.33 to 27.63)	50 more per 1000 (from 17 fewer to 666 more)	VERY LOW	CRITICAL
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Propranolol**	**Methyldopa**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Arterial pressure difference between groups during treatment (Better indicated by lower values)												
1 (Livingstone 1983)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[10]	none	14	14	-	MD 1.60 lower (7.78 lower to 4.58 higher)	VERY LOW	CRITICAL
Neonatal complications - Hypoglycaemia												
1 (Livingstone 1983)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	very serious[8]	none	2/14 (14.3%)	0/14 (0%)	RR 5.00 (0.26 to 95.61)	not calculable[11]	VERY LOW	CRITICAL
Neonatal complications - Bradycardia												
1 (Livingstone 1983)	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/14 (0%)	0/14 (0%)	not estimable [12]	not calculable[13]	MODERATE	CRITICAL

[a] *Target blood pressure was dBP ≤ 95 mmHg*

[1] *The quality of the evidence was downgraded by 2 levels due to an unclear risk of bias in random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors and a high risk of sponsorship bias*

[2] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (+/-0.5 x 1.9= 0.95)*

[3] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (+/-0.5 x 0.8 = +/- 0.4)*

[4] *The quality of the evidence was downgrade by 2 levels as the 95% CI crossed 2 default MID thresholds (+/- 0.5 X 1.9=+/-0.95)*

[5] *The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (+/-0.5 x 0.8= +/-0.4)*

[6] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default default MID threshold (1.25)*

[7] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default default MID threshold (0.8)*

[8]*The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)*
[9]*The quality of the evidence was downgraded by 1 level due to an unclear risk of bias in random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors; unclear isk of incomplete outcome data and unclear risk of selective reporting*
[10]*The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (+/- 0.5 x 6.8=+/-3.4)*
[11]*The corresponding absolute risk was not calculated as no events were reported in the control arm*
[12]*The corresponding relative risk was not estimable as no events were reported in the intervention or treatment arms*
[13]*The corresponding absolute risk was not calculated as no events were reported in the intervention or treatment arms*

Table 6: Clinical evidence profile. Comparison 2: beta blockers versus beta blockers. 2.1 atenolol versus metoprolol

Study	Milk concentrations of atenolol mean (SD)	Milk concentrations of metoprolol mean (SD)	Effect on new-borns	Number of participants (studies)	Risk of bias (The Newcastle-Ottawa Scale)	Importance
Kulas 1984	0 hours after dose (left breast): 1386.66 (555.81) nmol/l	0 hours after dose (left breast): Not reported	No adverse outcomes on new-borns were studied	7 (1 study)	VERY LOW[1]	CRITICAL
Kulas 1984	0 hours after dose (right breast): 1750 (809.03) nmol/l	0 hours after dose (right breast): Not reported	No adverse outcomes on new-borns were studied	7 (1 study)	VERY LOW[1]	CRITICAL
Kulas 1984	4 hours after dose (left breast): 5532.50 (1752.68) nmol/l	4 hours after dose (left breast): 271.66 (18.03) nmol/l	No adverse outcomes on new-borns were studied	7 (1 study)	VERY LOW[1]	CRITICAL
Kulas 1984	4 hours after dose (right breast): 3990 (1841.77) nmol/l	4 hours after dose (right breast): 320 (2.82) nmol/l	No adverse outcomes on new-borns were studied	7 (1 study)	VERY LOW[1]	CRITICAL
Kulas 1984	8 hours after dose (left breast): 4107.50 (932.28) nmol/l	8 hours after dose (left breast): 82 (49.78) nmol/l	No adverse outcomes on new-borns were studied	7 (1 study)	VERY LOW[1]	CRITICAL
Kulas 1984	8 hours after dose (right breast): 3720 (113.13) nmol/l	8 hours after dose (right breast): 84 (15.62) nmol/l	No adverse outcomes on new-borns were studied	7 (1 study)	VERY LOW[1]	CRITICAL

Study	Milk concentrations of atenolol mean (SD)	Milk concentrations of metoprolol mean (SD)	Effect on new-borns	Number of participants (studies)	Risk of bias (The Newcastle-Ottawa Scale)	Importance
Liedholm 1981	Maximum concentration recorded: 6.35 µmol	Maximum concentration recorded: 2.58 µmol	Estimated intake of 0.13mg of atenolol and 0.05 mg of metoprolol for 75 ml of milk	10 (1 study)	VERY LOW[2]	CRITICAL

[1]The quality of the evidence was considered very low due to the following factors: no definition of hypertension was provided, the study did not control for confounding factors, the ascertainment of exposure was obtained from self-reports or medical records and the response rate was different between groups.
[2] The quality of the evidence was considered very low due to the following factors: no definition of hypertension was provided, controls consisted of healthy women who agreed to take metoprolol four months after having given birth, study did not control for confounding factors and ascertainment of exposure was obtained from self-reports or medical records.

Table 7: Clinical evidence profile. Comparison 2: beta blockers versus beta blockers. 2.2 atenolol versus propranolol

Study	Milk concentrations of atenolol Mean (SD)	Milk concentrations of propranolol Mean (SD)	Effects on new-born	Number of participants (studies)	Risk of bias (The Newcastle-Ottowa Scale)	Importance
Thorley 1983	2 hours after dose: 630 (271) ng ml^{-1}	2 hours after dose: 27 (11) ng ml^{-1}	Estimated intake of 0.3 mg of atenolol and 0.01 mg of propranolol for 500 ml of milk/ day No adverse outcomes on new-borns were studied	10 (1 study)	VERY LOW[1]	CRITICAL

[1] The quality of the evidence was considered very low due to the following: no definition of hypertension was provided, the study did not control for confounding factors and the ascertainment of exposure was obtained from self-reports or medical records

Table 8: Clinical evidence profile. Comparison 3: beta blockers/mixed alpha-beta blockers versus placebo

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atenolol	Placebo	Relative (95% CI)	Absolute	Quality	Importance
Hypoglycaemic events in the new-born - 1st hour												
1 (Darcie 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	17/33 (51.5%)	2/13 (15.4%)	RR 3.35 (0.9 to 12.5)	362 more per 1000 (from 15 fewer to 1000 more)	LOW	CRITICAL
Hypoglycaemic events in the new-born - 3rd hour												
1 (Darcie 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	10/33 (30.3%)	1/13 (7.7%)	RR 3.94 (0.56 to 27.77)	226 more per 1000 (from 34 fewer to 1000 more)	VERY LOW	CRITICAL
Hypoglycaemic events in the new-born - 6th hour												
1 (Darcie 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/33 (24.2%)	1/13 (7.7%)	RR 3.15 (0.44 to 22.76)	165 more per 1000 (from 43 fewer to 1000 more)	VERY LOW	CRITICAL
Hypoglycaemic events in the new-born - 12th hour												
1 (Darcie 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	6/33 (18.2%)	2/13 (15.4%)	RR 1.18 (0.27 to 5.12)	28 more per 1000 (from 112 fewer to 634 more)	VERY LOW	CRITICAL
Hypoglycaemic events in the new-born - 24th hour												
1 (Darcie 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/33 (9.1%)	1/13 (7.7%)	RR 1.18 (0.13 to 10.35)	14 more per 1000 (from 67 fewer to 719 more)	VERY LOW	CRITICAL

[1] The quality of the evidence was downgraded by 1 level due to an unclear risk of bias in random sequence generation, allocation concealment and blinding of participants, personnel and outcome assessors
[2] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (1.25)
[3] The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)

Table 9: Clinical evidence profile. Comparison 4: centrally acting α2-adrenoceptor agonists versus ACE inhibitors

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clonidine	Captopril	Relative (95% CI)	Absolute	Quality	Importance
Number of very high blood pressure episodes per day (Better indicated by lower values)												
1 (Noronha- Neto 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	43	45	-	MD 1.40 lower (2.91 lower to 0.11 higher)	VERY LOW	CRITICAL
Percentage reduction in systolic blood pressure (Better indicated by lower values)												
1 (Noronha-Neto 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	43	45	-	MD 3.20 higher (0.44 lower to 6.84 higher)	VERY LOW	CRITICAL
Percentage reduction in diastolic blood pressure (Better indicated by lower values)												
1 (Noronha- Neto 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	43	45	-	MD 0.70 higher (3.23 lower to 4.63 higher)	VERY LOW	CRITICAL
Number of days until blood pressure control (Better indicated by lower values)												
1 (Noronh	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	43	45	-	MD 0.60 higher (0.35 lower	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clonidine	Captopril	Relative (95% CI)	Absolute		
a- Neto 2017)										to 1.55 higher)		
Systolic blood pressure - Day 1 (Better indicated by lower values)												
1 (Noronha- Neto 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43	45	-	MD 1.1 higher (5.34 lower to 7.54 higher)	LOW	CRITICAL
Diastolic blood pressure - Day 1 (Better indicated by lower values)												
1 (Noronha- Neto 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43	45	-	MD 2.6 higher (1.89 lower to 7.09 higher)	LOW	CRITICAL
Systolic blood pressure - Day 2 (Better indicated by lower values)												
1 (Noronha- Neto 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43	45	-	MD 3.20 lower (8.77 lower to 2.37 higher)	LOW	CRITICAL
Diastolic blood pressure - Day 2 (Better indicated by lower values)												
1 (Noronha- Neto 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43	45	-	MD 2.9 lower (7.34 lower to 1.54 higher)	LOW	CRITICAL
Systolic blood pressure - Day 3 (Better indicated by lower values)												
1 (Noronh	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	43	45	-	MD 6.2 lower	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clonidine	Captopril	Relative (95% CI)	Absolute		
a-Neto 2017)										(11.51 to 0.89 lower)		
Diastolic blood pressure- Day 3 (Better indicated by lower values)												
1 (Noronha- Neto 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43	45	-	MD 1.3 lower (4.98 lower to 2.38 higher)	LOW	CRITICAL
Systolic blood pressure - Day 4 (Better indicated by lower values)												
1 (Noronha- Neto 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43	45	-	MD 3 lower (8.66 lower to 2.66 higher)	LOW	CRITICAL
Diastolic blood pressure - Day 4 (Better indicated by lower values)												
1 (Noronha- Neto 2017)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	43	45	-	MD 1.3 lower (5.29 lower to 2.69 higher)	LOW	CRITICAL

[1] The quality of the evidence was downgraded by 2 levels due to an unclear risk of bias in random sequence generation, and unclear allocation concealment. The study was not blinded for participants, personnel and outcome assessors.
[2] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (+/- 0.5 x 4.7 =+/-2.35)
[3] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (+/- 0.5 x 8.8= +/-4.40)
[4] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (9.1 x +/- 0.5 = +/-4.55)
[5] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (+/-0.5 x 2 = +/- 1)
[6] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (+/- 0.5 x 21.6= +/-10.8)

Table 10: Clinical evidence profile. Comparison 5: calcium channel blockers versus placebo/ low sodium diet

Quality assessment							Number of patients		Effect			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nifedipine**	**Placebo**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
MAP during the 18 to 24 hours after delivery (Better indicated by lower values)												
1 (Barton 1990)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	16	15	-	MD 6.30 lower (7.83 to 4.77 lower)	MODERATE	CRITICAL
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Isradipine**	**Low sodium diet**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Hypoglycaemic events in the new-born - 1st hour												
1 (Darcie 2004)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	15/37 (40.5%)	2/13 (15.4%)	RR 2.64 (0.69 to 10)	252 more per 1000 (from 48 fewer to 1000 more)	VERY LOW	CRITICAL
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Isradipine**	**Low sodium diet**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Hypoglycaemic events in the new-born - 3rd hour												
1 (Darcie 2004)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	8/37 (21.6%)	1/13 (7.7%)	RR 2.81 (0.39 to 20.37)	139 more per 1000 (from 47 fewer to 1000 more)	VERY LOW	CRITICAL
Hypoglycaemic events in the new-born - 6th hour												
1 (Darcie 2004)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/37 (13.5%)	1/13 (7.7%)	RR 1.76 (0.23 to 13.67)	58 more per 1000 (from 59 fewer to	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect			
										975 more)		
Hypoglycaemic events in the new-born - 12th hour												
1 (Darcie 2004)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	3/37 (8.1%)	2/13 (15.4%)	RR 0.53 (0.10 to 2.81)	72 fewer per 1000 (from 138 fewer to 278 more)	VERY LOW	CRITICAL
Hypoglycaemic events in the new-born - 24th hour												
1 (Darcie 2004)	randomised trials	very serious[2]	no serious inconsistency	no serious indirectness	very serious[3]	none	5/37 (13.5%)	1/13 (7.7%)	RR 1.76 (0.23 to 13.67)	58 more per 1000 (from 59 fewer to 975 more)	VERY LOW	CRITICAL

[1] The quality of the evidence was downgraded by 1 level due to an unclear risk of bias in allocation concealment, no information was provided for drop-outs and a high risk of selective reporting of data
[2] The quality of the evidence was downgraded by 2 levels due to an unclear risk of bias in random sequence generation, allocation concealment and an unclear risk of blinding of participants, personnel and outcome assessors. No details regarding drop-out data were reported and there was an unclear risk of selective reporting
[3] The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)

Table 11: Clinical evidence profile. Comparison 6: calcium channel blockers versus beta blockers

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nifedipine**	**Labetalol**	**Relative (95% CI)**	**Absolute**		
Time elapsed to reach blood pressure control, hours (<=160/105 for at least 12h) (hours) (Better indicated by lower values)												

Quality assessment							Number of patients		Effect		Quality	Importance
1 (Sharma 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	25	-	MD 0.60 higher (16.11 lower to 17.13 higher)	LOW	CRITICAL
Systolic blood pressure at 72h, mmHg (Better indicated by lower values)												
1 (Sharma 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	25	25	-	MD 1 higher (1.11 lower to 13.11 higher)	LOW	CRITICAL
Diastolic blood pressure at 72h, mmHg (Better indicated by lower values)												
1 (Sharma 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	25	25	-	MD 2 lower (7.33 lower to 3.33 higher)	VERY LOW	CRITICAL
Systolic blood pressure at 1-2 weeks (Better indicated by lower values)												
1 (Sharma 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	25	25	-	MD 5 lower (12.07 lower to 2.07 higher)	LOW	CRITICAL
Diastolic blood pressure at 1-2 weeks (Better indicated by lower values)												
1 (Sharma 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	25	25	-	MD 1 higher (3.57 lower to 5.57 higher)	LOW	CRITICAL
Systolic blood pressure at 4-6 weeks (Better indicated by lower values)												
1 (Sharma 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[7]	none	25	25	-	MD 8 higher (1.68 lower to 14.32 higher)	LOW	CRITICAL
Diastolic blood pressure at 4-6 weeks (Better indicated by lower values)												
1 (Sharma 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[8]	none	25	25	-	MD 4 higher (1.02 lower to 9.02 higher)	LOW	CRITICAL
Required additional IV medication for control of blood pressure												
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Nifedipine**	**Labetalol**	**Relative (95% CI)**	**Absolute**		

Quality assessment							Number of patients		Effect		Quality	Importance
1 (Sharma 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[9]	none	9/25 (36%)	6/25 (24%)	RR 1.5 (0.63 to 3.59)	120 more per 1000 (from 89 fewer to 622 more)	VERY LOW	CRITICAL
Required additional oral agent for control of blood pressure												
1 (Sharma 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[9]	none	2/25 (8%)	3/25 (12%)	RR 0.67 (0.12 to 3.65)	40 fewer per 1000 (from 106 fewer to 318 more)	VERY LOW	CRITICAL
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Isradipine**	**Atenolol**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Hypoglycaemic events in the new-born - 1st hour												
1 (Darcie 2004)	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	very serious[9]	none	15/37 (40.5%)	17/33 (51.5%)	RR 0.79 (0.47 to 1.31)	108 fewer per 1000 (from 273 fewer to 160 more)	VERY LOW	CRITICAL
Hypoglycaemic events in the new-born - 3rd hour												
1 (Darcie 2004)	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	very serious[9]	none	8/37 (21.6%)	10/33 (30.3%)	RR 0.71 (0.32 to 1.59)	88 fewer per 1000 (from 206 fewer to 179 more)	VERY LOW	CRITICAL
Hypoglycaemic events in the new-born - 6th hour												
1 (Darcie 2004)	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	very serious[9]	none	5/37 (13.5%)	8/33 (24.2%)	RR 0.56 (0.2 to 1.54)	107 fewer per 1000 (from 194 fewer to 131 more)	VERY LOW	CRITICAL
Hypoglycaemic events in the new-born - 12th hour												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Isradipine	Atenolol	Relative (95% CI)	Absolute	Quality	Importance
1 (Darcie 2004)	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	very serious[9]	none	3/37 (8.1%)	6/33 (18.2%)	RR 0.45 (0.12 to 1.64)	100 fewer per 1000 (from 160 fewer to 116 more)	VERY LOW	CRITICAL
Hypoglycaemic events in the new-born - 24th hour												
1 (Darcie 2004)	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	very serious[9]	none	5/37 (13.5%)	3/33 (9.1%)	RR 1.49 (0.38 to 5.75)	45 more per 1000 (from 56 fewer to 432 more)	VERY LOW	CRITICAL

[1] *The quality of the evidence was downgraded by 1 level as this was an open label trial*
[2] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (32.5 x +/- 0.5 = +/- 16.25)*
[3] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (15 x +/-0.5= +/- 7.5)*
[4] *The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (4 x +/- 0.5 = +/-2)*
[5] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (15 x +/- 0.5= +/-7.5)*
[6] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (10 x +/- 0.5 = +/-5)*
[7] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (8 x +/- 0.5= +/4)*
[8] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (10 x +/- 0.5 = +/-5)*
[9] *The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)*
[10] *The quality of the evidence was downgraded by two levels due to an unclear risk of bias in random sequence generation, allocation concealment, blinding of participants, personnel and outcome assessors, incomplete outcome data and selective reporting*

Table 12: Clinical evidence profile. Comparison 7: diuretics versus placebo/no intervention

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Furosemide	No intervention	Relative (95% CI)	Absolute		
Systolic blood pressure on day 2 postpartum (Better indicated by lower values)												
1 (Ascarelli 2005)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	132	132	-	MD 11 lower (14.93 to 7.07 lower)[a]	VERY LOW	CRITICAL

a Blood pressure was not reported for other time points
[1] The quality of the evidence was downgraded by 2 levels due to an unclear risk of bias in random sequence generation, blinding of participants, personnel and outcome assessors, incomplete outcome data, and a high risk of selective reporting
[2] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (19 x +/- 0.5= +/- 8.5)

Table 13: Clinical evidence profile. Comparison 8: vasodilators versus beta blockers / mixed alpha-beta blockers

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydralazine	Labetalol	Relative (95% CI)	Absolute		
Mean arterial blood pressure (Better indicated by lower values)												
1 (Mabie 1987)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	20	40	-	MD 7.8 lower (14.55 to 1.05 lower)	LOW	CRITICAL
Total number of women with severe persistent hypertension post-treatment[a]												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydralazine	Labetalol	Relative (95% CI)	Absolute		
1 (Vigil-de Gracia 2007)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	0/42 (0%)	1/40 (2.5%)	RR 0.32 (0.01 to 7.58)	17 fewer per 1000 (from 25 fewer to 164 more)	VERY LOW	CRITICAL
Time (minutes) to maximal decrease in blood pressure (Better indicated by lower values)												
1 (Mabie 1987)	randomised trials	serious[1]	no serious inconsistency	serious[1]	serious[6]	none	20	40	-	MD 20.7 higher (3.82 to 37.58 higher)	VERY LOW	CRITICAL

[a] *severe persistent hypertension was defined as 160 or 110 mmHg after use of the maximum number of doses (5) of antihypertensive drug or ≥ 5 doses over 24 hours*
[1] *The quality of the evidence was downgraded by 1 level due to an unclear risk of bias in allocation concealment, it was unclear whether participants, personnel and outcome assessors were blinded to treatment allocation, and there was an unclear risk of reporting bias*
[2] *The quality of the evidence was downgraded by 1 level as 31.6% of included women were antenatal*
[3] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (11.2 x +/- 0.5= +/-5.6)*
[4] *The quality of the evidence was downgraded by 2 levels due to an unclear risk of bias in random sequence generation and allocation concealment, and the trial was open label*
[5] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)*
[6] *The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (0.5 x +/- 0.5= +/- 16.55)*

Table 14: Clinical evidence profile. Beta-blockers (non-comparative studies)

Study	Outcomes	Results	Number of Participants (studies)	Quality of the evidence (IHE Quality Appraisal Checklist)	Importance
Eyal 2010	Daily excretion of atenolol in breast milk (µg) at 2-4 weeks post-partum, dose 25 mg/day	Mean ± SD = 227 ± 80 Range = 138 - 345	8 (1 study)	VERY LOW[1]	CRITICAL
Eyal 2010	Daily excretion of atenolol in breast milk (µg) at 2-4 weeks post-partum, dose 50 mg/day	Mean ± SD = 350 ± 167 Range = 56 - 630	16 (1 study)	VERY LOW[1]	CRITICAL
Eyal 2010	Daily excretion of atenolol in breast milk (µg) at 2-4 weeks post-partum, dose 100 mg/day	Mean ± SD = 429 ± 126 Range = 307 - 596	4 (1 study)	VERY LOW[1]	CRITICAL
Eyal 2010	Daily excretion of atenolol in breast milk (µg) at 2-4 weeks post-partum, dose 200 mg/day	Mean ± SD = 350 ± 524 Range = 30 - 955	3 (1 study)	VERY LOW[1]	CRITICAL
Michael 1979	Breast milk concentrations of labetalol at a daily dose of 330 mg	Mean = 29 ng/l	4 (1 study)	VERY LOW[1]	CRITICAL
Michael 1979	Breast milk concentrations of labetalol at a daily dose of 400 mg	Mean = 27 ng/l	11 (1 study)	VERY LOW[2]	CRITICAL
Michael 1979	Breast milk concentrations of labetalol at a daily dose of 600 mg	Mean = 39 ng/l	6 (1 study)	VERY LOW[2]	CRITICAL
Michael 1979	Breast milk concentrations of labetalol at a daily dose of 700 mg	Mean = 46 ng/l	2 (1 study)	VERY LOW[2]	CRITICAL
Michael 1979	Breast milk concentrations of labetalol at a daily dose of 800 mg	Mean = 43 ng/l	1 (1 study)	VERY LOW[2]	CRITICAL

Study	Outcomes	Results	Number of Participants (studies)	Quality of the evidence (IHE Quality Appraisal Checklist)	Importance
Michael 1979	Breast milk concentrations of labetalol at a daily dose of 1200 mg	Mean = 600 ng/l	1 (1 study)	VERY LOW[2]	CRITICAL
Sioufi 1984	Breast milk concentrations of oxprenolol at a daily dose of 80 mg	Mean ± SD = 387 nmol/l ± 426 Range 0 to 1342 nmol/l	1 (1 study)	VERY LOW[3]	CRITICAL
Michael 1979	Number of new-borns with hypotension	1/27 (3.7%)	27 (1 study)	VERY LOW[2]	CRITICAL
Sioufi 1984	Neonatal hypoglycaemia during first 24 hours (glucose ≤ 1.6 mmol/l	5/32 (6.25%)	32 (1 study)	VERY LOW[3]	CRITICAL

[1] The quality of the evidence was considered very low due to the following: non-comparative case series; it was unclear whether consecutive recruitment was performed; the study was not blinded; estimates of random variability were not reported; adverse outcomes were not reported, and competing interests or support was not reported
[2] The quality of the evidence was considered very low due to the following: non-comparative case series; it was unclear whether consecutive recruitment was performed; the study was not blinded; estimates of random variability were not reported; it was unclear whether appropriate methods for outcome assessment were used and unclear whether follow-up duration was sufficient.
[3] The quality of the evidence was considered very low due to the following: non-comparative case series; it was unclear whether women entered the study at the same time point; the study was not blinded; it was unclear whether follow-up time was sufficient; estimates of random variability were not reported; competing interests of authors were not reported.

Table 15: Clinical evidence profile for calcium channel blockers (non-comparative studies)

Study	Outcomes	Results	Number of participants (studies)	Quality of the evidence (IHE Quality Appraisal Checklist)	Importance
Jarreau 2000	Breast milk concentrations of nicardipine at 20mg x 3 days	Mean (SD) maximum milk concentrations = 5.67 (3.20)	N=4 (1 study)	VERY LOW[1]	CRITICAL

Study	Outcomes	Results	Number of participants (studies)	Quality of the evidence (IHE Quality Appraisal Checklist)	Importance
		Mean (SD) maximum dose ingested by the infant = 851.25 (480.05) Mean (SD) maximum dose ingested by the infant as a percentage of the weight adjusted maternal daily dose = 0.09 (0.04)			
Jarreau 2000	Breast milk concentrations of nicardipine at 50mg x 2 days	Mean (SD) maximum milk concentrations = 6.41 (3.48) Mean (SD) maximum dose ingested by the infant = 931.33 (523.19) Mean (SD) maximum dose ingested by the infant as a percentage of the weight adjusted maternal daily dose = 0.05 (0.03)	N=6 (1 study)	VERY LOW[1]	CRITICAL
Jarreau 2000	Breast milk concentrations of IV nicardipine	Maximum milk concentrations = 18.8 Maximum dose ingested by the infant = 2823 Maximum dose ingested by the infant as a percentage of the weight adjusted maternal daily dose = 0.14	N=1 (1 study)	VERY LOW[1]	CRITICAL

Study	Outcomes	Results	Number of participants (studies)	Quality of the evidence (IHE Quality Appraisal Checklist)	Importance
Matsumura 2014	Breast milk concentrations of nicardipine	Mean (SD): 6.89 (8.28) ng/ml Range: 2.26 to 37.55 ng/ml	N=17 (1 study)	VERY LOW[1]	CRITICAL
Matsumura 2014	Infants admitted to the neonatal unit	14/21 (67%)	N=21 (1 study)	VERY LOW[2]	CRITICAL
Naito 2015	Breast milk concentrations of amlodipine (pre-dose)	Median = 11.5ng/mL IQR= 3.5-6.32 µg/kg	N=31 (1 study)	VERY LOW[2]	CRITICAL
Naito 2015	Daily dose of amlodipine in the infant via breast milk	4.17 µg/kg (IQR, 3.05-6.32 µg/kg)	N=31 (1 study)	VERY LOW[2]	CRITICAL

[1] The quality of the evidence was considered very low due to the following: non-comparative case series; it was unclear whether consecutive recruitment was performed; eligibility criteria of the study were not defined; the study was not blinded; it was unclear if the follow-up provided was sufficient; estimates of random variability were not provided; adverse events were not reported; competing interests were not reported.

[2] The quality of the evidence was considered very low due to the following: non-comparative case series; it was unclear whether consecutive recruitment was performed; the study was not blinded; estimates of random variability were not reported; it was unclear whether appropriate methods for outcome assessment were used and it was unclear whether follow-up duration was sufficient.

Appendix G – Economic evidence study selection

Appendix H – Economic evidence tables

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

No economic evidence was identified for this review question.

Appendix J – Health economic analysis

No health economic analysis was conducted for this review question.

Appendix K – Excluded studies

Clinical studies

Table 16: Clinical excluded studies with reasons for exclusion

Study	Reason for Exclusion
Alabdulrazzaq, Fatoumah, Koren, Gideon, Fetal safety of calcium channel blockers, Canadian family physician Medecin de famille canadien, 58, 746-7, 2012	Narrative review
Alfirevic,A., Alfirevic,Z., Pirmohamed,M., Pharmacogenetics in reproductive and perinatal medicine, Pharmacogenomics, 11, 65-79, 2010	Narrative review
Amorim, M. M. R., Noronha-Neto, C., Maia, S. B., Souza, A. S. R., Katz, L., Neto, A. H. F., Clonidine compared with captopril for severe postpartum hypertension, Obstetrics and Gynecology, 125, 42S, 2015	Abstract
Amorim, M., Katz, L., Cursino, T., Coutinho, I., Postpartum furosemide for accelerating recovery in women with severe preeclampsia: A randomized clinical trial, International Journal of Gynecology and Obstetrics, 131, E195, 2015	Abstract
Bartels, P. A., Hanff, L. M., Mathot, R. A. A., Steegers, E. A. P., Vulto, A. G., Visser, W., Nicardipine in pre-eclamptic patients: placental transfer and disposition in breast milk, BJOG : an international journal of obstetrics and gynaecology, 114, 230-3, 2007	Non-comparative study, n<10
Barton, J. R., Prevost, R. R., Wilson, D. A., Whybrew, W. D., Sibai, B. M., Nifedipine pharmacokinetics and pharmacodynamics during the immediate postpartum period in patients with preeclampsia, American Journal of Obstetrics and Gynecology, 165, 951-4, 1991	Non comparative study, n<10
Boutroy, M. J., Vert, P., Bianchetti, G., Infants born to hypertensive mothers treated by acebutolol. Pharmacological studies in the perinatal period, Developmental Pharmacology and Therapeutics, 4, 109-115, 1982	Women received treatment only during pregnancy
Buhimschi,C.S., Weiner,C.P., Medications in pregnancy and lactation: Part 2. drugs with minimal or unknown human teratogenic effect, Obstetrics and Gynecology, 113, 417-432, 2009	Narrative review
Caicedo, A., Thewissen, L., Naulaers, G., Lemmers, P., van Bel, F., Van Huffel, S., Effect of maternal use of labetalol on the cerebral autoregulation in premature infants, Advances in Experimental Medicine & Biology, 789, 105-11, 2013	No outcomes of interest (pulse pressure in the new-born)
Cairns, A., Tucker, K., Leeson, P., MacKillop, L., Crawford, C., Baker, N., Tebbutt, J.,	Abstract

Study	Reason for Exclusion
McManus, R., Self-management of postnatal antihypertensive treatment: A pilot randomised controlled trial, BJOG: An International Journal of Obstetrics and Gynaecology, 124, 36, 2017	
Cairns, Alexandra E., Pealing, Louise, Duffy, James M. N., Roberts, Nia, Tucker, Katherine L., Leeson, Paul, MacKillop, Lucy H., McManus, Richard J., Postpartum management of hypertensive disorders of pregnancy: a systematic review, BMJ open, 7, e018696, 2017	Not all the included studies in this systematic review were relevant (studies presented with mixed population of postnatal and perinatal women or used interventions not included in the protocol, such as selective 5-HT antagonists or urine curettage)
Cairns, Alexandra E., Tucker, Katherine L., Leeson, Paul, Mackillop, Lucy, McManus, Richard J., Survey of healthcare professionals regarding adjustment of antihypertensive medication(s) in the postnatal period in women with hypertensive disorders of pregnancy, Pregnancy Hypertension, 6, 256-258, 2016	No relevant outcomes (rates of antihypertensive prescriptions amongst clinicians)
Cordero, Leandro, Valentine, Christina J., Samuels, Philip, Giannone, Peter J., Nankervis, Craig A., Breastfeeding in women with severe preeclampsia, Breastfeeding medicine : the official journal of the Academy of Breastfeeding Medicine, 7, 457-63, 2012	No intervention of interest (magnesium sulphate)
Cursino, Telma, Katz, Leila, Coutinho, Isabela, Amorim, Melania, Diuretics vs. placebo for postpartum blood pressure control in preeclampsia (DIUPRE): a randomized clinical trial, Reproductive Health, 12, 66, 2015	Study protocol
Dhananjaya, B. S., Jamuna, R., Oral nifedipine versus intravenous labetalol in hypertensive emergencies of pregnancy: A randomised trial, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 6, 1673-1681, 2015	Antenatal study
Duley,Lelia, Meher,Shireen, Jones,Leanne, Drugs for treatment of very high blood pressure during pregnancy, Cochrane Database of Systematic Reviews, -, 2013	Postpartum women were excluded
Engeland, Anders, Bjorge, Tone, Klungsoyr, Kari, Skjaerven, Rolv, Skurtveit, Svetlana, Furu, Kari, Preeclampsia in pregnancy and later use of antihypertensive drugs, European journal of epidemiology, 30, 501-8, 2015	No outcomes of interest
Firoz, T, Magee, L, MacDonell, K, Payne, B, Gordon, R, Vidler, M, Dadelszen, P, Oral antihypertensive therapy for severe hypertension in pregnancy and postpartum: a systematic review (Provisional abstract), Database of Abstracts of Reviews of Effects, 1210-1220, 2014	In this systematic review, all the included studies included pregnant women, with the exception of 1, which included women in the postpartum period. This study cannot be included as is in Spanish
Franke, G., Pietsch, P., Schneider, T., Studies on the kinetics and distribution of dihydralazine	N <10 (n= 11 were included, but drug levels in breast milk were included for n=1/ no other relevant outcomes were studied)

Study	Reason for Exclusion
in pregnancy, Biological Research in Pregnancy and Perinatology, 7, 30-33, 1986	
Gaisin, I. R., Iskchakova, A. S., Shilina, L. V., Indapamide in the management of post-partum hypertension: A randomized, case-control study, European Heart Journal, 34, 271, 2013	Abstract
Ghanem, Firas A., Movahed, Assad, Use of antihypertensive drugs during pregnancy and lactation, Cardiovascular therapeutics, 26, 38-49, 2008	Narrative review
Goncalves, P. V. B., Cavalli, R. C., Cunha, S. P. d, Lanchote, V. L., Determination of pindolol enantiomers in amniotic fluid and breast milk by high-performance liquid chromatography: Applications to pharmacokinetics in pregnant and lactating women, Journal of Chromatography B: Analytical Technologies in the Biomedical and Life Sciences, 852, 640-645, 2007	No intervention of interest (racemic pindolol)
Griffis, K. R., Jr., Martin, J. N., Jr., Palmer, S. M., Martin, R. W., Morrison, J. C., Utilization of hydralazine or alpha-methyldopa for the management of early puerperal hypertension, American Journal of Perinatology, 6, 437-41, 1989	Only p-values were reported for the relevant outcome (mean arterial blood pressure) therefore, no abstractable data
Hebert, Mary F., Carr, Darcy B., Anderson, Gail D., Blough, David, Green, Grace E., Brateng, Debra A., Kantor, Eric, Benedetti, Thomas J., Easterling, Thomas R., Pharmacokinetics and pharmacodynamics of atenolol during pregnancy and postpartum, Journal of clinical pharmacology, 45, 25-33, 2005	Postpartum data was obtained at 3 months only
Heida, Karst Y., Zeeman, Gerda G., Van Veen, Teelkien R., Hulzebos, Christian V., Neonatal side effects of maternal labetalol treatment in severe preeclampsia, Early human development, 88, 503-7, 2012	Considers infants exposed to labetalol antenatally, not postpartum. No data on postpartum management, or breast milk levels.
Hennessy, A., Thornton, C. E., Makris, A., Ogle, R. F., Henderson-Smart, D. J., Gillin, A. G., Child, A., A randomized comparison of hydralazine and mini-bolus diazoxide for hypertensive emergencies in pregnancy: The PIVOT trial, Obstetrical and Gynecological Survey, 62, 776-778, 2007	Mixed population of antenatal/postnatal patients
Hugon-Rodin, J., Plu-Bureau, G., Hypertension and pregnancy: Post-partum period, Presse Medicale, 45, 651-658, 2016	Study in French
Hurst, A. K., Shotan, A., Hoffman, K., Johnson, J., Goodwin, T. M., Koda, R., Elkayam, U., Pharmacokinetic and pharmacodynamic evaluation of atenolol during and after pregnancy, Pharmacotherapy:The Journal of	No relevant outcomes

Study	Reason for Exclusion
Human Pharmacology & Drug Therapy, 18, 840-6, 1998	
Ilshat Gaisin, I. R., Iskchakova, A. S., Shilina, L. V., Control of cardiovascular risk factors with ursodeoxycholic acid and indapamide in postpreeclamptic nursing mothers: Results from a randomized, case-control 1-year study, European Journal of Preventive Cardiology, 1), S120, 2014	Conference abstract.
Janmohamed, Rahim, Montgomery-Fajic, Erin, Sia, Winnie, Germaine, Debbie, Wilkie, Jodi, Khurana, Rshmi, Nerenberg, Kara A., Cardiovascular risk reduction and weight management at a hospital-based postpartum preeclampsia clinic, Journal of obstetrics and gynaecology Canada : JOGC = Journal d'obstetrique et gynecologie du Canada : JOGC, 37, 330-7, 2015	No intervention of interest (counselling)
Jayanna, K., Ramesh,, Bhowmik, A., Thomas, A., Mony, P., Shankar, K., Schurmann, A., Moses, S., Avery, L., Blanchard, J., Management of eclampsia and postpartum hemorrhage: Challenges and opportunities to improve quality of care in northern Karnataka, India, International Journal of Gynecology and Obstetrics, 119, S379-S380, 2012	Abstract
Katz, L., Neto, C. N., Maia, S., Coutinho, I., Souza Sr, A., Amorim, M., Clonidine versus captopril for severe postpartum hypertension: A randomized controlled trial, Pregnancy Hypertension, 5, 29-30, 2015	Conference abstract. Full text of published study identified for inclusion.
Koniak-Griffin, D., Dodgson, J., Severe pregnancy-induced hypertension: postpartum care of the critically ill patient, Heart & Lung, 16, 661-9, 1987	Narrative review
Kovacs, C. S., Calcium and bone metabolism disorders during pregnancy and lactation, Endocrinology and Metabolism Clinics of North America, 40, 795-826, 2011	Narrative review, not related with hypertensive disorders during the postnatal period
Lindeberg, S., Sandstrom, B., Lundborg, P., Regardh, C. G., Disposition of the adrenergic blocker metoprolol in the late-pregnant woman, the amniotic fluid, the cord blood and the neonate, Acta Obstetricia et Gynecologica Scandinavica - Supplement, 118, 61-4, 1984	Non-comparative study, n<10
Lunell, N. O., Kulas, J., Rane, A., Transfer of labetalol into amniotic fluid and breast milk in lactating women, European Journal of Clinical Pharmacology, 28, 597-9, 1985	Non-comparative study, n<10
Magee,Laura, von Dadelszen,Peter, Prevention and treatment of postpartum hypertension,	No relevant clinical outcomes were reported

Study	Reason for Exclusion
Cochrane Database of Systematic Reviews, -, 2013	
Manninen, A. K., Juhakoski, A., Nifedipine concentrations in maternal and umbilical serum, amniotic fluid, breast milk and urine of mothers and offspring, International journal of clinical pharmacology research, 11, 231-6, 1991	n <10 (n= 11 were included, but drug levels in breast milk were included for n=6/ no other relevant outcoms were studied)
Matthews, G., Gornall, R., Saunders, N. J., A randomised placebo controlled trial of loop diuretics in moderate/severe pre-eclampsia, following delivery, Journal of obstetrics and gynaecology : the journal of the Institute of Obstetrics and Gynaecology, 17, 30-2, 1997	No extractable data
Mulders Annemarie, G. M. G. J., Van Der Wilk Eline, C., Jorgo, L., Roeters Van Lennep Jeanine, E., Duvekot Johannes, J., Hypertension evaluated by 24-hour ambulatory blood pressure measurements in previously preeclamptic women one year postpartum, Pregnancy Hypertension, 3, 91, 2013	Abstract
Noronha-Neto, C, Katz, L, Coutinho, Ic, Maia, Sb, Souza, As, Amorim, Mm, Clonidine versus captopril for treatment of postpartum very high blood pressure: study protocol for a randomized controlled trial (CLONCAP), Reproductive health, 10, 37, 2013	Study protocol
Rubin, P. C., Butters, L., Kelman, A. W., Fitzsimons, C., Reid, J. L., Labetalol disposition and concentration-effect relationships during pregnancy, British Journal of Clinical Pharmacology, 15, 465-70, 1983	n <10
Saotome, T., Minoura, S., Terashi, K., Sato, T., Echizen, H., Ishizaki, T., Labetalol in hypertension during the third trimester of pregnancy: its antihypertensive effect and pharmacokinetic-dynamic analysis, Journal of Clinical Pharmacology, 33, 979-88, 1993	n<10
Sharma, K. J., Greene, N., Kilpatrick, S. J., Oral labetalol compared to oral extended release nifedipine for persistent postpartum hypertension: A randomized controlled trial, American Journal of Obstetrics and Gynecology, 214, S27-S28, 2016	Conference abstract. Full published text included.
Shumard, K., Yoon, J., Huang, C., Nitsche, J. F., Peripartum anti-hypertensive choice affects time to blood pressure control in treating hypertensive disorders of pregnancy, American Journal of Obstetrics and Gynecology, 214, S378, 2016	Abstract
Too, Gloria T., Hill, James B., Hypertensive crisis during pregnancy and postpartum period, Seminars in Perinatology, 37, 280-7, 2013	Narrative review

Study	Reason for Exclusion
Veena, P, Perivela, L, Raghavan, Ss, Furosemide in postpartum management of severe preeclampsia: a randomized controlled trial, Hypertension in Pregnancy, 36, 84-89, 2017	Only p-values were reported for the relevant outcome (blood pressure in the postnatal period)therefore, no abstractable data
Vermillion, S. T., Scardo, J. A., Newman, R. B., Chauhan, S. P., A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy, American Journal of Obstetrics & Gynecology, 181, 858-61, 1999	58% of included women were antenatal
Vila Maior, C., Pipa, A., Portugal, A., Campos, S., Management of postpartum hypertension, International Journal of Gynecology and Obstetrics, 107, S685, 2009	Abstract
White, W. B., Andreoli, J. W., Cohn, R. D., Alpha-methyldopa disposition in mothers with hypertension and in their breast-fed infants, Clinical pharmacology and therapeutics, 37, 387-90, 1985	Non-comparative study, n<10

Economic studies

No economic evidence was identified for this review question.

Appendix L – Research recommendations

In women who require treatment for high blood pressure after birth, what is the effectiveness and safety (including in breastfeeding women) of antihypertensive agents in achieving adequate blood pressure control?

Why this is important

Hypertensive disorders of pregnancy often persist in the postnatal period, or maternal hypertension might present for the first time after the birth of a baby. In either situation, blood pressure control is required to reduce the potential for adverse events such as stroke and to avoid multiple attendances for additional medical review, either in primary or secondary care, costly to the woman and the health service. There is limited information about the safety and effectiveness of antihypertensive drugs in the postnatal period, including the use of antihypertensive drugs in breastfeeding women.

Table 17: Research recommendation rationale

Research question	In women who require treatment for high blood pressure after birth, what is the effectiveness and safety (including in breastfeeding women) of antihypertensive agents in achieving adequate blood pressure control?
Importance to 'patients' or the population	Information on the effectiveness and safety of antihypertensive drugs, including use while breastfeeding, will help women make informed choices about treatment selection in the postpartum period. If blood pressure is not adequately controlled after birth, the woman (and her baby) might need to be readmitted to hospital after primary discharge or attend additional appointments for medical review in the community.
Relevance to NICE guidance	The committee searched for evidence on this topic but found no high-quality evidence. The committee therefore made the recommendations to consider treatment in line with the Hypertension in adults guidelines, with treatment selection according to ethnicity and, where possible, taking into account any available information on the use of antihypertensive drugs in breastfeeding. However, clinical trials in this area would allow more definitive evidence-based recommendations to be made.
Relevance to the NHS	This question is of high and immediate priority for the NHS. Re-attendance and re-admission of women and their babies to hospital for severe hypertension after primary discharge is one of the leading causes of postnatal readmission, and so clear recommendations would help improve blood pressure control, reduce adverse events (for example stroke) and mortality, and reduce direct NHS costs by reducing the re-attendance and re-admission rate. Guidance will ensure the consistency of treatment and help clinicians managing women with hypertension in the postpartum period.
National priorities	Encouraging breastfeeding is a key priority for maternity care providers.
Current evidence base	Lack of evidence; some low or very low quality evidence available.
Equality	Women in the postpartum period should receive as adequate treatment for hypertension as other women, and those who chose to breastfeed should not be disadvantaged.

Table 18: Research recommendation modified PICO table

Criterion	Explanation
Population	Women who require treatment for high blood pressure after birth, including breast-feeding women. Setting: hospital and/or community
Intervention	Antihypertensive agents, to include ACE inhibitors and calcium channel blockers, with specific choice of these and other agents to be justified.
Comparator	Other antihypertensive agents in head-to-head trial.
Outcome	Important outcomes: Blood pressure control (to be defined and justified); severe hypertension, death, stroke. Other outcomes: Women: Other adverse maternal outcomes to be defined and justified by investigators, side-effects, re-admissions to hospital after primary discharge. Baby: Outcomes relating to safety and side-effects of antihypertensive agents. (Consideration should be given to use of routinely collected data for determination of some outcomes).
Study design	Randomised controlled trial with an internal pilot phase with clear progression criteria to the main trial, to test ability to recruit. Other designs could be considered, if justified. Setting: Hospital and/or community
Timeframe	Minimum duration of follow-up: Until 6 months after birth.