National Institute for Health and Care Excellence

FINAL

Hypertension in pregnancy

[A] Evidence review for interventions for chronic hypertension

NICE guideline NG133

Evidence reviews

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FINAL

These evidence reviews were developed by The National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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1. In women who require treatment for chronic hypertension in pregnancy, what is the effectiveness and safety of antihypertensive agents (compared in head-to-head trials) in improving maternal and perinatal outcomes? 145

2. In women who require treatment for hypertension in pregnancy, what are the adverse neonatal outcomes associated with maternal use of beta-blockers (or mixed alpha-beta blockers)? 146

Review question: What interventions for chronic hypertension are effective at improving outcomes for women and infants?

Introduction

Chronic hypertension in pregnancy is hypertension present at the booking visit or before 20 weeks, or if the woman is already taking antihypertensive medication when presenting to maternity services. It can be primary or secondary in aetiology. Its pathophysiology is likely to be different from gestational hypertension, and intervention in chronic hypertension which are successful in reducing complications in the mother and baby may be different from those interventions which improve outcomes in gestational hypertension.

This review will look at the evidence for interventions in chronic hypertension in pregnancy to determine which improve outcomes in the woman and her baby.

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	Pregnant women with chronic hypertension. This population includes women with: • Essential (primary) hypertension • Secondary hypertension e.g. secondary to chronic kidney disease, diabetes.
Intervention	• Centrally acting alpha2-adrenoceptor agonists • Beta-blockers/mixed alpha/beta-blockers • Calcium channel blockers • Diuretics • Angiotensin converting enzyme (ACE) inhibitors • Acetylsalicylic acid/aspirin • Elective (planned) delivery versus expectant management • Tight management (for example, diastolic target = 85mmHg) • Less-tight management (for example, diastolic target = 100 mmHg) • Automated monitoring of blood pressure • Ambulatory/self-monitoring of blood pressure • Exercise • Dietary interventions • Dietary salt reduction
Comparison	• No intervention • Placebo • Each other of the interventions outlined above • Combinations of the interventions outlined above
Outcome	**Outcomes for babies** **Critical outcomes:**

	• Perinatal mortality
	  ○ Stillbirth (include if reported as part of perinatal mortality)
	  ○ Neonatal death up to 7 days (include if reported as part of perinatal mortality)
	• Small-for-gestational age (birthweight <10th centile)
	
	Important outcomes:
	• Birth weight
	• Gestational age at birth
	• Preterm birth (<28 weeks, <34 weeks, <37 weeks)
	• Admission to neonatal unit
	• Neurodevelopmental outcomes:
	  ○ Cerebral palsy (CP) (dichotomous outcome, reported as present/absent, not severity of condition)
	  ○ Neurodevelopmental delay (dichotomous outcome, not continuous outcomes such as mean change in score):
	  - Severe (score of >2SD below normal on validated assessment scales, or Bayley assessment scale of mental development index [MDI] or psychomotor developmental index [PDI] <70, or complete inability to assign score due to CP or severe cognitive delay)
	  - Moderate (score of 1-2 SD below normal on validated assessment scales, or Bayley assessment scale MDI or PDI 70-84)
	  ○ Neurosensory impairment (dichotomous outcome, present or absent, not severity of condition)
	  - Severe hearing impairment (for example, deaf)
	  - Severe visual impairment (for example, blind)
	
	Outcomes for women:
	
	Critical outcomes:
	• Blood pressure control
	  ○ Severe hypertension
	
	Important outcomes:
	• Superimposed pre-eclampsia
	  ○ including eclampsia and HELLP syndrome
	• Placental abruption
	• Onset of labour
	• Mode of birth
	• Maternal death

ACE: angiotensin converting enzyme; CP: cerebral palsy; HELLP: haemolysis, elevated liver enzymes, low platelets; MDI: mental development index; mmHg: millimetres of mercury; PDI: psychomotor developmental index; SD: standard deviation

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

Included studies

Eighteen articles from 15 randomised controlled trials (RCTs) and 2 individual participant data (IPD) meta-analyses of RCT data have been included in this review (N=5377) (Askie 2007, Atallah 1996, Butters 1990, Cockburn 1982, Hamed 2014, Kasawara 2013, Magee 2015, Moore 1982, Moore 2015, Parazzini 1993, Poon 2017, Redman 1976, Sibai 1990, van Vliet 2017, Vigil-de Gracia 2014, Viinikka 1993, Webster 2017, Weitz 1987).

Summary estimates were reported in the two IPD meta-analyses. However, as the articles did not report the specific data from each of the original studies it was not possible to pool the estimates from the IPD meta-analyses with additional studies. Instead, data from the IPD meta-analyses are presented separately to that from the additional RCTs identified in this review.

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 exclusion, 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 the included studies

Study	Participants/ Diagnosis (*and definition*)	Intervention	Control	Outcomes
Askie 2007 Multicentre Individual participant data meta-analysis	N=3303 women with chronic hypertension *No definition provided*	Antiplatelet: predominantly aspirin (27 of the included studies), given in doses ranging from 50 to 150mg per day. 59% of women commenced treatment before 20 weeks' gestation. 3 trials used aspirin with dipyridamole and 3 used different antiplatelet agents	No intervention: either placebo or no treatment	• Pre-eclampsia
Atallah 1996 (ECPPA) Brazil RCT	N=473 women with chronic hypertension *No definition provided*	Aspirin: 60mg PO daily from 12 weeks' gestation (or immediately following randomisation, if this was after 12	No intervention: placebo tablets daily from 12 weeks' gestation (or immediately following randomisation, if this was after 12	• Stillbirth and neonatal death • Small-for-gestational age

Study	Participants/ Diagnosis (*and definition*)	Intervention	Control	Outcomes
		weeks) until delivery	weeks) until delivery	• Preterm delivery (<37 weeks)[a] • Pre-eclampsia[a]
Butters 1990 UK RCT	N=29 women with chronic hypertension *sBP between 140 and 170mmHg and dBP between 90 and 110mmHg on 2 occasions separated by at least 24 hours*	Atenolol: 50mg PO daily up to 200mg	No intervention: placebo tablets	• Stillbirth • Small-for-gestational age • Birth weight • Gestational age at delivery
Hamed 2014 Egypt and Saudi Arabia RCT	N=76 women with chronic hypertension *sBP between 140 and 160mmHg and dBP between 90 and 110mmHg at least 6 hours apart in the first half of pregnancy*	Induction of labour	Expectant management	• Perinatal death • Birth weight • Gestational age at delivery • Preterm birth • Admission to neonatal unit • Severe chronic hypertension • Superimposed pre-eclampsia • Placental abruption
Kasawara 2013 Brazil RCT	N=116 women with CHT (90.5%) or previous PE (9.5%) *BP ≥ 140/90mmHg diagnosed before pregnancy or before 20 weeks' gestation*	Exercise (30 minutes per week riding a stationary bike)	No intervention	• Birth weight (<2500; 2500 to 3999 and ≥ 4000g) • Admission to neonatal unit • Mode of birth
Magee 2015 South America, North America, Israel, Jordan, Oceania and Europe	N=981 women with CHT (75.02%) or GH (24.98%) *dBP ≥90mmHg before pregnancy or before 20^{+0} weeks' gestation*	Less-tight control (aiming for a target of dBP of 100mmHg)	Tight control (aiming for a target of dBP of 85mmHg)	• Stillbirth • Neonatal death up to 7 days • Small-for-gestational age • Birth weight • Gestational age at delivery

Study	Participants/ Diagnosis (*and definition*)	Intervention	Control	Outcomes
RCT				• Admission to neonatal unit • Severe hypertension • HELLP • Placental abruption • Onset of labour • Mode of birth
Moore 1982 UK RCT	N=72 women with CHT (65.2%) or PE (34.8%) *BP ≥110/170mmHg on two separate occasions before 20 weeks' gestational age*	Labetalol: 100mg x 4 times/day	Methyldopa: 250 mg x 4 times/day	• Stillbirth • Neonatal death up to 7 days • Small-for-gestational age • Birth weight; gestational age at delivery • Admission to neonatal unit • Maximum sBP and dBP after entry • Onset of labour • Mode of birth
Moore 2015 USA RCT	N=186 women with chronic hypertension *Defined as use of antihypertensive agent at baseline, or resting BP ≥ 140/90mmHg on two occasions at least four hours apart prior to pregnancy, or before 20 weeks' gestation*	Aspirin: 60mg PO once daily, started prior to 17 weeks' gestation	No intervention: placebo tablets started prior to 17 weeks' gestation	• Small-for-gestational age • Preterm delivery due to pre-eclampsia (<34 weeks)[a] • Pre-eclampsia[a]
Parazzini 1993 Italy RCT	N=240 women with chronic hypertension or nephropathy *Defined as diastolic BP 90 to 100mmHg or nephropathy with normal renal*	Aspirin: 50mg PO once daily from randomisation (at 16 to 32 weeks) until delivery	No intervention	• Small-for-gestational age[b]

Study	Participants/ Diagnosis (*and definition*)	Intervention	Control	Outcomes
	function and normal BP			
Poon 2017 Multicentre (UK, Spain, Italy, Belgium, Greece and Israel) RCT	N=110 women with chronic hypertension *Study participants self-reported a diagnosis of chronic hypertension at the 11-13 week visit*	Aspirin: 150mg PO once daily from randomisation (approximately 12-13 weeks) until 36 weeks' gestation	No intervention: placebo tablet to be taken once daily from randomisation until 36 weeks' gestation	• Pre-eclampsia
Redman 1976, Cockburn 1982 UK RCT	N=208 women with CHT *sBP >140 or dBP>90 on 2 occasions at least 24 hours apart before 28 weeks' GA*	Methyldopa: dose and administration route not reported	No intervention	• Stillbirth • Birth weight • GA at delivery • Impaired hearing • Impaired vision
Sibai 1990 USA RCT	N=263 women with CHT *Definition was not reported*	Methyldopa: 750 mg/day up to 4g/day Labetalol: 300 mg/day increased up to 2400 mg/day.	No intervention	• Perinatal death • Small-for-gestational age • Preterm birth • Superimposed pre-eclampsia • Placental abruption • Mode of birth
van Vliet 2017 Multicentre Individual participant data meta-analysis	N=2518 women with chronic hypertension *No definition provided*	Antiplatelet: predominantly aspirin (15 of the included studies), given in doses ranging from 60 to 150mg per day. 1 trial used aspirin with dipyridamole and 1 used dipyridamole alone.	No intervention: either placebo or no treatment	• Spontaneous preterm birth (<37 weeks, <34 weeks and <28 weeks)[b]
Vigil-De Gracia 2014 Panama	N=39 women with CHT *BP >140/90 mmHg present before pregnancy or for first time before the*	Amlodipine: 5mg/day PO	Aspirin: 75mg/day PO	• Stillbirth • Neonatal death • Small-for-gestational age • Birth weight • Preterm birth

Study	Participants/ Diagnosis (*and definition*)	Intervention	Control	Outcomes
RCT	*20th week of gestation*			• Severe hypertension • Placental abruption • Mode of birth
Viinikka 1993 Finland RCT	N=208 women with chronic hypertension (89%) or severe pre-eclampsia in a previous pregnancy *CHT defined as BP >140/90mmHg without treatment prior to pregnancy*	Aspirin: 50mg aspirin/day PO	No intervention: placebo tablets to be taken daily PO	• Perinatal mortality • Small-for-gestational age • Birth weight • Gestational age • Admission to neonatal unit • Severe hypertension • Superimposed pre-eclampsia • Onset of labour
Webster 2017 UK RCT	N=114 women with CHT *BP ≥140/90mmHg before 20 weeks' gestation requiring antihypertensive treatment before 27+ 6 weeks'*	Labetalol: 100 mg BID up to 1800 mg	Nifedipine: 10 mg BID up to 80 mg	• Stillbirth • Neonatal death • Small-for-gestational age • Birth weight • Admission to neonatal unit • Preterm birth • GA at delivery • Mode of delivery • Superimposed PE • Eclampsia • Maternal death
Weitz 1987 US RCT	N=25 women with CHT *BP ≥140/90 mmHg on 2 separate occasions at least 6 hours apart*	Methyldopa: 250 mg PO TID	No intervention: one placebo tablet PO TID	• Stillbirth • Neonatal death up to 7 days • GA at delivery • Superimposed PE

BID: twice a day; BP: blood pressure; CHT: chronic hypertension; dBP: diastolic blood pressure; GA: gestational age; GH: gestational hypertension; HELLP: haemolysis, elevated liver enzymes and low platelet count; mmHg: millimetres of mercury; N: total number of participants; PE: pre-eclampsia; PO: orally; sBP: systolic blood pressure; TID: three times a day

[a]*Data are included in individual participant data meta-analyses (by Askie 2007 or van Vliet 2017) therefore not analysed separately*

[b]*Participants in this report are also included in the IPD by Askie 2007*

See appendix D for clinical evidence tables.

Quality assessment of clinical outcomes included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

No economic evidence on the cost effectiveness interventions for chronic hypertension was identified by the systematic search of the economic literature undertaken for this guideline. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1. Induction of labour versus expectant management

Outcomes for babies

Critical outcomes

Perinatal mortality

- One randomised controlled trial (n=76) provided very low quality evidence to show that there were no clinically important differences in perinatal mortality between those who received induction of labour or expectant management.

Important outcomes

Birth weight

- One randomised controlled trial (n=76) provided low quality evidence to show a clinically important decrease in the weight of babies born of women who received induction of labour compared to those of women who received expectant management.

Gestational age at birth

- One randomised controlled trial (n=76) provided very low quality evidence to show a clinically important decrease in the gestational age at birth for babies born of women who received induction of labour as compared to those of women who received expectant management.

Preterm birth (number of weeks not reported)

- One randomised controlled trial (n=76) provided very low quality evidence to show no clinically important differences in the number of preterm births between those who received induction of labour or expectant management.

Admission to neonatal unit

- One randomised controlled trial (n=76) provided very low quality evidence to show a clinically important increase in the number of babies admitted to a neonatal unit between women who received induction of labour as compared to expectant management.

Outcomes for women

Critical outcomes

Severe hypertension

- One randomised controlled trial (n=76) provided very low quality evidence to show no clinically important difference in the occurrence of severe hypertension between those who received induction of labour or expectant management.

Important outcomes:

Superimposed pre-eclampsia

- One randomised controlled trial (n=76) provided very low quality evidence to show no clinically important difference in the incidence of superimposed pre-eclampsia between those who received induction of labour or expectant management.

Placental abruption

- One randomised controlled trial (n=76) provided very low quality evidence to show no clinically important difference in the occurrence of placental abruption between those who received induction of labour or expectant management.

Comparison 2. Exercise versus no intervention

Outcomes for babies

Important outcomes

Birth weight

- One randomised controlled trial (n=109) provided very low quality evidence to show that there were no clinically important differences in birth weight between the babies born of mothers who exercised and those who did not exercise, for weights of <2500g or 2500-3999g. There may be a clinically important reduction in the number of babies born weighing ≥4000g for those who exercise, but there was some uncertainty around the effect (RR 0.43, 95% CI 0.16-1.16).

Admission to neonatal unit

- One randomised controlled trial (n=109) provided very low quality evidence to show no clinically important difference in neonatal unit admission between babies born of mothers who exercised and those who did not exercise.

Outcomes for women

Important outcomes

Mode of birth (caesarean section)

- One randomised controlled trial (n=109) provided very low quality evidence to show no clinically important differences in mode of birth (caesarean section) between women who exercised and those who did not exercise.

Comparison 3. Less-tight versus tight control of blood pressure

Outcomes for babies

Critical outcomes

Stillbirth

- One randomised controlled trial (n=981) provided very low quality evidence to show no clinically important difference in the occurrence of stillbirth between those who received less-tight or tight control of blood pressure.

Neonatal death

- One randomised controlled trial (n=981) provided very low quality evidence to show no clinically important difference in the occurrence of neonatal death between those who received less-tight or tight control of blood pressure.

Small-for-gestational age (birthweight <10th centile)

- One randomised controlled trial (n=727) provided low quality evidence to show a clinically important decrease in the number of babies born small-for-gestational age for women who received less-tight control of blood pressure, as compared to women who received tight control of blood pressure.

Important outcomes

Birth weight

- One randomised controlled trial (n=981) provided low quality evidence to show no clinically important difference in the birth weight of babies born to women who received less-tight or tight control of blood pressure.

Gestational age at birth

- One randomised controlled trial (n=981) provided low quality evidence to show no clinically important difference in the gestational age at birth for babies born to women who received less-tight or tight control of blood pressure.

Admission to neonatal unit

- One randomised controlled trial (n=959) provided low quality evidence to show no clinically important difference in neonatal unit admissions for babies born to women who received less-tight or tight control of blood pressure.

Outcomes for women

Critical outcomes

Severe hypertension

- One randomised controlled trial (n=732) provided moderate quality evidence to show that less-tight blood pressure control resulted in a clinically important increase in the number of women experiencing severe hypertension, as compared to those with tight control.

Important outcomes

Haemolysis, elevated liver enzymes, low platelets (HELLP)

- One randomised controlled trial (n=981) provided very low quality evidence to show that there may be a clinically important increase in the occurrence of HELLP for those

receiving less-tight control, as compared to those receiving tight control, but there was some uncertainty around the estimate (RR 4.45, 95% CI 0.97 to 20.51).

Placental abruption

- One randomised controlled trial (n=981) provided very low quality evidence to show no clinically important difference in the occurrence of placental abruption between those who received less-tight or tight control of blood pressure.

Pre-eclampsia

- One randomised controlled trial (n=731) provided low quality evidence to show no clinically important difference in the occurrence of pre-eclampsia between those who received less-tight or tight control of blood pressure.

Onset of labour (spontaneous onset)

- One randomised controlled trial (n=981) provided very low quality evidence to show no clinically important difference in the number of women experiencing spontaneous onset of labour for those who received less-tight or tight control of blood pressure.

Onset of labour (induced onset)

- One randomised controlled trial (n=981) provided low quality evidence to show no clinically important difference in the number of women experiencing induction of labour for those who received less-tight or tight control of blood pressure.

Onset of labour (elective caesarean)

- One randomised controlled trial (n=981) provided low quality evidence to show no clinically important difference in the occurrence of elective caesarean section for those who received less-tight or tight control of blood pressure.

Mode of birth (caesarean section)

- One randomised controlled trial (n=981) provided low quality evidence to show no clinically important difference in the rate of caesarean section for those who received less-tight or tight control of blood pressure.

Comparison 4. Atenolol versus placebo

Outcomes for babies

Critical outcomes

Stillbirth

- One randomised controlled trial (n=29) provided very low quality evidence to show no clinically important difference in the occurrence of stillbirth between those who received placebo or atenolol.

Small-for-gestational age (birthweight <10th centile)

- One randomised controlled trial (n=29) provided low quality evidence to show a clinically important increase in the number of babies born small-for-gestational age for those who received atenolol, as compared to those who received placebo.

Important outcomes

Birth weight

- One randomised controlled trial (n=29) provided very low quality evidence to show a clinically important decrease in birth weight for babies of women who received atenolol, as compared to those who received placebo.

Gestational age at birth

- One randomised controlled trial (n=29) provided very low quality evidence to show a mean gestational age of 39.5 weeks for infants born to women taing placebo, and a mean gestational age of 38.5 weeks for infants born to women taking atenolol.

Outcomes for women

Critical outcomes

Blood pressure control

- One randomised controlled trial (n=29) provided very low quality evidence to show a clinically important decrease in diastolic blood pressure for those who received atenolol, as compared to those who received placebo. However, this same study provided very low quality evidence to show that there was no clinically important difference in the systolic blood pressure measurements between those who received atenolol and placebo.

Comparison 5. Labetalol versus no intervention

Outcomes for babies

Critical outcomes

Perinatal death up to 7 days

- One randomised controlled trial (n=176) provided very low quality evidence to show no clinically important difference in perinatal deaths between those who received labetalol or no intervention.

Small-for-gestational age (birthweight <10th centile)

- One randomised controlled trial (n=176) provided very low quality evidence to show that there was no clinically important difference in the number of babies born small-for-gestational age between those who received labetalol or no intervention.

Important outcomes

Preterm birth (<37 weeks)

- One randomised controlled trial (n=176) provided very low quality evidence to show that there was no clinically important difference in preterm birth (<37 weeks) for those who received labetalol or no intervention.

Outcomes for women

Important outcomes

Superimposed pre-eclampsia

- One randomised controlled trial (n=176) provided very low quality evidence to show that there was no clinically important difference in the number of women developing superimposed pre-eclampsia between those who received labetalol or no intervention.

Placental abruption

- One randomised controlled trial (n=176) provided very low quality evidence to show that there was no clinically important difference in the occurrence of placental abruption between those who received labetalol or no intervention.

Mode of birth (caesarean section)

- One randomised controlled trial (n=176) provided very low quality evidence to show that there was no clinically important difference in the number of women undergoing caesarean section between those who received labetalol or no intervention.

Comparison 6. Labetalol versus nifedipine

Outcomes for babies

Critical outcomes

Stillbirth

- One randomised controlled trial (n=112) provided very low quality evidence to show no clinically important difference in the occurrence of stillbirth between those who received labetalol or nifedipine.

Neonatal death up to 7 days

- One randomised controlled trial (n=112) provided moderate quality evidence to show that no neonatal deaths occurred in those who received labetalol or nifedipine.

Small-for-gestational age (birthweight <10th centile)

- One randomised controlled trial (n=112) provided very low quality evidence to show no clinically important difference in the number of babies born small-for-gestational age between those who received labetalol or nifedipine.

Important outcomes

Birth weight

- One randomised controlled trial (n=112) provided low quality evidence to show no clinically important difference in the birth weight of babies born to women who received labetalol or nifedipine.

Preterm birth (<37 weeks)

- One randomised controlled trial (n=112) provided low quality evidence to show no clinically important difference in the occurrence of preterm birth (<37 weeks) between those who received labetalol or nifedipine.

Preterm birth (<34 weeks)

- One randomised controlled trial (n=112) provided very low quality evidence to show no clinically important difference in the occurrence of preterm birth (<34 weeks) between those who received labetalol or nifedipine.

Admission to neonatal unit

- One randomised controlled trial (n=112) provided very low quality evidence to show no clinically important difference in the number of babies requiring neonatal unit admission between women who received labetalol or nifedipine.

Gestational age at birth

- One randomised controlled trial (n=112) provided moderate quality evidence to show a clinically important increase in the gestational age at birth for the babies of women who received labetalol compared to women who received nifedipine.

Outcomes for women

Important outcomes

Mode of birth (caesarean section)

- One randomised controlled trial (n=112) provided very low quality evidence to show no clinically important difference in the number of women giving birth by caesarean section between those who received labetalol or nifedipine.

Superimposed pre-eclampsia

- One randomised controlled trial (n=112) provided low quality evidence to show no clinically important difference in the number of women developing superimposed pre-eclampsia between those who received labetalol or nifedipine.

Superimposed pre-eclampsia <34 weeks

- One randomised controlled trial (n=112) provided very low quality evidence to show no clinically important difference in the occurrence of early onset superimposed pre-eclampsia (< 34 weeks) between those who received labetalol or nifedipine.

Eclampsia

- One randomised controlled trial (n=112) provided moderate quality evidence to show no occurrence of eclampsia in women who received labetalol or nifedipine.

Maternal death

- One randomised controlled trial (n=112) provided moderate quality evidence to show that no maternal deaths occurred in those who received labetalol or nifedipine.

Comparison 7. Labetalol versus methyldopa

Outcomes for babies

Critical outcomes

Stillbirth

- One randomised controlled trial (n=72) provided very low quality evidence to show that no stillbirths occurred in those who received labetalol or methyldopa.

Neonatal death up to 7 days

- One randomised controlled trial (n=72) provided very low quality evidence to show that there was no clinically important difference in neonatal death between those who received labetalol or methyldopa.

Small-for-gestational age

- Two randomised controlled trials (n=246) provided very low quality evidence to show no clinically important difference in the number of babies born small-for-gestational age between women who received labetalol or methyldopa.

Important outcomes

Birth weight

- One randomised controlled trial (n=72) provided very low quality evidence to show that there was no clinically important difference in infant birth weight between women who received labetalol or methyldopa.

Gestational age at birth

- One randomised controlled trial (n=72) provided very low quality evidence to show that there was no clinically important difference in the gestational age at birth for babies born to women who received labetalol or methyldopa.

Admission to neonatal unit

- One randomised controlled trial (n=72) provided very low quality evidence to show that there was no difference in the rate of admission to a neonatal unit for babies of women who received labetalol or methyldopa.

Outcomes for women

Critical outcomes

Blood pressure control

- One randomised controlled trial (n=72) provided very low quality evidence to show that there was no clinically important difference in the systolic or diastolic blood pressure measurements between those who received labetalol or methyldopa.

Important outcomes

Onset of labour (induction)

- One randomised controlled trial (n=72) provided very low quality evidence to show that there was no clinically important difference in the number of women undergoing induction of labour between those who received labetalol or methyldopa.

Mode of birth (caesarean section)

- Two randomised controlled trials (n=246) provided very low quality evidence to show that there was no clinically important difference in the incidence of caesarean section between those who received labetalol or methyldopa.

Comparison 8. Methyldopa versus placebo

Outcomes for babies

Critical outcomes

Stillbirth

- One randomised controlled trial (n=25) provided moderate quality evidence to show that no stillbirths occurred in those who received methyldopa or placebo.

Neonatal death

- One randomised controlled trial (n=25) provided moderate quality evidence to show that no neonatal deaths occurred in those who received methyldopa or placebo.

Important outcomes

Gestational age at birth

- One randomised controlled trial (n=25) provided moderate quality evidence to show a clinically important increase in the gestational age at birth for infants of women who received methyldopa compared to those of women who received placebo.

Outcomes for women

Important outcomes

Superimposed pre-eclampsia

- One randomised controlled trial (n=25) provided very low quality evidence to show no clinically important difference in the occurrence of superimposed pre-eclampsia between those who received methyldopa or placebo.

Comparison 9. Methyldopa versus no intervention

Outcomes for babies

Critical outcomes

Stillbirth

- One randomised controlled trial (n=190) provided very low quality evidence to show a clinically important reduction in stillbirths for those who received methyldopa, compared to no intervention.

Perinatal death

- One randomised controlled trial (n=178) provided very low quality evidence to show no clinically important difference in perinatal death rates between those who received methyldopa or no intervention.

Small-for-gestational age (birthweight <10th centile)

- One randomised controlled trial (n=178) provided very low quality evidence to show that there was no clinically important difference in the number of babies born small-for-gestational age between women who received methyldopa or no intervention.

Important outcomes

Birth weight

- One randomised controlled trial (n=190) provided low quality evidence to show no clinically important difference in the birth weight of babies born to women who received methyldopa or no intervention.

Gestational age at birth

- One randomised controlled trial (n=204) provided low quality evidence to show no clinically important difference in the gestational age of babies born to women who received methyldopa or no intervention.

Preterm birth (<37 weeks)

- One randomised controlled trial (n=178) provided very low quality evidence to show that there was no clinically important difference in preterm births (<37 weeks) between those who received methyldopa or no intervention.

Neurodevelopmental outcomes at ≥ 18 months: impaired vision at 7.5 years old

- One randomised controlled trial (n=190) provided very low quality evidence to show that there may be a clinically important decrease in the number of children with impaired vision at 7.5 years old for those who received methyldopa, as compared to placebo, but there was some uncertainty around the effect (RR 0.47, 95% CI 0.20 to 1.11).

Neurodevelopmental outcomes at ≥ 18 months: impaired hearing at 7.5 years old

- One randomised controlled trial (n=188) provided very low quality evidence to show that there was no clinically important difference in impaired hearing at 7.5 years follow-up between children born to women who received methyldopa or no intervention

Outcomes for women

Important outcomes

Superimposed pre-eclampsia

- One randomised controlled trial (n=178) provided very low quality evidence to show that there was no clinically important difference in the development of superimposed pre-eclampsia between those who received methyldopa or no intervention.

Placental abruption

- One randomised controlled trial (n=178) provided very low quality evidence to show that there was no clinically important difference in the incidence of placental abruption between those who received methyldopa or no intervention

Mode of birth (caesarean section)

- One randomised controlled trial (n=178) provided very low quality evidence to show that there was no clinically important difference in the number of women giving birth by caesarean section between those who received methyldopa or no intervention

Comparison 10. Amlodipine versus aspirin

Outcomes for babies

Critical outcomes

Stillbirth

- One randomised controlled trial (n=39) provided very low quality evidence to show no clinically important difference in the occurrence of stillbirth between those who received amlodipine or aspirin.

Neonatal death

- One randomised controlled trial (n=39) provided moderate quality evidence to show that no neonatal deaths occurred in those who received amlodipine or aspirin.

Small-for-gestational age (birthweight <10th centile)

- One randomised controlled trial (n=39) provided very low quality evidence to show no clinically important difference in the number of babies born small-for-gestational age between those who received amlodipine or aspirin.

Important outcomes:

Birth weight

- One randomised controlled trial (n=39) provided low quality evidence to show no clinically important difference in the birth weight of infants born to women who received amlodipine or aspirin.

Preterm birth (weeks not specified)

- One randomised controlled trial (n=39) provided very low quality evidence to show no clinically important difference in the occurrence of preterm birth between those who received amlodipine or aspirin.

Outcomes for women

Critical outcomes

Severe hypertension

- One randomised controlled trial (n=39) provided very low quality evidence to show no clinically important difference in the incidence of severe hypertension between those who received amlodipine or aspirin.

Important outcomes

Placental abruption

- One randomised controlled trial (n=39) provided very low quality evidence to show no clinically important difference in the occurrence of placental abruption between those who received amlodipine or aspirin.

Mode of birth (caesarean section)

- One randomised controlled trial (n=39) provided very low quality evidence to show no clinically important difference in the number of women giving birth by caesarean section between those who received amlodipine or aspirin.

Comparison 11. Aspirin versus no intervention

Outcomes for babies

Critical outcomes

Stillbirth and neonatal death

- Two randomised controlled trials (n=656) provided very low quality evidence to show no clinically important difference in the occurrence of stillbirth and neonatal death between those who received aspirin or no intervention.

Small for gestational age

- Four randomised controlled trials (n=1074) provided very low quality evidence to show no clinically important difference in the number of babies born small-for-gestational age between women who received aspirin or no intervention.

Important outcomes

Birth weight

- One randomised controlled trial (n=197) provided low quality evidence to show no clinically important difference in the birth weight of babies born to women who received aspirin or no intervention.

Gestational age

- One randomised controlled trial (n=197) provided moderate quality evidence to show that there was no clinically important difference in the gestational age at birth of babies born to women who received aspirin or no intervention.

Preterm birth <37 weeks

- Two randomised controlled trials (n=566) provided low quality evidence to show that there was no clinically important difference in in the number of preterm births (<37 weeks) for women who received aspirin, as compared to those who received no intervention.
- A meta-analysis of individual participant data from a further 17 RCTs (n=2518) provided moderate quality evidence to show there may be a clinically important reduction in the number of preterm births (<37 weeks) for women who received aspirin, but there was some uncertainty over the estimate (RR 0.73, 95% CI 0.53 to 1.00).

Preterm birth <34 weeks

- A meta-analysis of individual participant data from 17 RCTs (n=2518) provided low quality evidence to show no clinically important difference in the number of preterm births (<34 weeks) between those who received aspirin or no intervention.

Preterm birth <28 weeks

- A meta-analysis of individual participant data from 17 RCTs (n=2518) provided low quality evidence to show no clinically important difference in the number of preterm births (<28 weeks) between those who received aspirin or no intervention.

Admission to neonatal unit

- One randomised controlled trial (n=197) provided low quality evidence to show a clinically important reduction in the number of neonatal unit admissions for babies born to women who received aspirin, as compared to those who received no intervention.

Outcomes for women

Critical outcomes

Severe hypertension

- One randomised controlled trial (n=197) provided very low quality evidence to show no clinically important difference in the occurrence of worsening hypertension between those who received aspirin or no intervention.
- One randomised controlled trial (n=197) provided moderate quality evidence to show no clinically important difference in the diastolic blood pressure at 36 weeks' gestation between those who received aspirin or no intervention.

Important outcomes

Development of pre-eclampsia

- Two randomised controlled trials (n=307) provided very low quality evidence to show no clinically important difference in the development of pre-eclampsia between those who received aspirin or no intervention.
- A meta-analysis of individual participant data from 31 RCTs (n=3303) provided high quality evidence to show no clinically important difference in the development of pre-eclampsia between those who received aspirin or no intervention.

Spontaneous onset of labour

- One randomised controlled trial (n=197) provided low quality evidence to show no clinically important difference in the number of women who had a spontaneous onset of labour between those who received aspirin or no intervention.

See appendix E for Forest plots.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Treatment of chronic hypertension in pregnancy aims to control the mother's blood pressure without leading to any adverse effects on the baby. The committee therefore identified 3 outcomes of critical importance to allow the balance of benefits and harms of interventions to be assessed. These were control of blood pressure (outcome for women) and perinatal mortality (including stillbirth and neonatal death) and small for gestational age (both outcomes for babies).

The committee also identified 7 important outcomes for babies to provide further information on the potential harms to babies. These were birth weight, gestational age at birth, preterm birth (< 28 weeks, <34 weeks, <37 weeks), admission to a neonatal unit, cerebral palsy, neurodevelopmental delay, and neurosensory impairment. Six further important outcomes for women with chronic hypertension were identified, and these were superimposed pre-eclampsia, HELLP, placental abruption, onset of labour, mode of birth, and maternal death.

The quality of the evidence

Eighteen articles were included in the review. The quality of the evidence was assessed with the Cochrane Risk of Bias tool and ranged from moderate to very low. The main sources of potential bias were: lack of information on the randomisation method used, unreported or unclear concealment of allocation, and lack of blinding of participants and investigators.

The committee determined that there was sufficient evidence to allow them to make some recommendations relating to treatment initiation thresholds and treatment targets. However, there was not enough evidence to discriminate between different pharmacologic treatments, therefore they made a research recommendation relating to the choice of pharmacologic agents. There was also concern (based on the committee's clinical knowledge and expertise) over the potential neonatal adverse outcomes with the use of beta-blockers in women with hypertension, and so the committee made a research recommendation relating to this too.

Benefits and harms

The committee made an overarching recommendation on the advice that should be provided to pregnant women with chronic hypertension, in accordance with existing NICE guidelines on the treatment of hypertension in adults. This guideline does not provide specific advice for pregnant women, but the committee agreed that the principles of treatment and advice (such as exercise and healthy diet) are similar.

No specific evidence was available that demonstrated the blood pressure at which treatment for chronic hypertension should be initiated, but the committee identified that in the CHIPS study (Magee 2015) (which had identified that tight blood pressure control led to a reduced incidence of severe hypertension in women), the treatment threshold had been a diastolic blood pressure of ≥90mmHg. There was no equivalent systolic blood pressure treatment threshold in this study so the committee referred to the NICE guidelines on the treatment of hypertension in adults and used their treatment threshold of ≥140mmHg. Similarly, for the target blood pressure the committee adopted the CHIPS target of ≤85mmHg diastolic and the adult guideline target of ≤135mmHg systolic. There was some low quality evidence that a tighter control of blood pressure may slightly increase the number of babies who were small-for-gestational-age (but with no impact on need for high-level neonatal care or pregnancy loss). However, the committee noted that in the full CHIPS trial (including women with both chronic hypertension and gestational hypertension) no difference was seen in the number of babies who were born small for gestational age, after adjustment for baseline differences between the two groups of participants. Overall, the committee balanced the benefits and harms and made recommendations to adopt these treatment thresholds and treatment targets.

Chronic hypertension is associated with complications during pregnancy, including adverse maternal and neonatal outcomes. However, treatments such as antihypertensives and aspirin also carry potential risks such as side effects for the mother and the possibility of teratogenic effects. Clinicians continuing existing treatment or initiating treatments should inform women of these risks and benefits. There was evidence for beneficial effects on the mother's blood pressure with tight blood pressure control. There was no evidence of a benefit on placental abruption or preterm birth with any of the interventions, but some evidence for a reduction in stillbirths and increased gestational age at birth with some of the pharmacologic interventions. However, there was also some evidence for harm with interventions – a possible increase in small-for-gestational age babies with tight blood pressure control and atenolol. The committee weighed up the benefits and harms and, based on their clinical expertise as well, agreed that treatment with antihypertensive medication should be continued or initiated in pregnant women with chronic hypertension, in order to reduce the risk of serious complications such as severe hypertension, placental abruption or preterm birth.

The available evidence was not sufficient to recommend one antihypertensive medicine over another as it demonstrated no significant differences between labetalol, nifedipine and methyldopa. The only significant difference noted was a small increase in gestational age at delivery for infants of mothers treated with labetalol, as compared with nifedipine. However, the committee noted that this difference was not seen after adjustment for baseline differences in the treatment groups. When methyldopa was compared with no intervention or placebo, it showed that those who received the active intervention experienced a longer

gestational age and fewer stillbirths. The committee discussed the fact that labetalol was specifically licensed in pregnancy (after the 1st trimester) whereas other treatments are not, but that all three medicines had been used in pregnant women for many years with no reports of major adverse effects, had been recommended in the 2010 guideline for gestational hypertension and pre-eclampsia, and that it made sense for clinicians to use the same range of drugs to treat all types of hypertension. The committee therefore chose to recommend labetaolol as the first-line choice due to its licensed status, with nifedipine or methylodopa as alternative treatment options

Aspirin had been included as one of the interventions in the review and there was evidence to show that it may reduce preterm birth (<37 weeks) and neonatal unit admission. The committee therefore chose to retain the recommendation from the previous guideline to use aspirin from the second trimester of pregnancy (12 weeks). The committee noted that the studies used different doses of aspirin, ranging from 50 to 150mg daily, and that common practice in the UK was to offer 75 to 150mg, with there being little evidence to support the optimal dose.

Because of the lack of evidence on the effectiveness and safety of antihypertensives in pregnant women with chronic hypertension, the committee decided to repeat the research recommendation made in the previous version of the guideline, to determine the best agent to use. The committee agreed that as ethnicity has an impact on the choice of antihypertensives outside of pregnancy, this study should include an analysis by different ethnicities.

Labetalol is approved for use in pregnancy, and atenolol had shown some efficacy for blood pressure control but with very limited evidence and possibly some adverse effects. The committee were aware from their own clinical experience and knowledge that these adverse effects included hypoglycaemia, but as there is limited data for both of these medicines, the committee also made a research recommendation to establish whether beta-blockers (and mixed alpha-beta blockers) can be used safely in chronic hypertension in pregnancy.

The committee noted that since the previous guideline had been published, NICE had produced diagnostic guidance on the use of placental growth factor (PlGF) monitoring to help rule-out pre-eclampsia in women between 20^{+0} and 34^{+6} weeks. Since chronic hypertension is a risk factor for pre-eclampsia, the committee agreed that a cross-reference to this guidance should be included.

Cost effectiveness and resource use

No relevant studies were identified in a systematic review of the economic evidence.

The committee considered that these recommendations would not lead to an increase in resource use as they reflect standard practice for the majority of centres.

Other factors the committee took into account

The committee were aware of the findings from a recently updated Cochrane systematic review and meta-analysis on antihypertensive treatment in pregnancy, which indicated that beta-blockers and calcium channel blockers were more effective than methyldopa at preventing severe hypertension. The Cochrane review included a mixed population of women with any hypertension during pregnancy and so did not meet the protocol criteria for inclusion in this evidence report (which included women with chronic hypertension only). However, the committee agreed that it would be appropriate to recommend methyldopa as the third-line option, after labetalol and nifedipine, based on the findings of the Cochrane review and their experience of the side-effect profile of methyldopa.

The committee were also aware of 2 forthcoming studies which may provide further evidence in this area. The Chronic Hypertension and Pregnancy (CHAP) study will provide further advice on treatment initiation thresholds (estimated completion date December 2019) and the When to Induce Labour to Limit risk in pregnancy hypertension (WILL) study is investigating the optimal timing of birth.

The committee were aware of a recent publication from NHS England, Saving Babies' Lives, which recommended the use of low dose aspirin in higher risk women. The dose suggested in this document was 150mg at night, or lower doses (60 to 75 mg) in some circumstances, for example women with hepatic or renal disease. This corresponded with the range of 75mg to 150 mg suggested by the committee.

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Appendices

Appendix A – Review protocol

Table 3: Review protocol

Field (based on PRISMA-P)	Content
Key area in the scope	Management of pregnancy with chronic hypertension
Draft review question from the previous guideline	What interventions for chronic hypertension are effective at improving outcomes for women and infants?
Actual review question	What interventions for chronic hypertension are effective at improving outcomes for women and infants?
Type of review question	Intervention
Objective of the review	To update the recommendations in the previous guideline (CG107) for the treatment of pregnant women who have chronic hypertension – surveillance has indicated that the CHIPS study may have changed treatment targets (rec 1.2.3.1)
Eligibility criteria – population/disease/condition/issue/domain	Pregnant women with chronic hypertension. This population includes women with: • Essential (primary) hypertension • Secondary hypertension e.g. secondary to chronic kidney disease, diabetes.
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Centrally acting α2-Adrenoceptor Agonists

Field (based on PRISMA-P)	Content

Field (based on PRISMA-P)	Content

Field (based on PRISMA-P)	Content
	• Beta blockers/mixed alpha beta blockers • Calcium (Ca2+) channel blockers • Diuretics • ACE inhibitors • Acetylsalicylic acid (aspirin) • Elective (planned) delivery versus expectant management • Tight management (e.g. target = 85mmHg) • Less tight management (e.g. target = 100 mmHg) • Automated monitoring of blood pressure (BP) • Ambulatory/self-monitoring of blood pressure • Exercise • Dietary interventions • Dietary salt reduction
Eligibility criteria – comparator(s)/control or reference (gold) standard	• No intervention • Placebo • Each other of the interventions outlined above • Combinations of the interventions outlined above
Outcomes and prioritisation	Outcomes for babies:

Field (based on PRISMA-P)	Content

	Critical outcomes:
	• Perinatal mortality
	  ○ Stillbirth (include if reported as part of perinatal mortality)
	  ○ Neonatal death up to 7 days (include if reported as part of perinatal mortality)
	• Small-for-gestational-age (BW<10th centile)
	Important outcomes:
	• Birth weight
	• Gestational age at delivery
	• Preterm birth (<28 weeks, <34 weeks, <37 weeks)
	• Admission to neonatal unit
	• Neurodevelopmental outcome
	  ○ Cerebral palsy (dichotomous outcome, reported as present/absent, not severity of condition)
	  ○ Neurodevelopmental delay (dichotomous outcome, not continuous outcomes such as mean change in score):
	  - Severe (score of >2SD below normal on validated assessment scales, or Bayley's assessment scale of mental development index [MDI] or psychomotor developmental index [PDI] <70, or complete inability to assign score due to CP or severe cognitive delay)
	  - Moderate (Score of 1-2 SD below normal on validated assessment scales, or Bayley's assessment scale MDI or PDI 70-84)
	  ○ Neurosensory impairment (dichotomous outcome, present or absent, not severity of condition)
	  - Severe hearing impairment (e.g. deaf)
	  - Severe visual impairment (e.g. blind)

Field (based on PRISMA-P)	Content

	Outcomes for women:
	Critical outcome:
	• Blood pressure control
	  ○ Severe hypertension
	Important outcomes:
	• Superimposed pre-eclampsia
	  ○ including eclampsia and HELLP (haemolysis, elevated liver enzymes, low platelets)
	• Placental abruption
	• Onset of labour
	• Mode of birth
	• Maternal death

Eligibility criteria – study design	Only published full text papers in English language • Systematic reviews of RCTs • RCTs • Comparative cohort studies (only if RCTs unavailable or limited data to inform decision making) 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)
Exclusion criteria	• NA
Proposed stratified, sensitivity/sub-group analysis, or meta-regression	Stratify for mild/mod/severe hypertension Stratify for black ethnic group Stratify by the following types of interventions: ○ Centrally acting α2-Adrenoceptor Agonists

Field (based on PRISMA-P)	Content
	- Methyldopa o Beta blockers/mixed alpha beta blockers - Labetalol - Atenolol o Calcium (Ca2+) channel blockers - Amlodipine - Nicardipine - Nifedipine o Diuretics - Furosemide - Thiazides o ACE inhibitors - Enalapril - Captopril - ARB Sub-groups in case of heterogeneity for primary and secondary hypertension Sub-groups in case of heterogeneity for individual drugs
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.

Field (based on PRISMA-P)	Content
	STAR will be used for 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. Limits (e.g. date, study design): Study design limited to Systematic Reviews, RCTs and Comparative Cohort Studies. Apply standard animal/non-English language filters. No date limit. Supplementary search techniques: No supplementary search techniques were used. Key papers (from surveillance report): • Magee LA, von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez J, Singer J, Gafni A, Gruslin A. Less-tight versus tight control of hypertension in pregnancy. New England Journal of Medicine. 2015 Jan 29;372(5):407-17. (CHIPS study). • Brown M, Roberts L, Mackenzie C, Mangos G, Davis G. A Prospective Randomized Study Of Automated Versus Mercury Blood Pressure Recordings In Hypertensive Pregnancy (tram Study). Nephrology. 2008 Sep 1;13:A129. • Webster, Louise M., et al. "Impact of Antihypertensive Treatment on Maternal and Perinatal Outcomes in Pregnancy Complicated by Chronic Hypertension: A Systematic Review and Meta-Analysis." Journal of the American Heart Association 6.5 (2017): e005526. 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.

Field (based on PRISMA-P)	Content
Author contacts	Developer: National Guideline Alliance NGA-enquiries@RCOG.org.uk
Highlight if amendment to previous protocol	New items added in this protocol: New interventions were integrated to reflect those highlighted by the surveillance summary. These were: timing of delivery, tight versus less tight control, monitoring of blood pressure and exercise. New outcomes: neonatal death up to 7 days, neurodevelopmental outcomes Items removed from the previous protocol: Removed from the interventions: thiazide, dypiridamole, rest and bed rest were deleted. The population, comparisons and outcomes are the same as in the 2010 protocol for this review question.
Search strategy – for one database	For details please see appendix B
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).
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.

Field (based on PRISMA-P)	Content
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 • Randomised controlled trials – Cochrane Risk of Bias tool 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/. Studies included in the previous guideline (CG107) that meet the inclusion criteria of this protocol will be assessed with the above mentioned checklists (as appropriate) and outcomes will be evaluated using GRADE.
Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual

Field (based on PRISMA-P)	Content
Methods for quantitative analysis – combining studies and exploring (in)consistency	Synthesis of data: Meta-analysis will be conducted where appropriate using Review Manager. 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. 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.

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

Appendix B – Literature search strategies

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

Date of last search: 19/02/18

#	Searches
1	META-ANALYSIS/
2	META-ANALYSIS AS TOPIC/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	cochrane.jw.
10	or/1-9
11	randomized controlled trial.pt.
12	controlled clinical trial.pt.
13	pragmatic clinical trial.pt.
14	randomi#ed.ab.
15	placebo.ab.
16	randomly.ab.
17	CLINICAL TRIALS AS TOPIC/
18	trial.ti.
19	or/11-18
20	COHORT STUDIES/
21	(cohort adj3 (study or studies)).ti,ab.
22	(Cohort adj3 analy$).ti,ab.
23	FOLLOW-UP STUDIES/
24	(Follow$ up adj3 (study or studies)).ti,ab.
25	LONGITUDINAL STUDIES/
26	longitudinal$.ti,ab.
27	PROSPECTIVE STUDIES/
28	prospective$.ti,ab.
29	RETROSPECTIVE STUDIES/
30	retrospective$.ti,ab.
31	OBSERVATIONAL STUDY/
32	observational$.ti,ab.
33	or/20-32
34	HYPERTENSION, PREGNANCY-INDUCED/
35	PREGNANCY/ and HYPERTENSION/
36	PRE-ECLAMPSIA/
37	HELLP SYNDROME/
38	((pregnan$ or gestation$) adj5 hypertensi$).ti.
39	preeclamp$.ti,ab.
40	pre eclamp$.ti,ab.
41	HELLP.ti,ab.
42	tox?emi$.ti,ab.
43	or/34-42
44	exp ADRENERGIC ALPHA-2 RECEPTOR AGONISTS/
45	(alpha$ adj3 Agonist?).mp.
46	(Brimonidine Tartrate or Clonidine or exmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine).mp.
47	exp ADRENERGIC BETA-ANTAGONISTS/
48	(Adrenergic beta$ adj3 Antagonist?).mp.
49	Beta blocker?.mp.
50	(mixed adj3 blocker?).ti,ab.

#	Searches
51	(Alprenolol 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.
52	exp CALCIUM CHANNEL BLOCKERS/
53	(calcium channel adj3 (blocker? or antagonist?)).ti,ab.
54	(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 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.
55	Magnesium Sulfate.ti.
56	Magnesium Sulfate.ab. /freq=2
57	DIURETICS/
58	diuretic?.ti,ab.
59	(Acetazolamide or Amiloride or Bendroflumethiazide or Bumetanide or Chlorothiazide or Chlorthalidone or Clopamide or Cyclopenthiazide or Ethacrynic Acid or Ethoxzolamide or Furosemide or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Mefruside or Methazolamide or Methyclothiazide or Metolazone or Muzolimine or Polythiazide or Potassium Citrate or Spironolactone or Ticrynafen or Triamterene or Trichlormethiazide or Xipamide or Isosorbide or Mannitol or Canrenoic Acid or Canrenone).mp.
60	exp ANGIOTENSIN-CONVERTING ENZYME INHIBITORS/
61	(angiotensin converting enzyme adj3 (antagonist? or inhibitor?)).ti,ab.
62	(ACE adj3 (antagonist? or inhibitor?)).ti,ab.
63	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide).mp.
64	ASPIRIN/
65	(acetylsalicylic acid or aspirin?).ti.
66	(acetylsalicylic acid or aspirin?).ab. /freq=2
67	((elect$ or plan$) adj3 deliver$).ti,ab.
68	(expect$ adj3 manag$).ti,ab.
69	(tight$ adj3 (manag$ or control$)).ti,ab.
70	BLOOD PRESSURE DETERMINATION/
71	BLOOD PRESSURE MONITORING, AMBULATORY/
72	((Automat$ or ambulatory or self$) adj3 blood pressure?).ti,ab.
73	exp EXERCISE/
74	(exercis$ or physical$ activ$ or swim$ or cycl$ or sport? or run$ or jog$ or walk$ or stair climb$ or gym$ or resistance train$ or yoga or pilates).ti.
75	(exercis$ or physical$ activ$ or swim$ or cycl$ or sport? or run$ or jog$ or walk$ or stair climb$ or gym$ or resistance train$ or yoga or pilates).ab. /freq=2
76	exp DIET/
77	diet$.ti.
78	diet$.ab. /freq=2
79	(calor$ adj3 restrict$).ti,ab.
80	((portion? or serving) adj3 size?).ti,ab.
81	((low$ or restrict$) adj3 (salt or sodium)).ti,ab.
82	or/44-81
83	43 and 82
84	limit 83 to english language
85	LETTER/
86	EDITORIAL/
87	NEWS/
88	exp HISTORICAL ARTICLE/
89	ANECDOTES AS TOPIC/
90	COMMENT/
91	CASE REPORT/
92	(letter or comment*).ti.
93	or/85-92
94	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
95	93 not 94
96	ANIMALS/ not HUMANS/
97	exp ANIMALS, LABORATORY/
98	exp ANIMAL EXPERIMENTATION/
99	exp MODELS, ANIMAL/
100	exp RODENTIA/
101	(rat or rats or mouse or mice).ti.

#	Searches
102	or/95-101
103	84 not 102
104	10 and 103
105	19 and 103
106	33 and 103
107	or/104-106

Database: Embase; and Embase Classic

Date of last search: 19/02/18

#	Searches
1	SYSTEMATIC REVIEW/
2	META-ANALYSIS/
3	(meta analy* or metanaly* or metaanaly*).ti,ab.
4	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
5	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
6	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
7	(search* adj4 literature).ab.
8	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
9	((pool* or combined) adj2 (data or trials or studies or results)).ab.
10	cochrane.jw.
11	or/1-10
12	random*.ti,ab.
13	factorial*.ti,ab.
14	(crossover* or cross over*).ti,ab.
15	((doubl* or singl*) adj blind*).ti,ab.
16	(assign* or allocat* or volunteer* or placebo*).ti,ab.
17	CROSSOVER PROCEDURE/
18	SINGLE BLIND PROCEDURE/
19	RANDOMIZED CONTROLLED TRIAL/
20	DOUBLE BLIND PROCEDURE/
21	or/12-20
22	COHORT ANALYSIS/
23	(cohort adj3 (study or studies)).ti,ab.
24	(Cohort adj3 analy$).ti,ab.
25	FOLLOW UP/
26	(Follow$ up adj3 (study or studies)).ti,ab.
27	LONGITUDINAL STUDY/
28	longitudinal$.ti,ab.
29	PROSPECTIVE STUDY/
30	prospective$.ti,ab.
31	RETROSPECTIVE STUDY/
32	retrospective$.ti,ab.
33	OBSERVATIONAL STUDY/
34	observational$.ti,ab.
35	or/22-34
36	MATERNAL HYPERTENSION/
37	PREGNANCY/ and HYPERTENSION/
38	PREECLAMPSIA/
39	HELLP SYNDROME/
40	((pregnan$ or gestation$) adj5 hypertensi$).ti.
41	preeclamp$.ti,ab.
42	pre eclamp$.ti,ab.
43	HELLP.ti,ab.
44	tox?emi$.ti,ab.
45	or/36-44
46	exp *ALPHA 2 ADRENERGIC RECEPTOR STIMULATING AGENT/
47	(alpha$ adj3 Agonist?).mp.

#	Searches
48	(Brimonidine Tartrate or Clonidine or exmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine).mp.
49	exp *BETA ADRENERGIC RECEPTOR BLOCKING AGENT/
50	(adrenergic adj3 beta adj3 antagonist?).ti,ab.
51	Beta blocker?.mp.
52	(mixed adj3 blocker?).ti,ab.
53	(Alprenolol 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.
54	exp *CALCIUM CHANNEL BLOCKING AGENT/
55	(calcium channel adj3 (blocker? or antagonist?)).ti,ab.
56	(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 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.
57	Magnesium Sulfate.ti.
58	Magnesium Sulfate.ab. /freq=2
59	exp *DIURETIC AGENT/
60	diuretic?.ti,ab.
61	(Acetazolamide or Amiloride or Bendroflumethiazide or Bumetanide or Chlorothiazide or Chlorthalidone or Clopamide or Cyclopenthiazide or Ethacrynic Acid or Ethoxzolamide or Furosemide or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Mefruside or Methazolamide or Methyclothiazide or Metolazone or Muzolimine or Polythiazide or Potassium Citrate or Spironolactone or Ticrynafen or Triamterene or Trichlormethiazide or Xipamide or Isosorbide or Mannitol or Canrenoic Acid or Canrenone).mp.
62	exp *DIPEPTIDYL CARBOXYPEPTIDASE INHIBITOR/
63	(angiotensin converting enzyme adj3 (antagonist? or inhibitor?)).ti,ab.
64	(ACE adj3 (antagonist? or inhibitor?)).ti,ab.
65	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide).mp.
66	*ACETYLSALICYLIC ACID/
67	(acetylsalicylic acid or aspirin?).ti.
68	(acetylsalicylic acid or aspirin?).ab. /freq=2
69	((elect$ or plan$) adj3 deliver$).ti,ab.
70	(expect$ adj3 manag$).ti,ab.
71	(tight$ adj3 (manag$ or control$)).ti,ab.
72	*BLOOD PRESSURE MEASUREMENT/
73	*BLOOD PRESSURE MONITORING/
74	((Automat$ or ambulatory or self$) adj3 blood pressure?).ti,ab.
75	exp *EXERCISE/
76	(exercis$ or physical$ activ$ or swim$ or cycl$ or sport? or run$ or jog$ or walk$ or stair climb$ or gym$ or resistance train$ or yoga or pilates).ti.
77	(exercis$ or physical$ activ$ or swim$ or cycl$ or sport? or run$ or jog$ or walk$ or stair climb$ or gym$ or resistance train$ or yoga or pilates).ab. /freq=2
78	exp *DIET/
79	diet$.ti.
80	diet$.ab. /freq=2
81	(calor$ adj3 restrict$).ti,ab.
82	((portion? or serving) adj3 size?).ti,ab.
83	*SODIUM RESTRICTION/
84	((low$ or restrict$) adj3 (salt or sodium)).ti,ab.
85	or/46-84
86	45 and 85
87	limit 86 to english language
88	letter.pt. or LETTER/
89	note.pt.
90	editorial.pt.
91	CASE REPORT/ or CASE STUDY/
92	(letter or comment*).ti.
93	or/88-92
94	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
95	93 not 94
96	ANIMAL/ not HUMAN/
97	NONHUMAN/

#	Searches
98	exp ANIMAL EXPERIMENT/
99	exp EXPERIMENTAL ANIMAL/
100	ANIMAL MODEL/
101	exp RODENT/
102	(rat or rats or mouse or mice).ti.
103	or/95-102
104	87 not 103
105	11 and 104
106	21 and 104
107	35 and 104
108	or/105-107

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: 19/02/18

#	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: [HELLP SYNDROME] this term only
7	((pregnan* or gestation*) near/5 hypertensi*):ti
8	preeclamp*:ti,ab
9	pre eclamp*:ti,ab
10	HELLP:ti,ab
11	tox?emi*:ti,ab
12	#1 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13	MeSH descriptor: [ADRENERGIC ALPHA-2 RECEPTOR AGONISTS] 2 tree(s) exploded
14	(alpha* near/3 Agonist?):ti,ab
15	(Brimonidine Tartrate or Clonidine or exmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine):ti,ab
16	MeSH descriptor: [ADRENERGIC BETA-ANTAGONISTS] 2 tree(s) exploded
17	(Adrenergic beta* near/3 Antagonist?):ti,ab
18	Beta blocker?:ti,ab
19	(mixed near/3 blocker?):ti,ab
20	(Alprenolol 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
21	MeSH descriptor: [CALCIUM CHANNEL BLOCKERS] 2 tree(s) exploded
22	(calcium channel near/3 (blocker? or antagonist?)):ti,ab
23	(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 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
24	Magnesium Sulfate:ti
25	MeSH descriptor: [DIURETICS] this term only
26	diuretic?:ti,ab
27	(Acetazolamide or Amiloride or Bendroflumethiazide or Bumetanide or Chlorothiazide or Chlorthalidone or Clopamide or Cyclopenthiazide or Ethacrynic Acid or Ethoxzolamide or Furosemide or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Mefruside or Methazolamide or Methyclothiazide or Metolazone or Muzolimine or Polythiazide or Potassium Citrate or Spironolactone or Ticrynafen or Triamterene or Trichlormethiazide or Xipamide or Isosorbide or Mannitol or Canrenoic Acid or Canrenone):ti,ab
28	MeSH descriptor: [ANGIOTENSIN-CONVERTING ENZYME INHIBITORS] 1 tree(s) exploded
29	(angiotensin converting enzyme near/3 (antagonist? or inhibitor?)):ti,ab
30	(ACE near/3 (antagonist? or inhibitor?)):ti,ab
31	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide):ti,ab

#	Searches
32	MeSH descriptor: [ASPIRIN] this term only
33	(acetylsalicylic acid or aspirin?):ti
34	((elect* or plan*) near/3 deliver*):ti,ab
35	(expect* near/3 manag*):ti,ab
36	(tight* near/3 (manag* or control*)):ti,ab
37	MeSH descriptor: [BLOOD PRESSURE DETERMINATION] this term only
38	MeSH descriptor: [BLOOD PRESSURE MONITORING, AMBULATORY] this term only
39	((Automat* or ambulatory or self*) near/3 blood pressure?):ti,ab
40	MeSH descriptor: [EXERCISE] 2 tree(s) exploded
41	exercis*:ti
42	(physical* activ* or swim* or cycl* or sport? or run* or jog* or walk* or stair climb* or gym* or resistance train* or yoga or pilates):ti,ab
43	MeSH descriptor: [DIET] 1 tree(s) exploded
44	diet*:ti
45	(calor* near/3 restrict*):ti,ab
46	((portion? or serving) near/3 size?):ti,ab
47	((low* or restrict*) near/3 (salt or sodium)):ti,ab
48	#13 or #14 or #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 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47
49	#12 and #48

Health economics search strategies

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

Date of last search: 19/02/18

#	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	HELLP SYNDROME/
26	((pregnan$ or gestation$) adj5 hypertensi$).ti.
27	preeclamp$.ti,ab.
28	pre eclamp$.ti,ab.
29	HELLP.ti,ab.

#	Searches
30	tox?emi$.ti,ab.
31	or/22-30
32	exp ADRENERGIC ALPHA-2 RECEPTOR AGONISTS/
33	(alpha$ adj3 Agonist?).mp.
34	(Brimonidine Tartrate or Clonidine or exmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine).mp.
35	exp ADRENERGIC BETA-ANTAGONISTS/
36	(Adrenergic beta$ adj3 Antagonist?).mp.
37	Beta blocker?.mp.
38	(mixed adj3 blocker?).ti,ab.
39	(Alprenolol 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.
40	exp CALCIUM CHANNEL BLOCKERS/
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 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	Magnesium Sulfate.ti.
44	Magnesium Sulfate.ab. /freq=2
45	DIURETICS/
46	diuretic?.ti,ab.
47	(Acetazolamide or Amiloride or Bendroflumethiazide or Bumetanide or Chlorothiazide or Chlorthalidone or Clopamide or Cyclopenthiazide or Ethacrynic Acid or Ethoxzolamide or Furosemide or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Mefruside or Methazolamide or Methyclothiazide or Metolazone or Muzolimine or Polythiazide or Potassium Citrate or Spironolactone or Ticrynafen or Triamterene or Trichlormethiazide or Xipamide or Isosorbide or Mannitol or Canrenoic Acid or Canrenone).mp.
48	exp ANGIOTENSIN-CONVERTING ENZYME INHIBITORS/
49	(angiotensin converting enzyme adj3 (antagonist? or inhibitor?)).ti,ab.
50	(ACE adj3 (antagonist? or inhibitor?)).ti,ab.
51	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide).mp.
52	ASPIRIN/
53	(acetylsalicylic acid or aspirin?).ti.
54	(acetylsalicylic acid or aspirin?).ab. /freq=2
55	((elect$ or plan$) adj3 deliver$).ti,ab.
56	(expect$ adj3 manag$).ti,ab.
57	(tight$ adj3 (manag$ or control$)).ti,ab.
58	BLOOD PRESSURE DETERMINATION/
59	BLOOD PRESSURE MONITORING, AMBULATORY/
60	((Automat$ or ambulatory or self$) adj3 blood pressure?).ti,ab.
61	exp EXERCISE/
62	(exercis$ or physical$ activ$ or swim$ or cycl$ or sport? or run$ or jog$ or walk$ or stair climb$ or gym$ or resistance train$ or yoga or pilates).ti.
63	(exercis$ or physical$ activ$ or swim$ or cycl$ or sport? or run$ or jog$ or walk$ or stair climb$ or gym$ or resistance train$ or yoga or pilates).ab. /freq=2
64	exp DIET/
65	diet$.ti.
66	diet$.ab. /freq=2
67	(calor$ adj3 restrict$).ti,ab.
68	((portion? or serving) adj3 size?).ti,ab.
69	((low$ or restrict$) adj3 (salt or sodium)).ti,ab.
70	or/32-69
71	31 and 70
72	limit 71 to english language
73	LETTER/
74	EDITORIAL/
75	NEWS/
76	exp HISTORICAL ARTICLE/
77	ANECDOTES AS TOPIC/
78	COMMENT/
79	CASE REPORT/

#	Searches
80	(letter or comment*).ti.
81	or/73-80
82	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
83	81 not 82
84	ANIMALS/ not HUMANS/
85	exp ANIMALS, LABORATORY/
86	exp ANIMAL EXPERIMENTATION/
87	exp MODELS, ANIMAL/
88	exp RODENTIA/
89	(rat or rats or mouse or mice).ti.
90	or/83-89
91	72 not 90
92	21 and 91

Databases: Embase; and Embase Classic

Date of last search: 19/02/18

#	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	PREECLAMPSIA/
21	HELLP SYNDROME/
22	((pregnan$ or gestation$) adj5 hypertensi$).ti.
23	preeclamp$.ti,ab.
24	pre eclamp$.ti,ab.
25	HELLP.ti,ab.
26	tox?emi$.ti,ab.
27	or/18-26
28	exp *ALPHA 2 ADRENERGIC RECEPTOR STIMULATING AGENT/
29	(alpha$ adj3 Agonist?).mp.
30	(Brimonidine Tartrate or Clonidine or exmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine).mp.
31	exp *BETA ADRENERGIC RECEPTOR BLOCKING AGENT/
32	(adrenergic adj3 beta adj3 antagonist?).ti,ab.
33	Beta blocker?.mp.
34	(mixed adj3 blocker?).ti,ab.
35	(Alprenolol 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.
36	exp *CALCIUM CHANNEL BLOCKING AGENT/
37	(calcium channel adj3 (blocker? or antagonist?)).ti,ab.

#	Searches
38	(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 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.
39	Magnesium Sulfate.ti.
40	Magnesium Sulfate.ab. /freq=2
41	exp *DIURETIC AGENT/
42	diuretic?.ti,ab.
43	(Acetazolamide or Amiloride or Bendroflumethiazide or Bumetanide or Chlorothiazide or Chlorthalidone or Clopamide or Cyclopenthiazide or Ethacrynic Acid or Ethoxzolamide or Furosemide or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Mefruside or Methazolamide or Methyclothiazide or Metolazone or Muzolimine or Polythiazide or Potassium Citrate or Spironolactone or Ticrynafen or Triamterene or Trichlormethiazide or Xipamide or Isosorbide or Mannitol or Canrenoic Acid or Canrenone).mp.
44	exp *DIPEPTIDYL CARBOXYPEPTIDASE INHIBITOR/
45	(angiotensin converting enzyme adj3 (antagonist? or inhibitor?)).ti,ab.
46	(ACE adj3 (antagonist? or inhibitor?)).ti,ab.
47	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide).mp.
48	*ACETYLSALICYLIC ACID/
49	(acetylsalicylic acid or aspirin?).ti.
50	(acetylsalicylic acid or aspirin?).ab. /freq=2
51	((elect$ or plan$) adj3 deliver$).ti,ab.
52	(expect$ adj3 manag$).ti,ab.
53	(tight$ adj3 (manag$ or control$)).ti,ab.
54	*BLOOD PRESSURE MEASUREMENT/
55	*BLOOD PRESSURE MONITORING/
56	((Automat$ or ambulatory or self$) adj3 blood pressure?).ti,ab.
57	exp *EXERCISE/
58	(exercis$ or physical$ activ$ or swim$ or cycl$ or sport? or run$ or jog$ or walk$ or stair climb$ or gym$ or resistance train$ or yoga or pilates).ti.
59	(exercis$ or physical$ activ$ or swim$ or cycl$ or sport? or run$ or jog$ or walk$ or stair climb$ or gym$ or resistance train$ or yoga or pilates).ab. /freq=2
60	exp *DIET/
61	diet$.ti.
62	diet$.ab. /freq=2
63	(calor$ adj3 restrict$).ti,ab.
64	((portion? or serving) adj3 size?).ti,ab.
65	*SODIUM RESTRICTION/
66	((low$ or restrict$) adj3 (salt or sodium)).ti,ab.
67	or/28-66
68	27 and 67
69	limit 68 to english language
70	letter.pt. or LETTER/
71	note.pt.
72	editorial.pt.
73	CASE REPORT/ or CASE STUDY/
74	(letter or comment*).ti.
75	or/70-74
76	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
77	75 not 76
78	ANIMAL/ not HUMAN/
79	NONHUMAN/
80	exp ANIMAL EXPERIMENT/
81	exp EXPERIMENTAL ANIMAL/
82	ANIMAL MODEL/
83	exp RODENT/
84	(rat or rats or mouse or mice).ti.
85	or/77-84
86	69 not 85
87	17 and 86

Database: Cochrane Central Register of Controlled Trials

Date of last search: 19/02/18

#	Searches
1	MeSH descriptor: [ECONOMICS] this term only
2	MeSH descriptor: [VALUE OF LIFE] this term only
3	MeSH descriptor: [COSTS AND COST ANALYSIS] explode all trees
4	MeSH descriptor: [ECONOMICS, HOSPITAL] explode all trees
5	MeSH descriptor: [ECONOMICS, MEDICAL] explode all trees
6	MeSH descriptor: [RESOURCE ALLOCATION] explode all trees
7	MeSH descriptor: [ECONOMICS, NURSING] this term only
8	MeSH descriptor: [ECONOMICS, PHARMACEUTICAL] this term only
9	MeSH descriptor: [FEES AND CHARGES] explode all trees
10	MeSH descriptor: [BUDGETS] explode all trees
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 near/2 (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	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19
21	MeSH descriptor: [HYPERTENSION, PREGNANCY-INDUCED] this term only
22	MeSH descriptor: [PREGNANCY] this term only
23	MeSH descriptor: [HYPERTENSION] this term only
24	#2 and #3
25	MeSH descriptor: [PRE-ECLAMPSIA] this term only
26	MeSH descriptor: [HELLP SYNDROME] this term only
27	((pregnan* or gestation*) near/5 hypertensi*):ti
28	preeclamp*:ti,ab
29	pre eclamp*:ti,ab
30	HELLP:ti,ab
31	tox?emi*:ti,ab
32	#21 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31
33	MeSH descriptor: [ADRENERGIC ALPHA-2 RECEPTOR AGONISTS] 2 tree(s) exploded
34	(alpha* near/3 Agonist?):ti,ab
35	(Brimonidine Tartrate or Clonidine or exmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine):ti,ab
36	MeSH descriptor: [ADRENERGIC BETA-ANTAGONISTS] 2 tree(s) exploded
37	(Adrenergic beta* near/3 Antagonist?):ti,ab
38	Beta blocker?:ti,ab
39	(mixed near/3 blocker?):ti,ab
40	(Alprenolol 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
41	MeSH descriptor: [CALCIUM CHANNEL BLOCKERS] 2 tree(s) exploded
42	(calcium channel near/3 (blocker? or antagonist?)):ti,ab
43	(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 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
44	Magnesium Sulfate:ti
45	MeSH descriptor: [DIURETICS] this term only
46	diuretic?:ti,ab
47	(Acetazolamide or Amiloride or Bendroflumethiazide or Bumetanide or Chlorothiazide or Chlorthalidone or Clopamide or Cyclopenthiazide or Ethacrynic Acid or Ethoxzolamide or Furosemide or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Mefruside or Methazolamide or Methyclothiazide or Metolazone or Muzolimine or Polythiazide or Potassium Citrate or Spironolactone or Ticrynafen or Triamterene or Trichlormethiazide or Xipamide or Isosorbide or Mannitol or Canrenoic Acid or Canrenone):ti,ab
48	MeSH descriptor: [ANGIOTENSIN-CONVERTING ENZYME INHIBITORS] 1 tree(s) exploded

#	Searches
49	(angiotensin converting enzyme near/3 (antagonist? or inhibitor?)):ti,ab
50	(ACE near/3 (antagonist? or inhibitor?)):ti,ab
51	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide):ti,ab
52	MeSH descriptor: [ASPIRIN] this term only
53	(acetylsalicylic acid or aspirin?):ti
54	((elect* or plan*) near/3 deliver*):ti,ab
55	(expect* near/3 manag*):ti,ab
56	(tight* near/3 (manag* or control*)):ti,ab
57	MeSH descriptor: [BLOOD PRESSURE DETERMINATION] this term only
58	MeSH descriptor: [BLOOD PRESSURE MONITORING, AMBULATORY] this term only
59	((Automat* or ambulatory or self*) near/3 blood pressure?):ti,ab
60	MeSH descriptor: [EXERCISE] 2 tree(s) exploded
61	exercis*:ti
62	(physical* activ* or swim* or cycl* or sport? or run* or jog* or walk* or stair climb* or gym* or resistance train* or yoga or pilates):ti,ab
63	MeSH descriptor: [DIET] 1 tree(s) exploded
64	diet*:ti
65	(calor* near/3 restrict*):ti,ab
66	((portion? or serving) near/3 size?):ti,ab
67	((low* or restrict*) near/3 (salt or sodium)):ti,ab
68	#33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67
69	#12 and #48
70	#20 and #69

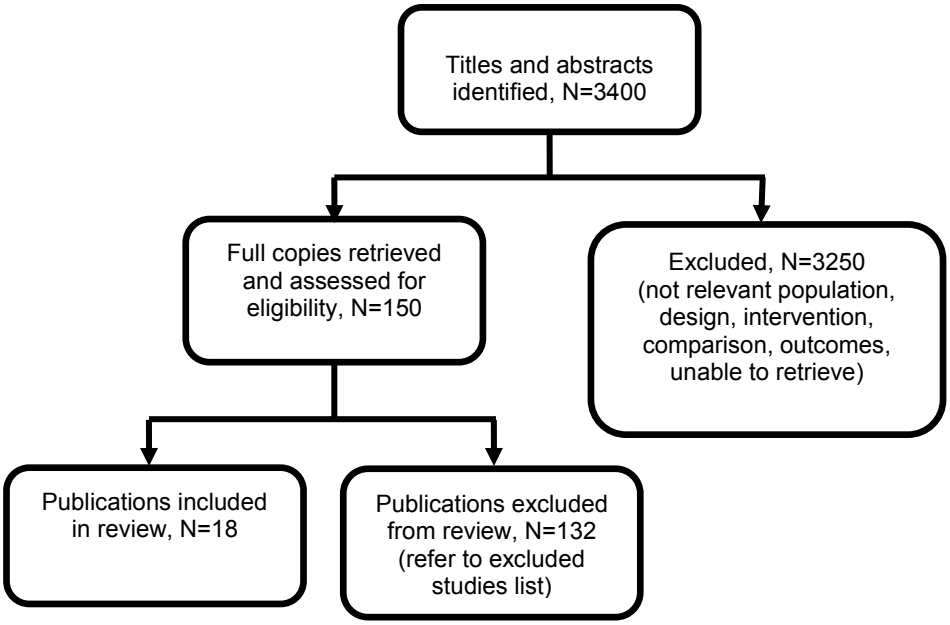
Databases: Health Technology Assessment; and NHS Economic Evaluation Database

Date of last search: 19/02/18

#	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: [HELLP SYNDROME] this term only
7	((pregnan* or gestation*) near/5 hypertensi*):ti
8	preeclamp*:ti,ab
9	pre eclamp*:ti,ab
10	HELLP:ti,ab
11	tox?emi*:ti,ab
12	#1 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
13	MeSH descriptor: [ADRENERGIC ALPHA-2 RECEPTOR AGONISTS] 2 tree(s) exploded
14	(alpha* near/3 Agonist?):ti,ab
15	(Brimonidine Tartrate or Clonidine or exmedetomidine or Guanabenz or Guanfacine or Medetomidine or Methyldopa or Xylazine):ti,ab
16	MeSH descriptor: [ADRENERGIC BETA-ANTAGONISTS] 2 tree(s) exploded
17	(Adrenergic beta* near/3 Antagonist?):ti,ab
18	Beta blocker?:ti,ab
19	(mixed near/3 blocker?):ti,ab
20	(Alprenolol 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
21	MeSH descriptor: [CALCIUM CHANNEL BLOCKERS] 2 tree(s) exploded
22	(calcium channel near/3 (blocker? or antagonist?)):ti,ab
23	(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 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
24	Magnesium Sulfate:ti

#	Searches
25	MeSH descriptor: [DIURETICS] this term only
26	diuretic?:ti,ab
27	(Acetazolamide or Amiloride or Bendroflumethiazide or Bumetanide or Chlorothiazide or Chlorthalidone or Clopamide or Cyclopenthiazide or Ethacrynic Acid or Ethoxzolamide or Furosemide or Hydrochlorothiazide or Hydroflumethiazide or Indapamide or Mefruside or Methazolamide or Methyclothiazide or Metolazone or Muzolimine or Polythiazide or Potassium Citrate or Spironolactone or Ticrynafen or Triamterene or Trichlormethiazide or Xipamide or Isosorbide or Mannitol or Canrenoic Acid or Canrenone):ti,ab
28	MeSH descriptor: [ANGIOTENSIN-CONVERTING ENZYME INHIBITORS] 1 tree(s) exploded
29	(angiotensin converting enzyme near/3 (antagonist? or inhibitor?)):ti,ab
30	(ACE near/3 (antagonist? or inhibitor?)):ti,ab
31	(Captopril or Cilazapril or Enalapril or Enalaprilat or Fosinopril or Lisinopril or Perindopril or Ramipril or Teprotide):ti,ab
32	MeSH descriptor: [ASPIRIN] this term only
33	(acetylsalicylic acid or aspirin?):ti
34	((elect* or plan*) near/3 deliver*):ti,ab
35	(expect* near/3 manag*):ti,ab
36	(tight* near/3 (manag* or control*)):ti,ab
37	MeSH descriptor: [BLOOD PRESSURE DETERMINATION] this term only
38	MeSH descriptor: [BLOOD PRESSURE MONITORING, AMBULATORY] this term only
39	((Automat* or ambulatory or self*) near/3 blood pressure?):ti,ab
40	MeSH descriptor: [EXERCISE] 2 tree(s) exploded
41	exercis*:ti
42	(physical* activ* or swim* or cycl* or sport? or run* or jog* or walk* or stair climb* or gym* or resistance train* or yoga or pilates):ti,ab
43	MeSH descriptor: [DIET] 1 tree(s) exploded
44	diet*:ti
45	(calor* near/3 restrict*):ti,ab
46	((portion? or serving) near/3 size?):ti,ab
47	((low* or restrict*) near/3 (salt or sodium)):ti,ab
48	#13 or #14 or #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 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47
49	#12 and #48

Appendix C – Clinical evidence study selection



Appendix D – Clinical evidence tables

Table 4: Clinical evidence 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

ECPPA: randomised trial of low dose aspirin for the prevention of maternal and fetal complications in high risk pregnant women. ECPPA (Estudo Colaborativo para Prevenção da Pré-eclampsia com Aspirina) Collaborative Group, British Journal of Obstetrics and Gynaecology, 103, 39-47, 1996

Ref Id

787414

Country/ies where the study was carried out

Brazil</td>
<td>Sample size

Total population:

N = 1009 (n = 498 randomised to aspirin, n = 511 randomised to placebo)

Women with chronic hypertension:

N = 473 (n = 242 randomised to aspirin, n = 231 randomised to placebo)

Characteristics

Demographics are reported for the entire population only, not the subgroup of women with chronic hypertension.
<table>
<tr><td></td><td>Aspirin

n = 498</td><td>Placebo

n = 511</td></tr>
<tr><td>Age, mean ± SD, years</td><td>27.5 ± 7.4</td><td>27.5 ± 7.4</td></tr>
<tr><td>Estimated gestation at randomisation</td><td>22.1 ± 6.2</td><td>22.4 ± 6.0</td></tr>
</table>
</td>
<td>Interventions

Aspirin group: 60mg aspirin to be taken daily

Placebo group: identical appearing placebo tablets containing cornstarch and microcrystalline cellulose.</td>
<td>Details

Women were instructed to take their allocated intervention daily from 12 weeks (or immediately after randomisation, if this was later than 12 weeks gestation) until delivery.

Computer generated randomisation lists were prepared by the Clinical Trial Service Unit, Oxford University. Baseline details of the women were recorded directly on the lists, and only after complete baseline information had been provided was a specific numbered trial treatment pack allocated.

The study was analysed on an intention to treat basis.

The study was double blind, with the contents of the treatment pack not to be revealed unless there was a clear medical reason for the treatment to be known.</td>
<td>Results

Pre-eclampsia in women with chronic hypertension†

Aspirin group: 23/231

Placebo group: 16/224

Preterm delivery < 37 weeks in women with chronic hypertension‡

Aspirin group: 56/231

Placebo group: 70/225

IUGR <3rd centile for sex and estimated maturity in women with chronic hypertension

Aspirin group: 26/233

Placebo group: 26/226</td>
<td>Limitations

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

Random sequence generation: low risk (computer generated randomisation lists prepared by third party)

Allocation concealment: unclear risk (no details reported. Authors state that allocation was only revealed if medically necessary during the trial, but no information as to how this data was released and who had access to the data)

Blinding of participants and personnel: low risk (double blinded trial)</td>
</tr>
</table>

Study details	Participants			Interventions	Methods	Outcomes and Results	Comments
Study type Multicentre RCT Aim of the study To determine whether low dose aspirin is effective in women at particularly high risk of adverse outcomes associated with pre-eclampsia. Study dates December 1989 to March 1993. Source of funding Sterling Drugs provided funding, and also supplied thee intervention and placebo drugs. Authors state that the study was designed, conducted, analysed and interpreted independently of the commercial sponsor.	mean ± SD, weeks				A sample size calculation is not reported. Pre-eclampsia was defined as the development of hypertension plus the detection of protein in the urine after randomisation. Hypertension was defined as a rise of ≥25 mmHg to a level of 90mmHg or higher for those with a baseline diastolic BP of <90mmHg. For those with a baseline diastolic of 90mmHg or above, an increment of 15mmHg was required.	**Stillbirths and neonatal deaths in women with chronic hypertension** Aspirin group: 22/233 Placebo group: 17/226 † data included in the individual participant meta-analysis by Askie 2007 ‡n.b. these data are not included in the individual participant meta-analysis by Van Vliet 2017. This is presumed to be because data on spontaneous onset of delivery versus induction were unavailable.	**Blinding of outcome assessment:** low risk (double blinded trial) **Blinding (performance bias and detection bias):** low risk (see above information) **Incomplete outcome data:** low risk (drop-out 4% and no difference between groups) **Selective reporting:** low risk **Other information** Note pharmaceutical company funded trial.
	< 12 weeks†, n (%)	18 (4)	20 (4)				
	12 ≤ 20 weeks, n (%)	186 (37)	161 (32)				
	> 20 ≤ 28 weeks, n (%)	194 (39)	233 (46)				
	> 28 weeks, n (%)	100 (20)	97 (19)				
	Systolic BP, mean ± SD, mmHg	127.3 ± 20.5	126.8 ± 20.5				
	< 120 mmHg, n (%)	153 (31)	159 (31)				
	120-139 mmHg, n (%)	171 (34)	183 (36)				
	≥ 140 mmHg, n (%)	174 (35)	169 (33)				

Study details	Participants			Interventions	Methods	Outcomes and Results	Comments
	Diastolic BP, mean ± SD, mmHg	81.3 ± 15.0	80.3 ± 14.8				
	< 90 mmHg, n (%)	314 (63)	333 (65)				
	90 - 109 mmHg, n (%)	155 (31)	159 (31)				
	≥ 110 mmHg, n (%)	29 (6)	19 (4)				
	Chronic hypertension, n (%)	242 (49)	231 (45)				
	† women randomised at < 12 weeks were to start the intervention at 12 weeks' gestation. **Inclusion criteria** Women between 12 and 32 weeks' gestation At sufficient risk of pre-eclampsia or its sequelae for the use of low dose aspirin to be contemplated, but without clear indications for or against its use (in the view of the responsible clinician). Reasons included, for example, chronic						

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	hypertension, primigravity (especially with other risk factors such as extremes of age), diabetes, renal disease, previous preeclampsia or IUGR. **Exclusion criteria** Women with an increased risk of bleeding, asthma, allergy to aspirin, gastric ulcer and placenta praevia.				
Full citation Askie, L. M., Duley, L., Henderson-Smart, D. J., Stewart, L. A., Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data, Lancet, 369, 1791-1798, 2007 **Ref Id** 787498 **Country/ies where the study was carried out** Multicentre	**Sample size** **Data for primary outcome (primary prevention of pre-eclampsia)** Total sample size N = 30822 (n = 15481 randomised to anti-platelet agents, n = 15341 randomised to control) Subgroup analysis for participants with chronic hypertension: N = 3303 (n = 1678 randomised to anti-platelet agents, n = 1625 randomised to control) **Characteristics** Demographics reported for entire population only, not for subgroup of women with chronic hypertension. 54% primigravida	**Interventions** **Antiplatelet group:** aspirin was given alone in 27 of the included studies, in doses ranging from 50 to 150mg per day (accounting for 98% women in the dataset). Aspirin was given in combination with dipyridamole in three trials (n = 177). Three further trials used different antiplatelet	**Details** Randomisation and therapy began before 20 weeks' gestation in 59% of the women enrolled. Data provided to the authors were checked for internal consistency, consistency with published reports and missing items. Inconsistencies of missing data were discussed with the trialists and amended as necessary. Quality and integrity of the randomisation processes were assessed by reviewing the chronological randomisation sequence and pattern of assignment, as well as the balance of	**Results** **Development of pre-eclampsia in women with pre-existing hypertension** Antiplatelet group: 293/1678 Control group: 295/1625 Relative risk 0.97 (0.84 to 1.12)	**Limitations** Assessed using the ROBIS tool Study eligibility criteria: Low risk of bias (clear inclusion/exclusion criteria with appropriate exclusions only) Identification and selection of studies: Low risk of bias (Cochrane database searched, supplemented by hand searching) Data collection and study appraisal: Unclear risk of bias (low risk generally, but method for assessing individual study quality is not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Meta-analysis of individual participant data from randomised controlled trials **Aim of the study** To assess the use of anti-platelet agents for the primary prevention of pre-eclampsia and identify which women are likely to benefit the most from their use. **Study dates** Included trials were identified from the period 1985 until 2005. 36 trials were identified, 31 of which included data relevant for primary prevention of pre-eclampsia.	92% singleton pregnancy 70% aged 20 to 35 years 90% had at least one risk factor for pre-eclampsia (which could include primiparity) **Inclusion criteria** Studies were included if they met the following criteria: women at risk of developing pre-eclampsia were randomised to receive one of more antiplatelet agents (e.g. low dose aspirin or dipyridamole) versus a placebo or no antiplatelet agent. for this analysis, only trials that included antiplatelet agent use for women deemed to be at risk of pre-eclampsia were included (i.e. primary prevention). Trials that recruited women in both primary and secondary prevention settings were divided in such a way that only women enrolled in a primary prevention setting were included. **Exclusion criteria** quasirandom study designs trials that included women who started treatment postpartum or had a diagnosis of pre-eclampsa at trial entry	agents (dypiridamole and/or heparin, ozagrel, n = 362). **Control group:** women received either placebo, or no treatment (numbers not reported)	baseline characteristics across treatment groups. The primary outcome (pre-eclampsia) was defined as hypertension with new onset proteinuria at or beyond 20 weeks' gestation.		Synthesis and findings: Low risk of bias (prespecified analyses reported) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding The main funding source was the National Health and Medical Research Council (NHMRC) of Australia, through a 3-year project grant and a Sidney Sax Public Health Postdoctoral Fellowship for the first author. Additional support was provided by the Resource Centre for Randomised Trials and the UK Cochrane Centre(Oxford, UK); the Medical Research Council Clinical Trials Unit (London, UK); and the NHMRC Clinical Trials Centre (University of Sydney, Australia).					

<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

Butters, L., Kennedy, S., Rubin, P. C., Atenolol in essential hypertension during pregnancy, BMJ, 301, 587-9, 1990

Ref Id

659083

Country/ies where the study was carried out

UK

Study type

RCT

Aim of the study

To assess the effectiveness of atenolol in women with chronic hypertension

Study dates

1970, month not specified</td>
<td>Sample size

N=29 women with chronic hypertension (n=15 randomised to atenolol and n=14 randomised to placebo)

Characteristics
<table>
<tr><th></th><th>Atenolol (n =15)</th><th>Placebo (n =14)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>NR</td><td>NR</td></tr>
<tr><td>No. with chronic hypertensio n n (%)</td><td>15 (100)</td><td>14 (100)</td></tr>
<tr><td>Gestational age at admission, weeks (mean)</td><td>15.8</td><td>15.9</td></tr>
<tr><td>Mean sBP/dBP at entry</td><td>144/86</td><td>148/86</td></tr>
</table>
[a]Chronic hypertension definition:sBP 140 to 170 and dBP 90 to 110 mmHg on 2 occasions separated by at least 24 hours

Inclusion criteria</td>
<td>Interventions

Atenolol 50 mg po daily. Number of tablets was increased at each visit until BP < 140/90 mmHg/ dose of 200 mg was reached.

No intervention: placebo tablets</td>
<td>Details

Method of randomisation or concealment allocation was not reported. Study was double blind.

Follow-up length: 20 weeks

Concurrent treatment, use of steroids, or whether a sample size calculation was performed was not reported.</td>
<td>Results

Neonatal outcomes

Stillbirth

Atenolol:1/ 15

Placebo: 0/14

Small-for-gestational-age (BW<10th centile)

Atenolol:10/15

Placebo:0/14

Birth weight

Atenolol:2620 g (SDs not reported)

Placebo:3530 g (SDs not reported)

MD -910, 95% CI: -440 to 1380, p<0.001

Gestational age at delivery

Atenolol: 39.5 (no SD was reported)

Placebo: 38.5 (no SD was reported)</td>
<td>Limitations

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

Random sequence generation: unclear risk (randomisation method was not reported)

Allocation concealment: unclear risk (not reported)

Blinding of participants and personnel: low risk (double blinded trial)

Blinding of outcome assessment: low risk (double blinded trial)

Blinding (performance bias and detection bias): low risk (see above information)

Incomplete outcome data: low risk (drop-out<20% and difference between groups <20%)

Selective reporting: high risk (basic demographic information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Not reported	sBP 140 to 170 and sBP 90 to 110 mmHg on 2 occasions separated by at least 24 hours. Women were recruited when they were between 12 and 24 weeks' gestation. **Exclusion criteria** Contraindications to the use of Beta-Blockers				and SD of the continuous outcomes have not been reported) **Other information**
Full citation Cockburn, J., Moar, V. A., Ounsted, M., Redman, C. W., Final report of study on hypertension during pregnancy: the effects of specific treatment on the growth and development of the children, Lancet (London, England), 1, 647-9, 1982 **Ref Id** 787716	**Sample size** See Redman 1976 **Characteristics** See Redman 1976 **Inclusion criteria** See Redman 1976 **Exclusion criteria** See Redman 1976	**Interventions** See Redman 1976	**Details** See Redman 1976	**Results** See Redman 1976	**Limitations** See Redman 1976 **Other information** See Redman 1976

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out **Study type** See Redman 1976 **Aim of the study** See Redman 1976 **Study dates** See Redman 1976 **Source of funding** See Redman 1976					
Full citation Gracia, P. V. D., Dominguez, L., Solis, A., Management of chronic hypertension during pregnancy with furosemide, amlodipine or aspirin: A pilot	**Sample size** N= 39(n= 20 randomised to amlodipine, and n=19 randomised to aspirin) **Characteristics**	**Interventions** Amlodipine 5mg/day PO Aspirin 75 mg/day PO If BP ≥160/110, women were admitted to the hospital and	**Details** Randomisation was performed to each of the treatments in a 1:1:1 ratio using a computer generated code with block size of six. Allocation was concealed using sealed envelopes. Open-label trial.	**Results** *Neonatal outcomes* **Stillbirth** Amlodipine: 0/20 Aspirin: 1/19 **Neonatal death** Amlodipine: 0/20	**Limitations** **Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias** **Random sequence generation:** low risk (randomisation was

Study details	Participants			Interventions	Methods	Outcomes and Results	Comments
clinical trial, Journal of Maternal-Fetal and Neonatal Medicine, 27, 1291-1294, 2014 **Ref Id** 337195 **Country/ies where the study was carried out** Panama **Study type** RCT **Aim of the study** To assess the efficacy of amolodipine, furosemide, and aspirin in women with chronic hypertension during pregnancy **Study dates** January 2010 to September 2012 **Source of funding**		**Amlodipine (n =20)**	**Aspirin (n=19)**	bolus doses of hydralazine or labetalol were administered to control severe hypertension, and the medication they were originally randomised to was not continued.	No details regarding use of concurrent treatment, use of antenatal steroids, duration of follow-up, or whether a sample size calculation was performed.	Aspirin: 0/19 **Small-for-gestational-age** (BW<10th centile) Amlodipine: 2/20 Aspirin: 2/19 **Birth weight** Amlodipine: 2873 (526) Aspirin: 2936 (740) **Preterm birth** (weeks not specified) Amlodipine: 3/20 Aspirin: 1/19 *Maternal outcomes:* **Severe hypertension (sBP/dBP ≥ 160/110 mmHg)** Amlodipine: 7/20 Aspirin: 6/19 **Placental abruption** Amlodipine: 1/20 Aspirin: 0/19	performed with computer generated code) **Allocation concealment:** low risk (opaque sealed enveloped were used) **Blinding of participants and personnel:** high risk (open-label trial) **Blinding of outcome assessment:** high risk (open-label trial) **Blinding (performance bias and detection bias):** high risk (see above information) **Incomplete outcome data:** low risk (drop-out<20% and difference between groups <20%) **Selective reporting:** unclear risk (protocol not reported but it appears that all outcomes reported) **Other information**
	Age, years (mean, SD)	34.1 (5.3)	33.9 (4.2)				
	No. with chronic hypertension [a] n (%)	20 (100)	19 (100)				
	Gestational age at treatment, weeks (mean, SD)	17.6 (2.2)	17.1 (2.6)				
	Primiparous	2 (10)	3 (10.5)				
	sBP at entry	130.5 (9.4)	135.2 (9)				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported	<table><tr><td>dBP at entry</td><td>84 (6.8)</td><td>85.2 (6.1)</td></tr></table> [a] Chronic hypertension: BP >140/90 present before pregnancy or for first time before the 20th week of gestation. Mild/moderate chronic hypertension: sBP between 140–159mmHg or dBP between 90–109 mmHg. **Inclusion criteria** Women with singleton or twin pregnancy and mild/moderate chronic hypertension at ≤ 20 weeks of gestation with live pregnancy **Exclusion criteria** Chronic hypertension with sBP/dBP≥160/110 mmHg; renal failure; pre-existing renal disease; diabetes mellitus; autoimmune disease; major fetal abnormalities; deficiency of amniotic fluid.			**Mode of birth** (C-section) Amlodipine: 12/20 Aspirin: 10/19	
Full citation Hamed, H. O., Alsheeha, M. A., Abu-Elhasan, A. M., Abd Elmoniem, A. E., Kamal, M. M., Pregnancy	**Sample size** N=76 (n=38 randomised to induction of labour and n=38 randomised to expectant management). **Characteristics**	**Interventions** Induction of labour: delivery was planned to take place immediately after completion of 37	**Details** Concurrent treatment: women in both groups were advised to continue their previous antihypertensive treatment, with a modification of dose to achieve control of blood pressure. *De novo*	**Results** *Neonatal outcomes* **Perinatal mortality** Induction of labour: 2/38	**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>outcomes of expectant management of stable mild to moderate chronic hypertension as compared with planned delivery, International Journal of Gynecology and Obstetrics, 127, 15-20, 2014

Ref Id

337201

Country/ies where the study was carried out

Egypt and Saudi Arabia

Study type

RCT

Aim of the study

To compare the outcomes between induction of labour and expectant management in pregnant women</td>
<td>
<table>
<tr><th></th><th>Induction of labour (n =38)</th><th>Expectant management (n =38)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>28.4 (5.7)</td><td>29.2 (6.6)</td></tr>
<tr><td>No. with chronic hypertension[a] n (%)</td><td>38 (100)</td><td>38 (100)</td></tr>
<tr><td>Parity 0-1</td><td>2 (5.3)</td><td>5 (13.2)</td></tr>
<tr><td>Parity 2-4</td><td>22 (57.9)</td><td>23 (60.5)</td></tr>
<tr><td>Parity ≥ 5</td><td>14 (36.8)</td><td>10 (26.3)</td></tr>
<tr><td>sBP ≥ at entry</td><td>153.2 (6.4)</td><td>154.8 (5.2)</td></tr>
<tr><td>dBP ≥ at entry</td><td>97.3 (5.1)</td><td>98.4 (4.5)</td></tr>
</table>
[a] sBP between 140 and 160 mmHg and dBP between 90 and 110 mmHg least 6 hours apart in the first half of pregnancy
</td>
<td>gestational weeks, provided no maternal or fetal complications were present (such as, superimposed pre-eclampsia; severe superimposed pre-eclampsia [BP ≥ 160/110; proteinuria >5g/24 hours]; severe chronic hypertension with a persistent high pressure [BP ≥ 160/110] not responding to antihypertensive medications or prepartum fetal asphyxia). For women with bishop score > 8, labour was induced by oxytocin infusion and amniotomy. For those with a Bishop score< 8, cervical</td>
<td>antihypertensive medications were started if women's BP ≥150/100 mmHg (methyldopa was the first line of choice, see the distribution in the table below). The target BP was to maintain it between 130/80 to 140/90 mmHg.
<table>
<tr><th></th><th>Induction</th><th>Expectant</th></tr>
<tr><td>None</td><td>17 (44.7)</td><td>16 (42.1)</td></tr>
<tr><td>Methyldopa</td><td>13 (43.2)</td><td>13 (34.2)</td></tr>
<tr><td>Labetalol</td><td>2 (5.3)</td><td>2 (5.3)</td></tr>
<tr><td>Combination</td><td>4 (10.5)</td><td>3 (7.9)</td></tr>
</table>
Women were randomised with a computer generated table and allocated by 1:1 ratio to induction of labour or expectant management or spontaneous onset of labour up to 41 weeks, whichever came first.</td>
<td>Expectant management: 1/38

Birth weight

Induction of labour: 2800 (600)

Expectant management: 3200 (600)

Gestational age at delivery

Induction of labour: 35.7 (1.2)

Expectant management:38.1 (2.7)

Preterm birth (weeks were not reported)

Induction of labour: 10/38

Expectant management:12/38

Admission to neonatal unit

Induction of labour: 12/38

Expectant management:3/38

Maternal outcomes:</td>
<td>Random sequence generation: low risk (randomised using a computer generated table)

Allocation concealment: unclear risk (not reported)

Blinding of participants and personnel: unclear risk (not reported)

Blinding of outcome assessment: unclear risk (not reported)

Blinding (performance bias and detection bias): unclear risk (see above information)

Incomplete outcome data: low risk (drop-out<20% and difference between groups <20%)

Selective reporting: unclear risk (protocol not reported but it appears that all outcomes reported)

Other information</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
with mild to moderate chronic hypertension. **Study dates** 1st of April 2012 to 31st of October 2013 **Source of funding** Qassim University	**Inclusion criteria** Mild to moderate chronic hypertension (dBP between 90 and 110 mmHg and sBP between 140 and 160 mmHg at least 6 hours apart in the first half of pregnancy) without proteinuria, singleton pregnancy, gestational age between 24 and 36 weeks. **Exclusion criteria** Severe chronic hypertension (dBP/sBP ≥ 160/110 mmHg); gestational hypertension; newly onset pre-eclampsia in a previously normotensive woman; women with secondary hypertension	ripening was induced by vaginal misoprostol at a dose of 50µg every 6 hours up to 200µg. Expectant management: this was continued until spontaneous labour. Elective delivery was carried out after 41 weeks, if the woman had completed 37 weeks and developed maternal or fetal complications (such as, superimposed pre-eclampsia; severe superimposed pre-eclampsia [BP ≥ 160/110; proteinuria >5g/24 hours]; severe chronic hypertension with a persistent high	Sample size calculations were performed and it was estimated that 74 participants would be needed to demonstrate a statistical difference between both groups with 80% power and type 1 error probability of 5%. Duration of follow-up was not reported	**Severe chronic hypertension (dBP between 90 and 110 mmHg and sBP between 140 and 160 mmHg at least 6 hours apart in the first half of pregnancy)** Induction of labour: 5/38 Expectant management: 3/38 **Superimposed pre-eclampsia** Induction of labour: 12/38 Expectant management: 13/38 **Placental abruption** Induction of labour: 3/38 Expectant management: 3/38	

<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>pressure [BP ≥ 160/110] not responding to anti-hypertensive medications, or prepartum fetal asphyxia).</td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Kasawara, K. T., Burgos, C. S. G., Do Nascimento, S. L., Ferreira, N. O., Surita, F. G., Pinto, E. Silva J. L., Maternal and perinatal outcomes of exercise in pregnant women with chronic hypertension and/or previous preeclampsia: A randomized controlled trial, ISRN Obstetrics and Gynecology, 2013, 857047, 2013

Ref Id

776154</td><td>Sample size

N=116 (n=58 randomised to the exercise group and n=58 randomised to the no intervention group)

Characteristics
<table>
<tr><th></th><th>Exercise (n = 58)</th><th>No intervention (n =58)</th></tr>
<tr><td>Age, years < 19 (n,%)</td><td>1 (1.7)</td><td>1 (1.7)</td></tr>
<tr><td>Age, years 20-29 (n,%)</td><td>21 (36.2)</td><td>20 (34.5)</td></tr>
<tr><td>Age, years 30-39 (n,%)</td><td>27 (46.6)</td><td>31 (53.5)</td></tr>
</table></td><td>Interventions

Exercise group: women rode a stationary bike once a week during 30 mins under the supervision of a physical therapist every week until the end of pregnancy. Heart rate was monitored with a wristband

Control group: not engaged in any physical exercise</td><td>Details

Randomisation was performed using sequentially numbered by a statistical program and opaque envelopes

Sample size calculations were performed. For a significance level of 5% and a power of 80%, n= 58 participants per arm would need to be included.

Follow-up: 10 weeks (approximately)

Concurrent treatment and use of steroids was not reported</td><td>Results

Neonatal outcomes

Birth weight (<2500)

Exercise: 9/56

No intervention: 11/53

Birth weight (2500-3999)

Exercise: 41/56

No intervention: 35/53

Birth weight (≥4000)

Exercise: 5/56

No intervention: 11/53

Admission to neonatal unit

Exercise: 12/56

No intervention: 13/53</td><td>Limitations

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

Random sequence generation: low risk (sequentially numbered enveloped using a statistical program)

Allocation concealment: low risk (sealed opaque envelopes were used)

Blinding of participants and personnel: high risk (not blinded)

Blinding of outcome assessment: unclear</td></tr>
</table>

Study details	Participants			Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Brazil **Study type** RCT **Aim of the study** To assess whether exercise improves outcomes in women with chronic hypertension **Study dates** January 2008 to November 2011 **Source of funding** Not reported	Age, years ≥ 40 (n,%)	9 (15.5)	6 (10.3)			**Mode of birth** (C-section) Exercise: 36/56 No intervention: 41/53	risk (no information was provided) **Blinding (performance bias and detection bias):** unclear risk (see above details) **Incomplete outcome data:** low risk (drop-out<20% and difference between groups <20%) **Selective reporting:** unclear risk (protocol not reported) **Other information**
	Chronic hypertension[a] n (%)	51 (87.9)	54 (93.1)				
	Previous pre-eclampsia[b] n (%)	7 (12.1)	4 (6.9)				
	Gestational age at treatment, weeks (mean, SD)	17.3 (3.4)	23 (39.7)				
	Ethnicity: white	41 (70.7)	35 (60.3)				
	Ethnicity: non-white	17 (29.3)	23 (39.7)				
	Parity 0	13 (22.4)	9 (15.5)				
	Parity ≥1	45 (77.6)	19 (84.5)				
	[a] Chronic hypertension definition: BP ≥ 140/90 mmHg diagnosed before pregnancy or before 20 week's gestation. [b] Pre-eclampsia definition: not reported						

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Inclusion criteria 12 to 20 week's gestation, ≥18 y/o, and presenting with chronic hypertension (BP ≥ 140/90 mmHg) diagnosed before pregnancy or before 20 week's gestation. Previous pre-eclampsia and proterinuria after 20 weeks' gestation was considered a reported history of hypertension. **Exclusion criteria** Not to be engaged in any supervised physical exercise at the time of the study.				
Full citation Magee, L. A., von Dadelszen, P., Rey, E., Ross, S., Asztalos, E., Murphy, K. E., Menzies, J., Sanchez, J., Singer, J., Gafni, A., Gruslin, A., Helewa, M., Hutton, E., Lee, S. K., Lee, T., Logan, A. G., Ganzevoort, W., Welch, R.,	**Sample size** N=981 (n=493 randomised to less-tight control and n=488 randomised to tight control) **Characteristics** **Less-tight control (n =493)** / **Tight control(n =488)** **Stillbirth** Less-tight control: 12/493 Tight control:7/488 **Neonatal death up to 7 days** Less-tight control: 2/493 Tight control:4/488 **Small-for-gestational-age** (BW<10th centile)	**Interventions** Less-tight control: aiming for a target diastolic blood pressure, 100 mm Hg Tight control: aiming for a target diastolic blood pressure, 85 mm Hg	**Details** No concurrent medications were used. Randomisation was stratified according to centre and type of hypertension. It was central and performed in permuted blocks of random size with the use of a telephone computerised randomisation service at the Data Co-ordinating Centre. Open trial.	**Results** *Neonatal outcomes*	**Limitations** **Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias** **Random sequence generation:** low risk (a telephone computerised randomisation service at the Data Co-ordinating Centre was used) **Allocation concealment:** low

Study details	Participants			Interventions	Methods	Outcomes and Results	Comments
Thornton, J. G., Moutquin, J. M., Less-tight versus tight control of hypertension in pregnancy, New England Journal of Medicine, 372, 407-17, 2015 **Ref Id** 377652 **Country/ies where the study was carried out** Argentina, Australia, Brazil, Canada, Chile, Colombia, Estonia, Hungary, Israel, Jordan, New Zealand, Poland, The Netherlands, UK, USA **Study type** RCT **Aim of the study** To assess the effects of tight versus less tight control of	Age at expected day of birth, years (mean, SD)	34 (5.7)	33.7 (5.8)		A sample size of 514 was estimated for 80% power at a two-tailed alpha level of 0.05 Duration of follow-up (median):12.1 weeks (IQR 6.4 to 18.8) in the less-tight control group and 11.4 weeks (IQR 6.6 to 19)	Less-tight control: 79/491 Tight control:96/488 **Birth weight** (mean, SD) *Median (IQR) transformed to mean using the calculator developed by Hozo et al., 2005 (equations 4 and 12) Less-tight control: 2920.34 (305.90) Tight control: 2951.41 (261.61) **Gestational age at delivery** Less-tight control: 36.8 (3.4) Tight control: 37.2 (3.1) **Admission to neonatal unit** Less-tight control:141/480 Tight control:139/479 *Maternal outcomes:* **Severe hypertension (BP ≥ 160/110 mmHg)**	risk (central randomisation) **Blinding of participants and personnel:** high risk (not blinded) **Blinding of outcome assessment:** high risk (not blinded) **Blinding (performance bias and detection bias):** high risk (see above details) **Incomplete outcome data:** low risk (drop-outs were reported in both groups, however ITT analysis was used) **Selective reporting:** low risk if (protocol reported and all outcomes included) **Other information**
	No. with chronic hypertension [a] n (%)	371 (74.6)	365 (74.5)				
	Gestational hypertension [b] n (%)	126 (25.4)	125 (25.5)				
	Gestational age at treatment, weeks (mean, SD)	23.7 (6.3)	24.2 (6.3)				
	Nulliparous	161 (32.4)	168 (34.3)				
	Ethnicity: Caucasian	298 (60)	315 (64.3)				
	Ethnicity: Black	62 (12.5)	61 (12.4)				
	Ethnicity: Asian	62 (12.5)	46 (9.4)				
	Ethnicity: Hispanic	58 (11.7)	63 (12.9)				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
hypertension in pregnancy outcomes **Study dates** 26th March to 2nd of August 2012 **Source of funding** Canadian Institutes of Health Research	<table><tr><td>Ethnicity: other</td><td>17 (3.4)</td><td>5 (1)</td></tr><tr><td>sBP 1 week before randomisation</td><td>140.4 (9.7)</td><td>139.7 (9.8)</td></tr><tr><td>dBP 1 week before randomisation</td><td>92.6 (4.8)</td><td>92.2 (5.2)</td></tr></table> [a] Chronic hypertension: dBP ≥90 mmHg before pregnancy or before 20 + 0 days gestation; [b] Gestational hypertension: dBP ≥90 mmHg at 20 weeks or more of gestation **Inclusion criteria** Non-severe, non-proteinuric women with either pre-existing hypertension (defined as dBP ≥90 mmHg before pregnancy or before 20 + 0 days gestation) or gestational hypertension (dBP ≥90 mmHg at 20 weeks or more of gestation), dBP 90 to 105 mmHg, not receiving antihypertensive medication, and with live singleton fetus with a gestational age of 14 to 33+6. If receiving antihypertensive medication, entry criteria was sBP 85 to 105 mmHg.			Less-tight control: 200/493 Tight control:134/488 **HELLP** Less-tight control: 9/493 Tight control:2/488 **Placental abruption** Less-tight control: 11/493 Tight control:11/488 **Onset of labour** (spontaneous onset) Less-tight control: 109/493 Tight control:104/488 **Onset of labour** (induced onset) Less-tight control: 224/493 Tight control:218/488 **Onset of labour** (no labour - caesarean prior to labour) Less-tight control: 159/493	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Exclusion criteria sBP ≥ 160 mmHg (although these patients were recruited subsequently if sBP <160 mmHg and met all other inclusion criteria); proteinuria; used an ACE inhibitor at 14 weeks+ 0 days gestation or later; a pre-existing condition; needed to be delivered for maternal or fetal reasons, had a fetus with a major anomaly, or had previously participated in CHIPS.			Tight control:164/488 **Mode of birth** (C-section) Less-tight control: 231/493 Tight control:250/488	
Full citation Moore, G. S., Allshouse, A. A., Post, A. L., Galan, H. L., Heyborne, K. D., Early initiation of low-dose aspirin for reduction in preeclampsia risk in high-risk women: a secondary analysis of the MFMU High-Risk Aspirin Study, Journal of perinatology :	**Sample size** Total sample size: N = 523 (n = 265 randomised to aspirin, n = 258 randomised to placebo) Women with pre-existing chronic hypertension: N = 186 (n = 93 randomised to aspirin, n = 93 randomised to placebo) **Characteristics** Demographics are reported for the full study group, not only for those women with chronic hypertension. | | Aspirin n = 265 | Placebo n = 258 |	**Interventions** **Aspirin group:** 60mg aspirin daily **Control group:** received a lactose containing, identical appearing placebo tablet daily	**Details** Aspirin and placebo packets were prepared and labelled at a central location. A computer generated permuted block randomisation sequence was used, stratified according to clinical centre and risk group. Packages were shipped to the clinical centres and each woman received the next labelled packet. Sample size calculation: an overall sample size of 2600 was chosen, to allow	**Results** **Development of pre-eclampsia in women with chronic hypertension†** Aspirin group: 23/93 Control group: 32/93 **Preterm delivery at <34 weeks (due to pre-eclampsia) in women with chronic hypertension‡** Aspirin group: 6/93	**Limitations** **Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias** **Random sequence generation:** low risk (computer generated block randomisation sequence, with stratification for centre and co-morbidities) **Allocation concealment:** low risk (placebo/active treatments were

Study details	Participants			Interventions	Methods	Outcomes and Results	Comments
official journal of the California Perinatal Association, 35, 328-31, 2015 **Ref Id** 657977 **Country/ies where the study was carried out** USA **Study type** RCT (multicentre) **Aim of the study** To assess whether low dose aspirin gives protection from pre-eclampsia when initiated prior to 17 weeks gestation, and to further characterise which women most benefit from low dose aspirin during pregnancy. **Study dates** 1991 to 1995	Age, mean (SE), years	26.7 (0.38)	27.5 (0.36)		detection of a 50% reduction in the risk of preeclampsia within each of the four risk groups, with a type I error of 0.05 (two sided) and 80% power.	Control group: 3/93 **Infants born small for gestational age in women with chronic hypertension** *defined as <10th percentile for gestational age, based on normative singleton birth weights* Aspirin group: 8/93 Control group: 11/93 † data included in the individual participant meta-analysis by Askie 2007 ‡ data included in the secondary analysis by Van Vliet (2017) of the above individual participant meta-analysis	packaged identically and centrally, then despatched to the individual centres. Women were given the next labelled package for their centre) **Blinding of participants and personnel:** low risk (double blinded trial) **Blinding of outcome assessment:** low risk (double blinded trial) **Blinding (performance bias and detection bias):** low risk (see above information) **Incomplete outcome data:** low risk (missing data for 1.5% in aspirin group, 1.3% in placebo group) **Selective reporting:** low risk (study considers secondary outcomes of the original trial, but within a pre-specified subgroup of interest) **Other information**
	Chronic hypertension, n (%)	93 (35.09)	93 (36.05)				
	Gestational age at randomisation mean (SE), days	106 (0.49)	106 (0.50)				
	Proteinuria, n (%)						
	< 300mg per 24 hours	69 (70.41)	59 (67.82)				
	≥ 300mg per 24 hours	29 (29.59)	28 (32.18)				
	Predominant race, n (%)						
	White	94 (35.47)	96 (37.21)				
	Hispanic	21 (7.92)	22 (8.53)				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
(this publication is a secondary analysis of the original trial - the High Risk Aspirin Study, performed by the Maternal-Fetal Medicine Units Network) **Source of funding** This analysis was supported by the University of Colorado Department of Obstetrics and Gynaecology. The original study was funded by the National Institute of Child Health and Human Development.	Black 150 (56.60) 138 (53.49) Other 0 2 (0.78) SE standard error **Inclusion criteria** For this subgroup analysis, women with chronic hypertension were identified as those who used an anti-hypertensive agent, or who had a resting blood pressure ≥ 140/90 mmHg on two occasions at least 4 hours apart, either prior to pregnancy, or during pregnancy prior to 20 weeks gestation. For the original study: women with pregestational, insulin-treated diabetes mellitus, or chronic hypertension, or multifetal gestations, or preeclampsia in a previous pregnancy **Exclusion criteria** Women with diabetes and chronic hypertension were included in the diabetes subgroup, therefore are not included in this analysis.				

<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

Moore, M. P., Redman, C. W. G., The treatment of hypertension in pregnancy, Current Medical Research and Opinion, 8, 39-46, 1982

Ref Id

776372

Country/ies where the study was carried out

UK

Study type

RCT

Aim of the study

To assess the effectiveness of methyldopa as compared with labetalol for the treatment of women with chronic hypertension

Study dates</td>
<td>Sample size

N=72 (n=38 randomised to the labetalol group and n=34 randomised to the methyldopa group)

Characteristics
<table>
<tr><th></th><th>Labetalol (n =38)</th><th>Methyldopa (n =34)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>NR</td><td>NR</td></tr>
<tr><td>No. with chronic hypertension [a] n (%)</td><td>22 (57.9)</td><td>25 (73.6)</td></tr>
<tr><td>Pre-eclampsia[b]</td><td>16 (42.1)</td><td>25 (73.6)</td></tr>
<tr><td>sBP/dBP at entry</td><td>170.1 (11)/111.7 (6.4)</td><td>173.4 (14.9)/111.3(9.1)</td></tr>
</table>
NR not reported

[a] Chronic hypertension:sBP/dBP ≥110/170 mmHg on two separate occasions before 20 weeks' gestational age; [b]</td>
<td>Interventions

Labetalol: 100 mg/4 times per day

Methyldopa: 250 mg 4 times per day

Both antihypertensive medications were increased as needed to maintain BP at about 140/90 mmHg.</td>
<td>Details

Follow-up time: 5 weeks

No information about concurrent treatment, use of statins, randomisation details, or sample size calculations was reported.</td>
<td>Results

Neonatal outcomes:

Stillbirth

Labetalol: 0/38

Methyldopa: 0/34

Neonatal death up to 7 days

Labetalol: 2/38

Methyldopa: 0/34

Small-for-gestational-age

Labetalol: 13/38

Methyldopa: 15/34

Birth weight

Labetalol: 2356 (724)

Methyldopa: 2349 (863)

Gestational age at delivery

Labetalol: 36.2 (2.3)

Methyldopa: 36.1 (3.2)

Admission to neonatal unit (report for medium</td>
<td>Limitations

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

Random sequence generation: unclear risk (method was not reported)

Allocation concealment: unclear risk (method for allocation concealment was not reported)

Blinding of participants and personnel: unclear risk (not reported)

Blinding of outcome assessment: unclear risk (not reported)

Blinding (performance bias and detection bias): unclear risk (see above details)

Incomplete outcome data: low risk (no drop outs were reported)

Selective reporting: unclear risk (protocol not</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Not reported **Source of funding** New Zealand Medical Research Council	pre-eclampsia: definition was not reported **Inclusion criteria** sBP/dBP ≥110/170 mmHg on two separate occasions **Exclusion criteria** Multiple pregnancy, insulin-dependent diabetes, rhesus isoimmunisation, those >36 weeks' GA.			care, high care, and intensive care) Labetalol: 19/38 Methyldopa: 16/34 *Maternal outcomes:* **Maximum sBP after entry (mean, SD)** Labetalol: 167.6 (15.6) Methyldopa: 164.9 (20.6) **Maximum dBP after entry (mean, SD)** Labetalol: 110 (8.7) Methyldopa: 110.9 (12.7) **Onset of labour** (induced) Labetalol: 20/38 Methyldopa: 14/34 **Mode of birth** (lower segment C-section in labour and not in labour) Labetalol: 19/38 Methyldopa: 20/34	reported but it appears that all outcomes reported) **Other bias:** 4 of the participants assigned to labetalol switched to methyldopa, and it is unclear whether this could have introduced bias as it was not reported whether patients were analysed per protocol or intention to treat **Other information**
Full citation	**Sample size**	**Interventions**	**Details**	**Results**	**Limitations**

<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>Parazzini, F., Benedetto, C., Frusca, T., Gregorini, G., Bocciolone, L., Marozio, L., Romero, M., Danesino, V., De Gaetano, G., Gastaldi, A., Massobrio, M., Remuzzi, G., Tognoni, G., Guaschino, S., Bianchi, C., Valcamonico, A., Giambuzzi, M., Ammendola, D., Casucci, F., Low-dose aspirin in prevention and treatment of intrauterine growth retardation and pregnancy-induced hypertension, Lancet, 341, 396-400, 1993

Ref Id

788545</td>
<td>Total population:

N = 1106 (n = 583 randomised to aspirin, n = 523 randomised to control)

Women with chronic hypertension or nephropathy:

N = 240 (n = 141 randomised to aspirin, n = 99 randomised to control

Characteristics

For chronic hypertension group:
<table>
<tr><th></th><th>Aspirin (n = 141)</th><th>Control (n = 99)</th></tr>
<tr><td>Gestational age, n (%)</td><td></td><td></td></tr>
<tr><td>16 to 24 weeks</td><td>115 (82)</td><td>78 (78)</td></tr>
<tr><td>25 to 32 weeks</td><td>26 (18)</td><td>21 (21)</td></tr>
</table>
Other demographic features are reported for the entire population, not the subgroup of women with chronic hypertension/nephropathy</td>
<td>Aspirin: 50mg aspirin daily from randomisation until delivery

Control: no treatment (no placebo was given)</td>
<td>Randomisation was performed by two randomisation centres, and participants were allocated by telephone. No details are provided as to the development of the randomisation lists.

Analysis was conducted on an intention to treat basis.

Sample size was calculated on the ability to detect a reduction of about one third in the frequency of babies born small for gestational age. The study had 80% power, with an α level of 0.05 (two tailed) to detect this change.

The study was open label, with no placebo given.</td>
<td>Number of infants born small for gestational age (<10th centile) in women with chronic hypertension†

Aspirin group: 25/134

Control group: 22/98

† denominator less than total group allocation, presumed due to exclusion of women who had miscarriage and those with no outcome data available</td>
<td>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

Random sequence generation: unclear risk (randomisation method was not reported. Authors report an error in randomisation process - same randomisation sheets were used by different centres. This reduces confidence in the process)

Allocation concealment: unclear risk (not reported)

Blinding of participants and personnel: high risk (open label trial, no blinding)

Blinding of outcome assessment: unclear risk (open label trial, no blinding but outcome measures not heavily influenced by subjectivity)

Blinding (performance bias and detection</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Italy **Study type** Multicentre RCT **Aim of the study** To determine the effect of aspirin in women at intermediate risk of pre-eclampsia or IUGR, and in women treated because of early signs of these disorders. **Study dates** September 1988 until September 1991. **Source of funding** Not reported	<table><tr><td></td><td>Aspirin (n = 583)</td><td>Control (n = 523)</td></tr><tr><td>Age, mean ± SD, years</td><td>30.7 ± 6.4</td><td>30.5 ± 6.7</td></tr><tr><td>Systolic BP, mean ± SD, mmHg</td><td>129 ± 17</td><td>128 ± 19</td></tr><tr><td>Diastolic BP, mean ± SD, mmHg</td><td>81 ± 11</td><td>81 ± 13</td></tr></table> **Inclusion criteria** Pregnant women between 16 and 32 weeks of gestation who satisfied one or more of the following criteria: For those treated prophylactically: age <18 or >40 years mild/moderate chronic hypertension (diastolic BP 90 to 100mmHg) nephropathy with normal renal function and normal BP history of PIH with/without proteinuria, developing after 32 weeks in a previous pregnancy history of IUGR (<10th percentile)				**bias):** high risk (see above information) **Incomplete outcome data:** low risk (drop-out 6% and difference between groups 5.7%) **Selective reporting:** high risk (basic demographic information and SD of the continuous outcomes have not been reported) **Other information** Note: subgroup analysis included women with hypertension or nephropathy, and numbers of women with each specific diagnosis are not reported.

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	multiple (twin) pregnancy For those treated therapeutically PIH (diastolic BP between 90 and 100mmHg) Early signs of IUGR (fetal abdominal circumference ≤2SD below the mean for gestation) **Exclusion criteria** History of chronic disease (other than hypertension, renal disease or diabetes without hypertension/nephropathy). Allergy to aspirin. Documented fetal malformations.				
Full citation Poon, L. C., Wright, D., Rolnik, D. L., Syngelaki, A., Delgado, J. L., Tsokaki, T., Leipold, G., Akolekar, R., Shearing, S., De Stefani, L., Jani, J. C., Plasencia, W., Evangelinakis, N., Gonzalez-	**Sample size** Total population: N = 1620 (n = 798 randomised to aspirin, n = 822 randomised to placebo) Subgroup of women with chronic hypertension: N = 110 (n = 49 randomised to aspirin, n = 61 randomised to placebo) **Characteristics**	**Interventions** Aspirin group: 150mg aspirin per day from randomisation until 36 weeks (or onset of labour, in the event of early delivery) Placebo group: identical appearing placebo to be	**Details** Randomisation was performed in a 1:1 manner with the use of a web based system (Sealed Envelope). Stratification was performed according to participating centre. Sample size calculation was performed on the hypothesis that low dose aspirin would reduce the incidence of preterm pre-eclampsia by 50%. Enrollment of 1600	**Results** **Development of preterm pre-eclampsia† in women with chronic hypertension** Aspirin group: 5/49 Control group: 5/61 Odds ratio 1.30 (0.33 to 5.12)	**Limitations** **Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias** **Random sequence generation:** low risk (web based randomisation program used)

<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>Vanegas, O., Persico, N., Nicolaides, K. H., Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history, American Journal of Obstetrics and Gynecology, 217, 585, 2017

Ref Id

788591

Country/ies where the study was carried out

Multicentre

Study type

Multicentre RCT

Countries included: UK,</td>
<td>Demographics reported for entire population, not subgroup of women with chronic hypertension
<table>
<tr><th></th><th>Aspirin

n = 798</th><th>Placebo

n = 822</th></tr>
<tr><td>Gestational age at randomisation median (IQR), weeks</td><td>12.7 (12.3 - 13.1)</td><td>12.6 (12.3 - 13.0)</td></tr>
<tr><td>Age, median (IQR), years</td><td>31.5 (27.3 - 35.8)</td><td>31.4 (26.9 - 35.8)</td></tr>
<tr><td>Ethnicity, n (%)</td><td></td><td></td></tr>
<tr><td>White</td><td>528 (66.2)</td><td>559 (68.0)</td></tr>
<tr><td>Black</td><td>208 (26.1)</td><td>201 (24.5)</td></tr>
<tr><td>South Asian</td><td>37 (4.6)</td><td>37 (4.5)</td></tr>
<tr><td>East Asian</td><td>13 (1.6)</td><td>16 (1.9)</td></tr>
<tr><td>Mixed race</td><td>12 (1.5)</td><td>9 (1.1)</td></tr>
</table>
</td>
<td>taken daily, as per the intervention group.</td>
<td>participants would give the trial 90% power to show a treatment effect with a two-sided α level of 0.05. Target recruitment was inflated to 1776 to allow for attrition.

Analyses were performed on an intention to treat basis.

The trial was double blind.</td>
<td>† defined as delivery with pre-eclampsia prior to 37 weeks gestation</td>
<td>Allocation concealment: unclear risk (no details reported)

Blinding of participants and personnel: low risk (double blinded trial)

Blinding of outcome assessment: low risk (double blinded trial)

Blinding (performance bias and detection bias): low risk (see above information)

Incomplete outcome data: low risk (drop-out <1%)

Selective reporting: low risk (full demographic details reported in primary paper, published protocol available)

Other information

Note: supplementary information obtained from primary trial publication, Rolnik et al. 2017</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Spain, Italy, Belgium, Greece and Israel. **Aim of the study** To examine whether there are differences in the effect of aspirin on the incidence of preterm pre-eclampsia in subgroups defined according to maternal characteristics, and medical and obstetrical history. **Study dates** Trial commenced April 2014, but stopped in June 2014 (after recruitment of 56 participants) because of administrative difficulties with the supply of the trial products. The trial was restarted in July 2015 and	**Inclusion criteria** Maternal age ≥ 18 years Singleton pregnancy with live fetus Estimated risk of preterm PE of >1 in 100 **Exclusion criteria** Unconsious/severely ill status Major fetal abnormality identified at 11-13 weeks scan Learning difficulties or serious mental illness Regular treatment with aspirin in the 28 days preceding screening Bleeding disorder e.g. von Willebrand's disease Peptic ulcer Hypersensitivity to aspirin Lon term use of non-steroidal anti-inflammatory medication Participation in another drug trial within 28 days of screening				

<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>continued until April 2016.

Source of funding

Grants from the European Union Seventh Framework Program and from the Fetal Medicine Foundation.</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Redman, C. W., Fetal outcome in trial of antihypertensive treatment in pregnancy, Lancet (London, England), 2, 753-6, 1976

Ref Id

776552

Country/ies where the study was carried out

UK</td><td>Sample size

N= 208 (n=107 randomised to methyldopa and n=101 randomised to no intervention)

Characteristics
<table><tr><th></th><th>Methyldopa (n = 107)</th><th>No intervention (n = 101)</th></tr><tr><td>Age, years (mean, SD)</td><td>28.6 (6.2)</td><td>27.9 (5.5)</td></tr></table></td><td>Interventions

Methyldopa: dose and route of administration was not reported

No intervention</td><td>Details

Concurrent treatment: other antihypertensive medications, such as hydralazine, were used as needed to control blood pressure in the methyldopa group. All women were managed in a special antenatal hypertension clinic, and most of them were managed as outpatients.

Follow-up: not reported

Randomisation method, sample size calculations, and use of statins were not reported</td><td>Results

Neonatal outcomes

Stillbirth

Methyldopa: 1/98

No intervention:9/92

Birth weight (kgs)

Methyldopa: 3.13 (0.50)

No intervention:3.09 (0.60)

Gestational age at delivery

Methyldopa: 267 (12) [n=103 ~ 4 excluded due</td><td>Limitations

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

Random sequence generation: unclear risk (not reported)

Allocation concealment: unclear risk (not reported)

Blinding of participants and personnel: unclear risk (not reported)</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** To assess the effectiveness of methyldopa in pregnancy outcomes of women with chronic hypertension **Study dates** Not reported **Source of funding** Merck, Sharp and Dohme Ltd.	<table><tr><td>No. with chronic hypertension [a] n (%)</td><td>107 (100)</td><td>101 (100)</td></tr><tr><td>Gestational age at entry, weeks (mean, SD)</td><td>20.5 (4.5)</td><td>21.8 (4.7)</td></tr><tr><td>Parity >4</td><td>6 (5.6%)</td><td>5 (5%)</td></tr></table> [a] sBP>140 or dBP>90 on 2 occasions at least 24 hours apart before 28 weeks' gestational age **Inclusion criteria** sBP>140 or dBP>90 on 2 occasions at least 24 hours apart before 28 weeks' gestational age **Exclusion criteria** Women with severe hypertension (≥170/110 mmHg on 2 occasions more than 4 hours apart; or 180 or 120 mmHg on 2 occasions more than 5 minutes apart); women with obstetric risk factors (diabetes, multiple pregnancy, rhesus immunisation) were also excluded			to mid trimester miscarriages] No intervention: 267 (11) [n=101] **Impaired hearing (At 7 1/2 years old; criteria was not reported) *[data extracted from Cockburn 1982]** Methyldopa: 7/96* (*the hearing test was not done in 2 children) No intervention:6/92 **Impaired vision (At 7 1/2 years old; criteria was not reported)*[data extracted from Cockburn 1982]** Methyldopa: 7/98 No intervention:14/92	**Blinding of outcome assessment:** unclear risk (not reported) **Blinding (performance bias and detection bias):** unclear risk (see above details) **Incomplete outcome data:** low risk if (drop-out<20% and difference between groups <20%) **Selective reporting:** unclear risk (protocol not reported but it appears that all outcomes reported) **Other bias (selection bias):** 11 of the participants assigned to no intervention were switched to methyldopa, and it is unclear whether this could have introduced bias as it was not reported whether patients were analysed per protocol or intention to treat **Other information** Trial sponsored by 3 pharmaceutical

<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>companies (Merck, Sharp, Dohme Ltd.)</td></tr>
<tr><td>Full citation

Sibai, B. M., Mabie, W. C., Shamsa, F., Villar, M. A., Anderson, G. D., A comparison of no medication versus methyldopa or labetalol in chronic hypertension during pregnancy, American Journal of Obstetrics & Gynecology, 162, 960-6; discussion 966-7, 1990

Ref Id

659222

Country/ies where the study was carried out

US

Study type

RCT</td><td>Sample size

N=263 (N=90 randomised to no intervention; n=88 randomised to methyldopa and n=86 randomised to labetalol)

Characteristics
<table><tr><th></th><th>No intervention (n =90)</th><th>Methyldopa (n = 88)</th><th>Labetalol (n=86)</th></tr><tr><td>Age, years (mean, SD)</td><td>29 (0.6)</td><td>30.9 (0.7)</td><td>28.9 (0.7)</td></tr><tr><td>No. with chronic hypertension [a] n (%)</td><td>90 (100)</td><td>88 (100)</td><td>86 (100)</td></tr><tr><td>Gestational age at entry, weeks (mean, SD)</td><td>11.3 (0.2)</td><td>11.2 (0.2)</td><td>11.2 (0.2)</td></tr></table></td><td>Interventions

Methyldopa: 750 mg/day an increased as needed up to 4g/day.

Labetalol: 300 mg/day increased up to 2400 mg/day.

If maximum doses of either medication were not sufficient to control blood pressure (sBP/dBP<140/90), hydralazine was added to a maximum oral dose of 300 mg/day

No intervention: patients were managed without medications, although if</td><td>Details

Randomisation was done with a computer-generated list of random numbers.

No details were provided regarding use of concurrent medication; sample size calculation; use of statins or duration of follow-up</td><td>Results

Neonatal outcomes

Perinatal deaths

No intervention:1/90

Methyldopa: 1/88

Labetalol: 1/86

Small-for-gestational-age

No intervention:8/90

Methyldopa: 6/88

Labetalol: 7/86

Preterm birth (<37 weeks)

No intervention:9/90

Methyldopa: 11/88

Labetalol: 10/86

Maternal outcomes:

Superimposed pre-eclampsia

No intervention:14/90</td><td>Limitations

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

Random sequence generation: low risk (randomisation was done with a computer-generated list of random numbers)

Allocation concealment: unclear risk (method for allocation concealment was not reported)

Blinding of participants and personnel: unclear risk (not reported)

Blinding of outcome assessment: unclear risk (not reported)

Blinding (performance bias and detection bias): unclear risk (see above details)</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess the effectiveness of methyldopa and labetalol as compared to no intervention in pregnancy outcomes of women with chronic hypertension **Study dates** Not reported **Source of funding** Not reported	<table><tr><td>sBP at entry</td><td>141 (0.8)</td><td>139 (0.9)</td><td>139 (0.8)</td></tr><tr><td>dBP at entry</td><td>92 (0.6)</td><td>91 (0.7)</td><td>91 (0.6)</td></tr></table> [a] Definition for chronic hypertension was not reported **Inclusion criteria** 6 to 13 weeks' gestational age with a history of chronic hypertension (definition not reported) **Exclusion criteria** Not reported	patients presented with severe hypertension (sBP >160 or dBP>110 mmHg) received methyldopa		Methyldopa: 16/88 Labetalol: 14/86 **Placental abruption** No intervention:2/90 Methyldopa: 1/88 Labetalol: 2/86 **Mode of birth** (C-section) No intervention:29/90 Methyldopa: 31/88 Labetalol: 30/86	**Incomplete outcome data:** low risk (drop-outs were reported, but these account for <20% in each of the groups and the difference between groups was < 20%) **Selective reporting:** unclear risk (protocol not reported but it appears that all outcomes reported) **Other bias:** some of the participants assigned to the no intervention group (N was not reported), switched to methyldopa, but for the analysis, remained in the non treatment group. It is unclear whether this could have introduced bias as it was not reported whether patients were analysed per protocol or intention to treat **Other information**
Full citation	**Sample size** (See also entry for Askie 2007)	**Interventions**	**Details**	**Results**	**Limitations**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
van Vliet, Elvira O. G., Askie, Lisa A., Mol, Ben W. J., Oudijk, Martijn A., Antiplatelet Agents and the Prevention of Spontaneous Preterm Birth: A Systematic Review and Meta-analysis, Obstetrics and Gynecology, 129, 327-336, 2017 **Ref Id** 788974 **Country/ies where the study was carried out** Multicentre **Study type** Meta-analysis of individual participant data from randomised controlled trials (see also entry for Askie 2007). **Aim of the study**	**Data for primary outcome (risk of spontaneous preterm birth)** Total sample size N = 27510 (n = 13825 randomised to antiplatelet treatment, n = 13685 randomised to control arm) Subgroup analysis for participants with chronic hypertension: N = 2518 (n = 1266 randomised to antiplatelet agent, n = 1252 randomised to control) **Characteristics** Demographics reported for entire population only, not for subgroup of women with chronic hypertension. 57% primigravida 96% singleton pregnancy 62% aged 20 - 35 years **Inclusion criteria** For the purpose of this analysis, only studies that reported on the primary outcome measure were included (spontaneous onset of labour as compared with induction/pre-labour caesarean section, and gestational age at delivery). **Exclusion criteria**	**Antiplatelet group:** aspirin was given alone in 15 of the included studies, in doses ranging from 60 to 150mg per day (accounting for 96%† of women in the dataset). One trial gave aspirin in combination with dipyridamole, and one trial gave dipyridamole alone. **Control group:** women received either placebo, or no treatment (number not reported) † calculated by the NGA from data reported in the article:	See entry from Askie for details of data collection and assessment. The primary outcome measures were: Spontaneous preterm birth of a liveborn neonate between 20 and 37 weeks of gestation Spontaneous preterm birth of a liveborn neonate between 20 and 34 weeks of gestation Spontaneous preterm birth of a liveborn neonate between 20 and 28 weeks of gestation Preterm birth was defined as spontaneous when it followed prelabour premature rupture of membranes, or spontaneous labour with intact membranes (i.e. no induced labour and no nonlabour caesarean delivery).	**Spontaneous preterm birth at <37 weeks' gestation in women with pre-existing hypertension** Antiplatelet group: 71/1266 Control group: 94/1252 Relative risk 0.73 (0.53 to 0.999) **Spontaneous preterm birth at <34 weeks' gestation in women with pre-existing hypertension** Antiplatelet group: 21/1266 Control group: 27/1252 Relative risk 0.76 (0.43 to 1.36) **Spontaneous preterm birth at <28 weeks' gestation in women with pre-existing hypertension** Antiplatelet group: 5/1266	Assessed using the ROBIS tool Study eligibility criteria: Low risk of bias (clear inclusion/exclusion criteria with appropriate exclusions only) Identification and selection of studies: Low risk of bias (Cochrane database searched, supplemented by hand searching) Data collection and study appraisal: Unclear risk of bias (low risk generally, but method for assessing individual study quality is not reported) Synthesis and findings: Low risk of bias (prespecified analyses reported) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To study whether antiplatelet agents reduce the risk of spontaneous preterm birth. **Study dates** Included studies were identified in the period between 1985 and 2005. 17 trials were identified which included data on the primary outcome (spontaneous onset of labour versus induction/non-labour caesarean delivery). **Source of funding** The first author was supported with a travel grant from the Dutch Ter Meulen Fund of the Royal Netherlands	Quasirandom study designs.	13294/13825 women in the intervention arm		Control group: 9/1252 Relative risk 0.56 (0.19 to 1.68)	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Academy of Arts and Sciences. The main funding source for the original study (Perinatal Antiplatelet Review of International Studies) was the National Health and Medical Research Council (NHMRC) of Australia, through a 3-year project grant and a Sidney Sax Public Health Postdoctoral Fellowship. Additional support was provided by the Resource Centre for Randomised Trials and the UK Cochrane Centre (Oxford, UK); the Medical Research Council Clinical Trials Unit (London, UK); and the NHMRC Clinical Trials Centre (University					

<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>of Sydney, Australia).</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Viinikka,L., Hartikainen-Sorri,A.L., Lumme,R., Hiilesmaa,V., Ylikorkala,O., Low dose aspirin in hypertensive pregnant women: effect on pregnancy outcome and prostacyclin-thromboxane balance in mother and newborn, British Journal of Obstetrics and Gynaecology, 100, 809-815, 1993

Ref Id

78531

Country/ies where the study was carried out

Finland</td><td>Sample size

N = 208 (n = 103 randomised to aspirin, n = 105 randomised to placebo)

Characteristics
<table><tr><th></th><th>Aspirin

n = 103</th><th>Placebo

n = 105</th></tr><tr><td>Age, mean ± SD, years</td><td>33.2 ± 4.9</td><td>32.7 ± 5.4</td></tr><tr><td>Gestation at randomisation, mean ± SD, weeks</td><td>15.3 ± 1.8</td><td>15.5 ± 1.9</td></tr><tr><td>Pre-existing hypertension, n (%)</td><td>89 (86.4)</td><td>96 (91.4)</td></tr><tr><td>Severe preeclampsia in previous pregnancy, n (%)</td><td>14 (13.6)</td><td>9 (8.6)</td></tr><tr><td>Diastolic BP at entry to study,</td><td>88.8 ± 10.6</td><td>88.8 ± 9.9</td></tr></table></td><td>Interventions

Aspirin group: 50mg aspirin to be taken daily

Control group: identically appearing and tasting tablets were to be taken daily</td><td>Details

Participants were randomly allocated to the groups by the use of sealed envelopes (no further details were provided).

Sample size was calculated on the basis of the risk of blood pressure elevation of 50%, and the protective effect of aspirin being at least 50%. The study population was calculated to be large enough to reveal the effect of aspirin with 95% probability. No further details were provided.</td><td>Results

Development of preeclampsia (study outcome reported as "exacerbation of hypertension with proteinuria")

Aspirin group: 9/97

Control group: 11/100

Exacerbation of hypertension

(defined as a level of >160/120mmHg, necessitating initiation of antihypertensives, or an increase in dose of antihypertensives, or a rise in BP to >160/110 in those participants without chronic hypertension)

Aspirin group: 21/97

Control group: 25/100</td><td>Limitations

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

Random sequence generation: unclear risk (insufficient details provided)

Allocation concealment: unclear risk (no details reported)

Blinding of participants and personnel: low risk (double blinded trial)

Blinding of outcome assessment: low risk (double blinded trial)

Blinding (performance bias and detection bias): low risk (see above information)

Incomplete outcome data: low risk (drop-out <6% and difference between groups <2%)</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type Single centre RCT **Aim of the study** To study the effect of aspirin on the complications in pregnancy of women with high risk pregnancy. **Study dates** Not reported. **Source of funding** Academy of Finlan and the Sigrid Juselius Foundation. Medication was provided by Orion Ltd.	mean ± SD, mmHg **Inclusion criteria** Chronic hypertension prior to pregnancy (BP >140/90 mmHg without treatment), or severe preeclampsia in a previous pregnancy. **Exclusion criteria** Presence of proteinuria (>300mg/ 24 hr) prior to pregnancy.			**Diastolic BP at 36th week of pregnancy, mean ± SD, mmHg** Aspirin group: 90.1 ± 12.5 Control group: 90.3 ± 10.9 **Gestational age at delivery, mean ± SD, weeks** Aspirin group: 38.6 ± 2.1 Control group: 38.2 ± 2.0 **Spontaneous onset of labour (comparator: induction or elective caesarean section)** Aspirin group: 45/97 Control group: 40/100 **Infant birthweight, mean ± SD (grams)** Aspirin group: 3348 **±** 707 Control group: 3170 **±** 665	**Selective reporting:** low risk (main outcomes fully reported, demographic details reported) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Number of infants born small for gestational age (≤2 SD below the mean) Aspirin group: 4/97 Control group: 9/100 **Admission to neonatal unit** Aspirin group: 10/97 Control group: 21/100 **Perinatal death** Aspirin group: 2/97 Control group: 0/100	
Full citation Webster, L. M., Myers, J. E., Nelson-Piercy, C., Harding, K., Kennedy	**Sample size** N=114 (n=56 randomised to the labetalol group and n=58 randomised to the nifedipine group) **Characteristics**	**Interventions** Labetalol: 100 mg BID up to 1800 mg (600 mg TID)	**Details** Concurrent treatment: women could be prescribed additional antihypertensive treatment in order to reach the BP target (dBP ≤85	**Results** *Neonatal outcomes* **Stillbirth** Labetalol: 2/55	**Limitations** **Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Cruickshank, J., Watt-Coote, I., Khalil, A., Wiesender, C., Seed, P. T., Chappell, L. C., Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy: A Randomized Controlled Trial, Hypertension, 70, 915-922, 2017 **Ref Id** 776893 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study** To assess the efficacy of labetalol as compared to nifedipine in	<table><tr><th></th><th>Labetalol (n = 56)</th><th>Nifedipine (n =58)</th></tr><tr><td>Age, years (n,%)</td><td>36 (32 to 39.1)</td><td>35 (30.3 to 38.5)</td></tr><tr><td>Chronic hypertension[a] n (%)</td><td>56 (100)</td><td>56 (100)</td></tr><tr><td>Gestational age at treatment, weeks (mean, SD)</td><td>16.6 (13.7 to 21.3)</td><td>16.9(14.6 to 21.1)</td></tr><tr><td>Ethnicity: White</td><td>17 (30)</td><td>18 (31)</td></tr><tr><td>Ethnicity: Black</td><td>30 (54)</td><td>32 (55)</td></tr><tr><td>Ethnicity: Asian</td><td>6 (11)</td><td>3(5)</td></tr><tr><td>Ethnicity: Other</td><td>3 (5)</td><td>5 (9)</td></tr><tr><td>Nulliparous</td><td>14 (25)</td><td>13 (22)</td></tr></table>	Nifedipine: 10 mg BID up to 80 mg (40 mg BID)	mmHg). Women also received 75mg/day aspirin for prevention of pre-eclampsia Randomisation was performed via MedSciNet online minimisation protocol. Stratification was performed by gestational age at randomisation, maternity centre, sBP, and ethnicity. Treatment was open-label. No information was reported regarding sample size calculations, use of statins or duration of follow-up	Nifedipine: 1/57 **Neonatal death** Labetalol: 0/55 Nifedipine: 0/57 **SGA (BW< 10th centile)** Labetalol: 16/55 Nifedipine: 17/57 **Birth weight** Labetalol: 2957 (790) Nifedipine: 2732 (883) **Admitted to neonatal unit** Labetalol: 11/55 Nifedipine:15/57 **Preterm birth (<37 weeks)** Labetalol: 12/55 Nifedipine: 20/57 **Preterm birth (<34 weeks)** Labetalol: 10/55 Nifedipine: 11/57	**Random sequence generation:** low risk (randomisation was performed using MedSciNet online minimisation protocol) **Allocation concealment:** unclear risk (not reported) **Blinding of participants and personnel:** high risk (open-label trial) **Blinding of outcome assessment:** high risk (open-label trial) **Blinding (performance bias and detection bias):** high risk (see above information) **Incomplete outcome data:** low risk (drop outs were not reported, ITT analysis was used) **Selective reporting:** low risk (protocol reported and all outcomes were covered) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
pregnancy outcomes of women with chronic hypertension **Study dates** August 2014 to October 2015 **Source of funding** King´s Health Partners Research and Development Challenge Fund and Tommy´s Charity	<table><tr><td>sBP at study entry</td><td>143 (133 to 150)</td><td>141 (132 to 151)</td></tr><tr><td>dBP at study entry</td><td>92 (85 to 98)</td><td>91 (86 to 96)</td></tr></table> [a] Chronic hypertension: BP ≥140/90 before 20 weeks gestation requiring antihypertensive treatment before 27 + 6 **Inclusion criteria** Aged > 18 years; prenatal diagnosis of chronic hypertension or BP ≥140/90 before 20 weeks gestation requiring antihypertensive treatment before 27 + 6; singleton pregnancies; gestation between 12+0 and 27+6 weeks. **Exclusion criteria** Contraindication to the use of nifedipine or labetalol.			*Mother outcomes* **Gestational age at delivery *[means calculated from medians using the calculator developed by Hozo et.al., 2005 (equations 4 and 12)** Labetalol: 38.5 (0.44) Nifedipine: 37.87 (0.71) **Mode of delivery (spontaneous)** Labetalol: 22/55 Nifedipine: 21/57 **Mode of delivery (assisted vaginal delivery)** Labetalol: 2/55 Nifedipine: 4/57	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Mode of delivery (elective prelabour LSCS) Labetalol: 9/55 Nifedipine: 13/57 **Mode of delivery (emergency prelabour LSCS)** Labetalol: 14/55 Nifedipine: 11/57 **Mode of delivery (emergency LSCS in labour)** Labetalol: 8/55 Nifedipine: 8/57 **Superimposed pre-eclampsia** Labetalol: 8/55 Nifedipine: 15/57	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Superimposed pre-eclampsia < 34 weeks Labetalol: 6/55 Nifedipine: 6/57 **Eclampsia** Labetalol: 0/55 Nifedipine: 0/57 **Maternal death** Labetalol: 0/55 Nifedipine: 0/57	
Full citation Weitz, C., Khouzami, V., Maxwell, K., Johnson, J. W., Treatment of hypertension in pregnancy with methyldopa: a randomized double blind study, International	**Sample size** N=25 (n=13 randomised to the methyldopa group and n=12 randomised to the placebo group) **Characteristics** Methyldopa (n =13) Placebo (n =12)	**Interventions** Methyldopa: 250 mg PO TID Placebo: one tablet PO TID	**Details** Concurrent medication: other antihypertensive medications (hydralazine and magnesium sulphate) were used if severe superimposed pre-eclampsia developed Patients were randomly allocated, double blind trial. No information was reported regarding sample size	**Results** *Neonatal outcomes* **Stillbirth** Methyldopa: 0/13 Placebo: 0/12 **Neonatal death up to 7 days** Methyldopa: 0/13	**Limitations** **Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias** **Random sequence generation:** unclear risk (method was not reported)

<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>Journal of Gynaecology & Obstetrics, 25, 35-40, 1987

Ref Id

392871

Country/ies where the study was carried out

US

Study type

RCT

Aim of the study

To asses the efficacy of methyldopa in the pregnancy outcomes of women with chronic hypertension

Study dates

Not reported

Source of funding

Not reported</td>
<td>
<table>
<tr><td>Age, years (median)</td><td>25.4</td><td>23.7</td></tr>
<tr><td>No. of women with chronic hypertension [a] n (%)</td><td>13 (100)</td><td>12 (100)</td></tr>
<tr><td>Ethnicity: black</td><td>9 (62)</td><td>8 (67)</td></tr>
<tr><td>Primipara</td><td>8 (61.5)</td><td>6 (50)</td></tr>
</table>
[a] BP ≥140/90 mmHg on 2 separate occasion at least 6 hours apart

Inclusion criteria

BP ≥140/90 mmHg on 2 separate occasion at east 6 hours apart; no evidence of proteinuria (24 h urine protein < 100mg); presumed chronic hypertension

Exclusion criteria

Not reported
</td>
<td></td>
<td>calculations, use of statins or duration of follow-up.</td>
<td>Placebo: 0/12

Gestational age at delivery

Methyldopa: 273 (2.93)

Placebo: 263 (3.48)

Maternal outcomes:

Superimposed pre-eclampsia

Methyldopa: 5/13

Placebo: 4/12</td>
<td>Allocation concealment: unclear risk (method was not reported)

Blinding of participants and personnel: low risk (double blind)

Blinding of outcome assessment: low risk (double blind)

Blinding (performance bias and detection bias): low risk (see above information)

Incomplete outcome data: low risk (no drop outs were reported)

Selective reporting: unclear risk (protocol not reported but all outcomes appear to have been reported)

Other information</td>
</tr>
</table>

Appendix E – Forest plots

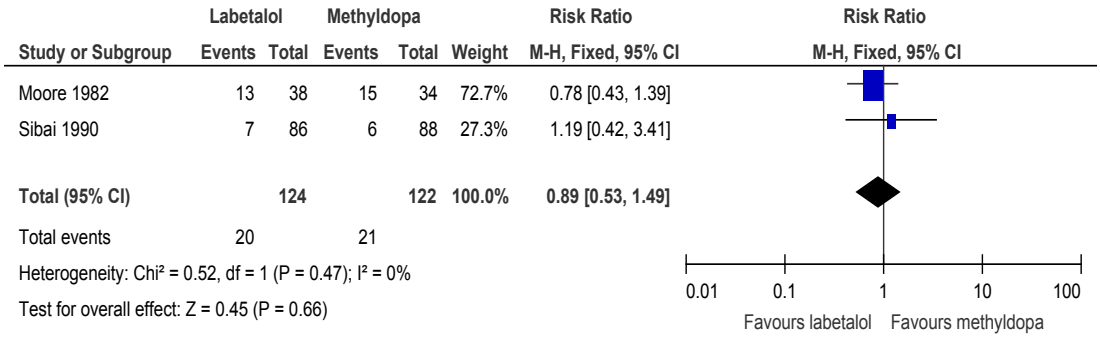
No forest plots were generated for comparisons 1- 6 and 8-10, as no meta-analyses were performed

Figure 1: Comparison 7. Labetalol versus methyldopa

Outcomes for babies

Critical outcomes:

Small-for-gestational-age (BW<10th centile)



Outcomes for women

Important outcomes:

Mode of birth (C-section)

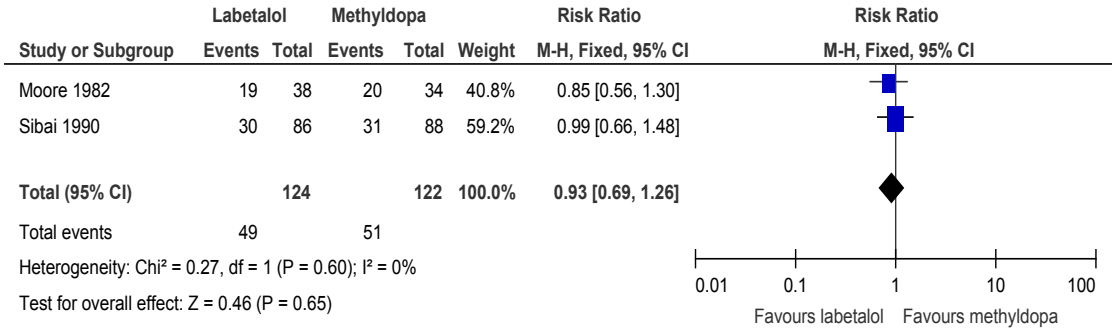


Figure 2: Comparison 11. Aspirin versus no intervention

Outcomes for babies

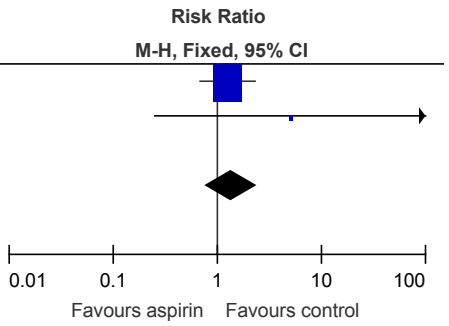
Critical outcomes:

Stillbirth and neonatal death

Study or Subgroup	Aspirin Events	Aspirin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Atallah 1996	22	233	17	226	97.2%	1.26 [0.68, 2.30]
Viinikka 1993	2	97	0	100	2.8%	5.15 [0.25, 105.98]
Total (95% CI)		**330**		**326**	**100.0%**	**1.36 [0.76, 2.46]**
Total events	24		17			

Heterogeneity: Chi² = 0.81, df = 1 (P = 0.37); I² = 0%

Test for overall effect: Z = 1.03 (P = 0.30)

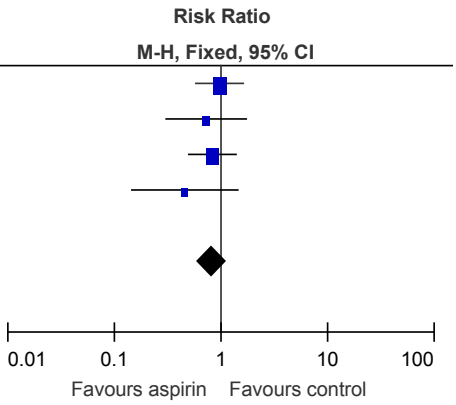


Small-for-gestational age

Study or Subgroup	Aspirin Events	Aspirin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Atallah 1996	26	233	26	226	36.8%	0.97 [0.58, 1.62]
Moore 2015	8	93	11	93	15.3%	0.73 [0.31, 1.73]
Parazzini 1993	25	134	22	98	35.5%	0.83 [0.50, 1.38]
Viinikka 1993	4	97	9	100	12.4%	0.46 [0.15, 1.44]
Total (95% CI)		**557**		**517**	**100.0%**	**0.82 [0.60, 1.13]**
Total events	63		68			

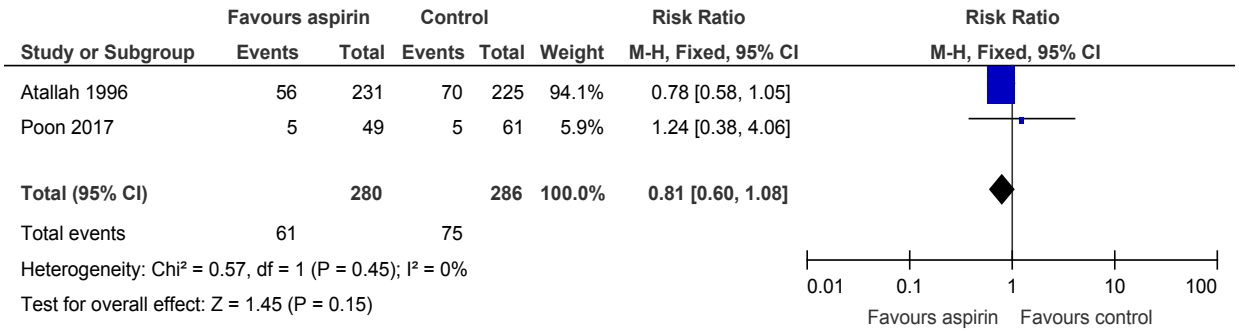
Heterogeneity: Chi² = 1.48, df = 3 (P = 0.69); I² = 0%

Test for overall effect: Z = 1.22 (P = 0.22)



Important outcomes:

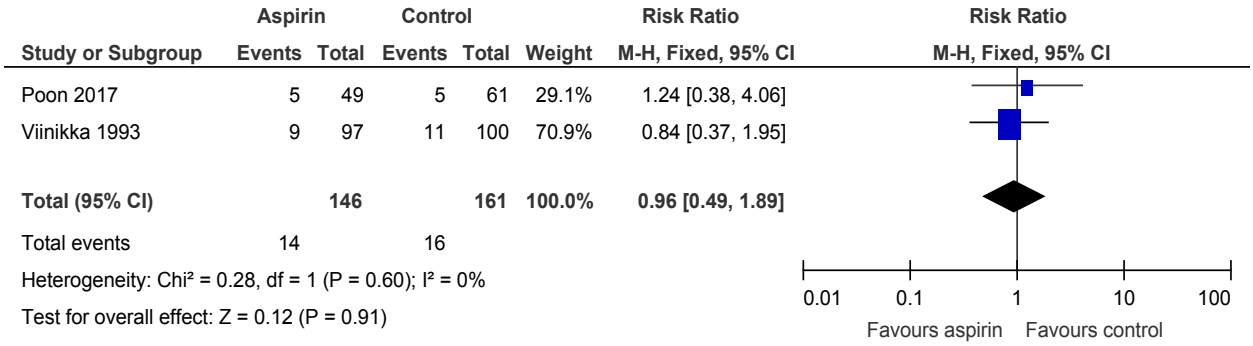
Preterm birth < 37 weeks



Outcomes for women

Important outcomes:

Development of pre-eclampsia



Appendix F – GRADE tables

Table 5: Clinical evidence profile. Comparison 1. Induction of labour versus expectant management

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Induction of labour	Expectant management	Relative (95% CI)	Absolute	Quality	Importance
Perinatal mortality												
1 (Hamed 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/38 (5.3%)	1/38 (2.6%)	RR 2 (0.19 to 21.14)	26 more per 1000 (from 21 fewer to 530 more)	VERY LOW	CRITICAL
Birth weight (grams) (Better indicated by higher values)												
1 (Hamed 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	38	38	-	MD 400 lower (669.79 to 130.21 lower)	LOW	IMPORTANT
Gestational age at birth (weeks) (Better indicated by higher values)												
1 (Hamed 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	38	38	-	MD 2.40 lower (3.34 to 1.46 lower)	VERY LOW	IMPORTANT
Preterm birth (number of weeks were not reported)												
1 (Hamed 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/38 (26.3%)	12/38 (31.6%)	RR 0.83 (0.41 to 1.69)	54 fewer per 1000 (from 186 fewer to 218 more)	VERY LOW	IMPORTANT
Admission to neonatal unit												
1 (Hamed 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	12/38 (31.6%)	3/38 (7.9%)	RR 4.00 (1.23 to 13.05)	237 more per 1000 (from 18 more to 951 more)	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Induction of labour	Expectant management	Relative (95% CI)	Absolute		
Severe hypertension												
1 (Hamed 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/38 (13.2%)	3/38 (7.9%)	RR 1.67 (0.43 to 6.49)	53 more per 1000 (from 45 fewer to 433 more)	VERY LOW	CRITICAL
Superimposed pre-eclampsia												
1 (Hamed 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/38 (31.6%)	13/38 (34.2%)	RR 0.92 (0.49 to 1.76)	27 fewer per 1000 (from 174 fewer to 260 more)	VERY LOW	IMPORTANT
Placental abruption												
1 (Hamed 2014)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/38 (7.9%)	3/38 (7.9%)	RR 1.00 (0.22 to 4.65)	0 fewer per 1000 (from 62 fewer to 288 more)	VERY LOW	IMPORTANT

1 The quality of the evidence was downgraded by two levels due to unclear risk of allocation concealment, performance and selection bias, and selective reporting
2 The quality of the evidence was downgraded by two levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)
3 The quality of the evidence was downgraded by one level as the 95% CI crossed 1 MID threshold (3.9 x +/- 0.5 = +/-1.95)
4 The quality of the evidence was downgraded by one level as the 95% CI crossed 1 default MID threshold (1.25)

Table 6: Clinical evidence profile. Comparison 2. Exercise versus no intervention

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	No intervention	Relative (95% CI)	Absolute		
Birth weight <2500 grams												
1 (Kasawara 2013)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	9/56 (16.1%)	11/53 (20.8%)	RR 0.77 (0.35 to 1.72)	48 fewer per 1000 (from 135	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise	No intervention	Relative (95% CI)	Absolute		
										fewer to 149 more)		
Birth weight 2500-3999 grams												
1 (Kasawara 2013)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	41/56 (73.2%)	35/53 (66%)	RR 1.11 (0.86 to 1.42)	73 more per 1000 (from 92 fewer to 277 more)	VERY LOW	IMPORTANT
Birth weight ≥4000 grams												
1 (Kasawara 2013)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[5]	none	5/56 (8.9%)	11/53 (20.8%)	RR 0.43 (0.16 to 1.16)	118 fewer per 1000 (from 174 fewer to 33 more)	VERY LOW	IMPORTANT
Admission to neonatal unit												
1 (Kasawara 2013)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	12/56 (21.4%)	13/53 (24.5%)	RR 0.87 (0.44 to 1.74)	32 fewer per 1000 (from 137 fewer to 182 more)	VERY LOW	IMPORTANT
Mode of birth (caesarean section)												
1 (Kasawara 2013)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	36/56 (64.3%)	41/53 (77.4%)	RR 0.83 (0.65 to 1.06)	132 fewer per 1000 (from 271 fewer to 46 more)	VERY LOW	IMPORTANT

1 The quality of the evidence was downgraded by 2 levels as participants and personnel were not blinded to treatment allocation; it was unclear whether outcome assessors were blinded to treatment allocation and there was an unclear risk of selective reporting
2 The quality of the evidence was downgraded by 1 level as 9.49% of women did not present with chronic hypertension
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)
4 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (1.25)
5 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (0.8)

Table 7: Clinical evidence profile. Comparison 3. Less-tight versus tight control of blood pressure

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Less-tight control	Tight control	Relative (95% CI)	Absolute	Quality	Importance
Stillbirth												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	12/493 (2.4%)	7/488 (1.4%)	RR 1.70 (0.67 to 4.27)	10 more per 1000 (from 5 fewer to 47 more)	VERY LOW	CRITICAL
Neonatal death												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/493 (0.41%)	4/488 (0.82%)	RR 0.49 (0.09 to 2.69)	4 fewer per 1000 (from 7 fewer to 14 more)	VERY LOW	CRITICAL
Small for gestational age (birthweight <10th percentile)												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	51/366 (13.9%)	71/361 (19.7%)	RR 0.71 (0.51 to 0.98)	57 fewer per 1000 (from 4 fewer to 96 fewer)	LOW	CRITICAL
Birth weight (grams) (Better indicated by higher values)												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	493	488	-	MD 31.07 lower (66.68 lower to 4.54 higher)	LOW	IMPORTANT
Gestational age at delivery (weeks) (Better indicated by higher values)												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	493	488	-	MD 0.40 lower (0.81 lower to 0.01 higher)	LOW	IMPORTANT
Admission to neonatal unit												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	141/480 (29.4%)	139/479 (29%)	RR 1.01 (0.83 to 1.23)	3 more per 1000 (from 49 fewer to 67 more)	LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Less-tight control	Tight control	Relative (95% CI)	Absolute	Quality	Importance
Severe hypertension												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	159/369 (43.1%)	96/363 (26.4%)	RR 1.63 (1.32 to 2.01)	167 more per 1000 (from 85 more to 267 more)	MODERATE	CRITICAL
HELLP												
1 (Magee 2015)	randomised trials	serious[2]	no serious inconsistency	serious[2]	very serious[3]	none	9/493 (1.8%)	2/488 (0.41%)	RR 4.45 (0.97 to 20.51)	14139 more per 1,000,000 (from 123 fewer to 79959 more)	VERY LOW	IMPORTANT
Placental abruption												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	11/493 (2.2%)	11/488 (2.3%)	RR 0.99 (0.43 to 2.26)	0 fewer per 1000 (from 13 fewer to 28 more)	VERY LOW	IMPORTANT
Pre-eclampsia												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	176/368 (47.8%)	155/363 (42.7%)	RR 1.12 (0.95 to 1.31)	51 more per 1000 (from 21 fewer to 132 more)	LOW	IMPORTANT
Onset of labour (spontaneous onset)												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	serious[2]	serious[5]	none	109/493 (22.1%)	104/488 (21.3%)	RR 1.04 (0.82 to 1.32)	9 more per 1000 (from 38 fewer to 68 more)	VERY LOW	IMPORTANT
Onset of labour (induced)												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	224/493 (45.4%)	218/488 (44.7%)	RR 1.02 (0.89 to 1.17)	9 more per 1000 (from 49 fewer to 76 more)	LOW	IMPORTANT
Onset of labour (elective caesarean section)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Less-tight control	Tight control	Relative (95% CI)	Absolute		
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	159/493 (32.3%)	164/488 (33.6%)	RR 0.96 (0.80 to 1.15)	13 fewer per 1000 (from 67 fewer to 50 more)	LOW	IMPORTANT
Mode of birth (C-section)												
1 (Magee 2015)	randomised trials	serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	231/493 (46.9%)	250/488 (51.2%)	RR 0.91 (0.80 to 1.04)	46 fewer per 1000 (from 102 fewer to 20 more)	LOW	IMPORTANT

1 The quality of the evidence was downgraded by 1 level due to a high risk of performance and detection bias
2 The quality of the evidence was downgraded by 1 level as 25.5% of women did not present with chronic hypertension
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)
4 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (0.8)
5 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (1.25)

Table 8: Clinical evidence profile. Comparison 4. Atenolol versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atenolol	Placebo	Relative (95% CI)	Absolute		
Stillbirth												
1 (Butters 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/15 (6.7%)	0/14 (0%)	RR 2.81 (0.12 to 63.83)[5]	-	VERY LOW	CRITICAL
Small-for-gestational age												
1 (Butters 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/15 (66.7%)	0/14 (0%)	RR 19.69 (1.26 to 307.41)[5]	-	LOW	CRITICAL
Birth weight (grams) (Better indicated by higher values)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atenolol	Placebo	Relative (95% CI)	Absolute		
1 (Butters 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	15	14	-	MD 910 lower (440 to 1380)	VERY LOW	IMPORTANT
Gestational age at birth (weeks) (Better indicated by higher values)												
1 (Butters 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	15	14	-	not calculable[4]	VERY LOW	IMPORTANT
sBP after treatment												
1 (Butters 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	-	-	-	MD 4 higher (1.4 lower to 8.6 higher)	VERY LOW	IMPORTANT
dBP after treatment												
1 (Butters 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	-	-	-	MD 7 lower (2.9 to 10 lower)	VERY LOW	IMPORTANT

1 The quality of the evidence was downgraded by 2 levels due to an unclear risk of random sequence generation and allocation concealment and a high risk of selective reporting
2 The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)
3 The quality of the evidence was downgraded by 2 levels as imprecision could not be assessed as SDs have not been reported
4 Not enough information was provided to allow calculation (SDs have not been reported). The mean gestational age in the atenolol group was 39.5 weeks and in the placebo group was 38.5 weeks
5 Corresponding absolute risk was not calculated as there were no events reported in the control arm.

Table 9: Clinical evidence profile. Comparison 5. Labetalol versus no intervention

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Labetalol	No intervention	Relative (95% CI)	Absolute		
Perinatal death												
1 (Sibai 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/86 (1.2%)	1/90 (1.1%)	RR 1.05 (0.07 to 16.47)	1 more per 1000 (from 10 fewer to	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Labetalol	No intervention	Relative (95% CI)	Absolute		
										172 more)		
Small-for-gestational age												
1 (Sibai 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/86 (8.1%)	8/90 (8.9%)	RR 0.92 (0.35 to 2.42)	7 fewer per 1000 (from 58 fewer to 126 more)	VERY LOW	CRITICAL
Preterm birth (<37 weeks)												
1 (Sibai 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/86 (11.6%)	9/90 (10%)	RR 1.16 (0.50 to 2.72)	16 more per 1000 (from 50 fewer to 172 more)	VERY LOW	IMPORTANT
Superimposed pre-eclampsia												
1 (Sibai 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/86 (16.3%)	14/90 (15.6%)	RR 1.05 (0.53 to 2.06)	8 more per 1000 (from 73 fewer to 165 more)	VERY LOW	IMPORTANT
Placental abruption												
1 (Sibai 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/86 (2.3%)	2/90 (2.2%)	RR 1.05 (0.15 to 7.26)	1 more per 1000 (from 19 fewer to 139 more)	VERY LOW	IMPORTANT
Mode of birth (caesarean section)												
1 (Sibai 1990)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	30/86 (34.9%)	29/90 (32.2%)	RR 1.08 (0.71 to 1.64)	26 more per 1000 (from 93 fewer to 206 more)	VERY LOW	IMPORTANT

1 The quality of the evidence was downgraded by 2 levels due to an unclear risk of allocation concealment, performance and selection bias, and selective reporting
2 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 10: Clinical evidence profile. Comparison 6. Labetalol versus nifedipine

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Labetalol	Nifedipine	Relative (95% CI)	Absolute		
Stillbirth												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/55 (3.6%)	1/57 (1.8%)	RR 2.07 (0.19 to 22.21)	19 more per 1000 (from 14 fewer to 372 more)	VERY LOW	CRITICAL
Neonatal death												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/55 (0%)	0/57 (0%)	not calculable	not calculable	MODERATE	CRITICAL
Small-for-gestational age												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	16/55 (29.1%)	17/57 (29.8%)	RR 0.98 (0.55 to 1.73)	6 fewer per 1000 (from 134 fewer to 218 more)	VERY LOW	CRITICAL
Birth weight (grams) (Better indicated by higher values)												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	55	57	-	MD 225 higher (85.06 lower to 535.06 higher)	LOW	IMPORTANT
Preterm birth (<37 weeks)												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	12/55 (21.8%)	20/57 (35.1%)	RR 0.62 (0.34 to 1.15)	133 fewer per 1000 (from 232 fewer to 53 more)	LOW	IMPORTANT
Preterm birth (<34 weeks)												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	10/55 (18.2%)	11/57 (19.3%)	RR 0.94 (0.44 to 2.04)	12 fewer per 1000 (from 108	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Labetalol	Nifedipine	Relative (95% CI)	Absolute		
										fewer to 201 more)		
Admission to neonatal unit												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	11/55 (20%)	15/57 (26.3%)	RR 0.76 (0.38 to 1.51)	63 fewer per 1000 (from 163 fewer to 134 more)	VERY LOW	IMPORTANT
Gestational age at birth, weeks (Better indicated by higher values)												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55	57	-	MD 0.63 higher (0.41 to 0.85 higher)	MODERATE	IMPORTANT
Mode of birth (caesarean section)												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	17/55 (30.9%)	21/57 (36.8%)	RR 0.84 (0.50 to 1.41)	59 fewer per 1000 (from 184 fewer to 151 more)	VERY LOW	IMPORTANT
Superimposed pre-eclampsia												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	8/55 (14.5%)	15/57 (26.3%)	RR 0.55 (0.25 to 1.20)	118 fewer per 1000 (from 197 fewer to 53 more)	LOW	IMPORTANT
Superimposed pre-eclampsia < 34 weeks												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/55 (10.9%)	6/57 (10.5%)	RR 1.04 (0.36 to 3.02)	4 more per 1000 (from 67 fewer to 213 more)	VERY LOW	IMPORTANT
Eclampsia												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Labetalol	Nifedipine	Relative (95% CI)	Absolute		
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/55 (0%)	0/57 (0%)	not calculable	not calculable	MODERATE	IMPORTANT
Maternal death												
1 (Webster 2017)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/55 (0%)	0/57 (0%)	not calculable	not calculable	MODERATE	IMPORTANT

1 The quality of the evidence was downgraded by 1 level due to unclear risk of allocation concealment and a high risk of performance and detection bias
2 The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)
3 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (883 x +/- 0.5= +/- 441.5)
4 95% CI crossed 1 default MID threshold (0.8)

Table 11: Clinical evidence profile. Comparison 7. Labetalol versus methyldopa

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Labetalol	Methyldopa	Relative (95% CI)	Absolute		
Stillbirth												
1 (Moore 1982)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	0/38 (0%)	0/34 (0%)	not calculable	not calculable	VERY LOW	CRITICAL
Neonatal death												
1 (Moore 1982)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	2/38 (5.3%)	0/34 (0%)	RR 4.49 (0.22 to 90.30)[6]	-	VERY LOW	CRITICAL
Small for gestational age												
2 (Moore 1982, Sibai 1990)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20/124 (16.1%)	21/122 (17.2%)	RR 0.89 (0.53 to 1.49)	19 fewer per 1000 (from 81 fewer to 84 more)	VERY LOW	CRITICAL
Birth weight (grams) (Better indicated by higher values)												
1 (Moore 1982)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	38	34	-	MD 7 higher	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Labetalol	Methyldopa	Relative (95% CI)	Absolute		
										(363.32 lower to 377.32 higher)		
Gestational age at birth (weeks) (Better indicated by higher values)												
1 (Moore 1982)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	no serious imprecision	none	38	34	-	MD 0.1 higher (1.2 lower to 1.4 higher)	VERY LOW	IMPORTANT
Admission to neonatal unit												
1 (Moore 1982)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	19/38 (50%)	16/34 (47.1%)	RR 1.06 (0.66 to 1.71)	28 more per 1000 (from 160 fewer to 334 more)	VERY LOW	IMPORTANT
Maximum sBP after entry (mmHg) (Better indicated by lower values)												
1 (Moore 1982)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	38	34	-	MD 2.7 higher (5.82 lower to 11.22 higher)	VERY LOW	CRITICAL
Maximum dBP after entry (mmHg) (Better indicated by lower values)												
1 (Moore 1982)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[5]	none	38	34	-	MD 0.9 lower (5.99 lower to 4.19 higher)	VERY LOW	CRITICAL
Onset of labour (induction)												
1 (Moore 1982)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	20/38 (52.6%)	14/34 (41.2%)	RR 1.28 (0.77 to 2.11)	115 more per 1000 (from 95 fewer to	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Labetalol	Methyldopa	Relative (95% CI)	Absolute		
										457 more)		
Mode of birth (C-section)												
2 (Moore 1982, Sibai 1990)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	49/124 (39.5%)	51/122 (41.8%)	RR 0.93 (0.69 to 1.26)	29 fewer per 1000 (from 130 fewer to 109 more)	VERY LOW	IMPORTANT

1 The quality of the evidence was downgraded by 2 levels due to an unclear risk of random sequence generation, allocation concealment, performance and selection bias, and selective reporting
2 The quality of the evidence was downgraded by 1 level as 34.8% of participants did not present with chronic hypertension
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)
4 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (14.9 x +/- 0.5 = +/- 7.45)
5 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)
6 The corresponding absolute risk was not calculated as there were no events reported in the control arm.

Table 12: Clinical evidence profile. Comparison 8. Methyldopa versus placebo

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methyldopa	Placebo	Relative (95% CI)	Absolute		
Stillbirth												
1 (Weitz 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/13 (0%)	0/12 (0%)	not calculable	not calculable	MODERATE	CRITICAL
Neonatal death												
1 (Weitz 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/13 (0%)	0/12 (0%)	not calculable	not calculable	MODERATE	CRITICAL
Gestational age at birth, weeks (Better indicated by higher values)												
1 (Weitz 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	13	12	-	MD 1.43 higher (1.07 to	MODERATE	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methyldopa	Placebo	Relative (95% CI)	Absolute		
										1.79 higher)		
Superimposed pre-eclampsia												
1 (Weitz 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/13 (38.5%)	4/12 (33.3%)	RR 1.15 (0.40 to 3.31)	50 more per 1000 (from 200 fewer to 770 more)	VERY LOW	IMPORTANT

1 The quality of the evidence was downgraded by 1 level due to an unclear risk of random sequence generation, allocation concealment and selective reporting
2 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 13: Clinical evidence profile. Comparison 9. Methyldopa versus no intervention

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methyldopa	No intervention	Relative (95% CI)	Absolute		
Stillbirth												
1 (Redman 1976)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	1/98 (1%)	9/92 (9.8%)	RR 0.1 (0.01 to 0.81)	88 fewer per 1000 (from 19 fewer to 97 fewer)	VERY LOW	CRITICAL
Perinatal death												
1 (Sibai 1990)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/88 (1.1%)	1/90 (1.1%)	RR 1.02 (0.06 to 16.10)	0 more per 1000 (from 10 fewer to 168 more)	VERY LOW	CRITICAL
Small for gestational age												
1 (Sibai 1990)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/88 (6.8%)	8/90 (8.9%)	RR 0.77 (0.28 to 2.12)	20 fewer per 1000 (from 64 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methyldopa	No intervention	Relative (95% CI)	Absolute		
										100 more)		
Birth weight (grams) (Better indicated by higher values)												
1 (Redman 1976)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	98	92	-	MD 40 higher (117.58 lower to 197.58 higher)	LOW	IMPORTANT
Gestational age at birth (weeks) (Better indicated by higher values)												
1 (Redman 1976)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	103	101	-	MD 0.03 lower (0.48 lower to 0.42 higher)	LOW	IMPORTANT
Preterm birth (<37 weeks)												
1 (Sibai 1990)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	11/88 (12.5%)	9/90 (10%)	RR 1.25 (0.54 to 2.87)	25 more per 1000 (from 46 fewer to 187 more)	VERY LOW	IMPORTANT
Impaired vision at 7.5 years old												
1 (Cockburn 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	7/98 (7.1%)	14/92 (15.2%)	RR 0.47 (0.20 to 1.11)	81 fewer per 1000 (from 122 fewer to 17 more)	VERY LOW	IMPORTANT
Impaired hearing at 7.5 years old												
1 (Cockburn 1982)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[4]	none	7/96 (7.3%)	6/92 (6.5%)	RR 1.12 (0.39 to 3.20)	8 more per 1000 (from 40 fewer to 143 more)	VERY LOW	IMPORTANT
Superimposed pre-eclampsia												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methyldopa	No intervention	Relative (95% CI)	Absolute		
1 (Sibai 1990)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	16/88 (18.2%)	14/90 (15.6%)	RR 1.17 (0.61 to 2.25)	26 more per 1000 (from 61 fewer to 194 more)	VERY LOW	IMPORTANT
Placental abruption												
1 (Sibai 1990)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/88 (1.1%)	2/90 (2.2%)	RR 0.51 (0.05 to 5.54)	11 fewer per 1000 (from 21 fewer to 101 more)	VERY LOW	IMPORTANT
Mode of birth (caesarean section)												
1 (Sibai 1990)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	31/88 (35.2%)	29/90 (32.2%)	RR 1.09 (0.72 to 1.65)	29 more per 1000 (from 90 fewer to 209 more)	VERY LOW	IMPORTANT

1 The quality of the evidence was downgraded by 2 levels due to an unclear risk of random sequence generation, allocation concealment, performance and detection bias, 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 (0.8)
3 The quality of the evidence was downgraded by 2 levels due to an unclear risk of allocation concealment, performance and selection bias, and selective reporting
4 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 14: Clinical evidence profile. Comparison 10.Amlodipine versus aspirin

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amlodipine	Aspirin	Relative (95% CI)	Absolute		
Stillbirth												
1 (Vigil de	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/20 (0%)	1/19 (5.3%)	RR 0.32 (0.01 to 7.35)	36 fewer per 1000 (from 52	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amlodipine	Aspirin	Relative (95% CI)	Absolute		
Gracia 2014)										fewer to 334 more)		
Neonatal death												
1 (Vigil de Gracia 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/20 (0%)	0/19 (0%)	not calculable	not calculable	MODERATE	CRITICAL
Small-for-gestational age												
1 (Vigil de Gracia 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/20 (10%)	2/19 (10.5%)	RR 0.95 (0.15 to 6.08)	5 fewer per 1000 (from 89 fewer to 535 more)	VERY LOW	CRITICAL
Birth weight (grams) (Better indicated by higher values)												
1 (Vigil de Gracia 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	20	19	-	MD 63 lower (467.79 lower to 341.79 higher)	LOW	IMPORTANT
Preterm birth (weeks not specified)												
1 (Vigil de Gracia 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/20 (15%)	1/19 (5.3%)	RR 2.85 (0.32 to 25.07)	97 more per 1000 (from 36 fewer to 1000 more)	VERY LOW	IMPORTANT
Severe hypertension												
1 (Vigil de Gracia 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/20 (35%)	6/19 (31.6%)	RR 1.11 (0.45 to 2.70)	35 more per 1000 (from 174 fewer to 537 more)	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amlodipine	Aspirin	Relative (95% CI)	Absolute		
Placental abruption												
1 (Vigil de Gracia 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/20 (5%)	0/19 (0%)	RR 2.86 (0.12 to 66.11)[4]	-	VERY LOW	IMPORTANT
Mode of birth (caesarean section)												
1 (Vigil de Gracia 2014)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	12/20 (60%)	10/19 (52.6%)	RR 1.14 (0.65 to 1.99)	74 more per 1000 (from 184 fewer to 521 more)	VERY LOW	IMPORTANT

1 The quality of the evidence was downgraded by 1 level due to a high risk of performance and selection bias and an unclear risk of selective reporting
2 The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)
3 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (740 x +/- 0.5= +/- 370)
4 The corresponding absolute risk was not calculated as there were no events reported in the control arm.

Table 15: Comparison 11. Aspirin versus no intervention

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Control	Relative (95% CI)	Absolute		
Stillbirth and neonatal death												
2 (Atallah 1996, Viinikka 1993)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	24/330 (7.3%)	17/326 (5.2%)	RR 1.36 (0.76 to 2.46)	19 more per 1000 (from 13 fewer to 76 more)	VERY LOW	CRITICAL
Small-for-gestational age												
4 (Atallah 1996, Moore	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	63/557 (11.3%)	68/517 (13.2%)	RR 0.82 (0.60 to 1.13)	24 fewer per 1000 (from 53	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Control	Relative (95% CI)	Absolute	Quality	Importance
2015, Parazzini 1993, Viinikka 1993)										fewer to 17 more)		
Birthweight (grams; Better indicated by higher values)												
1 (Viinikka 1993)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[6]	none	97	100	-	MD 178 higher (13.79 lower to 369.79 higher)	LOW	IMPORTANT
Gestational age (number of weeks; Better indicated by higher values)												
1 (Viinikka 1993)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	97	100	-	MD 0.4 higher (0.17 lower to 0.97 higher)	MODERATE	IMPORTANT
Preterm birth <37 weeks												
2 (Atallah 1996, Poon 2017)	randomised trials	no serious risk of bias	no serious inconsistency	serious[7]	serious[5]	none	61/280 (21.8%)	75/286 (26.2%)	RR 0.81 (0.60 to 1.08)	50 fewer per 1000 (from 105 fewer to 21 more)	LOW	IMPORTANT
1 (van Vliet 2017)	IPD meta-analysis of randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	71/1266 (5.6%)	94/1252 (7.5%)	RR 0.73 (0.53 to 1.00)	20 fewer per 1000 (from 35 fewer to 0 more)	MODERATE	IMPORTANT
Preterm birth <34 weeks												
1 (van Vliet 2017)	IPD meta-analysis of randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	21/1266 (1.7%)	27/1252 (2.2%)	RR 0.77 (0.44 to 1.35)	5 fewer per 1000 (from 12 fewer to 8 more)	LOW	IMPORTANT
Preterm birth <28 weeks												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Control	Relative (95% CI)	Absolute	Quality	Importance
1 (van Vliet 2017)	IPD meta-analysis of randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	5/1266 (0.39%)	9/1252 (0.72%)	RR 0.55 (0.18 to 1.63)	3 fewer per 1000 (from 6 fewer to 5 more)	LOW	IMPORTANT
Admission to neonatal unit												
1 (Viinikka 1993)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[5]	none	10/97 (10.3%)	21/100 (21%)	RR 0.49 (0.24 to 0.99)	107 fewer per 1000 (from 2 fewer to 160 fewer)	LOW	IMPORTANT
Worsening of hypertension												
1 (Viinikka 1993)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	very serious[2]	none	21/97 (21.6%)	25/100 (25%)	RR 0.87 (0.52 to 1.44)	32 fewer per 1000 (from 120 fewer to 110 more)	VERY LOW	CRITICAL
Diastolic BP at 36 weeks' gestation (mmHg; Better indicated by lower values)												
1 (Viinikka 1993)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	no serious imprecision	none	97	100	-	MD 0.2 lower (3.48 lower to 3.08 higher)	MODERATE	CRITICAL
Development of pre-eclampsia												
2 (Poon 2017, Viinikka 1993)	randomised trials	no serious risk of bias	no serious inconsistency	serious[8]	very serious[2]	none	14/146 (9.6%)	16/161 (9.9%)	0.96 (0.49 to 1.89)	50 fewer per 1000 (from 105 fewer to 21 more)	VERY LOW	IMPORTANT
1 (Askie 2007)	IPD meta-analysis of randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	293/ 1678 (17.5%)	295/ 1625 (18.2%)	0.97 (0.84 to 1.12)	5 fewer per 1000 (from 29 fewer to 22 more)	HIGH	IMPORTANT
Spontaneous onset of labour												

1 (Viinikka 1993)	randomised trials	no serious risk of bias	no serious inconsistency	serious[1]	serious[9]	none	45/97 (46.4%)	40/100 (40%)	RR 1.16 (0.84 to 1.60)	64 more per 1000 (from 64 fewer to 240 more)	LOW	IMPORTANT

1 The quality of the evidence was downgraded by 1 level as the study by Viinikka et al. 1993 included a mixed population of women, 89% of whom had chronic hypertension, and 11% had a history of pre-eclampsia in a previous pregnancy.
2 The quality of the evidence was downgraded by 2 levels as the 95% CI crosses 2 default MID thresholds (0.8 and 1.25)
3 The quality of the evidence was downgraded by 1 level as one study was at high risk of performance and detection bias (open label study)
4 Note that the outcomes reported have slight differences in the individual trials: Moore 2015 and Parazzini 1993 report <10th centile, Atallah 1996 reports <3rd centile and Viinikka 1993 reports <2SD below the mean for gestational age.
5 The quality of the evidence was downgraded by 1 level as the 95% CI crosses 1 default MID threshold (0.8)
6 The quality of the evidence was downgraded by 1 level as the 95% CI crosses 1 MID threshold (MID calculated as 0.5 x 665 = +/-332.5g)
7 Note that the outcomes reported have slight differences for individual trials: Atallah 1996 reports on all preterm delivery <37 weeks, Poon 2017 reports on preterm birth <37 weeks due to pre-eclampsia
8 Note that the outcomes reported have slight differences in the individual trials: Askie 2007 reports on hypertension with new onset proteinuria after 20 weeks' gestation, Poon 2017 reports on delivery with pre-eclampsia before 37 weeks' gestation.
9 The quality of the evidence was downgraded by 1 level as the 95% CI crosses 1 default MID threshold (1.25)

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
Aalami-Harandi, Rezvan, Karamali, Maryam, Asemi, Zatollah, The favorable effects of garlic intake on metabolic profiles, hs-CRP, biomarkers of oxidative stress and pregnancy outcomes in pregnant women at risk for pre-eclampsia: randomized, double-blind, placebo-controlled trial, The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstetricians, 28, 2020-7, 2015	Women with chronic hypertension were not included
Abalos,E., Duley,L., Steyn,D.W., Henderson-Smart,D.J., Antihypertensive drug therapy for mild to moderate hypertension during pregnancy, Cochrane Database of Systematic Reviews, 2007. Article Number, -, 2007	Studies included covered women with any type of hypertensive disorder. Studies including women with chronic hypertension have been considered for inclusion in this systematic review
Abramovici, Adi, Jauk, Victoria, Wetta, Luisa, Cantu, Jessica, Edwards, Rodney, Biggio, Joseph, Tita, Alan, Low-dose aspirin, smoking status, and the risk of spontaneous preterm birth, American Journal of Perinatology, 32, 445-50, 2015	No stratified analysis for women with chronic hypertension. Compares smokers and non-smokers only.
Allshouse, A. A., Jessel, R. H., Heyborne, K. D., The impact of low-dose aspirin on preterm birth: Secondary analysis of a randomized controlled trial, Journal of Perinatology, 36, 427-31, 2016	Only 41.5% of participants had chronic hypertension. No stratified analysis for women with chronic hypertension.
Anca-Daniela, S., Banica, R., Sima, R. M., Ples, L., Low dose aspirin for preventing fetal growth restriction: A randomised trial, Journal of Perinatal Medicine, 43, 2015	Participants had high risk first trimester screening result. No data on prevalence of chronic hypertension in population, and no stratified analysis for women with chronic hypertension.
Anonymous,, Nifedipine versus expectant management in mild to moderate hypertension in pregnancy. Gruppo di Studio Ipertensione in Gravidanza, British Journal of Obstetrics and Gynaecology, 105, 718-22, 1998	Less than 66% of participants presented with chronic hypertension
Anonymous,, CLASP: a randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women. CLASP (Collaborative Low-dose Aspirin Study in Pregnancy) Collaborative Group, Lancet (London, England), 343, 619-29, 1994	20% of participants had chronic hypertension. No stratified analysis for this group of women only
Anonymous,, Low dose aspirin in pregnancy and early childhood development: follow up of the collaborative low dose aspirin study in pregnancy. CLASP collaborative group, British Journal of Obstetrics and Gynaecology, 102, 861-8, 1995	20% of participants had chronic hypertension, but results are not presented with stratified analysis for this group of women.
Aparna, J., A randomized, double-blind, comparative trial of nifedipine and methyldopa in	Paper unavailable

Study	Reason for exclusion
moderate pregnancy induced hypertension, Der Pharmacia Lettre, 5, 274-277, 2013	
Arias, F., Zamora, J., Antihypertensive treatment and pregnancy outcome in patients with mild chronic hypertension, Obstetrics and Gynecology, 53, 489-94, 1979	Some of the participants received hydroclorothiazide
Atallah, A., Lecarpentier, E., Goffinet, F., Doret-Dion, M., Gaucherand, P., Tsatsaris, V., Aspirin for Prevention of Preeclampsia, Drugs, 77, 1819-1831, 2017	Narrative review article.
Baker, P. A., Chadd, M. A., Humphreys, D. M., Leather, H. M., Controlled trial of hypotensive agents in hypertension in pregnancy, British heart journal, 30, 871, 1968	Abstract
Baschat, A. A., Dewberry, D., Seravalli, V., Miller, J. L., Block-Abraham, D., Blitzer, M. G., Maternal blood pressure trends throughout pregnancy and development of pre-eclampsia in women receiving first trimester aspirin prophylaxis, Ultrasound in obstetrics & gynecology : the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 2017	Only 14.8% of participants had chronic hypertension, and no stratified analysis is presented for this subgroup.
Beaufils, M., Donsimoni, R., Uzan, S., Colau, J. C., Prevention of pre-elcampsia by early antiplatelet therapy, Lancet, 1, 840-842, 1985	Participants were recruited due to obstetric history (stillbirth, IUGR or miscarriage). Only 1 participant had hypertension.
Bergel, E., Carroli, G., Althabe, F., Ambulatory versus conventional methods for monitoring blood pressure during pregnancy, Cochrane Database of Systematic Reviews, CD001231, 2002	No trials were included
Bijvank,S.W.A.N., Duvekot,J.J., Nicardipine for the treatment of severe hypertension in pregnancy: A review of the literature, Obstetrical and Gynecological Survey, 65, 341-347, 2010	The studies included in this review were either not randomised or included women with pre-eclampsia
Bonnin, P, Mintz, P, Kedra, Aw, Pruna, A, Ciraru-Vigneron, N, Savin, E, Lefevre, V, Szyller, A, Belmont, C, Ferrand, S, Ravina, Jh, Idatte, Jm, Bailliart, O, Martineaud, Jp, Effects of nifedipine and atenolol on the fetal-maternal circulation in moderate hypertension in pregnancy, Therapie, 45, 525, 1990	Paper unavailable
Bortolus, R., Ricci, E., Chatenoud, L., Parazzini, F., Nifedipine administered in pregnancy: Effect on the development of children at 18 months, British Journal of Obstetrics and Gynaecology, 107, 792-794, 2000	Follow-up of a study that presented with less than 66% of participants presented with chronic hypertension
Brennecke, S. P., Brown, M. A., Crowther, C. A., Hague, W. M., King, J., McCowan, L., Morris, J., North, R., Pattison, N., Tippett, C., Wilson, D., Aspirin and prevention of preeclampsia, Australian and New Zealand Journal of Obstetrics and Gynaecology, 35, 38-41, 1995	Position statement only, no analysis or clinical data reported.
Broekhuijsen, K., Van Baaren, G. J., Van Pampus, M., Sikkema, M., Woiski, M., Oudijk, M., Bloemenkamp, K., Scheepers, H., Bremer, H., Rijnders, R., Van Loon, A., Perquin, D.,	Abstract

Study	Reason for exclusion
Sporken, J., Papatsonis, D., Van Huizen, M., Vredevoogd, C., Brons, J., Van Kaam, A., Groen, H., Porath, M., Mol, B., Franssen, M., Langenveld, J., Delivery versus expectant monitoring for late preterm hypertensive disorders of pregnancy (HYPITAT-II): A multicenter, open label, randomized controlled trial, American Journal of Obstetrics and Gynecology, 210, S2-S3, 2014	
Brown, M. A., Budle, M. L., Cario, G. M., Whitworth, J. A., Ambulatory blood pressure monitoring during pregnancy. Comparison with mercury sphygmomanometry, American Journal of Hypertension, 6, 745-749, 1993	Not a randomised trial
Brown, M. A., Roberts, L. M., Mackenzie, C., Mangos, G., Davis, G. K., A prospective randomized study of automated versus mercury blood pressure recordings in hypertensive pregnancy (PRAM Study), Hypertension in Pregnancy, 31, 107-19, 2012	Less than 66% of participants presented with chronic hypertension
Brown,M.A., Buddle,M.L., Farrell,T., Davis,G.K., Efficacy and safety of nifedipine tablets for the acute treatment of severe hypertension in pregnancy, American Journal of Obstetrics and Gynecology, 187, 1046-1050, 2002	Study compared two different types of nifedipine tables
Bujold, E., Roberge, S., Nicolaides, K. H., Low-dose aspirin for prevention of adverse outcomes related to abnormal placentation, Prenatal Diagnosis, 34, 642-8, 2014	Review article. No subgroup analysis for women with chronic hypertension.
Bujold,E., Roberge,S., Lacasse,Y., Bureau,M., Audibert,F., Marcoux,S., Forest,J.C., Giguere,Y., Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy: a meta-analysis, Obstetrics and Gynecology, 116, 402-414, 2010	No subgroup analysis for women with chronic hypertension.
Byaruhanga, R. N., Chipato, T., Rusakaniko, S., A randomized controlled trial of low-dose aspirin in women at risk from pre-eclampsia, International Journal of Gynecology and Obstetrics, 60, 129-135, 1998	Relevant data from this trial is included in the IPD meta-analysis by Askie et al. 2007.
Cameron, Ad, Walker, Jj, Bonduelle, M, Calder, Aa, A randomised trial of the antihypertensive agent, labetalol, against bed rest in pregnancy hypertension, Archives of gynecology, 237 Suppl, 295, 1985	Abstract
Cantu, J. A., Jauk, V. R., Owen, J., Biggio, J. R., Abramovici, A. R., Edwards, R. K., Tita, A. T., Is low-dose aspirin therapy to prevent preeclampsia more efficacious in non-obese women or when initiated early in pregnancy?, Journal of Maternal-Fetal & Neonatal Medicine, 28, 1128-1132, 2015	Relevant data are included in the IPD meta-analysis by Askie et al 2007
Cao, N. T., Vu, Q. H. N., Truong, Q. V., Vo, V. D., Tran, M. L., Effectiveness of low-dose aspirin for the prevention of pre-eclampsia, Journal of Obstetrics and Gynaecology Research, 43, 69, 2017	Conference abstract

Study	Reason for exclusion
Carbonne, B., Jannet, D., Touboul, C., Khelifati, Y., Milliez, J., Nicardipine treatment of hypertension during pregnancy, Obstetrics and Gynecology, 81, 908-14, 1993	Not a randomised trial
Caritis, S., Sibai, B., Hauth, J., Lindheimer, M. D., Klebanoff, M., Thom, E., Vandorsten, P., Landon, M., Paul, R., Miodovnik, M., Meis, P., Thurnau, G., Bottoms, S., McNellis, D., Roberts, J. M., Low-dose aspirin to prevent preeclampsia in women at high risk, New England Journal of Medicine, 338, 701-705, 1998	Relevant subgroup analysis from this trial in included in the papers by Askie et al 2007 (and van Vliet 2017).
Chiaffarino, F., Parazzini, F., Paladini, D., Acaia, B., Ossola, W., Marozio, L., Facchinetti, F., Giudice, A. D., A small randomised trial of low-dose aspirin in women at high risk of pre-eclampsia, European Journal of Obstetrics Gynecology and Reproductive Biology, 112, 142-144, 2004	No stratified analysis for participants with chronic hypertension.
Ciraru-Vigneron, N, Pruna, A, Akposso, K, Bonnin, P, Kedra, W, Mintz, P, Ferrand, S, Smadja, S, Martineaud, Jp, Idatte, Jm, Ravina,, Comparison of the effects of nefedipine and atenolol in the treatment of uncomplicated hypertension in pregnancy, Therapie, 47, 221, 1992	Paper unavailable
Cluver, C., Novikova, N., Koopmans, C. M., West, H. M., Planned early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term, Cochrane Database of Systematic Reviews, 2017, CD009273, 2017	Mixed population of women with PE, GE and CHT. The study that included women with CHT has already been included in this systematic review (Hamed 2014)
Coomarasamy,A., Honest,H., Papaioannou,S., Gee,H., Khan,K.S., Aspirin for prevention of preeclampsia in women with historical risk factors: A systematic review, Obstetrics and Gynecology, 101, 1319-1332, 2003	No subgroup analysis for women with chronic hypertension.
Cristina Rossi, A., D'Addario, V., Prevention of preeclampsia with low-dose aspirin or vitamins C/E: A systematic review with metaanalysis, American Journal of Obstetrics and Gynecology, 201, S266-S267, 2009	No subgroup analysis for women with chronic hypertension.
Cruickshank, D. J., Campbell, D., Robertson, A. A., MacGillivray, I., Intra-uterine growth retardation and maternal labetalol treatment in a random allocation controlled study, Journal of Obstetrics and Gynaecology, 12, 223-227, 1992	Women presented with gestational hypertension
Cruickshank, D. J., Robertson, A. A., Campbell, D. M., MacGillivray, I., Does labetalol influence the development of proteinuria in pregnancy hypertension? A randomised controlled study, European journal of obstetrics, gynecology, and reproductive biology, 45, 47-51, 1992	Women presented with gestational hypertension
Cruickshank, Dj, Campbell, Dm, Atenolol in essential hypertension during pregnancy, BMJ (Clinical research ed.), 301, 1103, 1990	Women presented with gestational hypertension
Cruickshank,D.J., Robertson,A.A., Campbell,D.M., MacGillivray,I., Maternal	Women presented with gestational hypertension

Study	Reason for exclusion
obstetric outcome measures in a randomised controlled study of labetalol in the treatment of hypertension in pregnancy, Clinical and Experimental Hypertension - Part B Hypertension in Pregnancy, 10, 333-344, 1991	
da Silva, S. G., Hallal, P. C., Domingues, M. R., Bertoldi, A. D., Silveira, M. F., Bassani, D., da Silva, I. C. M., da Silva, B. G. C., Coll, C. V. N., Evenson, K., A randomized controlled trial of exercise during pregnancy on maternal and neonatal outcomes: Results from the PAMELA study, International Journal of Behavioral Nutrition and Physical Activity, 14, 175, 2017	Women with CHT were not included
da Silva, Shana G., Ricardo, Luiza I., Evenson, Kelly R., Hallal, Pedro C., Leisure-Time Physical Activity in Pregnancy and Maternal-Child Health: A Systematic Review and Meta-Analysis of Randomized Controlled Trials and Cohort Studies, Sports medicine (Auckland, N.Z.), 47, 295-317, 2017	Women with CHT were not included
Di Mascio, D., Magro-Malosso, E. R., Saccone, G., Marhefka, G. D., Berghella, V., Exercise during pregnancy in normal-weight women and risk of preterm birth: a systematic review and meta-analysis of randomized controlled trials, American Journal of Obstetrics and Gynecology, 215, 561-571, 2016	Women with CHT were not included
Duggan,P.M., McCowan,L.M., Stewart,A.W., Antihypertensive drug effects on placental flow velocity waveforms in pregnant women with severe hypertension, Australian and New Zealand Journal of Obstetrics and Gynaecology, 32, 335-338, 1992	Non extractable data (only p-values have been reported)
Duley, L., Henderson-Smart, D. J., Meher, S., King, J. F., Antiplatelet agents for preventing pre-eclampsia and its complications, Cochrane Database of Systematic Reviews, CD004659, 2007	No data on number of women with chronic hypertension, and no subgroup analysis for this group of women.
Duley, L., Meher, S., Jones, L., Drugs for treatment of very high blood pressure during pregnancy, Cochrane Database of Systematic Reviews, CD001449, 2013	The majority of studies included in this review are not relevant for the protocol either because are abstracts, have been published in a foreign language or have no relevant interventions. The remaining studies have been considered for inclusion in this systematic review
Ebrashy,A., Ibrahim,M., Marzook,A., Yousef,D., Usefulness of aspirin therapy in high-risk pregnant women with abnormal uterine artery Doppler ultrasound at 14-16 weeks pregnancy: randomized controlled clinical trial, Croatian Medical Journal, 46, 826-831, 2005	35% participants had chronic hypertension. No subgroup analysis is reported for these women.
El Guindy, A. A., Nabhan, A. F., A randomized trial of tight vs. less tight control of mild essential and gestational hypertension in pregnancy, Journal of Perinatal Medicine, 36, 413-418, 2008	Less than 66% of participants presented with chronic hypertension
Elder, M. G., de Swiet, M., Sullivan, M., A randomised trial of low dose aspirin for primiparae in pregnancy (Golding)/Barbados low	Women did not present with CHT

Study	Reason for exclusion
dose aspirin study in pregnancy (BLASP) (Rotchell et al.), British Journal of Obstetrics and Gynaecology, 106, 180, 1999	
Farrell, B., Heineman, J., Handoll, H., Pearson, M., Collingwood, M., Belcher, J., Grant, A., Mutch, L., De Swiet, M., Redman, C., Collins, R., Elder, M., Rubin, P., Symonds, M., Wallenberg, H., Doll, R., Chalmers, I., Elstein, M., Peto, R., Low dose aspirin in pregnancy and early childhood development: Follow up of the collaborative low dose aspirin study in pregnancy, British Journal of Obstetrics and Gynaecology, 102, 861-868, 1995	<20% participants had chronic hypertension. No subgroup analysis reported for these women.
Finnstrom, O., Ezitis, J., Ryden, G., Wichman, K., Neonatal effects of beta-blocking drugs in pregnancy, Acta Obstetricia et Gynecologica Scandinavica - Supplement, 118, 91-3, 1984	No relevant intervention (metoprolol)
Firoz, T., Magee, L. A., Lalani, S., Sawchuck, D., Payne, B., Vidler, M., Gordon, R., Von Dadelszen, P., Oral antihypertensive therapy for severe hypertension in pregnancy, Pregnancy Hypertension, 2, 288, 2012	Some of the studies in this review are not relevant for the protocol either because included women with PE, published in a foreign language or presented with no relevant interventions. The relevant studies have been considered for inclusion
Fitton, C. A., Steiner, M. F. C., Aucott, L., Pell, J. P., Mackay, D. F., Fleming, M., McLay, J. S., In-utero exposure to antihypertensive medication and neonatal and child health outcomes: a systematic review, Journal of Hypertension, 11, 11, 2017	The majority of studies in this review are not relevant for the protocol either because included women with PE or presented with no relevant interventions. The relevant trials have been considered for inclusion
Gallery,E.D.M., Ross,M.R., Hawkins,M., Leslie,G., Gyory,A.Z., Low-dose aspirin in high-risk pregnancy?, Hypertension in Pregnancy, 16, 229-238, 1997	55.5% participants had chronic hypertension, but no stratified analysis is presented for these women.
Golding, J., A randomised trial of low dose aspirin for primiparae in pregnancy, British Journal of Obstetrics and Gynaecology, 105, 293-299, 1998	No data on number of participants with chronic hypertension, or subgroup analysis for these women.
Gonzalez, Jc, Andolcetti, R, Labetalol vs alpha methyldopa in the treatment of hypertension in pregnancy, Boletin medico de postgrado, 13, 3-8, 1997	Study in Spanish
Grab, D., Paulus, W. E., Erdmann, M., Terinde, R., Oberhoffer, R., Lang, D., Muche, R., Kreienberg, R., Effects of low-dose aspirin on uterine and fetal blood flow during pregnancy: Results of a randomized, placebo-controlled, double-blind trial, Ultrasound in Obstetrics and Gynecology, 15, 19-27, 2000	No data on number of women included with chronic hypertension.
Gresham, E., Bisquera, A., Byles, J. E., Hure, A. J., Effects of dietary interventions on pregnancy outcomes: a systematic review and meta-analysis, Maternal & Child Nutrition, 12, 5-23, 2016	The studies included were not specific to women presenting with chronic hypertenion
Gresham, E., Bisquera, A., Hure, A., Byles, J., Gil, A., Martinez, J. A., A systematic review and meta-analysis of dietary intervention during pregnancy on maternal hypertensive disorders	Abstract

Study	Reason for exclusion
and preterm delivery, Annals of Nutrition and Metabolism, 63, 607, 2013	
Haapsamo,M., Martikainen,H., Tinkanen,H., Heinonen,S., Nuojua-Huttunen,S., Rasanen,J., Low-dose aspirin therapy and hypertensive pregnancy complications in unselected IVF and ICSI patients: a randomized, placebo-controlled, double-blind study, Human Reproduction, 25, 2972-2977, 2010	Women did not present with chronic hypertension
Henderson, J. T., Whitlock, E. P., O'Connor, E., Senger, C. A., Thompson, J. H., Rowland, M. G., Low-dose aspirin for prevention of morbidity and mortality from preeclampsia: A systematic evidence review for the u.s. preventive services task force, Annals of Internal Medicine, 160, 695-703, 2014	No subgroup analysis presented for women with chronic hypertension.
Hennessy,A., Thornton,C.E., Makris,A., Ogle,R.F., Henderson-Smart,D.J., Gillin,A.G., Child,A., A randomised comparison of hydralazine and mini-bolus diazoxide for hypertensive emergencies in pregnancy: the PIVOT trial, Australian and New Zealand Journal of Obstetrics and Gynaecology, 47, 279-285, 2007	No relevant intervention (diazoxide)
Hermida, R. C., Ayala, D. E., Fernandez, J. R., Mojon, A., Alonso, I., Silva, I., Ucieda, R., Codesido, J., Iglesias, M., Administration time-dependent effects of aspirin in women at differing risk for preeclampsia, Hypertension, 34, 1016-23, 1999	No data on muber of participants with chronic hypertension. No subgroup analysis for women with chronic hypertension.
Holbrook, B., Nirgudkar, P., Mozurkewich, E., Efficacy of hydralazine, labetalol, and nifedipine for the acute reduction of severe hypertension in pregnancy: A systematic review, American Journal of Obstetrics and Gynecology, 212, S287, 2015	Abstract
Horvath, J. S., Phippard, A., Korda, A., Clonidine hydrochloride - A safe and effective antihypertensive agent in pregnancy, Obstetrics and Gynecology, 66, 634-638, 1985	No relevant intervention (clonidine)
Imperiale,T.F., Petrulis,A.S., A meta-analysis of low-dose aspirin for the prevention of pregnancy-induced hypertensive disease, JAMA, 266, 260-264, 1991	No subgroup analysis for women with chronic hypertension
Jabeen, M., Yakoob, M. Y., Imdad, A., Bhutta, Z. A., Impact of interventions to prevent and manage preeclampsia and eclampsia on stillbirths, BMC Public Health, 11 Suppl 3, S6, 2011	No subgroup analysis for women with chronic hypertension.
Jiang, N., Liu, Q., Liu, L., Yang, W. W., Effect of calcium channel blockers plus low-dosage aspirin on hypertensive pregnancy outcomes, Obstetrics and Gynecology, 123, 57S, 2014	Abstract
Kasawara, K. T., Burgos, C. S. G., Nascimento, S. L., Costa, M. L., Surita, F., E Silva, J. L. Pinto, OS020. Effects of exercise on maternal and neonatal outcomes in pregnantwomen with	Abstract

Study	Reason for exclusion
chronic hypertension and/or previous preecampsia: A randomized clinical trial, Pregnancy Hypertension, 2, 185-6, 2012	
Koren,G., Systematic review of the effects of maternal hypertension in pregnancy and antihypertensive therapies on child neurocognitive development, Reproductive Toxicology, 39, 1-5, 2013	This review included not relevant studies, asesseing the effects of maternal hypertension in pregnancy. For those studies assessing the relationship between antihypertensive medications and neurodevelopmental outcomes, not all of them were relevant for the study protocol. Those which are relevant have been asessed for inclusion
Leather, H. M., Humphreys, D. M., Baker, P., Chadd, M. A., A controlled trial of hypotensive agents in hypertension in pregnancy, Lancet, 2, 488-90, 1968	For most of the relevant outcomes, data was not presented stratified by CHT, SDs were not reported for continuous outcomes.
Leslie, G. I., Gallery, E. D., Arnold, J. D., Ross, M. R., Gyory, A. Z., Neonatal outcome in a randomized, controlled trial of low-dose aspirin in high-risk pregnancies, Journal of Paediatrics & Child Health, 31, 549-52, 1995	No data on number of participants with chronic hypertension.
Liu, F. M., Zhao, M., Wang, M., Yang, H. L., Li, L., Effect of regular oral intake of aspirin during pregnancy on pregnancy outcome of high-risk pregnancy-induced hypertension syndrome patients, European Review for Medical & Pharmacological Sciences, 20, 5013-5016, 2016	Women with chronic (pre-existing) hypertension were excluded.
Liu, F., Yang, H., Li, G., Zou, K., Chen, Y., Effect of a small dose of aspirin on quantitative test of 24-h urinary protein in patients with hypertension in pregnancy, Experimental and Therapeutic Medicine, 13, 37-40, 2017	No data on number of participants with chronic hypertension.
Liu, J., Trivedi, T., Blair, S. N., Ness, A., Macdonald-Wallis, C., Lawlor, D. A., Physical activity and hypertensive disorders of pregnancy among british women, American Journal of Epidemiology, 175, S22, 2012	Abstract
Luchini, L., Bortolus, R., Parazzini, F., Multicentric, randomized, clinical trial on the efficacy of long-acting nifedipine in improving the prognosis of pregnancy in women with mild or moderate, chronic or pregnancy-induced hypertension, Journal of Nephrology, 6, 51-54, 1993	Study proposal
Magee,L.A., Duley,L., Oral beta-blockers for mild to moderate hypertension during pregnancy, Cochrane database of systematic reviews (Online), 2003. Date of Publication, -, 2003	The majority of studies included in this review are not relevant for the protocol either because are abstracts, have been published in a foreign language or have no relevant interventions. The remaining studies have been considered for inclusion in this systematic review
Magee,L.A., Elran,E., Bull,S.B., Logan,A., Koren,G., Risks and benefits of beta-receptor blockers for pregnancy hypertension: Overview of the randomized trials, European Journal of Obstetrics Gynecology and Reproductive Biology, 88, 15-26, 2000	The majority of studies included in this review are not relevant for the protocol either because are abstracts, have been published in a foreign language or have no relevant interventions. The remaining studies have been considered for inclusion in this systematic review
Meher, S., Duley, L., Hunter, K., Askie, L., Antiplatelet therapy before or after 16 weeks'	No subgroup data for women with chronic hypertension.

Study	Reason for exclusion
gestation for preventing preeclampsia: an individual participant data meta-analysis, American Journal of Obstetrics & Gynecology, 216, 121-128.e2, 2017	
Mutch, L. M., Moar, V. A., Ounsted, M. K., Redman, C. W., Hypertension during pregnancy, with and without specific hypotensive treatment. II. The growth and development of the infant in the first year of life, Early human development, 1, 59-67, 1977	Most of the participants included in this trial overlapped with those included in the Redman 1976 trial
Mutch,L.M., Moar,V.A., Ounsted,M.K., Redman,C.W., Hypertension during pregnancy, with and without specific hypotensive treatment. I. Perinatal factors and neonatal morbidity, Early Human Development, 1, 47-57, 1977	Most of the participants included in this trial overlapped with those included in the Redman 1976 trial
Nielsen, L. H., Ovesen, P., Hansen, M. R., Brantlov, S., Jespersen, B., Bie, P., Jensen, B. L., Changes in the renin-angiotensin-aldosterone system in response to dietary salt intake in normal and hypertensive pregnancy. A randomized trial, Journal of the american society of hypertension, 10, 881-890.e4, 2016	Women with chronic hypertension were not included
Nij, Bijvank Sw, Duvekot, Jj, Nicardipine for the treatment of severe hypertension in pregnancy: a review of the literature (Provisional abstract), Obstetrical and Gynecological Survey, 65, 341-347, 2010	This review included observational studies only
Novikova, N., Cluver, C., Koopmans, C. M., Delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term, Cochrane Database of Systematic Reviews, 2011, CD009273, 2011	The majority of studies included in this review are not relevant for the protocol either because are abstracts, have been published in a foreign language or have no relevant interventions. The remaining studies have been considered for inclusion in this systematic review
Odibo, A. O., Goetzinger, K. R., Odibo, L., Tuuli, M. G., Early prediction and aspirin for prevention of pre-eclampsia (EPAPP) study: a randomized controlled trial, Ultrasound in Obstetrics & Gynecology, 46, 414-8, 2015	53% of participants had chronic hypertension. No subgroup analysis presented for these women.
Park, F., Russo, K., Pellosi, M., Puddephat, R., Walter, M., Leung, C., Saiid, R., Rawashdeh, H., Hyett, J., The impact of aspirin on the prevalence of early onset pre-eclampsia after first trimester screening, Prenatal Diagnosis, 34, e4, 2014	No subgroup analysis for women with chronic hypertension.
Patel, P., Koli, D., Maitra, N., Sheth, T., Vaishnav, P., Comparison of Efficacy and Safety of Intravenous Labetalol Versus Hydralazine for Management of Severe Hypertension in Pregnancy, Journal of Obstetrics and Gynecology of India, 1-6, 2017	No relevant comparator (hydralazine)
Peacock, Iv W. F., Hilleman, D. E., Levy, P. D., Rhoney, D. H., Varon, J., A systematic review of nicardipine vs labetalol for the management of hypertensive crises, American Journal of Emergency Medicine, 30, 981-993, 2012	This study did not cover women with chronic hypertension
Phippard, A. F., Fischer, W. E., Horvath, J. S., Child, A. G., Korda, A. R., Henderson-Smart, D.,	Women presented with gestational hypertension

Study	Reason for exclusion
Duggin, G. D., Tiller, D. J., Early blood pressure control improves pregnancy outcome in primigravid women with mild hypertension, Medical Journal of Australia, 154, 378-382, 1991	
Pickles, C. J., Broughton Pipkin, F., Symonds, E. M., A randomised placebo controlled trial of labetalol in the treatment of mild to moderate pregnancy induced hypertension, British Journal of Obstetrics & Gynaecology, 99, 964-8, 1992	Women presented with gestational hypertension
Raheem, I. A., Saaid, R., Omar, S. Z., Tan, P. C., Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: a randomised trial, BJOG: An International Journal of Obstetrics & Gynaecology, 119, 78-85, 2012	Women presented with gestational hypertension
Ramaiya, C., Mgaya, H. N., Low dose aspirin in prevention of pregnancy-induced hypertension in primigravidae at the Muhimbili Medical Center, Dar es Salaam, East African medical journal, 72, 690-3, 1995	No data on number of participants with chronic hypertension.
Redman, C. W., Beilin, L. J., Bonnar, J., Treatment of hypertension in pregnancy with methyldopa: blood pressure control and side effects, British Journal of Obstetrics & Gynaecology, 84, 419-26, 1977	No relevant outcomes were reported
Rey,E., Morin,F., Boudreault,J., Pilon,F., Vincent,D., Ouellet,D., Blood pressure assessments in different subtypes of hypertensive pregnant women: office versus home patient- or nurse-measured blood pressure, Hypertension in Pregnancy, 28, 168-177, 2009	Observational study
Rezaei, Z., Sharbaf, F. R., Pourmojieb, M., Youefzadeh-Fard, Y., Motevalian, M., Khazaeipour, Z., Esmaeili, S., Comparison of the efficacy of nifedipine and hydralazine in hypertensive crisis in pregnancy, Acta Medica Iranica, 49, 701-6, 2011	No relevant comparison (hydralazine)
Rhodes, C. A., Beevers, D. G., Churchill, D., A randomized trial of ambulatory blood pressure monitoring versus clinical blood pressure measurement in the management of hypertension in pregnancy. A feasibility study, Pregnancy Hypertension, 2017	Less than 66% of participants presented with chronic hypertension
Roberge, S., Bujold, E., Nicolaides, K. H., Aspirin for the prevention of preterm and term preeclampsia: Systematic review and metaanalysis, American Journal of Obstetrics and Gynecology, 2017	No subgroup analysis for women with chronic hypertension.
Roberge, S., Giguere, Y., Villa, P., Nicolaides, K., Vainio, M., Forest, J. C., Von Dadelzen, P., Vaiman, D., Tapp, S., Bujold, E., Early administration of low-dose aspirin for the prevention of severe and mild preeclampsia: A systematic review and meta-analysis, American Journal of Perinatology, 29, 551-556, 2012	No information on number of women with chronic hypertension, or subgroup analysis for these women.

Study	Reason for exclusion
Roberge, S., Nicolaides, K. H., Demers, S., Villa, P., Bujold, E., Prevention of perinatal death and adverse perinatal outcome using low-dose aspirin: a meta-analysis, Ultrasound in Obstetrics & Gynecology, 41, 491-9, 2013	No subgroup analysis for women with chronic hypertension.
Roberge, S., Nicolaides, K., Demers, S., Hyett, J., Chaillet, N., Bujold, E., The role of aspirin dose on the prevention of preeclampsia and fetal growth restriction: systematic review and meta-analysis, American Journal of Obstetrics & Gynecology, 216, 110-120.e6, 2017	No subgroup analysis for women with chronic hypertension.
Roberge, S., Sibai, B., McCaw-Binns, A., Bujold, E., Low-Dose Aspirin in Early Gestation for Prevention of Preeclampsia and Small-for-Gestational-Age Neonates: Meta-analysis of Large Randomized Trials, American Journal of Perinatology, 33, 781-785, 2016	No subgroup analysis for women with chronic hypertension.
Roberge, S., Villa, P., Nicolaides, K., Giguere, Y., Vainio, M., Bakthi, A., Ebrashy, A., Bujold, E., Early administration of low-dose aspirin for the prevention of preterm and term preeclampsia: a systematic review and meta-analysis, Fetal Diagnosis & Therapy, 31, 141-6, 2012	No subgroup analysis for women with chronic hypertension.
Roberge, Stephanie, Bujold, Emmanuel, Nicolaides, Kypros H., Meta-analysis on the effect of aspirin use for prevention of preeclampsia on placental abruption and antepartum hemorrhage, American Journal of Obstetrics and Gynecology, 2018	No subgroup analysis for women with chronic hypertension.
Rogers, M. S., Fung, H. Y., Hung, C. Y., Calcium and low-dose aspirin prophylaxis in women at high risk of pregnancy-induced hypertension, Hypertension in Pregnancy, 18, 165-72, 1999	Women with chronic hypertension were not included.
Rolnik, Dl, Wright, D, Poon, Lc, O'Gorman, N, Syngelaki, A, Paco, Matallana C, Akolekar, R, Cicero, S, Janga, D, Singh, M, Molina, Fs, Persico, N, Jani, Jc, Plasencia, W, Papaioannou, G, Tenenbaum-Gavish, K, Meiri, H, Gizurarson, S, Maclagan, K, Nicolaides, Kh, Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia, New England Journal of Medicine, 377, 613-622, 2017	No subgroup analysis presented for women with chronic hypertension. Data from secondary publication of this trial (Poon 2017) are included.
Rotchell, Y. E., Cruickshank, J. K., Gay, M. P., Griffiths, J., Stewart, A., Farrell, B., Ayers, S., Hennis, A., Grant, A., Duley, L., Collins, R., Barbados Low Dose Aspirin Study in Pregnancy (BLASP): a randomised trial for the prevention of pre-eclampsia and its complications, British Journal of Obstetrics and Gynaecology, 105, 286-92, 1998	<1% participants had chronic hypertension.
Rubin, P. C., Butters, L., Clark, D. M., Reynolds, B., Sumner, D. J., Steedman, D., Low, R. A., Reid, J. L., Placebo-controlled trial of atenolol in treatment of pregnancy-associated hypertension, Lancet, 1, 431-4, 1983	Women presented with gestational hypertension

Study	Reason for exclusion
Rubin,P.C., Butters,L., Low,R.A., Reid,J.L., Atenolol in the treatment of essential hypertension during pregnancy, British Journal of Clinical Pharmacology, 14, 279-281, 1982	Non randomised trial
Sabir, S., Yasmin, S., Abbas, G., Comparison of oral nifedipine with intravenous hydralazine for acute hypertensive emergencies of pregnancy, Journal of Postgraduate Medical Institute, 30, 328-330, 2016	Women presented with gestational hypertension
Schiff, E., Peleg, E., Goldenberg, M., Rosenthal, T., Ruppin, E., Tamarkin, M., Barkai, G., Ben-Baruch, G., Yahal, I., Blankstein, J., Goldman, B., Mashiach, S., The use of aspirin to prevent pregnancy-induced hypertension and lower the ratio of thromboxane A2 to prostacyclin in relatively high risk pregnancies, New England Journal of Medicine, 321, 351-356, 1989	Women with chronic hypertension were excluded.
Sharma, C., Soni, A., Gupta, A., Verma, A., Verma, S., Hydralazine vs nifedipine for acute hypertensive emergency in pregnancy: A randomized controlled trial, American Journal of Obstetrics and Gynecology, 2017	Women with chronic hypertension were excluded
Shekhar, S., Gupta, N., Kirubakaran, R., Pareek, P., Oral nifedipine versus intravenous labetalol for severe hypertension during pregnancy: a systematic review and meta-analysis, BJOG: An International Journal of Obstetrics & Gynaecology, 123, 40-7, 2016	No relevant studies were included
Shekhar, S., Sharma, C., Thakur, S., Verma, S., Oral nifedipine or intravenous labetalol for hypertensive emergency in pregnancy: a randomized controlled trial, Obstetrics & Gynecology, 122, 1057-63, 2013	Women with chronic hypertension were excluded
Sibai, B. M., Grossman, R. A., Grossman, H. G., Effects of diuretics on plasma volume in pregnancies with long-term hypertension, American Journal of Obstetrics and Gynecology, 150, 831-835, 1984	Type or dose of diuretics was not specified
Souza, Mesquita Mr, Atallah, An, Bertini, Am, The use of hydralazine and nifedipine as treatment for hypertension emergency during pregnancy, Proceedings of 14th european congress of perinatal medicine;1994 june 5-8; helsinki, finland, Abstract no: 163, 1994	Abstract
Stanescu, A. D., Banica, R., Sima, R. M., Ples, L., Low dose aspirin for preventing fetal growth restriction: A randomised trial, Journal of Perinatal Medicine, 2018	No data on prevalence of chronic hypertension in participants.
Subtil, D, Goeusse, P, Houfflin-Debarge, V, Puech, F, Lequien, P, Breart, G, Uzan, S, Quandalle, F, Delcourt, Ym, Malek, Ym, Randomised comparison of uterine artery Doppler and aspirin (100 mg) with placebo in nulliparous women: the Essai Régional Aspirine Mère-Enfant study (Part 2), Bjog, 110, 485-491, 2003	Women with chronic hypertension were excluded.

Study	Reason for exclusion
Subtil, D, Goeusse, P, Puech, F, Lequien, P, Biausque, S, Breart, G, Uzan, S, Marquis, P, Parmentier, D, Churlet, A, Aspirin (100 mg) used for prevention of pre-eclampsia in nulliparous women: the Essai Régional Aspirine Mère-Enfant study (Part 1), Bjog, 110, 475-484, 2003	Women with chronic hypertension were excluded.
Sureau, C., Prevention of perinatal consequences of pre-eclampsia with low-dose aspirin: Results of the epreda trial, European Journal of Obstetrics Gynecology and Reproductive Biology, 41, 71-73, 1991	All participants received aspirin.
Tewari,S., Kaushish,R., Sharma,S., Gulati,N., Role of low dose aspirin in prevention of pregnancy induced hypertension, Journal of the Indian Medical Association, 95, 43-44, 1997	No details on inclusion/exclusion of women with chronic hypertension.
Trivedi, N. A., A meta-analysis of low-dose aspirin for prevention of preeclampsia, Journal of Postgraduate Medicine, 57, 91-5, 2011	No subgroup analysis for women with chronic hypertension.
Tuimala, R., Hartikainen-Sorri, A. L., Randomized comparison of atenolol and pindolol for treatment of hypertension in pregnancy, Current Therapeutic Research - Clinical and Experimental, 44, 579-584, 1988	Women presented with gestational hypertension
Villa, P. M., Kajantie, E., Raikkonen, K., Pesonen, A. K., Hamalainen, E., Vainio, M., Taipale, P., Laivuori, H., Aspirin in the prevention of pre-eclampsia in high-risk women: A randomised placebo-controlled PREDO Trial and a meta-analysis of randomised trials, BJOG: An International Journal of Obstetrics and Gynaecology, 120, 64-74, 2013	16.5% participants had chronic hypertension, but no stratified analysis is reported for these women.
Vogel, S. A., Rajaii, R., Ottaviano, G., Kim, L., Yeaton-Massey, A., Caughey, A. B., Low-dose aspirin for prevention of preeclampsia and its complications: A cost effectiveness analysis, Archives of Disease in Childhood: Fetal and Neonatal Edition, 95, 2010	Conference abstract
Voto, Ls, Lapidus, Am, Neira, J, Magulies, M, Treatment of hypertension in pregnancy: atenolol versus alpha-methyldopa, Obstetricia y ginecologia latino-americanas, 43, 335-341, 1985	Study in Spanish
Walker, J. J., Greer, I., Calder, A. A., Treatment of acute pregnancy-related hypertension: Labetalol and hydralazine compared, Postgraduate Medical Journal, 59, 168-170, 1983	Unclear whether women presented with CHT; only p-values were reported, therefore non abstractable data
Walker, K. F., Bugg, G. J., Macpherson, M., McCormick, C., Grace, N., Wildsmith, C., Bradshaw, L., Smith, G. C. S., Thornton, J. G., Randomized trial of labor induction in women 35 years of age or older, New England Journal of Medicine, 374, 813-822, 2016	Inclusion criteria for the trial covered diferent conditions, and a minority of women presented with hypertension
Wallenburg, H. C., Dekker, G. A., Makovitz, J. W., Rotmans, P., Low-dose aspirin prevents pregnancy-induced hypertension and pre-eclampsia in angiotensin-sensitive	Trial did not include women with chronic hypertension.

Study	Reason for exclusion
primigravidae, Lancet (London, England), 1, 1-3, 1986	
Webster, L. M., Conti-Ramsden, F., Seed, P. T., Webb, A. J., Nelson-Piercy, C., Chappell, L. C., Impact of antihypertensive treatment on maternal and perinatal outcomes in pregnancy complicated by chronic hypertension: A systematic review and meta-analysis, Journal of the American Heart Association, 6, e005526, 2017	Some of the included studies used antihypertensive medications not relevant for the protocol of this review. The remaining included studies have been considered for inclusion
Welt, S. I., Dorminy, J. H., 3rd, Jelovsek, F. R., Crenshaw, M. C., Gall, S. A., The effects of prophylactic management and therapeutics on hypertensive disease in pregnancy: preliminary studies, Obstetrics and Gynecology, 57, 557-65, 1981	No relevant comparator (hydralazine)
Xu, T. T., Zhou, F., Deng, C. Y., Huang, G. Q., Li, J. K., Wang, X. D., Low-Dose Aspirin for Preventing Preeclampsia and Its Complications: A Meta-Analysis, Journal of Clinical Hypertension, 17, 567-73, 2015	No stratified analysis for women with chronic hypertension.

Economic studies

Table 17: Economic excluded studies with reasons for exclusion

Study	Reason for exclusion
Ahmed RJ, Gafni A, Hutton EK, Hu ZJ, Pullenayegum E, Von Dadelszen P, Rey E, Ross S, Asztalos E, Murphy KE, Menzies J, Sanchez JJ, Ganzevoort W, Helewa M, Lee SK, Lee T, Logan AG, Moutquin JM, Singer J, Thornton JG, Welch R, Magee LA. The Cost Implications of Less Tight Versus Tight Control of Hypertension in Pregnancy (CHIPS Trial). Hypertension 68(4):1049-1055. 2016	Not cost-effectiveness analysis. Costs consider Canadian healthcare system and are therefore of limited relevance to UK setting.
Barton JR, Istwan NB, Rhea D, Collins A, Stanziano GJ. Cost-savings analysis of an outpatient management program for women with pregnancy-related hypertensive conditions. Dis Manag 9(4):236-41. 2006	Not cost-effectiveness analysis. Costs considered reflect US healthcare setting therefore of limited relevance to UK.
Caughey AB, Sundaram V, Kaimal AJ, Cheng YW, Gienger A, Little SE, Lee JF, Wong L, Shaffer BL, Tran SH, Padula A, McDonald KM, Long EF, Owens DK, Bravata DM. Maternal and neonatal outcomes of elective induction of labor. Evidence report/technology assessment (176) 1-257. 2009	Not specific to women with chronic hypertension
Lai J, Niu B, Caughey AB. A cost-effectiveness analysis on the optimal timing of delivery for women with preeclampsia without severe features. American Journal of Obstetrics and Gynecology, 214(1):S237-S238 2016	Different population - women with pre-eclampsia
Meads CA, Cnossen JS, Meher S, Juarez-Garcia A, ter Riet G, Duley L, Roberts TE, Mol	Not specific to women with chronic hypertension.

Study	Reason for exclusion
BW, Van der Post JA, Leeflang MM, Barton PM, Hyde CJ, Gupta JK, Khan KS. Methods of prediction and prevention of pre-eclampsia: systematic reviews of accuracy and effectiveness literature with economic modelling. Health Technol Assess;12(6). 2008	
Meertens LJE, Scheepers HCJ, Willemse JPMM, Spaanderman MEA, Smits LJM. Should women be advised to use calcium supplements during pregnancy? A decision analysis. Matern Child Nutr 14:e12479. 2018	Not specific to women with chronic hypertension
Merrill M, Aviram A, Niu B, Kuo K, Caughey AB. Tight versus less tight control of blood pressure in pregnant women with chronic hypertension - a cost-effective analysis. American Journal of Obstetrics & Gynecology 214(1):S406-S407 2016	Available as abstract only (conference poster)
O'Mahony JF, Mone F, Tyrrell E, Mulcahy C, McParland P, Breathnach F, Morrison JJ, Higgins J, Daly S, Cotter A, Hunter A, Dicker P, Tully E, Malone FD, Normand C, McAuliffe FM. The cost effectiveness of a policy of universal aspirin versus aspirin indicated by a positive pre-eclampsia screening test. American Journal of Obstetrics & Gynecology 216(1): S483 2017 2016	Not specific to women with chronic hypertension.
Rogozinska E, Marlin N, Jackson L, Rayanagoudar G, Ruifrok AE, Dodds J, Molyneaux E, van Poppel MNM, Poston L, Vinter CA, McAuliffe F, Dodd JM, Owens J, Barakat R, Perales M, Cecatti JG, Surita F, Yeo SA, Bogaerts A, Devlieger R, Teede H, Harrison C, Haakstad L, Shen GX, Shub A, El Beltagy N, Motahari N, Khoury J, Tonstad S, Luoto R, Kinnunen TI, Guelfi K, Facchinetti F, Petrella E, Phelan S, Scudeller TT, Rauh K, Hauner H, Renault K, de Groot CJM, Sagedal LR, Vistad I, Stafne SN, Morkved S, Salvesen KA, Jensen DM, Vitolo M, Astrup A, Geiker NRW, Kerry S, Barton P, Roberts T, Riley RD, Coomarasamy A, Mol BW, Khan KS, Thangaratinam S. Effects of antenatal diet and physical activity on maternal and fetal outcomes: individual patient data meta-analysis and health economic evaluation. Health Technol Assess;21(41) 2017	Not specific to chronic hypertension
van Baaren G-J, Broekhuijsen K, van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, Oudijk MA, Bloemenkamp KWM, Scheepers HCJ, Bremer HA, Rijnders RJP, van Loon AJ, Perquin DAM, Sporken JMJ, Papatsonis DNM, van Huizen ME, Vredevoogd CB, Brons JTJ, Kaplan M, van Kaam AH, Groen H, Porath M, van den Berg PP, Mol BWJ, Franssen MTM, Langenveld J, for the HYPITAT-II Study Group. An economic analysis of immediate delivery and expectant monitoring in women with hypertensive disorders of pregnancy, between	Not cost-utility analysis. Costs considered reflect US healthcare setting therefore of limited relevance to UK.

Study	Reason for exclusion
34 and 37 weeks of gestation (HYPITAT-II). BJOG 2017;124:453–461 2017	
Vijgen S, Koopmans C, Opmeer B, Groen H, Bijlenga D, Aarnoudse J, Bekedam D, van den Berg P, de Boer K, Burggraaff J, Bloemenkamp K, Drogtrop A, Franx A, de Groot C, Huisjes A, Kwee A, van Loon A, Lub A, Papatsonis D, van der Post J, Roumen F, Scheepers H, Stigter R, Willekes C, Mol B, Van Pampus M. An economic analysis of induction of labour and expectant monitoring in women with gestational hypertension or pre-eclampsia at term (HYPITAT trial). BJOG, 117: 1577-1585. 2010	Not specific to women with chronic hypertension
Vogel SA, Rajaii R, Ottaviano G, Kim L, Yeaton-Massey A, Caughey AB. Low-dose aspirin for prevention of pre-eclampsia and its complications: a cost-effectiveness analysis. Archives of Disease in Childhood - Fetal and Neonatal Edition;95:Fa46. 2010	Not specific to women with chronic hypertension.
Werner EF, Hauspurg AK, Rouse DJ. A Cost-Benefit Analysis of Low-Dose Aspirin Prophylaxis for the Prevention of Preeclampsia in the United States. Obstet Gynecol 126(6):1242-50 2015	Not specific to women with chronic hypertension
Yeaton-Massey A, Ohno M, Caughey A. Optimal delivery timing for mild gestational hypertension: a decision analysis. American Journal of Obstetrics & Gynecology 210(1): S192 2014	Different population - mild gestational hypertension not chronic hypertension.

Appendix L – Research recommendations

1. In women who require treatment for chronic hypertension in pregnancy, what is the effectiveness and safety of antihypertensive agents (compared in head-to-head trials) in improving maternal and perinatal outcomes?

Why this is important

There is a lack of head-to-head evidence comparing the effectiveness and safety of antihypertensive agents in pregnancy. It is not therefor possible to determine the optimal treatment to reduce blood pressure and improve clinical outcomes, while minimising the risk of adverse effects to both the woman and her baby.

Table 18: Research recommendation rationale

Research question	In women who require treatment for chronic hypertension in pregnancy, what is the effectiveness and safety of antihypertensive agents (compared in head-to-head trials) in improving maternal and perinatal outcomes?
Importance to 'patients' or the population	Use of treatments shown to be effective and safe in pregnancy may reduce the risk of adverse events due to high blood pressure, reduce the burden of monitoring for the woman and reduce the incidence of adverse effects for both the woman and her baby.
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 based on limited available evidence, ensuring that choices of medication take into account pre-existing treatment and the safe use of medicines in pregnancy. However, clinical trials in this area would allow more definitive evidence-based recommendations to be made.
Relevance to the NHS	Evidence in this area would lead to better care of women with hypertension in pregnancy, may reduce the need for admission and progression to pre-eclampsia, and lead to better outcomes for both women and their babies (with fewer adverse effects).
National priorities	The Department of Health and Social Care Single Departmental Plan (May 2018) aims to reduce variation in health outcomes, and reduce maternal deaths by 20% by 2020 and 50% by 2025. This research recommendation is in response to an identified need in the population.
Current evidence base	Lack of evidence; some low or very low quality evidence available.
Equality	Pregnant women are entitled to safe pharmacological treatment of their chronic hypertension, without risk to either themselves or their baby

Table 19: Research recommendation modified PICO table

Criterion	Explanation
Population	Women who require treatment for chronic hypertension, including in the first trimester. Setting – hospital-based care.
Intervention	Antihypertensive agents, to include labetalol, calcium channel blocker, and to consider use of methyldopa, with specific choice of these and other agents to be justified.
Comparator	• Comparator antihypertensive agents in head-to-head trial.
Outcome	• Women: severe hypertension, adverse maternal outcomes to be defined, side-effects. • Baby: pregnancy loss; congenital anomalies; birthweight centile; neonatal care admission; neonatal hypoglycaemia.
Study design	Randomised controlled trial with an internal pilot phase with clear progression criteria to the main trial.

Criterion	Explanation
Timeframe	Minimum duration of follow-up: To primary discharge of woman and baby.

2. In women who require treatment for hypertension in pregnancy, what are the adverse neonatal outcomes associated with maternal use of beta-blockers (or mixed alpha-beta blockers)?

There is evidence that beta-blockers and mixed alpha-beta blockers used in pregnancy result in an increased incidence of neonatal hypoglycaemia. However, there is a known transient physiological nadir in glucose levels in well neonates in the immediate postnatal period. It is not clear if the use of beta-blockers/mixed alpha-beta blockers in pregnancy results in a significant decrease in the plasma glucose concentration of a term or preterm neonate, associated with signs and symptoms, resulting in increased hospital length of stay, separation of baby from woman in the immediate postnatal period, or long term adverse outcomes in the baby.

Table 20: Research recommendation rationale

Research question	In women who require treatment for hypertension in pregnancy, what are the adverse neonatal outcomes associated with maternal use of beta-blockers (or mixed alpha/beta-blockers)?
Importance to 'patients' or the population	Further studies would clarify if beta or mixed alpha/beta-blockers are associated with neonatal hypoglycaemia and may reduce or eliminate the need for invasive heel prick testing to monitor blood glucose in some or all of these babies.
Relevance to NICE guidance	The committee searched for evidence on this topic but found no high-quality evidence. Clinical studies in this area would allow more definitive evidence-based recommendations to be made.
Relevance to the NHS	Clear recommendations in this area would reduce the likelihood of morbidity and separation of woman and baby in the immediate postnatal period.
National priorities	The Department of Health and Social Care Single Departmental Plan (May 2018) aims to reduce the 2010 rate of neonatal deaths and brain injuries in babies that occur during or soon after birth by 20% by 2020 and 50% by 2025
Current evidence base	A systematic review published in 2016 found that there is an increased risk of neonatal blood glucose levels falling below 2.6mmol/L shortly after birth if their mothers received beta blockers or labetalol, a mixed alpha and beta blocker in late pregnancy. However, it is physiological for a newborn's blood glucose level to fall below this threshold in the immediate postnatal period. This systematic review does not address whether these neonatal blood glucose levels below 2.6mmol/L were associated with any clinical problems or long-term morbidity.
Equality	Babies born to women with hypertension in pregnancy are entitled to safe care without risk of long term morbidity.

Table 21: Research recommendation modified PICO table

Criterion	Explanation
Population	Women who require treatment for hypertension. Setting: hospital or community
Intervention/Exposure	Maternal use of beta-blocker or mixed alpha/beta-blocker during late pregnancy and peripartum period, with consideration of timing and duration of use.
Comparator	Women not using these agents in late pregnancy.
Outcome	Important outcomes:

Criterion	Explanation
	Baby: hypoglycaemia, need for additional treatment for hypoglycaemia, birthweight centile. (Consideration should be given to use of routinely collected data for determination of some outcomes)
Study design	A variety of study designs may be suitable, but consideration of a cohort design (with comparator data) should be included.
Timeframe	Minimum duration of follow-up: To primary discharge of woman and baby.