National Institute for Health and Care Excellence

FINAL

Hypertension in pregnancy

[D] Evidence review for interventions for pre-eclampsia

NICE guideline NG133

Evidence review

June 2019

FINAL

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

Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government, and Northern Ireland Executive. All NICE guidance is subject to regular review and may be updated or withdrawn.

ISBN: 978-1-4731-3434-8

Contents

Review question: What interventions are effective at improving outcomes for women and infants in women with pre-eclampsia?

Introduction

Pre-eclampsia is defined as new hypertension presenting after 20 weeks with one or more new-onset features, including significant proteinuria or maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological complications or haematological complications[a]. Severe pre-eclampsia is defined as having a blood pressure of >160 mmHg systolic or 110 mmHg diastolic, with worsening maternal organ dysfunction (such as haemolysis, elevated liver function tests and low platelets, also known as HELLP syndrome) or worsening fetal growth restriction. Early onset-preeclampsia refers to an onset of the disorder before 34 weeks[b].

The presence of pre-eclampsia is known to increase the risk of maternal and perinatal mortality and morbidity, and worsening pre-eclampsia can influence the timing of birth, with early birth being considered in some women to avoid compromise to babies and women.

There is ongoing debate about the appropriate treatment of pre-eclampsia, particularly the place of management (inpatient versus outpatient) and the blood pressure treatment thresholds and targets.

The aim of this review is to identify the efficacy and safety of different interventions for the treatment of pre-eclampsia.

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 pre-eclampsia
Intervention	**Acute management:** • Labetalol • Hydralazine • Nifedipine • Nicardipine • Timing of birth • Magnesium **Non-acute management:** • Methyldopa

a. The classification, diagnosis and management of the hypertensive disorders of pregnancy: A revised statement from the ISSHP: Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 3 (2014): 97-104

b. Tranquilli AL, Brown MB, Zeeman GG , Dekker G, Sibai BM: The definition of severe and early-onset preeclampsia. Statements from the International Society for the Study of Hypertension in Pregnancy (ISSHP): Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health 3 (2013) 44–47

	• Labetalol • Nifedipine • Timing of birth • Magnesium • Statins • Place of management (inpatient versus outpatient) • Abdominal decompression • Tight management (e.g. target dBP 85mmHg) • Less tight management (e.g. target dBP 100 mmHg)
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 (SGA, BW<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:
	• Eclampsia
	• HELLP (haemolysis, elevated liver enzymes, low platelet count)

	• Placental abruption • Onset of labour • Mode of birth • Maternal death

BW: birth weight; CP: cerebral palsy; dBP; diastolic blood pressure; MDI: mental development index; mmHg: millimetres of mercury; PDI: psychomotor developmental index; SD: standard deviation; SGA: small-for-gestational age

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

One Cochrane systematic review (Churchill 2013) including 4 randomised controlled trials (RCTs) was included (n=425) (GRIT 2003; Mesbah 2003; Odendaal 1990; Sibai 1994). In addition, 18 RCTs and 1 retrospective cohort study were included in this systematic review (n= 2,797) (Aali 2001; Broekhuijsen 2015; Dhananjaya 2015; Elatrous 2002; Elhassan 2002; Fenakel 1991; Harper 1991; Koopmans 2009; Kwawukume 1995; Martins-Costa 1992; Owens 2014; Rezaei 2011; Schoen 2017; Sibai 1987; Sibai 1992; Subhedar 2016; Vermillion 1999; Vigil-De Gracia 2006; Vigil-De Gracia 2013). Participants consisted of pregnant women with pre-eclampsia, although 6 RCTs also included participants with other hypertensive disorders of pregnancy in variable proportions (Elatrous 2002; GRIT 2003; Koopmans 2009; Odendaal 1990; Vigil-De Gracia 2006; Vigil-De Gracia 2013). Evidence was found for all interventions, except for statins, abdominal decompression, tight management and less-tight management. Evidence was found for all the main outcomes.

Some of the identified trials were suitable for meta-analyses and these have been performed as appropriate. Furthermore, stratified analyses were conducted by gestational age at trial entry, severity of hypertension at trial entry and income setting where the study was carried out. For severity of hypertension, mild hypertension was defined as <149/99 mmHg; moderate hypertension was defined as 150/100 to 159/109 mmHg; and severe hypertension was defined as ≥ 160/110 mmHg. Studies were classified as low/middle and high income setting as per the classification of the Organisation of Economic Co-Operation and Development (OECD).

As per the protocol, some of the interventions have been categorised as acute and non-acute care. Studies were classified as acute care when including women with sudden, uncontrolled hypertension, very high blood pressure levels or with acute symptoms of pre-eclampsia (headache, visual disturbance, upper abdominal pain).

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 included studies

Study	Participants/ Diagnosis *(and definition of pre-eclampsia)*	Intervention	Control	Outcomes
Churchill 2013 Cochrane SR UK, Egypt, South Africa, and US	N=425 women with PE <u>GRIT 2003</u> *>0.3 g/l proteinuria; hypertension: 140/90 mmHg* <u>Mesbah 2003</u> *Not reported* <u>Odendaal 1990</u> *BP≥180/120 mmHg on 2 occasions at least 30 mins apart with ≥2+ of proteinuria on dipstick; or BP 160/110 to 180/120 mmHg on 2 occasions at least 6 hours apart with ≥2+ of proteinuria; or BP 150/110 – 160/110 mmHg on two occasions at least 6 hours apart with ≥3+ proteinuria or BP≥ 140/90 mmHg with proteinuria and clinical signs of imminent eclampsia* <u>Sibai 1994</u> *BP ≥ 160/110 during the initial 24 hours of hospitalisation and proteinuria > 500 mg per 24 hours*	Induction of labour	Expectant management	• Stillbirth • Neonatal death • SGA • Gestational age at birth • Admission to neonatal unit • Birth weight • Cerebral palsy • Severe hearing impairment (poor hearing/ hearing aid) • Impaired vision • HELLP • Onset of labour (induction) • Mode of birth (C-section)
Aali 2002	N=126 women with PE.	Hydralazine 5mg IV with further doses of 10mg at	Nifedipine 8mg (4 drops) sl.	• Blood pressure control (minutes

Study	Participants/ Diagnosis *(and definition of pre-eclampsia)*	Intervention	Control	Outcomes
RCT Iran	*BP ≥ 160/110 mmHg and met the ACOG criteria for severe pre-eclampsia* All participants were receiving IV magnesium sulfate during participation in the trial (loading dose 4 g, maintenance dose 1-2 g/hour), stopped 24 hours after birth	intervals according to the protocol recommended by ACOG.	Doses were repeated if target blood pressure was not achieved (dBP between 90 and 100 mmHg, and not lower than 90 mmHg).	needed to achieve dBP between 90 and 100mmHg)
Dhananjaya 2015 RCT India	N=60 women with PE (83.3%); GHT (8.3%); CHT + superimposed PE (1.6%) *Definition was not reported.*	Nifedipine PO 10mg with repeated doses of 10mg every 15 minutes up to a maximum of 5 doses or until goal BP was achieved (150/110 mmHg)	Labetalol IV 20mg duplicating the dose every 15 mins until goal BP was achieved (150/110 mmHg)	• Neonatal mortality • Birth weight • Admission to neonatal unit • Gestational age • Blood pressure control (minutes needed to achieve effective control of BP) • Eclampsia • HELLP
Broekhuijsen 2015 RCT The Netherlands	N=423 women with pre-eclampsia (75.5%) or superimposed pre-eclamspia (23.4%) *Pre-eclampsia was defined as dBP ≥90 mmHg on at least 2 occasions 6 hours apart in combination with proteinuria (spot protein: creatinine ratio ≥ of 30 mg/mmol or at*	Immediate birth	Expectant monitoring	• Eclampsia • HELLP

Study	Participants/ Diagnosis *(and definition of pre-eclampsia)*	Intervention	Control	Outcomes
	least 300mg protein in a 24 hours urine collection. *Superimposed pre-eclampsia was defined as new onset proteinuria in women with pre-existing hypertension.*			
Elatrous 2002 RCT Tunisia	N=60 women with PE (96.6%) or CHT (3.3%) *Definition was not reported.* All participants were classified as having hypertensive emergencies (either sustained systolic BP ≥ 170mmHg, or diastolic BP ≥ 110mmHg on two measurements, 30 minutes apart) All participants were receiving IV magnesium sulfate (loading dose 4g, maintenance dose 1g/hour)	Nicardipine 10mg IV over 5 minutes. If BP did not fall 20% in the next 5 minutes, 12.5 mg/hur over 5 minutes was administered, followed by 15 mg/hour if 20% reduction of blood pressure was not achieved. If BP did not fall 20% in the next 5 minutes, the intervention was ceased.	Labetalol 1mg/kg IV loading dose over 1 minute. If BP did not fall 20%, 5 minutes after a second dose of 1.5mg/kg was administered over 1 minute. If BP did not fall 20% in the next 5 minutes, the intervention was ceased. If BP was achieved at any point, a maintenance dose of 100-150mg/kg/hour was infused for the remaining study period.	• Blood pressure control (minutes needed to achieve a fall of 20% compared to baseline)
Elhassan 2002 RCT Sudan	N= 70 women with PE *dBP between 90-109 mmHg in 2 readings 6 hours apart showing 2+ or more albumin by dipstick.*	Methyldopa 750mg/day and increased as needed (maximum dose was 4000mg)	No intervention	• Perinatal death up to 7 days • Blood pressure control (sBP at the start of labour, dBP at the start of labour) • Eclampsia • Mode of birth (C-section)
Fenakel 1991	N= 49 women with PE (~37%) or	Hydralazine 6.25mg IV followed by	Nifedipine 10mg sl. Doses were repeated every	• Neonatal death up to 7 days

Study	Participants/ Diagnosis *(and definition of pre-eclampsia)*	Intervention	Control	Outcomes
RCT Israel	superimposed PE (~63%). *PE: BP ≥160/110 mmHg + any of the following factors: proteinuria, generalised oedema, or hyperreflexia. 26-36 weeks' gestation* All participants received IV magnesium sulfate (loading dose 4g, maintenance dose 1-2g/hour) stopped 24 hours after stabilisation of BP	boluses of 12.5mg at intervals determined by the BP. After 24 hours of stabilisation of sBP/dBP ≤ 160, IV therapy was stopped and po hydralazine therapy was started (20-30mg every 6 hours until birth).	20 and 40 minutes later if sBP/dBP ≥ 160 and increased to 20mg every 4 hours if sBP/dBP continued to be ≥ 160. Thereafter, nifedipine was given in doses of 10mg every 6 hours until birth.	• Birth weight • Gestational age at birth • Severe hypertension • Eclampsia • Onset of labour (induction), • Mode of birth (C-section)
Harper 1991 RCT Northern Ireland	N= 30 women with PE *Definition was not reported*	Hydralazine 10mg IV (single injection)	Labetalol 100mg IV (single injection)	• Stillbirth • Neonatal death • SGA • Birth weight • Gestational age at birth • Mode of birth (C-section)
Koopmans 2009 RCT Netherlands	N=246 women with PE	Induction of labour: labour was induced within 24 hours of randomisation.	Expectant management: women were monitored until the onset of spontaneous labour	• Mode of birth (C-section)
Kwawukume 1995 RCT Ghana	N=98 women with PE *Proteinuria of at least 1+ as measured by dipstick in a random urine sample; sBP or dBP of 160/110 mmHg measured twice,4-6 hours apart*	Hydralazine 5mg IV. Escalating doses of 10mg were repeated at intervals determined by the BP level. Once dBP was stabilised at around 90 to 100 mmHg, 20mg to 80mg	Nifedipine 10mg sl. Escalating doses of 10mg every 30 minutes were given if BP was ≥ 160/110 mmHg. The dose was escalated to 20mg every 6 to 8 hours if the BP readings	• Neonatal death • Birth weight • Admission to neonatal unit • Eclampsia • Mode of birth (C-section)

Study	Participants/ Diagnosis *(and definition of pre-eclampsia)*	Intervention	Control	Outcomes
		hydralazine tablets in divided doses were administered until birth	approached 160/110 mmHg	
Martins-Costa 1992 RCT Brazil	N=37 women with PE *dBP ≥ 110 mmHg and significant proteinuria (at least 300 mg in 24 hour collection urine, or a minimum of 3+ as measured by dipstick)*	Hydralazine 5mg IV + placebo capsule PO	Nifedipine 10mg PO + placebo IV	• Stillbirth • SGA • Birth weight • Gestational age at birth • Severe hypertension • Placental abruption • Mode of birth (C-section)
Owens 2014 RCT US	N=169 women with PE *BP ≥140/90 mmHg on 2 occasions at least 4 hours apart after 24 weeks GA ; or BP ≥ 160/110 mmHg plus proteinuria; or in the absence of proteinuria, new onset hypertension with clinical signs of imminent eclampsia*	Induction of labour: women underwent induction of labour or caesarean birth within 12 hours of randomisation. Magnesium sulphate prophylaxis was administered intrapartum and immediately postpartum	Expectant management: women were admitted to hospital until birth, which was delayed until 37 weeks gestation unless there was deterioration in their clinical condition. Magnesium sulfate prophylaxis was administered intrapartum and immediately postpartum	• SGA • Birth weight • Admission to neonatal unit • Severe hypertension • Eclampsia • HELLP • Mode of birth (C-section)
Rezaei 2011 RCT Iran	N=50 women with PE or superimposed PE (% was not reported) *Definition was not reported*	Hydralazine 5mg IV and repeated in doses of 10 mg , up to 5 injections in 10mg doses, up to a maximum of 5 injections in intervals of 20 minutes + magnesium sulfate (dose was not reported)	Nifedipine 10mg capsules and repeated in doses of 20mg with intervals of 20 minutes up to 5 doses, or when target BP was reached (150/90-100) + magnesium sulfate (dose was not reported)	• Blood pressure control (minutes to achieve BP of 150/90-100mmHg)

Study	Participants/ Diagnosis *(and definition of pre-eclampsia)*	Intervention	Control	Outcomes
Schoen 2017 Retrospective cohort study Italy and US	N= 365 women with CHT and superimposed PE without severe features. *CHT: history of hypertension prior to the pregnancy or a BP ≥ 140/90 prior to 20 weeks.* *Superimposed PE without severe features: sudden increase in BP that was previously well controlled, or a need to increase antihypertensive medication; new onset proteinuria ≥ 300mg per 24 h or > 0.3 PCR (mg/dL),or a sudden increase in proteinuria in a women who had proteinuria before or early in pregnancy.*	Outpatient management: 1 visit per week to clinician or high-risk nurse practitioner; 2 per week non-stress tests; ultrasound for fetal growth once every 3 to 4 weeks. Complete blood count and a comprehensive metabolic panel was done regularly (at the clinician´s discretion). All women had daily monitoring of blood pressure (home device) + methyldopa, labetalol, nifedipine or, rarely, amlodipine to control BP (doses were not reported)	Inpatient management: women were monitored 2 to 3 times daily non-stress tests + methyldopa, labetalol, nifedipine or, rarely, amlodipine to control BP (doses were not reported)	• Stillbirth • SGA • Birth weight • Gestational age at birth • Admission to neonatal unit • HELLP • Placental abruption • Mode of birth (C-section)
Sibai 1987 RCT US	N=186 women with PE. *sBP 140 to 160 and dBP 90 to 110 with proteinuria (more than 300mg/24h) and elevated uric acid levels (≥6 mg/dl)*	Labetalol 300mg/day increased every 2 to 3 days as needed, maximum 2400mg/day (method of administration was not reported)	No intervention	• Stillbirth • Neonatal death • Birth weight • SGA • Admission to neonatal unit • Mode of birth (C-section)
Sibai 1992 RCT US	N= 200 women with PE. *sBP 140 to 160 mmHg and dBP 90 to 110 mmHg with proteinuria (more than 300mg/24hours) and elevated uric acid levels (≥6 mg/dl)*	Nifedipine: 40mg/day increased every 2 to 3 days as needed to a maximum of 120 mg/day to keep sBP/dBP below 140/90 mmHg (method of administration was not reported)	No intervention	• Stillbirth • Neonatal death • SGA • Gestational age at birth • Preterm birth (<37 weeks) • Admission to neonatal unit • HELLP

Study	Participants/ Diagnosis *(and definition of pre-eclampsia)*	Intervention	Control	Outcomes
				• Placental abruption • Onset of labour (induction) • Mode of birth (C-section)
Subhedar 2016 RCT India	N=180 women with PE *BP >140/90 mmHg on two separate occasion 6 hours apart, proteinuria 1+ dipstick in two urine samples collected 4 hours apart.*	Labetalol 100mg tid	Methyldopa 250 mg tid	• Blood pressure control (MAP) • Onset of labour
Vermillion 1999 RCT US	N=50 women with PE and chronic hypertension with PE. *Defined according to the ACOG criteria*	Nifedipine po in combination with placebo IV (50g of isotonic sodium chloride solution)	Labetalol IV in combination with oral placebo (cornstarch powder)	• Blood pressure control (minutes to achieve effective control of blood pressure)
Vigil-De Gracia 2006 RCT Panama	N=200 women with: • severe PE (~55%) • severe PE with HELLP (~1%) • superimposed PE (~15%) • CHT (~8%) • GH (~20%). *Severe PE: elevated BP 140/90 mmHg + proteinuria (1+ or more on dipstick) + and clinical signs of imminent eclampsia or BP ≥160/110 mmHg + proteinuria in the absence of any of the above mentioned features.*	Hydralazine 5mg IV every 20 minutes until dBP ≤ 110 mmHg or sBP ≤ 160 mmHg (up to 5 consecutive doses)	Labetalol 20mg IV every 20 minutes until dBP ≤ 110 mmHg or sBP ≤ 160 mmHg (up to 5 consecutive doses)	• Neonatal death • Birth weight • Admission to neonatal unit • Maternal death • Severe hypertension • Eclampsia • HELLP • Placental abruption • Mode of birth (C-section)

Study	Participants/ Diagnosis *(and definition of pre-eclampsia)*	Intervention	Control	Outcomes
Vigil-De Gracia 2013 RCT Panama	N=264 women with: • severe PE (~80%) • superimposed PE (~13%) • severe GH (~7%) *Severe PE: elevated BP (at least 140/90 mmHg) with proteinuria (0.3 g or greater in a 24 h urine specimen) associated with clinical signs of imminent eclampsia.*	Induction of labour: women received glucocorticoid therapy followed by birth in 24 to 72 hours	Expectant management: women were treated expectantly and received glucocorticoid therapy followed by birth only for fetal or maternal indications or reaching 34 weeks' gestation	• Stillbirth • SGA • Birth weight • Admission to neonatal unit • Eclampsia • HELLP • Placental abruption • Mode of birth (C-section)

ACOG: The American College of Obstetricians and Gynecologists; BP: blood pressure; C-section: caesarean section; CHT: chronic hypertension; dBP: diastolic blood pressure; GA: gestational age; GH: gestational hypertension; HELLP: haemolysis, elevated liver enzymes and low platelet count; IV: intravenous; MAP: mean arterial pressure; ml: millilitre; mmHg: millimetres of mercury; N: total number of participants; NST: non stress test; OD: once daily; PCR: protein:creatinine ratio; PE: pre-eclampsia; PO: oral administration; sBP: systolic blood pressure; SGA: small-for-gestational age; SL: sublingual; SR: systematic review; tid: three times a day

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 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. Labetalol versus nicardipine (acute management)

Outcomes for women

Critical outcomes

Blood pressure control

Minutes needed to achieve effective control of blood pressure

- One randomised controlled trial (n=60) provided low quality evidence to show no clinically important difference in the time taken to achieve effective control of blood pressure between those who received labetalol or nicardipine.

Comparison 2. Labetalol versus no intervention (non-acute management)

Outcomes for babies

Critical outcomes

Stillbirth

- One randomised controlled trial (n=191) provided moderate quality evidence to show that no stillbirths occurred in those who received labetalol or no intervention.

Neonatal death

- One randomised controlled trial (n=191) provided very low quality evidence to show that there was no clinically important difference in neonatal deaths between those who received labetalol or no intervention.

Small-for-gestational age

- One randomised controlled trial (n=191) provided low quality evidence to show that there may be a clinically important increase in the number of babies born SGA for women taking labetalol, as compared to no intervention, but there was uncertainty around the estimate (RR 2.06, 95% CI 0.98 to 4.36).

Important outcomes

Birth weight

- One randomised controlled trial (n=191) provided moderate quality evidence to show that there was no clinically important difference in birth weight between those who received labetalol or no intervention.

Gestational age at birth

- One randomised controlled trial (n=191) provided moderate quality evidence to show that there was no clinically important difference in gestational age at birth between those who received labetalol or no intervention.

Admission to neonatal unit

- One randomised controlled trial (n=191) provided very low quality evidence to show that there was no clinically important difference in the number of babies requiring admission to a neonatal unit between those who received labetalol or no intervention.

Outcomes for women

Critical outcomes

Severe hypertension

- One randomised controlled trial (n=191) provided low quality evidence to show that those who received labetalol experienced a clinically important decrease in the number of episodes of severe hypertension, as compared to those who received no intervention.

Important outcomes

Placental abruption

- One randomised controlled trial (n=191) 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 (C-section)

- One randomised controlled trial (n=191) provided low quality evidence to show that there was no clinically important difference in the mode of birth (caesarean section) between those who received labetalol or no intervention.

Comparison 3. Labetalol versus methyldopa (acute management)

Outcomes for women

Critical outcomes

Blood pressure control: Mean arterial pressure

- One randomised controlled trial (n=180) provided very low quality evidence to show that those who received labetalol experienced a clinically important reduction in mean arterial pressure as compared to those who received methyldopa.

Important outcomes

Onset of labour (induction)

- One randomised controlled trial (n=180) provided very low quality evidence to show that there was no clinically important difference in the number of women having induction of labour between those who received labetalol or methyldopa.

Comparison 4. Hydralazine versus nifedipine (acute management)

Outcomes for babies

Critical outcomes

Stillbirth

- One randomised controlled trial (n=37) provided very low quality evidence to show that there was no clinically important difference in the rate of stillbirth between those who received hydralazine or nifedipine.

Neonatal death

- Two randomised controlled trials (n=132) provided very low quality evidence to show that there was no clinically important difference in neonatal deaths between those who received hydralazine or nifedipine. Subgroup analyses by gestational age, severity of hypertension or income setting provided low to very low quality evidence and did not detect any differences between groups.

Small-for-gestational age

- One randomised controlled trial (n=37) provided moderate quality evidence to show that there was no clinically important difference in the number of neonates born small-for-gestational age between those who received hydralazine or nifedipine.

Important outcomes

Birth weight

- Three randomised controlled trials (n=184) provided low quality evidence to show that there was no clinically important difference in birth weight between those who received hydralazine or nifedipine. Subgroup analyses by gestational age, severity of hypertension or income setting provided low to very low quality evidence and did not detect any differences between groups.

Gestational age at birth

- Two randomised controlled trials (n=86) provided very low quality evidence to show that there was no clinically important difference in the gestational age at birth for babies of those who received hydralazine or nifedipine. Subgroup analyses by gestational age, severity of hypertension or income setting provided low to very low quality evidence and did not detect any differences between groups.

Admission to neonatal unit

- One randomised controlled trial (n=79) provided very low quality evidence to show that there was no clinically important difference in the number of neonates admitted to the neonatal unit between those who received hydralazine or nifedipine.

Outcomes for women

Critical outcomes

Blood pressure control

Minutes needed to achieve effective control of blood pressure

- Two randomised controlled trials (n=176) provided very low quality evidence to show that there was no clinically important difference in the number of minutes taken to achieve effective control of blood pressure between those who received hydralazine or nifedipine. However, there was very high inconsistency in the effect estimates between these trials.

Minutes needed to achieve effective control of blood pressure, gestational age 34^{+0} to 36^{+6} weeks, severe hypertension, and from a low/middle income setting

- One randomised controlled trial (n= 50) provided very low quality evidence to show that those who received nifedipine, whose gestational age was 34^{+0} to 36^{+6} weeks, presenting with severe hypertension at study entry, and from a low/middle income setting, had a clinically important reduction in the time needed to achieve target blood pressure, as compared with those who received hydralazine. No differences were found between treatment arms in the remaining subgroup analyses.

Severe hypertension

- Two randomised controlled trials (n=86) provided very low quality evidence to show that those who received nifedipine, whose gestational age was <34/40, presenting with severe hypertension at study entry, and from a high-income setting, had a clinically important reduction in the occurrence of severe hypertension, as compared to those who received hydralazine. No difference was found in the remaining subgroup analysis.

Important outcomes

Eclampsia

- Two randomised controlled trials (n=128) provided low quality evidence to show no occurrence of eclampsia in those who received hydralazine or nifedipine.

Placental abruption

- One randomised controlled trial (n=37) provided very low quality evidence to show that there was no clinically important difference in placental abruption between those who received hydralazine or nifedipine.

Onset of labour (induction)

- One randomised controlled trial (n=49) provided very low quality evidence to show that there was no difference in the onset of labour (number of women undergoing induction of labour) in those who received nifedipine compared to those who received hydralazine.

Mode of birth (C-section)

- Three randomised controlled trials (n=116) provided very low quality evidence to show that there was no clinically important difference in mode of birth between those who received hydralazine or nifedipine. Subgroup analyses by gestational age, severity of hypertension or income setting provided very low quality evidence to show no differences between groups.

Comparison 5. Hydralazine versus labetalol (acute management)

Outcomes for babies

Critical outcomes

Stillbirth

- One randomised controlled trial (n=30) provided very low quality evidence to show no clinically important difference in stillbirths between those who received hydralazine or labetalol.

Neonatal death

- Two randomised controlled trials (n=235) provided very low quality evidence to show no clinically important difference in neonatal deaths between those who received hydralazine or labetalol. Subgroup analyses by gestational age, severity of hypertension or income setting did not detect any differences between treatment arms.

Small-for-gestational age

- One randomised controlled trial (n=30) 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 hydralazine or labetalol.

Important outcomes

Birth weight

- Two randomised controlled trials (n=230) provided very low quality evidence to show no clinically important difference in infant birth weight between those who received hydralazine and labetalol. Subgroup analyses by gestational age, severity of hypertension or income setting provided moderate to very low quality evidence to show no difference between treatment arms.

Admission to neonatal unit

- One randomised controlled trial (n=205) provided very low quality evidence to show no clinically important difference in the number of neonates admitted to neonatal units between those who received hydralazine or labetalol.

Outcomes for women

Critical outcomes

Severe hypertension

- One randomised controlled trial (n=200) provided very low quality evidence to show no clinically important difference in severe hypertension between those who received hydralazine or labetalol.

Important outcomes

Eclampsia

- One randomised controlled trial (n=200) provided moderate quality evidence to show no episodes of eclampsia in those who received hydralazine or labetalol.

HELLP

- One randomised controlled trial (n=200) provided very low quality evidence to show no clinically important difference in the occurrence of HELLP syndrome between those who received hydralazine or labetalol.

Placental abruption

- One randomised controlled trial (n=200) provided moderate quality evidence to show no clinically important difference in the occurrence of placental abruption between those who received hydralazine or labetalol.

Mode of birth (C-section)

- Two randomised controlled trials (n=230) provided very low quality evidence to show no clinically important difference in the mode of birth (occurrence of C-section) between those who received hydralazine or labetalol. Subgroup analyses by gestational age, severity of hypertension or income setting provided low to very low quality evidence to show no differences between treatment arms.

Maternal death

- One randomised controlled trial (n=200) provided moderate quality evidence to show that no maternal deaths occurred in those who received hydralazine or labetalol.

Comparison 6. Nifedipine versus labetalol (acute management)

Outcomes for babies

Critical outcomes

Neonatal mortality

- One randomised controlled trial (n=59) provided very low quality evidence to show that there was no clinically important difference in neonatal mortality between those who received labetalol or nifedipine.

Important outcomes

Birth weight

- One randomised controlled trial (n=59) provided very low quality evidence to show that there was no clinically important difference in infant birth weight between those who received labetalol or nifedipine.

Gestational age at birth

- One randomised controlled trial (n=59) provided very low quality evidence to show that there was no clinically important difference in the gestational age at birth of infants born to women who received labetalol or nifedipine.

Admission to neonatal unit

- One randomised controlled trial (n=59) provided very low quality evidence to show that there was no clinically important difference in the number of infants requiring neonatal unit admission between those who received labetalol or nifedipine.

Outcomes for women

Critical outcomes

Minutes needed to achieve effective control of BP

- Two randomised controlled trials (n=109) provided very low quality evidence to show a clinically important reduction in the time needed to control blood pressure for those who received nifedipine, as compared to those who received labetalol.

Gestational age 34^{+0} to 36^{+6} weeks, severe hypertension, and from a low/middle income setting

- One randomised controlled trial (n=59) provided very low quality evidence to show to show a clinically important reduction in the time needed to control blood pressure for those who received nifedipine, as compared to those who received labetalol, for women with a gestational age 34^{+0} to 36^{+6} weeks, severe hypertension, and from a low/middle income setting.

Gestational age 34^{+0} to 36^{+6} weeks, severe hypertension, and from a high income setting

- One randomised controlled trial (n=50) provided very low quality evidence to show a clinically important reduction in the time needed to control blood pressure for those who received nifedipine, as compared to those who received labetalol, for women with a gestational age 34^{+0} to 36^{+6} weeks, severe hypertension, and from a high income setting.

Important outcomes

HELLP syndrome

- One randomised controlled trial (n=59) provided very low quality evidence to show that there was no clinically important difference in the incidence of HELLP syndrome between those who received labetalol or nifedipine.

Eclampsia

- One randomised controlled trial (n=59) provided very low quality evidence to show that there was no clinically important difference in the incidence of eclampsia between those who received labetalol or nifedipine.

Comparison 7. Nifedipine versus no intervention (non-acute management)

Outcomes for babies

Critical outcomes

Stillbirth

- One randomised controlled trial (n=200) provided moderate quality evidence to show that no stillbirths occurred in those who received nifedipine or no intervention.

Neonatal death

- One randomised controlled trial (n=200) provided moderate quality evidence to show that no neonatal deaths occurred in those who received nifedipine or no intervention.

Small-for-gestational age

- One randomised controlled trial (n=200) provided very low quality evidence to show that there was no clinically important difference in the number of neonates born small-for-gestational age between those who received nifedipine or no intervention.

Important outcomes

Gestational age at birth

- One randomised controlled trial (n=200) provided moderate quality evidence to show that there were no differences in gestational age at birth for infants born to women who received nifedipine or no intervention.

Preterm birth (<37 weeks)

- One randomised controlled trial (n=200) provided moderate quality evidence to show a clinically important increase in the number of preterm births (<37 weeks) for those who received nifedipine, as compared to those who received no intervention.

Admission to neonatal unit

- One randomised controlled trial (n=200) provided low quality evidence to show that there was no clinically important difference in the number of infants requiring admission to a neonatal unit between those who received nifedipine or no intervention.

Outcomes for women

Important outcomes

HELLP syndrome

- One randomised controlled trial (n=197) provided very low quality evidence to show that there was no clinically important difference in the incidence of HELLP syndrome between those who received nifedipine or no intervention.

Placental abruption

- One randomised controlled trial (n=197) provided very low quality evidence to show that there was no clinically important difference in the occurrence of placental abruption between those who received nifedipine or no intervention.

Onset of labour (induction)

- One randomised controlled trial (n=197) provided very low quality evidence to show that there was no difference in the onset of labour (occurrence of induction) between those who received nifedipine or no intervention.

Mode of birth (C-section)

- One randomised controlled trial (n=197) provided low quality evidence to show that there was no clinically important difference in the mode of birth (birth by C-section) between those who received nifedipine or no intervention.

Comparison 8. Methyldopa versus no intervention (non-acute management)

Outcomes for babies

Critical outcomes

Perinatal mortality

- One randomised controlled trial (n=70) provided very low quality evidence to show that there was no clinically important difference in perinatal mortality between those who received methyldopa or no intervention.

Outcomes for women

Critical outcomes

Control of blood pressure: Systolic blood pressure

- One randomised controlled trial (n=70) provided very low quality evidence to show a clinically important reduction in systolic blood pressure for those women who received methyldopa as compared to no intervention, but no clinically important change in diastolic blood pressure.

Important outcomes

Eclampsia

- One randomised controlled trial (n=70) provided very low quality evidence to show no clinically important difference in the occurrence of eclampsia between those who received methyldopa or no intervention.

Mode of birth (C-section)

- One randomised controlled trial (n=70) provided very low quality evidence to show no clinically important difference in the mode of birth (birth by C-section) between those who received methyldopa or no intervention.

Comparison 9. Immediate birth versus expectant management

Outcomes for babies

Critical outcomes

Stillbirth

- Five randomised controlled trials (n=700) provided very low quality evidence to show that there was no clinically important difference in the number of stillbirths between those who received immediate birth or expectant management. Subgroup analyses by gestational age, severity of hypertension or income setting provided very low quality evidence to show no differences between treatment arms.

Neonatal death

- Five randomised controlled trials (n=700) provided very low quality evidence to show that there was no clinically important difference in neonatal deaths between those who underwent immediate birth or expectant management. Subgroup analyses by gestational age, severity of hypertension or income setting provided very low quality evidence to show no differences between treatment arms.

Small-for-gestational age

- Four randomised controlled trials (n=569) provided very low quality evidence to show that there was no clinically important difference in the number of neonates born small-for-gestational age between those who received expectant management as compared to those who received immediate birth. There was considerable inconsistency in the effect estimates between the different trials, although this improved with subgroup analysis by gestational age and severity of hypertension.

Gestational age <34 weeks

- Three randomised controlled trials (n=400) provided very low quality evidence to show that those with a gestational age <34 weeks who received immediate birth had a clinically important reduction in the number of neonates born small-for-gestational age as compared to those who received expectant management.

Gestational age 34 to 36^{+6} weeks

- One randomised controlled trial (n=169) provided very low quality evidence to show that, for those with a gestational age 34^{+0} to 36^{+6} weeks, no clinically important difference was identified in the number of neonates born small-for-gestational age between those who received immediate birth compared with those who received expectant management.

Severe hypertension

- Three randomised controlled trials (n=400) provided very low quality evidence to show that those with severe hypertension who received immediate birth experienced fewer neonates born small-for-gestational age as compared to those who received expectant management.

Mild hypertension

- One randomised controlled trial (n=169) provided very low quality evidence to show, for those with mild hypertension, no clinically important difference was identified in the number of neonates born small-for-gestational age between those who received immediate birth compared with those who received expectant management.

High income setting

- Two randomised controlled trials conducted in a high income setting (n=264) provided very low quality evidence to show no clinically important difference was identified in the number of neonates born small-for-gestational age between those who received immediate birth compared with those who received expectant management.

Low/middle income setting

- Two randomised controlled trials conducted in a low/middle income setting (n=305) provided very low quality evidence to show that those who received immediate birth and experienced fewer neonates born small-for-gestational-age as compared to those who received expectant management

Important outcomes

Birth weight

Gestational age <34 weeks

- Three randomised controlled trials (n=338) provided very low quality evidence to show that there was no clinically important difference in the birth weight of those with a gestational age <34 weeks who received immediate birth or expectant management. However, there was very high inconsistency in the effect estimates for the individual trials.

Gestational age 34^{+0} to 36^{+6} weeks

- One randomised controlled trial (n=169) provided very low quality evidence to show that those with a gestational age of 34^{+0} to 36^{+6} weeks who received immediate birth had neonates of higher birth weight as compared to those who received expectant management.

Gestational age at birth

- Four randomised controlled trials (n=425) provided very low quality evidence to show that those who received immediate birth had a lower gestational age at birth as compared to those who received expectant management. However, there was considerable inconsistency in the effect estimates between the individual trials, which remained despite subgroup analysis by severity of hypertension and income setting.

Severe hypertension

- One randomised controlled trial (n=125) provided very low quality evidence to show that, for those with severe hypertension, there was no clinically important difference in the gestational age at birth between those who received immediate birth and those who received expectant management.

Moderate hypertension

- One randomised controlled trial (n=38) provided very low quality evidence to show that those with moderate hypertension who received immediate birth had a lower gestational age at birth than those who received expectant management.

Mild hypertension

- One randomised controlled trial (n=262) provided low quality evidence to show that, for those with mild hypertension, there was no clinically important difference in the gestational age at birth for those who received immediate birth compared to those who received expectant management.

- No other differences were found in the remaining subgroup analyses (income setting).

Admission to neonatal unit

- Four randomised controlled trials (n=569) provided very low quality evidence to show that there was no clinically important difference in the number of neonates admitted to neonatal units between those who received immediate birth as compared to expectant management. However, there was considerable inconsistency in the effect estimates between the individual trials, which remained despite subgroup analysis.

High income setting

- Two randomised controlled trials conducted in a high income setting (n= 264) provided very low quality evidence to show that infants of those who received expectant management experienced fewer admissions to a neonatal unit as compared to those who received immediate birth.

Low/middle income setting

- Two randomised controlled trials conducted in a low/middle income setting (n=305) provided very low quality evidence to show no clinically important difference in the number of infants requiring admission to a neonatal unit, between those who received expectant management or immediate birth.

- Subgroup analyses by gestational age or severity of hypertension showed no differences between the treatment arms.

Neurodevelopmental outcomes ≥ 18 months: cerebral palsy

- One randomised controlled trial (n=262) provided very low quality evidence to show no clinically important difference in the number of infants with cerebral palsy between those who received immediate birth or expectant management.

Neurodevelopmental outcomes ≥ 18 months: impaired vision

- One randomised controlled trial (n=262) provided very low quality evidence to show no clinically important difference in the number of infants with impaired vision between those who received induction of labour or expectant management.

Neurodevelopmental outcomes ≥ 18 months: moderate hearing impairment

- One randomised controlled trial (n=262) provided very low quality evidence to show no clinically important difference in the number of infants with moderate hearing impairment between those who received induction of labour or expectant management.

Outcomes for women

Critical outcomes

Severe hypertension

- One randomised controlled trial conducted in a high income setting (n=169) provided low quality evidence to show that those who presented with mild hypertension at study entry, with a gestational age of 34^{+0} to 36^{+6}, experienced fewer episodes of severe hypertension with immediate birth, as compared to expectant management.

Important outcomes

Eclampsia

- Four randomised controlled trials (n=962) provided very low quality evidence to show no clinically important difference in the incidence of eclampsia between those with immediate birth or expectant management. Subgroup analyses by gestational age, severity of hypertension or income setting provided very low quality evidence to show no differences between the treatment arms.

HELLP syndrome

- Four randomised controlled trials (n=962) provided very low quality evidence to show no clinically important difference in the incidence of HELLP syndrome between those with immediate birth or expectant management. Subgroup analyses by gestational age, severity of hypertension or income setting provided very low quality evidence to show no differences between the treatment arms.

Placental abruption

- Three randomised controlled trials (n=397) (all conducted with participants at <34 weeks' gestation) provided very low quality evidence to show that there may be a clinically important reduction in placental abruption with immediate birth as compared to expectant management, although there was some uncertainty around the estimate (RR 0.42, 95% CI 0.18 to 1.00).

<u>Severe hypertension</u>

- Two randomised controlled trials (n=359) including participants with severe hypertension provided very low quality evidence to show that there may be a clinically important reduction in placental abruption with immediate birth as compared to expectant

management, although there was some uncertainty around the estimate (RR 0.34, 95% CI 0.11 to 1.02).

Moderate hypertension

- One randomised controlled trial (n=38) including participants with moderate hypertension provided very low quality evidence to show no clinically important difference in the incidence of placental abruption between those who had immediate birth as compared to expectant management.

High income setting

- One randomised controlled trial, conducted in a high income setting (n=95) provided very low quality evidence to show no clinically important difference in the occurrence of placental abruption between those who received immediate birth as compared to those who received expectant management.

Low/middle income setting

- Two randomised controlled trials (n=302) provided very low quality evidence to show that those from a low/middle income setting who received immediate birth experienced fewer episodes of placental abruption as compared to those who received expectant management.

Mode of birth (C-section)

- Six randomised controlled trials (n=1002) provided low quality evidence to show no clinically important difference in mode of birth (occurrence of C-section) between those who received immediate birth as compared to those who received expectant management. Subgroup analyses by gestational age, severity of hypertension or income setting provided low to very low quality evidence to show no differences between the treatment arms.

Maternal death

- One randomised controlled trials (n=200) provided low quality evidence to show that no maternal deaths occurred in the immediate birth group or in the expectant management group.

Comparison 10. Outpatient management versus inpatient management

Outcomes for babies

Critical outcomes

Stillbirth

- One observational study (n=365) provided very low quality evidence to show no clinically important difference in stillbirths between those who were managed in an inpatient or outpatient setting. However, this study included women with chronic hypertension with superimposed pre-eclampsia only.

Small-for-gestational age

- One observational study (n=365) provided very low quality evidence to show that those who were managed in an outpatient setting had a clinically important reduction in the number of neonates born small-for-gestational age, as compared to those who were managed in the inpatient setting. However, this study included women with chronic hypertension with superimposed pre-eclampsia only.

Important outcomes

Birth weight

- One observational study (n=365) provided very low quality evidence to show that those who were managed in an outpatient setting had neonates with a clinically important increase in birth weight, as compared to those who were managed in an inpatient setting. However, this study included women with chronic hypertension with superimposed pre-eclampsia only.

Gestational age at birth (weeks)

- One observational study (n=365) provided low quality evidence to show a clinically important increase in the gestational age at birth for infants born to women who were managed in an outpatient setting as compared to those who were managed in an inpatient setting. However, this study included women with chronic hypertension with superimposed pre-eclampsia only.

Admission to neonatal unit

- One observational study (n=365) provided very low quality evidence to show no clinically important difference in the number of infants requiring admission to a neonatal unit between those who were managed in an inpatient or outpatient setting. However, this study included women with chronic hypertension with superimposed pre-eclampsia only.

Outcomes for women

Important outcomes

HELLP syndrome

- One observational study (n=365) provided low quality evidence to show no occurrence of HELLP syndrome in those who were managed in an inpatient or outpatient setting. However, this study included women with chronic hypertension with superimposed pre-eclampsia only.

Placental abruption

- One observational study (n=365) provided low quality evidence to show no clinically important difference between the number of placental abruptions in those who were managed in an inpatient or outpatient setting. However, this study included women with chronic hypertension with superimposed pre-eclampsia only.

Mode of birth (C-section)

- One observational study (n=365) provided low quality evidence to show no clinically important difference in the mode of birth (C-section) between those who were managed in an inpatient or outpatient setting. However, this study included women with chronic hypertension with superimposed pre-eclampsia only.

See appendix E for Forest plots.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Treatment of pre-eclampsia in pregnancy aims to control the mother's blood pressure and prevent progression to eclampsia, without leading to any adverse effects on the baby. The committee therefore identified 3 outcomes of critical importance to allow the balance of

benefit 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 (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 neonatal unit, cerebral palsy, neurodevelopmental delay, and neurosensory impairment. Six further important outcomes for women with pre-eclampsia were identified, and these were eclampsia, HELLP, placental abruption, onset of labour, mode of birth, and maternal death.

The quality of the evidence

Eighteen RCTs, 1 systematic review and 1 retrospective cohort study were included in this review. For the RCTs, the quality of the evidence was assessed with the Cochrane Risk of Bias tool and ranged from very low to moderate. 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.

For the systematic review, the quality of the evidence was assessed with the AMSTAR checklist. The quality of this systematic review was high.

The retrospective cohort study was considered a good quality study, although the committee agreed that due to its design it is very likely to be subject to selection bias, and only relates to women with chronic hypertension with superimposed pre-eclampsia, therefore they interpreted its results cautiously.

Benefits and harms

The committee discussed the potential harms of pre-eclampsia in pregnant women and noted that it could lead to preterm birth, as well as placental abruption, stroke, small for gestational age babies, and that it could develop, if undetected or not treated appropriately, into eclampsia with associated convulsions and potentially maternal and fetal death. The committee therefore agreed that treatment with antihypertensive medication should be initiated and that other possible management options may include admission to hospital and induction of labour to achieve a planned early birth. The committee reviewed the recommendations from the 2010 guideline table relating to admission to hospital, thresholds for pharmacological treatment, and monitoring of blood pressure, proteinuria and blood tests. The committee simplified the table from the 2010 guideline for the management of pre-eclampsia and agreed that, based on their clinical experience and knowledge, women only need to be stratified into those with hypertension, and those with severe hypertension.

There was some evidence that in women with chronic hypertension and superimposed pre-eclampsia, outpatient care led to benefits to the baby (reduction in the number of babies who were small for gestational age, increased birthweight and increased gestational age) compared to inpatient care, but the committee noted that this evidence was from an observational cohort study. In this study women were admitted at their physician's discretion so the women who were thought to be more at risk or more ill would have been more likely to have been admitted and induced, thus leading to babies who were smaller for gestational age, with decreased birthweight and decreased gestational age in the inpatient arm. The committee did not therefore think that this evidence was robust enough for them to make recommendations, but noted that the review of clinical prediction models for eclampsia (evidence review C) had shown that it was possible to predict which women with pre-eclampsia were at a high risk of complications, and this would allow for the identification of which women should be admitted for closer surveillance and monitoring, and which women could be cared for as outpatients. However, the committee recognised that there may be women who do not reach the suggested score of 30% using the fullPIERS or PREP-S prediction model, but who for other reasons should be admitted, and these would include

women with systolic blood pressure of 160 mmHg or higher and women with any biochemical or haematological investigations, or clinical signs that caused concern, or any signs of fetal compromise. The committee therefore cross-referenced to the recommendations to use the fullPIERS or PREP-S prediction models, but also made it clear that the decision on place of care whould be made on the basis of a full clinical assessment and that women should be admitted if there were concerns for the wellbeing of the woman or her baby.. However, because of the lack of evidence for the best place of care for women with pre-eclampsia the committee made a research recommendation.

No evidence was available from this review that demonstrated the blood pressure at which treatment for pre-eclampsia should be initiated, but the committee adopted the recommendations from the chronic hypertension review (see evidence review A). This review had identified that in the CHIPS study (Magee 2015) tight blood pressure control led to a reduced incidence of severe hypertension in mothers with no adverse effects on the baby, and the treatment initiation 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 guideline on the treatment of hypertension in adults and used their treatment initiation 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.

The committee amended the previous recommendations on blood pressure monitoring, because if women with pre-eclampsia were not admitted to hospital then it would be difficult to monitor their blood pressure four times a day, so they agreed to change this to at least every 48 hours if women were not in hospital, but more frequently if they were. They also agreed, based on their clinical experience, that dipstick proteinuria testing should only be continued if there were changes in the women's clinical condition, or uncertainty about the diagnosis, and adopted the recommendations from the previous guideline on blood tests. The committee noted that the management table did not include guidance on how often to monitor fetal growth (this is covered in a separate section of the guideline) but agreed that it was important to include this in the table so it was not omitted from the ongoing monitoring of women and their babies, and so they added this information based on the recommendations already in section 1.6 of the guideline.

There was some evidence for the benefit of labetalol, nifedipine and methyldopa on maternal blood pressure but not enough evidence to recommend one agent over another and the committee therefore adopted the recommendation from the previous guideline which recommended labetalol first-line as it is specifically licensed for use in pregnancy, with nifedipine and methyldopa as alternatives. There was no evidence of adverse effects on the baby from these medicines, although the committee were aware from their clinical experience and knowledge that beta-blockers can lead to neonatal hypoglycaemia, and there was some evidence that labetalol may increase babies born small for gestational age, but there was uncertainty around this estimate. The committee also noted that in the comparison of intravenous labetalol and oral nifedipine, oral nifedipine led to a more rapid decrease in blood pressure (with no difference in neonatal outcomes); however, the optimal speed of reduction of blood pressure is unclear and this may not have been beneficial to the baby as a steep decrease in blood pressure may lead to a reduction in blood flow to the baby. There was also some evidence comparing intravenous hydralazine to labetalol and nifedipine but this was in the acute management of pre-eclampsia, and the committee agreed that this intravenous formulation was not appropriate to treat ongoing hypertension associated with pre-eclampsia during pregnancy and therefore they did not recommend its use.

The committee reviewed the other existing recommendations from the 2010 guideline on timing of birth, and agreed that there was no evidence to change the majority of these, although they updated the language and included a link to the NICE guideline on preterm labour and birth in reference to the use of maternal corticosteroids and magnesium sulfate. However, the committee expanded the recommendation from the previous guideline about

the indications to offer planned early birth, and based these on the recommendations from the International Society for the Study of Hypertension in Pregnancy (Brown 2018) which were used by members of the committee in clinical practice, and are widely used in the UK.

There was some evidence that planned birth compared to expectant birth reduced the number of babies who were born small for gestational age (in those less than 34 weeks), increased birthweight (in those more than 34 weeks), may reduce placental abruption (but there was uncertainty around this estimate) and reduced neonatal admissions (in high income settings), with no evidence of any adverse effects.

The committee discussed the sub-analyses that had been carried out for low/middle income settings versus high income settings, but noted that these compared low/middle income versus high income countries, and not different settings within the UK as they had hoped, and so they did not use these sub-analyses to inform any of the recommendations.

In addition, the previous guideline had recommended that pre-eclampsia could be managed conservatively (that is, without same-day birth) in women with severe hypertension only until 34 weeks. The committee were aware that this cut-off date was based on very little evidence and that a research recommendation had been made. Based on the data from the HYPITAT II study the committee therefore agreed that, in the absence of any of the 'red flag' features they had already identified as indications for early birth this should be changed from 34 to 37 weeks. The main benefit of prolonging pregnancy until 37 weeks is to improve the outcome for the baby, although as in the previous recommendations the committee retained the caveat that if there was severe hypertension, abnormal biochemical or haematological investigations, clinical signs, or fetal compromise, planned early birth should be offered. As in the previous guideline the committee recommended that the decision to offer planned early birth would depend on the woman and baby's condition, risk factors and availability of neonatal care.

Cost effectiveness and resource use

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

The recommendations aimed to standardise management and largely reflect current best clinical practice and so should not have a significant resource impact. However, at present, there is some variation in whether pre-eclampsia is managed on an inpatient or outpatient basis. The recommendations could therefore increase or decrease the number of women who will be admitted, depending on current practice. Thus, there is the potential for a resource impact at the local level but it is thought that inpatient management is more common than outpatient management overall and therefore an overall reduction in the number if women admitted is more likely.

The recommendation to offer admission with a fullPIERS risk of 30% or more was partly based on a cost-effectiveness model conducted for question 3 (see evidence review C). There was uncertainty around the results but they suggest that a strategy to offer admission with a fullPIERS risk of 30% or more may be the most cost-effective strategy overall. Furthermore, a strategy to offer admission with a fullPIERS risk of 30% or more was very likely to be cost effective compared to managing everyone on an inpatient basis, which is thought to be the most common strategy in current practice.

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 pre-eclampsia 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 aware of a forthcoming study which may provide further evidence on timing of birth: the PHOENIX trial is investigating the optimal timing of birth in women with late preterm pre-eclampsia (between 34^{+0} and 36^{+6} weeks' gestation).

References

Aali 2002

Aali, Bibi Shahnaz, and Samira Shahabi Nejad. "Nifedipine or hydralazine as a first-line agent to control hypertension in severe preeclampsia." Acta obstetricia et gynecologica Scandinavica 81.1 (2002): 25-30.

Broekhuijsen 2015

Broekhuijsen K, van Baaren GJ, Van Pampus MG, Ganzevoort W, Sikkema JM, Woiski MD, Oudijk MA, Bloemenkamp KW, Scheepers HC, Bremer HA, Rijnders RJ. Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of gestation (HYPITAT-II): an open-label, randomised controlled trial. The Lancet. 2015 Jun 20;385(9986):2492-501.

Brown 2018

Brown, M., Magee, L., Kenny, L., Karumanchi, A., McCarthy, F., Saito, S., Hall, D., Warren, C., Adoyi, G., Ishaku, S., on behalf of the International Society for the Study of Hypertension in Pregnancy (ISSHP). The hypertensive disorders of pregnancy: ISSHP classification, diagnosis and management recommendations for international practice. Pregnancy Hypertension 2018; 13:291-310.

Churchill 2013

Churchill D, Duley L. Interventionist versus expectant care for severe pre-eclampsia before term. Cochrane Database Syst Rev. 2002;3(3).

Dhananjaya 2015

Dhananjaya BS, Jamuna R. Oral nifedipine versus intravenous labetalol in hypertensive emergencies of pregnancy: a randomised trial. Research Journal of Pharmaceutical Biological and Chemical Sciences. 2015 Mar 1;6(2):1673-81.

Elatrous 2002

Elatrous, S., Nouira, S., Besbes, L. O., Marghli, S., Boussarssar, M., Sakkouhi, M., & Abroug, F. (2002). Short-term treatment of severe hypertension of pregnancy: prospective comparison of nicardipine and labetalol. Intensive Care Medicine, 28(9), 1281-1286.

Ehassan 2002

Elhassan, E. M., et al. "Methyldopa versus no drug treatment in the management of mild pre-eclampsia." East African Medical Journal 79.4 (2002): 172-175.

Fenakel 1991

Fenakel, K., Fenakel, G., Appelman, Z. V. I., Lurie, S., Katz, Z. V. I., & Shoham, Z. E. E. V. (1991). Nifedipine in the treatment of severe preeclampsia. Obstet Gynecol, 77(3), 331-337.

Harper 1991

Harper, A. N. N., & Murnaghan, G. A. (1991). Maternal and fetal haemodynamics in hypertensive pregnancies during maternal treatment with intravenous hydralazine or labetalol. BJOG: An International Journal of Obstetrics & Gynaecology, 98(5), 453-459

Koopmans 2009

Koopmans, C. M., Bijlenga, D., Groen, H., Vijgen, S. M., Aarnoudse, J. G., Bekedam, D. J. & Drogtrop, A. P. (2009). Induction of labour versus expectant monitoring for gestational hypertension or mild pre-eclampsia after 36 weeks' gestation (HYPITAT): a multicentre, open-label randomised controlled trial. The Lancet, 374(9694), 979-988.

Kwawukume 1995

Kwawukume, E. Y., & Ghosh, T. S. (1995). Oral nifedipine therapy in the management of severe preeclampsia. International Journal of Gynecology & Obstetrics, 49(3), 265-269.

Martins-Costa 1992

Martins-Costa, S., Ramos, J. G., Barros, E., Bruno, R. M., Costa, C. A., & Goldin, J. R. (1992). Randomized, controlled trial of hydralazine versos nifedipine in preeclamptic women with acute hypertension. Clinical and Experimental Hypertension. Part B: Hypertension in Pregnancy, 11(1), 25-44.

Owens 2014

Owens, M. Y., Thigpen, B., Parrish, M. R., Keiser, S. D., Sawardecker, S., Wallace, K., & Martin, J. J. (2014). Management of preeclampsia when diagnosed between 34-37 weeks gestation: deliver now or deliberate until 37 weeks?.Journal of the Mississippi State Medical Association, 55(7), 208-211.

Rezaei 2011

Rezaei, Z., Sharbaf, F. R., Pourmojieb, M., Youefzadeh-Fard, Y., Motevalian, M., Khazaeipour, Z., & Esmaeili, S. (2011). Comparison of the efficacy of nifedipine and hydralazine in hypertensive crisis in pregnancy. Acta Medica Iranica, 49(11), 701.

Schoen 2017

Schoen, Corina N., et al. Outpatient versus inpatient management for superimposed preeclampsia without severe features: a retrospective, multicenter study. The Journal of Maternal-Fetal & Neonatal Medicine (2017): 1-7.

Sibai 1987

Sibai BM, Gonzalez AR, Mabie WC, Moretti M. A comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term. Obstetrics and Gynecology. 1987 Sep;70(3 Pt 1):323-7.

Sibai 1992

Sibai, Baha M., et al. "A randomized prospective comparison of nifedipine and bedrest versus bed rest alone in the management of preeclampsia remote from term." American Journal of Obstetrics and Gynecology 167.4 (1992): 879-884.

Subhedar 2016

Subhedar V, Inamdar S, Hariharan C, Subhedar S. Comparison of efficacy of labetalol and methyldopa in patients with pregnancy-induced hypertension. International Journal of Reproduction, Contraception, Obstetrics and Gynecology. 2016 Dec 8;2(1):27-34.

Vermillion 1999

Vermillion, S. T., Scardo, J. A., Newman, R. B., & Chauhan, S. P. (1999). A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy. American Journal of Obstetrics & Gynecology, 181(4), 858-861.

Vigil-De Gracia 2006

Vigil-De Gracia, P., Lasso, M., Ruiz, E., Vega-Malek, J. C., de Mena, F. T., & López, J. C. (2006). Severe hypertension in pregnancy: Hydralazine or labetalol: A randomized clinical trial. European Journal of Obstetrics and Gynecology and Reproductive Biology, 128(1), 157-162.

Vigil-De Gracia 2013

Vigil-De Gracia, P., Tejada, O. R., Miñaca, A. C., Tellez, G., Chon, V. Y., Herrarte, E., & Ludmir, J. (2013). Expectant management of severe preeclampsia remote from term: the MEXPRE Latin Study, a randomized, multicenter clinical trial. American Journal of Obstetrics & Gynecology, 209(5), 425-e1.

Appendices

Appendix A – Review protocol

Table 3: Review protocol

Field (based on PRISMA-P)	Content
Key area in the scope	Management of pregnancy with pre-eclampsia
Draft review question from previous guideline (to be deleted in the final version)	What interventions are effective in improving outcomes for women and infants in women with pre-eclampsia?
Actual review question	What interventions are effective at improving outcomes for women and infants in women with pre-eclampsia?
Type of review question	Intervention
Objective of the review	To update the recommendations in CG107 (2010) for the treatment of pre-eclampsia – surveillance has identified that that nicardipine is now licensed for the indication of severe pre-eclampsia
Eligibility criteria – population/disease/condition/issue/domain	Pregnant women with pre-eclampsia
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Acute management: • Labetalol • Hydralazine • Nifedipine • Nicardipine • Timing of birth

Field (based on PRISMA-P)	Content
	• Magnesium Non-acute management: • Methyldopa • Labetalol • Nifedipine • Timing of birth • Magnesium • Statins • Place of management (inpatient vs. outpatient) • Abdominal decompression • Tight management (e.g. target = 85mmHg) • Less tight management (e.g. target = 100 mmHg)
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: Critical outcomes: • Perinatal mortality o Stillbirth (include if reported as part of perinatal mortality) o Neonatal death up to 7 days (include if reported as part of perinatal mortality) • Small-for-gestational-age (BW<10th centile) • Important outcomes:

Field (based on PRISMA-P)	Content

	• Birth weight
	• Gestational age at birth
	• 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 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 (e.g. deaf)
	  - Severe visual impairment (e.g. blind)
	Outcomes for women:
	Critical outcome:
	• Blood pressure control
	  ○ Severe hypertension
	• Important outcomes:
	• Eclampsia
	• HELLP (hemolysis, elevated liver enzymes, low platelet count)
	• Placental abruption

Field (based on PRISMA-P)	Content
	• 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 • Cohort studies –only when no RCT data (anticipated for place of management) 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)
Proposed stratified, sensitivity/sub-group analysis, or meta-regression	Stratify for mild/moderate/severe hypertension Stratify for gestational age: ○ <34/40 ○ 34+0 to 36+6 ○ ≥37+0
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. STAR will be used bibliographies/citations, text mining, and study sifting, data extraction and quality assessment/critical appraisal.

Field (based on PRISMA-P)	Content
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. See appendix B for full strategies.
Identify if an update	This is an update. Studies meeting the current protocol criteria and previously included in the 2010 guideline (CG107) will be included in this update.
Author contacts	Developer: National Guideline Alliance NGA-enquiries@RCOG.org.uk

Field (based on PRISMA-P)	Content
Highlight if amendment to previous protocol	Items added in this protocol: • As part of the interventions: timing of birth, magnesium, statins, place of management (inpatient versus outpatient), tight versus less tight management and abdominal decompression • As part of the outcomes: neonatal death, gestational age at birth, severe hypertension, and placental abruption • Items removed from the previous protocol: • As part of the interventions (for the mother): prazosine, atenolol, oxypranolol, amlodipine, thiazide, bendrofluazide, aspirin, dipyridamole, ACE inhibitors, angiotensin receptor blockers. • As part of the interventions (for the baby): betamethasone, dexamethasone, hydrocortisone, and prednisone • As part of the outcomes (for the mother): severe maternal complications, such as stroke, cerebral haemorrhage, admission to HDU (High dependency unit)/ITU (Intensive care unit)). • As part of the outcomes (for the baby): preterm birth (< 34 weeks), neonatal hypoglycaemia, preterm birth, and breastfeeding. • The population and comparisons are the same as in the 2010 protocol for this review question.
Search strategy – for one database	For details please see appendix B of the full guideline
Data collection process – forms/duplicate	Studies included in the previous guideline (CG107) that meet the inclusion criteria of this protocol will be re-extracted in a standardised evidence table and published in appendix D (clinical evidence tables) or H (economic evidence tables).

Field (based on PRISMA-P)	Content
Data items – define all variables to be collected	For clinical evidence tables (appendix D), the following data items will be collected: full reference, study ID, type of study, objective country/ies where the study was carried out, inclusion criteria, exclusion criteria, methods, results and limitations.
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • Systematic review and Meta-analyses – AMSTAR • Randomised controlled trials – Cochrane risk of bias tool • Cohort studies – Newcastle-Ottowa scale • 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 in the full guideline.

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

Review question search strategies

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

Date of last search: 07/02/18

#	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	PRE-ECLAMPSIA/
35	HELLP SYNDROME/
36	preeclamp$.ti,ab.
37	pre eclamp$.ti,ab.
38	HELLP.ti,ab.
39	tox?emi$.ti,ab.
40	or/34-39
41	LABETALOL/
42	labetalol.mp.
43	exp HYDRALAZINE/
44	hydralazine.mp.
45	dihydralazine.mp.
46	NIFEDIPINE/
47	nifedipine.mp.
48	NICARDIPINE/
49	nicardipine.mp.
50	MAGNESIUM/
51	MAGNESIUM SULFATE/
52	magnesium.mp.
53	METHYLDOPA/
54	methyldopa.mp.
55	exp HYDROXYMETHYLGLUTARYL-COA REDUCTASE INHIBITORS/

#	Searches
56	Hydroxymethylglutaryl-CoA Reductase Inhibitor?.mp.
57	HMG-CoA reductase inhibitor?.mp.
58	(statin or statins).mp.
59	(Atorvastatin Calcium or Lovastatin or Meglutol or Pravastatin or Rosuvastatin Calcium or Simvastatin).mp.
60	WATCHFUL WAITING/
61	((time or timing) adj3 deliver$).ti,ab.
62	((early or delay$) adj3 deliver$).ti,ab.
63	((early or delay$) adj3 birth$).ti,ab.
64	((conservative$ or expectant$ or active$) adj2 manag$).ti,ab.
65	HOSPITALIZATION/
66	PATIENT ADMISSION/
67	PATIENT READMISSION/
68	INPATIENTS/
69	hospitali$.ti.
70	hospitali$.ab. /freq=2
71	((hospital? or department? or unit? or patient?) adj3 (admission? or admit$ or readmi$)).ti.
72	((hospital? or department? or unit? or patient?) adj3 (admission? or admit$ or readmi$)).ab. /freq=2
73	inpatient?.ti,ab.
74	(place? adj3 manag$).ti,ab.
75	(place? adj3 care).ti,ab.
76	LOWER BODY NEGATIVE PRESSURE/
77	lower body negative pressure.ti,ab.
78	LBNP.ti,ab.
79	(abdom$ adj3 decompress$).ti,ab.
80	BLOOD PRESSURE/ and (Optimal$ or Target? or Goal?).ti,ab.
81	((Optimal$ or Target? or Goal? or Aim$) adj5 blood adj3 pressure?).ti,ab.
82	or/41-81
83	40 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.
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; Appendix B – Literature search strategies

Date of last search: 07/02/18

#	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.

#	Searches
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	PREECLAMPSIA/
37	HELLP SYNDROME/
38	preeclamp$.ti,ab.
39	pre eclamp$.ti,ab.
40	HELLP.ti,ab.
41	tox?emi$.ti,ab.
42	or/36-41
43	*LABETALOL/
44	labetalol.mp.
45	*HYDRALAZINE/
46	hydralazine.mp.
47	*DIHYDRALAZINE/
48	dihydralazine.mp.
49	*NIFEDIPINE/
50	nifedipine.mp.
51	*NICARDIPINE/
52	nicardipine.mp.
53	*MAGNESIUM/
54	*MAGNESIUM SULFATE/
55	magnesium.mp.
56	*METHYLDOPA/
57	methyldopa.mp.
58	exp *HYDROXYMETHYLGLUTARYL COENZYME A REDUCTASE INHIBITOR/
59	Hydroxymethylglutaryl-CoA Reductase Inhibitor?.mp.
60	Hydroxymethylglutaryl Coenzyme A Reductase Inhibitor?.mp.
61	HMG-CoA reductase inhibitor?.mp.
62	(statin or statins).mp.
63	(Atorvastatin Calcium or Lovastatin or Meglutol or Pravastatin or Rosuvastatin Calcium or Simvastatin).mp.
64	WATCHFUL WAITING/
65	((early or delay$) adj3 deliver$).ti,ab.
66	((early or delay$) adj3 birth$).ti,ab.
67	((conservative$ or expectant$ or active$) adj2 manag$).ti.
68	((conservative$ or expectant$ or active$) adj2 manag$).ab. /freq=2
69	*HOSPITALIZATION/
70	*HOSPITAL ADMISSION/
71	*HOSPITAL READMISSION/
72	*HOSPITAL PATIENT/
73	hospitali$.ti.
74	hospitali$.ab. /freq=2
75	((hospital? or department? or unit? or patient?) adj3 (admission? or admit$ or readmi$)).ti.
76	((hospital? or department? or unit? or patient?) adj3 (admission? or admit$ or readmi$)).ab. /freq=2
77	inpatient?.ti,ab.

#	Searches
78	(place? adj3 manag$).ti,ab.
79	(place? adj3 care).ti,ab.
80	*LOWER BODY NEGATIVE PRESSURE/
81	ABDOMINAL DECOMPRESSION/
82	lower body negative pressure.ti,ab.
83	LBNP.ti,ab.
84	(abdom$ adj3 decompress$).ti,ab.
85	*BLOOD PRESSURE/ and (Optimal$ or Target? or Goal?).ti,ab.
86	((Optimal$ or Target? or Goal? or Aim$) adj5 blood adj3 pressure?).ti,ab.
87	or/43-86
88	42 and 87
89	limit 88 to english language
90	letter.pt. or LETTER/
91	note.pt.
92	editorial.pt.
93	CASE REPORT/ or CASE STUDY/
94	(letter or comment*).ti.
95	or/90-94
96	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
97	95 not 96
98	ANIMAL/ not HUMAN/
99	NONHUMAN/
100	exp ANIMAL EXPERIMENT/
101	exp EXPERIMENTAL ANIMAL/
102	ANIMAL MODEL/
103	exp RODENT/
104	(rat or rats or mouse or mice).ti.
105	or/97-104
106	89 not 105
107	11 and 106
108	21 and 106
109	35 and 106
110	or/107-109

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: 07/02/18

#	Searches
1	MeSH descriptor: [PRE-ECLAMPSIA] this term only
2	MeSH descriptor: [HELLP SYNDROME] this term only
3	preeclamp*.ti,ab.
4	pre eclamp*.ti,ab.
5	HELLP.ti,ab.
6	tox?emi*.ti,ab.
7	#1 or #2 or #3 or #4 or #5 or #6
8	MeSH descriptor: [LABETALOL] this term only
9	labetalol.mp.
10	MeSH descriptor: [HYDRALAZINE] explode all trees
11	hydralazine.mp.
12	dihydralazine.mp.
13	MeSH descriptor: [NIFEDIPINE] this term only
14	nifedipine.mp.
15	MeSH descriptor: [NICARDIPINE] this term only
16	nicardipine.mp.
17	MeSH descriptor: [MAGNESIUM] this term only
18	MeSH descriptor: [MAGNESIUM SULFATE] this term only
19	magnesium.mp.
20	MeSH descriptor: [METHYLDOPA] this term only
21	methyldopa.mp.
22	MeSH descriptor: [HYDROXYMETHYLGLUTARYL-COA REDUCTASE INHIBITORS] explode all trees
23	Hydroxymethylglutaryl-CoA Reductase Inhibitor?.mp.
24	HMG-CoA reductase inhibitor?.mp.

#	Searches
25	(statin or statins).mp.
26	(Atorvastatin Calcium or Lovastatin or Meglutol or Pravastatin or Rosuvastatin Calcium or Simvastatin).mp.
27	MeSH descriptor: [WATCHFUL WAITING] this term only
28	((time or timing) near] this term only3 deliver*).ti,ab.
29	((early or delay*) near] this term only3 deliver*).ti,ab.
30	((early or delay*) near] this term only3 birth*).ti,ab.
31	((conservative* or expectant* or active*) near] this term only2 manag*).ti,ab.
32	MeSH descriptor: [HOSPITALIZATION] this term only
33	MeSH descriptor: [PATIENT ADMISSION] this term only
34	MeSH descriptor: [PATIENT READMISSION] this term only
35	MeSH descriptor: [INPATIENTS] this term only
36	hospitali*.ti,ab.
37	((hospital? or department? or unit? or patient?) near] this term only3 (admission? or admit* or readmi*)).ti,ab.
38	inpatient?.ti,ab.
39	(place? near] this term only3 manag*).ti,ab.
40	(place? near] this term only3 care).ti,ab.
41	MeSH descriptor: [LOWER BODY NEGATIVE PRESSURE] this term only
42	lower body negative pressure.ti,ab.
43	LBNP.ti,ab.
44	(abdom* near] this term only3 decompress*).ti,ab.
45	"blood pressure?" .ti,ab.
46	#8 or #9 or #10 or #11 or #12 or #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
47	#7 and #46

Health economics search strategies

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

Date of last search: 07/02/18

#	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	PRE-ECLAMPSIA/
23	HELLP SYNDROME/
24	preeclamp$.ti,ab.
25	pre eclamp$.ti,ab.
26	HELLP.ti,ab.
27	tox?emi$.ti,ab.
28	or/22-27
29	LABETALOL/
30	labetalol.mp.
31	exp HYDRALAZINE/

#	Searches
32	hydralazine.mp.
33	dihydralazine.mp.
34	NIFEDIPINE/
35	nifedipine.mp.
36	NICARDIPINE/
37	nicardipine.mp.
38	MAGNESIUM/
39	MAGNESIUM SULFATE/
40	magnesium.mp.
41	METHYLDOPA/
42	methyldopa.mp.
43	exp HYDROXYMETHYLGLUTARYL-COA REDUCTASE INHIBITORS/
44	Hydroxymethylglutaryl-CoA Reductase Inhibitor?.mp.
45	HMG-CoA reductase inhibitor?.mp.
46	(statin or statins).mp.
47	(Atorvastatin Calcium or Lovastatin or Meglutol or Pravastatin or Rosuvastatin Calcium or Simvastatin).mp.
48	WATCHFUL WAITING/
49	((time or timing) adj3 deliver$).ti,ab.
50	((early or delay$) adj3 deliver$).ti,ab.
51	((early or delay$) adj3 birth$).ti,ab.
52	((conservative$ or expectant$ or active$) adj2 manag$).ti,ab.
53	HOSPITALIZATION/
54	PATIENT ADMISSION/
55	PATIENT READMISSION/
56	INPATIENTS/
57	hospitali$.ti.
58	hospitali$.ab. /freq=2
59	((hospital? or department? or unit? or patient?) adj3 (admission? or admit$ or readmi$)).ti.
60	((hospital? or department? or unit? or patient?) adj3 (admission? or admit$ or readmi$)).ab. /freq=2
61	inpatient?.ti,ab.
62	(place? adj3 manag$).ti,ab.
63	(place? adj3 care).ti,ab.
64	LOWER BODY NEGATIVE PRESSURE/
65	lower body negative pressure.ti,ab.
66	LBNP.ti,ab.
67	(abdom$ adj3 decompress$).ti,ab.
68	BLOOD PRESSURE/ and (Optimal$ or Target? or Goal?).ti,ab.
69	((Optimal$ or Target? or Goal? or Aim$) adj5 blood adj3 pressure?).ti,ab.
70	or/29-69
71	28 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/
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: 07/02/18

#	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	PREECLAMPSIA/
19	HELLP SYNDROME/
20	preeclamp$.ti,ab.
21	pre eclamp$.ti,ab.
22	HELLP.ti,ab.
23	tox?emi$.ti,ab.
24	or/18-23
25	*LABETALOL/
26	labetalol.mp.
27	*HYDRALAZINE/
28	hydralazine.mp.
29	*DIHYDRALAZINE/
30	dihydralazine.mp.
31	*NIFEDIPINE/
32	nifedipine.mp.
33	*NICARDIPINE/
34	nicardipine.mp.
35	*MAGNESIUM/
36	*MAGNESIUM SULFATE/
37	magnesium.mp.
38	*METHYLDOPA/
39	methyldopa.mp.
40	exp *HYDROXYMETHYLGLUTARYL COENZYME A REDUCTASE INHIBITOR/
41	Hydroxymethylglutaryl-CoA Reductase Inhibitor?.mp.
42	Hydroxymethylglutaryl Coenzyme A Reductase Inhibitor?.mp.
43	HMG-CoA reductase inhibitor?.mp.
44	(statin or statins).mp.
45	(Atorvastatin Calcium or Lovastatin or Meglutol or Pravastatin or Rosuvastatin Calcium or Simvastatin).mp.
46	WATCHFUL WAITING/
47	((early or delay$) adj3 deliver$).ti,ab.
48	((early or delay$) adj3 birth$).ti,ab.
49	((conservative$ or expectant$ or active$) adj2 manag$).ti.
50	((conservative$ or expectant$ or active$) adj2 manag$).ab. /freq=2
51	*HOSPITALIZATION/
52	*HOSPITAL ADMISSION/
53	*HOSPITAL READMISSION/
54	*HOSPITAL PATIENT/
55	hospitali$.ti.
56	hospitali$.ab. /freq=2
57	((hospital? or department? or unit? or patient?) adj3 (admission? or admit$ or readmi$)).ti.
58	((hospital? or department? or unit? or patient?) adj3 (admission? or admit$ or readmi$)).ab. /freq=2
59	inpatient?.ti,ab.
60	(place? adj3 manag$).ti,ab.
61	(place? adj3 care).ti,ab.
62	*LOWER BODY NEGATIVE PRESSURE/
63	ABDOMINAL DECOMPRESSION/
64	lower body negative pressure.ti,ab.
65	LBNP.ti,ab.
66	(abdom$ adj3 decompress$).ti,ab.
67	*BLOOD PRESSURE/ and (Optimal$ or Target? or Goal?).ti,ab.
68	((Optimal$ or Target? or Goal? or Aim$) adj5 blood adj3 pressure?).ti,ab.
69	or/25-68

#	Searches
70	24 and 69
71	limit 70 to english language
72	letter.pt. or LETTER/
73	note.pt.
74	editorial.pt.
75	CASE REPORT/ or CASE STUDY/
76	(letter or comment*).ti.
77	or/72-76
78	RANDOMIZED CONTROLLED TRIAL/ or random*.ti,ab.
79	77 not 78
80	ANIMAL/ not HUMAN/
81	NONHUMAN/
82	exp ANIMAL EXPERIMENT/
83	exp EXPERIMENTAL ANIMAL/
84	ANIMAL MODEL/
85	exp RODENT/
86	(rat or rats or mouse or mice).ti.
87	or/79-86
88	71 not 87
89	17 and 88

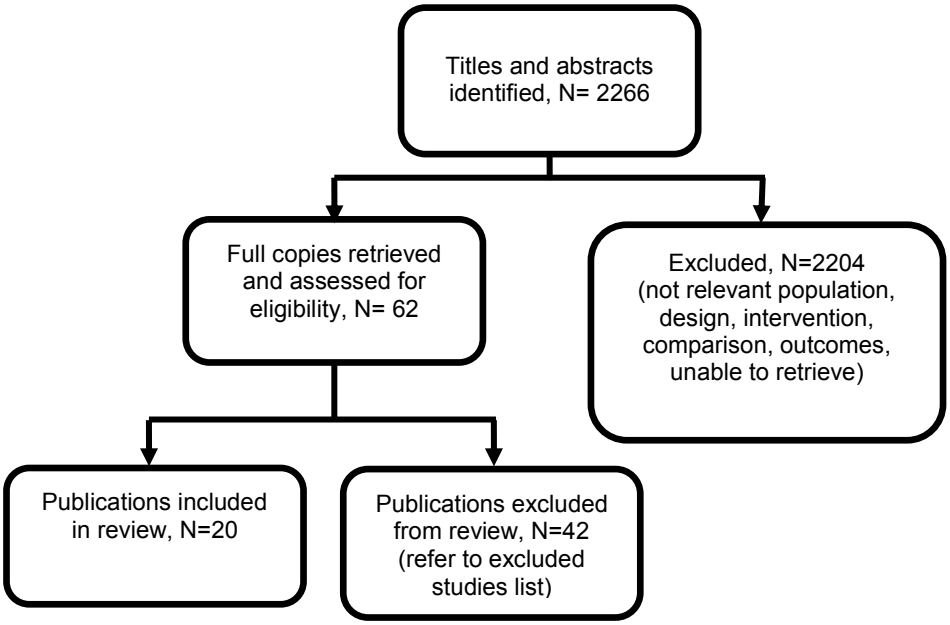
Databases: Cochrane Central Register of Controlled Trials; Health Technology Assessment; and NHS Economic Evaluation Database

Date of last search: 07/02/18

#	Searches
1	MeSH descriptor: [PRE-ECLAMPSIA] this term only
2	MeSH descriptor: [HELLP SYNDROME] this term only
3	preeclamp*.ti,ab.
4	pre eclamp*.ti,ab.
5	HELLP.ti,ab.
6	tox?emi*.ti,ab.
7	#1 or #2 or #3 or #4 or #5 or #6
8	MeSH descriptor: [LABETALOL] this term only
9	labetalol.mp.
10	MeSH descriptor: [HYDRALAZINE] explode all trees
11	hydralazine.mp.
12	dihydralazine.mp.
13	MeSH descriptor: [NIFEDIPINE] this term only
14	nifedipine.mp.
15	MeSH descriptor: [NICARDIPINE] this term only
16	nicardipine.mp.
17	MeSH descriptor: [MAGNESIUM] this term only
18	MeSH descriptor: [MAGNESIUM SULFATE] this term only
19	magnesium.mp.
20	MeSH descriptor: [METHYLDOPA] this term only
21	methyldopa.mp.
22	MeSH descriptor: [HYDROXYMETHYLGLUTARYL-COA REDUCTASE INHIBITORS] explode all trees
23	Hydroxymethylglutaryl-CoA Reductase Inhibitor?.mp.
24	HMG-CoA reductase inhibitor?.mp.
25	(statin or statins).mp.
26	(Atorvastatin Calcium or Lovastatin or Meglutol or Pravastatin or Rosuvastatin Calcium or Simvastatin).mp.
27	MeSH descriptor: [WATCHFUL WAITING] this term only
28	((time or timing) near] this term only3 deliver*).ti,ab.
29	((early or delay*) near] this term only3 deliver*).ti,ab.
30	((early or delay*) near] this term only3 birth*).ti,ab.
31	((conservative* or expectant* or active*) near] this term only2 manag*).ti,ab.
32	MeSH descriptor: [HOSPITALIZATION] this term only
33	MeSH descriptor: [PATIENT ADMISSION] this term only
34	MeSH descriptor: [PATIENT READMISSION] this term only
35	MeSH descriptor: [INPATIENTS] this term only
36	hospitali*.ti,ab.
37	((hospital? or department? or unit? or patient?) near] this term only3 (admission? or admit* or readmi*)).ti,ab.
38	inpatient?.ti,ab.
39	(place? near] this term only3 manag*).ti,ab.

#	Searches
40	(place? near] this term only3 care).ti,ab.
41	MeSH descriptor: [LOWER BODY NEGATIVE PRESSURE] this term only
42	lower body negative pressure.ti,ab.
43	LBNP.ti,ab.
44	(abdom* near] this term only3 decompress*).ti,ab.
45	"blood pressure?" .ti,ab.
46	#8 or #9 or #10 or #11 or #12 or #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
47	#7 and #46

Appendix C – Clinical evidence study selection



Appendix D – Clinical evidence tables

Table 4: Clinical evidance tables

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

Aali, Bs, Nejad, Ss, Nifedipine or hydralazine as a first-line agent to control hypertension in severe preeclampsia, Acta Obstetricia et Gynecologica Scandinavica, 81, 25-30, 2002

Ref Id

775557

Country/ies where the study was carried out

Iran

Study type

RCT

Aim of the study</td>
<td>Sample size

126 (n= 61 in the hydralazine group and n= 65 in the nifedipine group)

Characteristics
<table>
<tr><th></th><th>Hydralazine (n =61)</th><th>Nifedipine (n =65)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>26.8 (6.4)</td><td>27.1 (6.4)</td></tr>
<tr><td>No. with severe pre-eclampsiaa n (%)</td><td>61 (100%)</td><td>65 (100%)</td></tr>
<tr><td>Gestational age at treatment, weeks (mean, SD)</td><td>37.7 (8.3)</td><td>37 (3.3)</td></tr>
</table>
[a] Definition for severe pre-eclampsia was as defined by the American College of Obstetricians and Gynaecologists

Inclusion criteria</td>
<td>Interventions

Hydralazine 5mg IV with further doses of 10mg at intervals according to the protocol recommended by ACOG. Doses were repeated if target blood pressure was not achieved (dBP between 90 and 100 mmHg, and not lower than 90 mmHg)

Nifedipine 8mg (4 drops) sl. Doses were repeated if target blood pressure was not achieved (dBP between 90 and 100 mmHg, and not lower than 90 mmHg)</td>
<td>Details

Consecutive treatment: all patients received IV magnesium sulfate (loading dose 4 g, maintenance dose 1-2 g/hr), which was stopped 24 hours after birth.

Women were randomised using the block randomisation technique. Women were allocated using consecutive numbered, opaque, sealed envelopes. Single blind trial.

Unclear whether a sample size calculation was performed.

Follow-up time was not reported.</td>
<td>Results

Minutes needed to achieve effective control of blood pressure (dBP between 90 and 100 mmHg, and not lower than 90 mmHg), mean (SD)

Hydralazine 10.4 (3.8)

Nifedipine 9.6 (3.4)</td>
<td>Limitations

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

Random sequence generation: unclear risk (no method of randomisation was reported)

Allocation concealment: low risk (women were allocated with "consecutive, numbered, opaque, sealed envelopes"

Blinding of participants and personnel: high risk (single blind, only outcome assessor blinded)

Blinding of outcome assessment: low risk</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>To determine the most effective treatment for the control of severe pre-eclampsia - acute treatment

Study dates

April to December 1999

Source of funding

Kerman Medical University.</td>
<td>BP ≥ 160/110; met the criteria of severe pre-eclampsia according to the American College of Obstetrics & Gynaecology

Exclusion criteria

Previous history of heart failure; history of treatment with an antihypertensive agent during the course of the current pregnancy.</td>
<td></td>
<td></td>
<td></td>
<td>Blinding (performance bias and detection bias): high risk (see details above)

Incomplete outcome data: low risk (no drop out was reported)

Selective reporting: unclear risk (study protocol does not appear to have been registered)

Other information</td>
</tr>
<tr>
<td>Full citation

Broekhuijsen, Kim, van Baaren, Gert-Jan, van Pampus, Maria G., Ganzevoort, Wessel, Sikkema, J. Marko, Woiski, Mallory D., Oudijk, Martijn A., Bloemenkamp, Kitty W. M., Scheepers, Hubertina C. J., Bremer, Henk A., Rijnders, Robbert J. P., van Loon, Aren J., Perquin,</td>
<td>Sample size

N= 423 (n=211 randomised to immediate birth and n=212 randomised to expectant monitoring)*

*The original manuscript included n=703 women, but a subgroup of women with pre-eclampsia and superimposed pre-eclampsia have been included for the purposes of this review

Characteristics of the total sample*
<table>
<tr><td></td><td>Outpatient management (n =352)</td><td>Inpatient management (n =351)</td></tr>
<tr><td>Age, years (mean, SD)</td><td>30.4 (5.3)</td><td>30.4 (5.2)</td></tr>
</table>
</td>
<td>Interventions

Immediate birth: labour was induced by ammniotomy followed by augmentation with oxytocin if needed. For those with contraindications for vaginal deliveries, a c-section was planned.

Expectant management: women were monitored as outpatients. Monitoring was done according to local protocol.</td>
<td>Details

Randomisation was performed in a 1:1 ratio by block randomisation with a web-based application system. Open-label trial.

Sample size calculations indicated that 680 women were needed</td>
<td>Results

Maternal outcomes:

Eclampsia*

Immediate birth:0/211

Expectant management:1/212

HELLP*

Immediate birth:1/211

Expectant management:4/212

*A subgroup of women with pre-eclampsia and</td>
<td>Limitations

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

Random sequence generation: low risk (randomisation was performed in a 1:1 ratio by block randomisation with a web-based application system)

Allocation concealment: low risk</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Denise A. M., Sporken, Jan M. J., Papatsonis, Dimitri N. M., van Huizen, Marloes E., Vredevoogd, Corla B., Brons, Jozien T. J., Kaplan, Mesrure, van Kaam, Anton H., Groen, Henk, Porath, Martina M., van den Berg, Paul P., Mol, Ben W. J., Franssen, Maureen T. M., Langenveld, Josje, Hypitat-Ii study group, Ganzevoort W, van der Akker E. S. Fong C. B. Hummel P. Muller M. A. Bax C. Hermsen B. B. Hemelaar M. Kleiverda G. Doekhie B. Visser H. Pernet P. J. Mozes A. van Zandvoort H. van Beek E. Kwee A. Oudijk M. A. Huisjes A. J. Zanders E. H. Schuitemaker N. W. Deurlo K. Evers I. Bloemenkamp K. W. van Meir C. A.	<table><tr><td>Gestational hypertension[a]</td><td>92 (26)</td><td>90 (26)</td></tr><tr><td>Pre-eclampsia[b]</td><td>165 (47)</td><td>129 (45)</td></tr><tr><td>Deteriorating hypertension[c]</td><td>49 (14)</td><td>49 (14)</td></tr><tr><td>Superimposed pre-eclampsia[d]</td><td>46 (13)</td><td>53 (15)</td></tr><tr><td>Gestational age at study entry, weeks (median, IQR)</td><td>$35^{+6/7}$($35^{+0/7}$ - $36^{+3/7}$)</td><td>$35^{+5/7}$($35^{+0/7}$ - $36^{+2/7}$)</td></tr><tr><td>Parity (≥1)</td><td>142 (40)</td><td>145 (41)</td></tr></table> [a]Gestational hypertension: dBP ≥ 100 mmHG on at least 2 occasions 6h apart in women with no pre-existing hypertension [b]Pre-eclamspia: dBP≥ 90 mmHg on at least 2 occasions, 6h apart + proteinuria (spot protein:creation ratio ≥ 30 mg/mmol or at least 300 mg protein ina 24h protein collection) [c]Deteriorating pre-existing hypertension: need for new antihypertensive medication after 34 weeks gestational age in a person with pre-existing hypertension [d]Superimposed pre-ecla,soia:new onset proteinuria in those with pre-existing hypertension *The characteristics of the subgroup of women included for the purpose of this review (n=423 women with pre-elampsia and superimposed pre-eclampsia)			superimposed pre-eclampsia have been included	(allocation of women was concealed) **Blinding of participants and personnel:** high risk (open label) **Blinding of outcome assessment:** high risk (open label) **Blinding (performance bias and detection bias):** high risk (open label) **Incomplete outcome data:** low risk (drop-out<20% and difference between groups <20%) **Selective reporting:** low risk (protocol reported and all outcomes included) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Vredevoogd C. B. van Huizen M. E. van Unnik G. A. Porath M. M. van Oirschot C. M. Rijnders R. J. Scheepers L. C. Langenveld J. Langenveld J. Roumen F. Langenveld J. Wijnen E. J. Aardenburg R. Franssen M. T. van Loon A. J. Perquin D. Koops A. Bremer H. A. Papatsonis D. N. van Gemund N. Akerboom B. M. Smid-Koopman E. de Boer K. Woiski M. D. Sporken J. M. de Wit A. C. van Ginkel A. A. Verhagen T. E. Stigter R. H. Brons J. T. Sikkema J. M. Kaplan M., Immediate delivery versus expectant monitoring for hypertensive disorders of pregnancy between 34 and 37 weeks of	have not been reported, therefore characteristics of the total sample were reported **Inclusion criteria** Not reported **Exclusion criteria** sBP≥ 170 mmHg, severe proteinuria, oliguria, HELLP, pulmonary oedema, cyanosis, non-reassuring fetal condition, HIV, women with comorbidities, and women with ruptured membranes or other contraindications to prolong pregnancy. Multiple pregnancies and fetus in breech position were not excluded.				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
gestation (HYPITAT-II): an open-label, randomised controlled trial, Lancet (London, England), 385, 2492-501, 2015 **Ref Id** 864970 **Country/ies where the study was carried out** The Netherlands **Study type** RCT **Aim of the study** To assess the effect of expectant management as compared to immediate birth in women with pre-eclampsia **Study dates** 1st March 2009 to 21st February 2013 **Source of funding**					

<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>ZonMw</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Churchill,David, Duley,Lelia, Thornton,Jim G., Jones,Leanne, Interventionist versus expectant care for severe pre-eclampsia between 24 and 34 weeks' gestation, Cochrane Database of Systematic Reviews, -, 2013

Ref Id

272558

Country/ies where the study was carried out

Europe, Egypt, South Africa and US*

Study type

Cochrane systematic review

Aim of the study</td><td>Sample size

4 RCTs (n=425)

Characteristics

GRIT 2003*

<table><tr><th></th><th>Induction of labour

(n =273)</th><th>Expectant management

(n =274)</th></tr><tr><td>Age, years (median, IQR)</td><td>28 (24-33)</td><td>29 (25-33)</td></tr><tr><td>No. of women with hypertension (>140/90 mm Hg) n (%)</td><td>125 (46)</td><td>109 (40)</td></tr><tr><td>Number of women with proteinuria (>0.3 g/l) n (%)</td><td>57 (21)</td><td>51 (19)</td></tr><tr><td>Primiparous n (%)</td><td>154 (56)</td><td>156 (57)</td></tr></table></td><td>Interventions

GRIT 2003

Induction of labour: women gave birth within 48 hours to permit completion of a steroid course

Expectant management: birth was deferred until it could safely be delayed no longer

Mesbah 2003

Induction of labour: women were administered steroids and allowed 48 hours to lapse before an induction or c-section

Expectant management: women were administered steroids and then were managed conservatively with bed rest, observations and nifedipine to control their blood pressure. Indications for birth were imminent eclampsia, deteriorating renal function, spontaneous preterm labour, absent EDF, or a non-reassuring CTG, and reaching 34 weeks.

Odendaal 1990</td><td>Details

GRIT 2003*

No information was provided regarding concurrent treatment

Randomisation was performed using either an experimental internet randomisation programme; a paper-based number sequence with balanced blocked of 8-12, or a computer-generated sequence. Open label trial

Duration of follow-up was not reported

Whether a sample size calculation was performed was not reported

Mesbah 2003*</td><td>Results

GRIT 2003

Neonatal outcomes

Stillbirth

Induction of labour: 1/141

Expectant management: 5/121

Neonatal death up to 7 days

Induction of labour: 21/141

Expectant management: 15/121

Gestational age at birth, mean days (SD)

Induction of labour: 217 (17)

Expectant management: 223 (21)

Cerebral palsy</td><td>Limitations

Limitations Quality of the Cochrane SR*

Systematic review assessed using AMSTAR checklist. Total score:15/16

Limitations for each of the included studies assessed with the Cochrane Risk of Bias Tool

GRIT 2003

Random sequence generation: low risk (randomisation was performed using either an experimental internet randomisation programme; a paper-based number sequence with balanced blocked of 8-12, or a computer-generated sequence)

Allocation concealment: low risk (an individual</td></tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>To assess the risks and benefits of induction of labour as compared to expectant management in women with severe pre-eclampsia (acute management)

Study dates

Last search: February 2013

Source of funding

National Institute of Health Research (NIHR)</td>
<td>
<table>
<tr><td>Multiple pregnancy n (%)</td><td>22 (8)</td><td>17 (6)</td></tr>
</table>
Mesbah 2003*
<table>
<tr><th></th><th>Induction of labour

(n =15)</th><th>Expectant management

(n =15)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>25.6 (6.3)</td><td>23.7 (5.5)</td></tr>
<tr><td>No. with pre-eclampsia[a] n (%)</td><td>12 (80)</td><td>14 (93)</td></tr>
<tr><td>No. of women with chronic hypertension[b] n (%)</td><td>3 (20)</td><td>1 (7)</td></tr>
<tr><td>Proteinuria (gm/24)</td><td>3.4 (2.3)</td><td>2.7 (2.5)</td></tr>
<tr><td>Gestational age at entry between 28 to 30</td><td>6 (40)</td><td>7 (47)</td></tr>
<tr><td>Nulliparous</td><td>12 (80)</td><td>10 (679</td></tr>
<tr><td>sBP at entry</td><td>168 (11)</td><td>171 (10)</td></tr>
</table>
</td>
<td>Induction of labour: women were prepared for birth, either by C-section or induction depending on the obstetric condition (for example, C-section was done for babies weighting < 1000 g; in breech presentation or in women with unfavourable cervix). Magnesium sulphate was restarted when labour was induced and continue for 24 hours post birth.

Expectant management: women were managed with bed rest in the high-risk obstetric ward. BP was controlled with prazosin 3-20 mg/day. Bethamethasone was repeated weekly after the initial administration. Indications for birth were: uncontrollable BP; imminent eclampsia, abruption placentae, decline in renal function, and fetal death.

Sibai 1994

Induction of labour: 48 hours after the first dose of betamethasone, women were prepared for birth, either by birth or C-section depending on the obstetric circumstances.

Expectant management: women were managed in an</td>
<td>Odendaal 1990*

Concurrent treatment: Magnesium sulphate 4g IV and 10g IM, followed by 5g IM every 4 hours for at least 24 hours. Dihydralazine 6.25mg IV every 30 minutes if BP was ≥ 160/110 mmHg. Balanced electrolute solution was started at a rate of 80 ml/hour. After admission, betamethasone 12mg IM was repeated after 24 hours if it had not been administered previously.

Randomisation method was not reported

Duration of follow-up was not reported

Whether a sample size calculation was performed was not reported</td>
<td>Induction of labour: 7/141

Expectant management: 1/121

Severe hearing impairment (poor hearing/hearing aid)

Induction of labour: 2/141

Expectant management: 5/121

Impaired vision

Induction of labour: 5/141

Expectant management: 1/121

Maternal outcomes:

Mode of birth (c-section)

Induction of labour: 137/141

Expectant management: 107/121

Mesbah 2003

Neonatal outcomes</td>
<td>independent from the study organised allocation)

Blinding of participants and personnel: low risk (study not blinded as it is not possible, but this is unlikely to change the outcomes)

Blinding of outcome assessment: low risk (study not blinded as it is not possible, but this in unlikely to change the outcomes)

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

Incomplete outcome data: unclear risk (an individual patient data subset was reported for this study, this was extracted from the Cochrane review, whose authors requested the data. It is not possible to tell whether this data is incomplete)

Selective reporting: low risk (all expected outcomes appear to be reported)</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	dBP at entry: 110 (7); 112 (6) [a,b] Definition was not reported **Odendaal 1990*** Induction of labour (n =20); Expectant management (n = 18) Age, years (mean, SD): 23 (5); 23 (3) No. with pre-eclampsia[a] n (%): 20 (100); 18 (100) Number of women with proteinuria 3+, 4+: 17; 14 Primigravidas: 10; 10 sBP at entry: 159 (18); 159 (19) dBP at entry: 107 (8); 108 (11) [a]BP≥180/120 mmHg on 2 occasions at least 30 mins apart with 2+ of proteinuria on dipstick; BP 160/110 to 180/120 mmHg on 2 occasions at least 6 hours apart with 3+ of proteinuria, or BP≥ 140/90 mmHg with proteinuria and clinical signs of imminent eclampsia **Sibai 1994***	antenatal ward. BP was controlled with antihypertensive medication at the clinicians' discretion. Antihypertensives used were either oral labetalol (initial dose 200g every 8 hours up to 2400 mg/day [600 mg every 6 hours]) or nifedipine (initial dose was 10 mg every 6 hours up to a maximum dose of 120 mg/day [20 mg every 4 hours]).	**Sibai 1994*** Concurrent treatment: betamethasone 2 doses x 12 mg administered 24 hours apart; magnesium sulphate: loading dose of 6 mg over 20 minutes, followed by 2 mg/h as a maintenance dose Randomisation was performed by "computer-generated assignments" and treatment allocation was concealed using "consecutively numbered, sealed, opaque envelopes" Duration of follow-up was not reported Whether a sample size calculation was performed was not reported	**Stillbirth** Induction of labour: 0/15 Expectant management: 0/15 **Neonatal death up to 7 days** Induction of labour: 6/15 Expectant management: 4/15 **Small-for-gestational-age (BW<10th centile)** Induction of labour: 2/15 Expectant management: 9/15 **Gestational age at birth, mean days (SD)** Induction of labour: 213 (12) Expectant management: 217 (11) **Admission to neonatal unit**	**Other bias:** unclear risk (since a subset of patients was used, it if not clear whether this could have introduced additional bias) **Mesbah 2003** **Random sequence generation:** low risk ("random sequence generate by going through random number till we obtained 30 pairs of numbers from 01 to 30") **Allocation concealment:** low risk ("randomly assigned to one of two management groups by withdrawing the next envelope in a series of 30 consecutively numbered, sealed, opaque envelopes) **Blinding of participants and personnel:** unclear risk (no blinding was reported) **Blinding of outcome assessment:** unclear risk (no blinding was reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	<table><tr><td></td><td>Induction of labour (n =49)</td><td>Expectant management (n = 46)</td></tr><tr><td>Age, years (mean, SD)</td><td>22.6 (5.8)</td><td>21.9 (4.4)</td></tr><tr><td>No. with pre-eclampsia[a] n (%)</td><td>49 (100)</td><td>46 (100)</td></tr><tr><td>Ethnicity: white</td><td>15</td><td>16</td></tr><tr><td>Ethnicity: black</td><td>34</td><td>30</td></tr><tr><td>Nulliparous</td><td>40</td><td>37</td></tr><tr><td>sBP at entry</td><td>172 (9.4)</td><td>170 (9.7)</td></tr><tr><td>dBP ≥ XY mmHg at entry</td><td>112 (4.2)</td><td>110 (5.4)</td></tr></table> [a]BP ≥ 160/110 during the initial 24 hours of hospitalisation and proteinuria > 500 mg per 24 hours **Inclusion criteria** Studies with women with severe pre-eclampsia (BP ≥ 140/90 on 2 occasions 4 or more hours apart and with proteinuria > 300 mg/24 hours) and a gestational age ≥ 34 weeks'.			Induction of labour: 15/15 Expectant management: 10/15 **Mode of birth (c-section)** Induction of labour: 11/15 Expectant management: 9/15 **Odendaal 1990** ***Neonatal outcomes*** **Neonatal death up to 7 days** Induction of labour: 1/20 Expectant management: 1/ 18 **Gestational age at birth,** mean days (SD) Induction of labour: 211 (15) Expectant management: 223 (13)	**Blinding (performance bias and detection bias):** unclear risk (see above details) **Incomplete outcome data:** high risk ("41 women were recruited, but 11 (27%) judged too compromised for expectant management and were delivered by CS. 5 patients from the expectant group appear to be missing from results table 2 - no explanation") **Selective reporting:** unclear risk (study protocol does not appear to have been registered) **Odendaal 1990** **Random sequence generation:** unclear risk (not reported) **Allocation concealment:** unclear risk (not reported) **Blinding of participants and personnel:** unclear risk (not reported)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	Studies including women with severe hypertension alone (BP ≥ 160/110 mmHg) were also included. Additionally, studies of women with severe hypertension alone (BP ≥ 160/110 mmHg) and one of the following symptoms were also included: severe proteinuria (3+ on a dipstick or 3 g [range 2-5g] protein in 24 h]; oliguria (less than 1/2 litre in 24 h) , upper abdominal pain, pulmonary oedema; neurological problems; impaired liver function and suspected IUGR. **Exclusion criteria** NR			**Birthweight*** Induction of labour: 1272 (357) Expectant management: 1420 (350) ***Maternal outcomes:*** **Placental abruption** Induction of labour: 3/20 Expectant management: 4/18 **Mode of birth (C-section)** Induction of labour: 14/20 Expectant management: 15/18 **Sibai 1994** ***Neonatal outcomes*** **Stillbirth** Induction of labour: 0/46 Expectant management: 0/49	**Blinding of outcome assessment:** unclear risk (not reported) **Blinding (performance bias and detection bias):** unclear risk (not reported) **Incomplete outcome data:** unclear risk (34.4% of women had to be delivered before randomisation because of severe maternal complications or fetal distress, and there is no clear from result table how many were analysed) **Selective reporting:** unclear risk (study protocol does not appear to have been registered) **Sibai 1994** **Random sequence generation:** low risk

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Neonatal death up to 7 days Induction of labour: 0/46 Expectant management: 0/49 **Small-for-gestational-age (BW<10th centile)** Induction of labour: 5/46 Expectant management: 15/49 **Gestational age at birth, mean days (SD)** Induction of labour: 216 (14) Expectant management: 233 (11) **Admission to neonatal unit** Induction of labour: 46/46 Expectant management: 37/49	("random computer generated") **Allocation concealment:** low risk ("consecutively numbered, sealed opaque envelopes") **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 (not reported) **Incomplete outcome data:** low risk **Selective reporting:** unclear risk (study protocol does not appear to have been registered)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Birthweight* Induction of labour: 1233 (287) Expectant management: 1622 (360) ***Maternal outcomes:*** **Eclampsia** Induction of labour: 0/46 Expectant management: 0/49 **HELLP** Induction of labour: 1/46 Expectant management: 2/49 **Placental abruption** Induction of labour: 2/46 Expectant management: 2/49 **Mode of birth (C-section)**	**Other information** GRIT 2003: following the Cochrane review this data extraction is based on, only a subset of women were included as part of the results. These women presented with hypertension plus either proteinuria or IUGR (total % was not reported). The characteristics of the patients are based on the whole sample of women. The data presented in this section has been adapted from the Cochrane systematic review. We present the data that is relevant to the aims of this review. Individual studies were retrieved for accuracy and to check of other outcomes of interest were reported. Data extracted by the review team from the original study has been marked with an *.

<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>Induction of labour: 39/46

Expectant management: 36/49</td><td></td></tr>
<tr><td>Full citation

Dhananjaya, B. S., Jamuna, R., Oral nifedipine versus intravenous labetalol in hypertensive emergencies of pregnancy: A randomised trial, Research Journal of Pharmaceutical, Biological and Chemical Sciences, 6, 1673-1681, 2015

Ref Id

755903

Country/ies where the study was carried out

India

Study type</td><td>Sample size

N= 60 (n= 30 randomised to nifedipine and n=30 randomised to labetalol)

Characteristics
<table>
<tr><th></th><th>Nifedipine
(n =30)</th><th>Labetalol
(n = 30)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>23.73±4.57</td><td>23.80±3.09</td></tr>
<tr><td>No. with pre-eclampsia[a] n</td><td>28†</td><td>24</td></tr>
<tr><td>No. of women with chronic hypertension [b] n</td><td>1†</td><td>1</td></tr>
<tr><td>No. of women with gestational hypertension [c] n (%)</td><td>8†</td><td>5</td></tr>
</table></td><td>Interventions

Nifedipine PO 10 mg with repeated doses of 10 mg every 15 minutes up to a maximum of 5 doses or until goal BP was achieved (150/110 mmHg)

Labetalol IV 20 mg duplicating the dose every 15 mins until goal BP was achieved (150/110 mmHg)</td><td>Details

In cases where the goal blood pressure was not achieved after 5 doses, crossover of the trial medication was done. If clinically significant maternal hypotension occurred, intravenous fluid bolus challenge or intravenous ephedrine was administered.

Sample size calculations were conducted and it was estimated that a sample size of 30 in each group was</td><td>Results

Baby outcomes

Neonatal mortality

Nifedipine: 0/30

Labetalol: 1/29

Birth weight (kg)

Nifedipine: 2.17 ± 0.52

Labetalol: 2.13 ± 0.66

Admission to neonatal unit

Nifedipine: 10/30

Labetalol: 14/29

Gestational age at birth, mean weeks (SD)

Nifedipine: 36.23 ±2.47

Labetalol: 35.55 ± 3.05

Maternal outcomes</td><td>Limitations

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

Random sequence generation: unclear (no information was provided)

Allocation concealment: unclear (no information was provided)

Blinding of participants and personnel: unclear (no information was provided)

Blinding of outcome assessment: low risk (blinded)

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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
RCT **Aim of the study** To assess whether nifedipine as compared to labetalol improves pregnancy outcomes in women with pre-eclampsia **Study dates** 10 October 2013 to 30 March 2014 **Source of funding** Not reported	<table><tr><td>Number of women with proteinuria[d]</td><td>22 (73.3)</td><td>26 (86.2)</td></tr><tr><td>Gestational age at treatment, weeks (mean, SD)</td><td>36.10 (2.22)</td><td>35.40 (3.27)</td></tr><tr><td>Primigravida</td><td>18 (60)</td><td>17 (57.7)</td></tr><tr><td>sBP at entry</td><td>171.40±13.39</td><td>172.13±15.28</td></tr><tr><td>dBP at entry</td><td>110.87±9.26</td><td>112.80±13.13</td></tr></table> [a,b,c,d] Definition was not reported † Percentage of women in each group is reported by the study authors, but data do not sum to 100%, therefore presumed typographical error. **Inclusion criteria** GA ≥28weeks, pregnant women with sBP ≥160mm Hg or dBP ≥ of 110mmHg, maternal heart rate > 60 and < 120 beats per minute. **Exclusion criteria**		needed to reduce BP and IV labetalol required 43.6 min (x2=43.6) to reduce blood pressure. Level of significance was taken as 5% and the power of test was taken as 80% . An additional 10% is added for lose to follow up cases. Details regarding randomisation were not provided.	**Time (minutes) taken to achieve BP target** Nifedipine 14 ± 6.87 Labetalol 25.17 ± 12.76 **HELLP** Nifedipine 1/30 Labetalol: 0/29 **Eclampsia** Nifedipine: 3/30 Labetalol:2/29	**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 registered) **Other information**

<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>Women with history of heart rhythm abnormality and/ or heart failure, exposure to either study medication within 24hrs of enrolment, asthma or allergic disorders with predisposition to bronchospasm, severe Hepatic/ Renal impairment, secondary hypertension and hypovolaemic shock.</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Elatrous, S., Nouira, S., Ouanes Besbes, L., Marghli, S., Boussarssar, M., Sakkouhi, M., Abroug, F., Short-term treatment of severe hypertension of pregnancy: prospective comparison of nicardipine and labetalol, Intensive Care Medicine, 28, 1281-6, 2002

Ref Id

659102

Country/ies where the study was carried out

Tunisia</td><td>Sample size

N=60 (n= 30 in the labetalol group and n=30 in the nicardipine group)

Characteristics
<table><tr><th></th><th>Labetalol (n=30)</th><th>Nicardipine (n=30)</th></tr><tr><td>Age, years (mean, SD)</td><td>31 (6)</td><td>31 (7)</td></tr><tr><td>No. with pre-eclampsia[a], n (%)</td><td>29 (96.6%)</td><td>29 (96.6%)</td></tr><tr><td>No. of women with chronic hypertension[b], n (%)</td><td>1 (3.3%)</td><td>1 (3.3%)</td></tr><tr><td>Gestational age at treatment,</td><td>36 (2)</td><td>35 (4)</td></tr></table></td><td>Interventions

Nicardipine: 10 mg IV over 5 minutes. If BP did not fall 20% in the next 5 minutes, 12.5 mg/h over 5 minutes was administered, followed by 15 mg/h if 20% reduction of blood pressure was not achieved. If BP did not fall 20% in the next 5 minutes, the intervention was ceased.

Labetalol: 1 mg/kg IV loading dose over 1 minute. If BP did not fall 20%, 5 minutes after a second dose of 1.5 mg/kg was administered over 1 minute. If BP did not fall 20% in the next 5 minutes, the intervention was ceased. If BP was achieved at any point, a maintenance dose of 100-150 mg/ kg hour was infused for the remaining study period.</td><td>Details

Concurrent mediation: all women were receiving IV magnesium sulfate for seizure prophylaxis (loading dose was 4 g and maintenance dose was 1g/h)

Randomisation was computer generated. Women were assigned to each of the treatment arms using sealed sequentially numbered opaque envelopes. Single blind study.

Follow-up period: 1 hour

Unclear whether a sample size</td><td>Results

Minutes (mean, SD) to effective control of blood pressure (target was lowering BP by a 20% in comparison with baseline levels)

Labetalol = 12.38 (6.25)

Nicardipine = 11.09 (3.68)</td><td>Limitations

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

Random sequence generation: low risk (computerised random number generated)

Allocation concealment: low risk (sequentially numbered opaque envelopes)

Blinding of participants and personnel: high risk (single blind)

Blinding of outcome assessment: low risk

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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** To assess the efficacy and safety of nicardipine compared to labetalol in the management of women with pre-eclampsia or chronic hypertension - **acute treatment** **Study dates** January 1995 to December 1996 **Source of funding** NR	**weeks (mean, SD)** | | | **Parity, mean (SD)** | 3.2 (2) | 2.8 (2) **sBP at entry, mean (SD)** | 171 (8) | 176 (10) **dBP at entry, mean (SD)** | 110 (10) | 10 (9) [a,b]Definitions for pre-eclampsia and chronic hypertension were not reported, however all the study participants were classified as having hypertensive emergencies, defined as "a sustained systolic BP of 170 mmHg or higher, or diastolic BP of 110 mmHg or higher on two repeated measurements 30 min apart". **Inclusion criteria** Women ≥ 18 years old; with severe hypertension beyond the 24th week of gestation. **Exclusion criteria** Contraindications to beta-blockers or calcium channel blockers, or who had taken either of the study medications within 4 hours of enrollment to the study.		calculation was performed No information regarding sample size calculations was provided.		**Incomplete outcome data:** low risk (no drop-out data was reported) **Selective reporting:** unclear risk (study protocol does not appear to have been registered) **Other information**
Full citation Elhassan, E. M., Mirghani, O. A., Habour, A. B.,	**Sample size** N= 70, n= 34 randomised to methyldopa treatment and n= 36 randomised to the control group	**Interventions** Methyldopa: 750 mg/day and increased as needed (maximum dose was 4000mg)	**Details** No relevant methods regarding method	**Results** *Neonatal outcomes*	**Limitations** **Methodological limitations assessed using the Cochrane**

<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>Adam, I., Methyldopa versus no drug treatment in the management of mild pre-eclampsia, East African medical journal, 79, 172-5, 2002

Ref Id

742779

Country/ies where the study was carried out

Sudan

Study type

RCT

Aim of the study

To assess the efficacy of methyldopa in the treatment of mild pre-eclampsia

Study dates

Not reported

Source of funding

Not reported</td>
<td>Characteristics
<table>
<tr><th></th><th>Methyldopa (n=34)</th><th>Control (n=36)</th></tr>
<tr><td>Age</td><td>22.3 (5.2)</td><td>21.1 (5.4)</td></tr>
<tr><td>Pre-eclampsia[a]</td><td>34 (100)</td><td>36 (100)</td></tr>
<tr><td>sBP (mmHg)</td><td>174.4 (8.6)</td><td>144.7 (6.5)</td></tr>
<tr><td>dBP (mmHg)</td><td>102.4 (2.5)</td><td>101.4 (2.3)</td></tr>
</table>
[a]Pre-eclampsia: dBP between 90 to 109 mmHg in 2 readings 6 hours apart showing 2+ or more albumin by dip stick

Inclusion criteria

Mild pre-eclampsia (dBP between 90-109 mmHg) in 2 readings 6 hours apart showing 2+ or more albumin by dip stick

Exclusion criteria

Not reported</td>
<td>Control group received no treatment, but were observed in the hospital</td>
<td>of randomisation, follow-up time, sample power calculations or additional treatment were reported.</td>
<td>Perinatal death up to 7 days

Methyldopa: 4/34

No intervention group:6/36

Maternal outcomes:

sBP at the start of labour

Methyldopa: 131.8 (7.5)

No intervention: 137.5(6.8)

dBP at the start of labour

Methyldopa: 91.8 (6.03)

No intervention: 89.6 (4.6)

Eclampsia

Methyldopa: 3/34

No intervention group: 10/36

Mode of birth (C-section)

Methyldopa: 14/34

No intervention group:14/36</td>
<td>collaboration's tool for assessing risk of bias

Random sequence generation: unclear risk (no details as to how random sequence generation was performed)

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

Blinding of participants and personnel: high risk (open-label)

Blinding of outcome assessment: high risk (open-label)

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

Incomplete outcome data: unclear risk

Selective reporting: unclear risk (study protocol does not appear to have been registered)

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

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

Fenakel,K., Fenakel,G., Appelman,Z., Lurie,S., Katz,Z., Shoham,Z., Nifedipine in the treatment of severe preeclampsia, Obstetrics and Gynecology, 77, 331-337, 1991

Ref Id

169213

Country/ies where the study was carried out

Israel

Study type

RCT

Aim of the study

To assess whether hydralazine as compared to nifedipine improves maternal and</td>
<td>Sample size

N=49 (n=25 in the hydralazine group and n= 24 in the nifedipine group)

Characteristics

<table>
<tr><th></th><th>Hydralazine (n=25)</th><th>Nifedipine (n=24)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>28.6 (4.8)</td><td>30.6 (6.4)</td></tr>
<tr><td>No. with pre-eclampsia[a] n (%)</td><td colspan="2">18 (36.7%)</td></tr>
<tr><td>Superimposed pre-eclampsia[b] n (%)</td><td colspan="2">31 (63.2%)</td></tr>
<tr><td>Gestational age at treatment, weeks (mean, SD)</td><td>32.3 (2.9)</td><td>32.4 (2.5)</td></tr>
<tr><td>Nulliparas</td><td>6 (24%)</td><td>12 (50%)</td></tr>
<tr><td>sBP at entry</td><td>170.0 (no SD reported)</td><td>171.6 (no SD reported)</td></tr>
</table>
</td>
<td>Interventions

Hydralazine: 6.25 mg IV followed by boluses of 12.5mg at intervals determined by the BP. After 24h of stabilisation of sBP/dBP ≤ 160, IV therapy was stopped and po hydralazine therapy was started (20-30 mg every 6 hours until birth).

Nifedipine: 10 mg sl. Doses were repeated every 20 and 40 minutes later if sBP/dBP ≥ 160 and increased to 20 mg every 4 hours if sBP/dBP continued to be ≥ 160. Thereafter, nifedipine was given in doses of 10mg every 6 hours until birth.</td>
<td>Details

Concurrent treatment: magnesium sulphate IV (loading dose 4g, maintenance dose 1-2 g/hour) stopped after 24 hour of stabilisation of BP.

Steroids to accelerate lung maturation were not used in any of the groups.

Follow-up: 4 weeks

No information regarding sample size calculations was provided. Randomisation method was not reported.</td>
<td>Results

Neonatal outcomes

Neonatal death up to 7 days (include if reported as part of perinatal mortality)

Hydralazine: 2/27

Nifedipine: 1/26

Birth weight

Hydralazine: 1580 (499)

Nifedipine: 1826 (456)

Gestational age at birth, mean weeks (SD)

Hydralazine: 33.6 (2.4)

Nifedipine: 34.6 (2.3)

Women outcomes:

Severe hypertension (sBP/dBP ≥ 160/110 mmHg)

Hydralazine: 8/25

Nifedipine: 1/24</td>
<td>Limitations

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

Random sequence generation: unclear risk (method not reported)

Allocation concealment: unclear risk (method 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 (drop-out<20% and difference between groups <20%)</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>neonatal outcomes in women with pre-eclampsia or superimposed pre-elampsia

Study dates

January 1985 to December 1988

Source of funding

NR</td>
<td>[a]dBP/sBP ≥160/110 mmHg and presence of any of the following factors: proteinuria, generalised oedema, or hyperreflexia, 26-36 weeks' gestation. Total N was only provided at study level and not per treatment arm;[b] No definition for superimposed pre-eclampsia was provided. Total N was only provided at study level and not per treatment arm

Inclusion criteria

dBP/sBP ≥160/110 mmHg and presence of any of the following factors: proteinuria, generalised edema, or hyperreflexia, 26-36 weeks' gestation

Exclusion criteria

NR</td>
<td></td>
<td></td>
<td>Eclampsia

Hydralazine:0/25

Nifedipine: 0/24

Onset of labour (induction)

Hydralazine: 8/25

Nifedipine: 1/24

Mode of birth (C-section)

Hydralazine: 15/25

Nifedipine: 14/24</td>
<td>Selective reporting: unclear risk (study protocol does not appear to have been registered)

Other information</td>
</tr>
<tr>
<td>Full citation

Harper, A., Murnaghan, G. A., Maternal and fetal haemodynamics in hypertensive pregnancies during maternal treatment with intravenous hydralazine or labetalol, British Journal of Obstetrics & Gynaecology, 98, 453-9, 1991</td>
<td>Sample size

N=30 (n=15 in the hydralazine group and n=15 in the labetalol group)

Characteristics

<table>
<tr><th></th><th>Hydralazine (n =15)</th><th>Labetalol (n =15)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>25.9 (6.3)</td><td>28.1 (6.2)</td></tr>
<tr><td>No. with pre-eclampsia n (%)[a]</td><td>15 (100%)</td><td>15 (100%)</td></tr>
</table>
</td>
<td>Interventions

Hydralazine 10mg IV (single injection)

Labetalol 100mg IV (single injection)</td>
<td>Details

Randomisation was done by sequentially numbered sealed envelopes.

Follow-up: 120 minutes

No information re: concurrent treatment or power analysis was reported</td>
<td>Results

Neonatal outcomes

Stillbirth (include if reported as part of perinatal mortality)

Hydralazine: 1/15

Labetalol: 0/15

Neonatal death up to 7 days (include if reported</td>
<td>Limitations

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

Random sequence generation: unclear risk (no randomisation method was reported)

Allocation concealment: low risk (sequentially numbered sealed envelopes)</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 659128 **Country/ies where the study was carried out** Northern Ireland **Study type** RCT **Aim of the study** To assess the efficacy of hydralazine or labetalol in lowering blood pressure- **acute treatment** **Study dates** NR **Source of funding** NR	<table><tr><td>**No. with multiple pregnancy**</td><td>0</td><td>0</td></tr><tr><td>**No. of primigravida**</td><td>9 (60%)</td><td>10 (66.6%)</td></tr><tr><td>**Gestational age at treatment, weeks (mean, SD)**</td><td>31.2 (3.2)</td><td>32.1 (3.1)</td></tr></table> [a]No definition for pre-eclampsia was provided, women presented with "*acutely elevated or labile blood pressure which did not respond to bed rest. Most women had clinically significant non-infective proteinuria and many have headaches, visual symptoms or hyper-reflexia*" **Inclusion criteria** Not having received any previous antihypertensive treatment (no more details were provided) **Exclusion criteria** NR			**as part of perinatal mortality)** Hydralazine: 1/15 Labetalol: 1/15 **Small-for-gestational-age (BW<10th centile)** Hydralazine: 8/15 Labetalol: 10/15 **Birth weight (Mean, SD)** Hydralazine: 1898 (962) Labetalol: 1833 (845) **Gestational age at birth** Hydralazine: 33.7 (3.3) Labetalol: 33.8 (3.4) *Women outcomes* **Mode of birth (C-section)** Hydralazine: 9/15 Labetalol: 9/15	**Blinding of participants and personnel:** unclear risk (not reported whether participants and personnel were blinded) **Blinding of outcome assessment:** unclear risk (not reported whether outcome assessors were blinded) **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 does not appear to have been registered) **Other information**

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

Koopmans, Corine M., Bijlenga, Denise, Aarnoudse, Jan G., van Beek, Erik, Bekedam, Dick J., van den Berg, Paul P., Burggraaff, Jan M., Birnie, Erwin, Bloemenkamp, Kitty W. M., Drogtrop, Addi P., Franx, Arie, de Groot, Christianne J. M., Huisjes, Anjoke J. M., Kwee, Anneke, le Cessie, Saskia, van Loon, Aren J., Mol, Ben W. J., van der Post, Joris A. M., Roumen, Frans J. M. E., Scheepers, Hubertina C. J., Spaanderman, Marc E. A., Stigter, Rob H., Willekes, Christine, van Pampus, Maria G., Induction of</td>
<td>Sample size

N=246 (n=123 in induction of labour and n=123 in expectant management)*

*The original manuscript included n=756 women, but a subgroup of women with pre-eclampsia have been included for the purpose of this review

Characteristics of the total sample*
<table>
<tr><th></th><th>Induction of labour (n =377)</th><th>Expectant management (n =379)</th></tr>
<tr><td>Age, years (median, IQR)</td><td>29 (26-33)</td><td>29 (26-33)</td></tr>
<tr><td>No. with mild pre-eclampsia[a] n (%)</td><td>123 (33%)</td><td>123 (32%)</td></tr>
<tr><td>No. of women with unknown diagnosis n (%)</td><td>10 (3%)</td><td>4 (1%)</td></tr>
<tr><td>No. of women with gestational hypertension[b] n (%)</td><td>244 (65%)</td><td>252 (66%)</td></tr>
</table>
</td>
<td>Interventions

Induction of labour: women were induced within 24 hours of randomisation. Women with a Bishop score > 6 at vaginal examination, labour was induced with amniotomy and augmentation with oxytocin was provided, if needed. For women with a Bishop score > 6, cervical ripening was stimulated with intracervical or intravaginal prostaglandins or a balloon catherer. Use of oxytocin or prostaglandins were subject to local protocols.

Expectant management: women were monitored until the onset of spontaneous birth. Monitoring consisted on measurement of BP, screening of urine for protein with a dipstick specimen or with the ratio of protein to creatinine. This was done in either outpatient or inpatient setting.</td>
<td>Details

Randomisation was performed in a 1:1 ratio by block randomisation with a web-based application system. Open-label trial.

No information regarding use of concurrent treatment, including steroid use, follow-up length or power sample calculations was provided.</td>
<td>Results

Maternal outcomes

Mode of birth (C-section)*

Induction of labour: 22/123

Expectant management: 29/123

*Only women with pre-eclampsia have been included</td>
<td>Limitations

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

Random sequence generation: low risk (block randomisation with a web-based application system)

Allocation concealment: unclear risk (no information was provided)

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 (open label trial)</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>labour versus expectant monitoring in women with pregnancy induced hypertension or mild preeclampsia at term: the HYPITAT trial, BMC Pregnancy and Childbirth, 7, 14, 2007

Ref Id

776205

Country/ies where the study was carried out

Netherlands

Study type

RCT

Aim of the study

To assess whether induction of labour improves outcomes of women with hypertensive disorders of pregnancy as compared to</td>
<td>
<table>
<tr><td>Proteinuria in women with pre-eclampsia (median [IQR] mg per 24)</td><td>450 (300 - 1140)</td><td>600 (350-970)</td></tr>
<tr><td>Gestational age at treatment, weeks (median, IQR)</td><td>38.4 (37.6-39.4)</td><td>38.6 (37.6-39.4)</td></tr>
<tr><td>Ethnicity: white</td><td>317 (84%)</td><td>298 (79%)</td></tr>
<tr><td>Ethnicity: other</td><td>35 (9%)</td><td>47 (12%)</td></tr>
<tr><td>sBP at baseline (median, IQR)</td><td>140 (140-150)</td><td>144 (140-150)</td></tr>
<tr><td>dBP at baseline (median, IQR)</td><td>100 (95-100)</td><td>100 (95-100)</td></tr>
<tr><td>No of nulliparous women</td><td>269 (71.3%)</td><td>272 (71.7%)</td></tr>
</table>
[a] pre-eclampsia: dBP ≥ 90 mmHg measures on 2 occasions at least 6 h apart, combined with proteinuria (2 or more occurrences of protein on a dipstick, > 300 mg total protein within a 24h urine collction, or ratio protein: creatinin >30mg/mmol
</td>
<td></td>
<td></td>
<td></td>
<td>Incomplete outcome data: low risk (no drop outs were reported)

Selective reporting: low risk (all pre specified outcomes have been reported)

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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
expectant management. **Non-acute** **Study dates** October 2005 and March 2008 **Source of funding** ZonMw	[b] gestational hypertension: dBP ≥ 95 mmHg measured on 2 occasions at least 6 hours apart *The characteristics of the subgroup of women included for the purpose of this review (n= 246 women with pre-eclampsia) have not been reported, therefore characteristics of the total sample were reported **Inclusion criteria** Women with a singleton pregnancy at 36 to 41 weeks´gestation. In order to be included, women should present with gestational hypertension or pre-eclampsia **Exclusion criteria** Women with severe gestational hypertension or severe pre-eclampsia (sBP/dBP ≥ 170/110 mmHg), or proteinuria of 5g or higher per 24 hours. Pre-existing hypertension treated with antihypertensive medications, diabetes, gestational diabetes needing insulin, renal disease, heart disease, previous C-section, HELLP, oliguria < 500 ml in 24 hours, pulmonary oedema, HIV, use of IV antihypertensive drugs, fetal abnormalities or IUGR.				
Full citation Kwawukume, E. Y., Ghosh, T. S., Oral nifedipine therapy in the management of severe preeclampsia,	**Sample size** N=98 (n=49 in the hydralazine group and n=49 in the nifedipine group) **Characteristics**	**Interventions** Hydralazine 5mg IV. Escalating doses of 10mg were repeated at intervals determined by the BP level. Once dBP was stabilised at around 90 to 100 mmHg, 20 to 80 mg hydralazine tablets	**Details** Concurrent treatment of antihypertensive drugs (including methyldopa and propranolol) was used in 14 of the	**Results** *Neonatal outcomes* **Neonatal death up to 7 days (include if reported as part of perinatal mortality)**	**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>International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 49, 265-9, 1995

Ref Id

776221

Country/ies where the study was carried out

Ghana

Study type

RCT

Aim of the study

To compare the efficacy of nifedipine and hydralazine in lowering blood pressure in women with severe pre-eclampsia
- acute treatment

Study dates</td>
<td>
<table>
<tr><th></th><th>Hydralazine (n = 49)</th><th>Nifedipine (n = 49)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>29.2 (7.2)</td><td>30.7 (7.2)</td></tr>
<tr><td>No. pre-eclamptic women (n, %)</td><td>49 (100%)</td><td>49 (100%)</td></tr>
<tr><td>Primigravida</td><td>16 (32.6%)</td><td>19 (38.7)</td></tr>
<tr><td>Multigravida</td><td>33 (67.4%)</td><td>30 (61.3%)</td></tr>
<tr><td>Gestational age at treatment, weeks (mean, SD)</td><td>34 (3.4)</td><td>34.3 (2.9)</td></tr>
<tr><td>Mean sBP at entry (mean, SD)</td><td>189 (19.5)</td><td>190.7 (19.1)</td></tr>
<tr><td>Mean dBP at entry (mean, SD)</td><td>134.1 (9.2)</td><td>125.3 (11.3)</td></tr>
</table>
Inclusion criteria

Proteinuria of at least 1+ as measured by dipstick in a random urine sample; sBP or dBP of 160/110 mmHg measured twice 4 to 6 hours apart at rest; pregnancy above 28 weeks gestation with no previous history of hyperension during pregnancies; women normotensive during the first 20 weeks of gestation</td>
<td>in divided doses were administered until birth.

Nifedipine 10mg sublingual. Escalating doses of 10mg every 30 minutes were given if BP was ≥ 160/110 mmHg. The dose was escalated to 20mg every 6 to 8 hours if the BP readings approached 160/110 mmHg.</td>
<td>women randomised to the hydralazine arm and 5 of the women randomised to the nifedipine arm because their dBP were persistently above 110 mmHg.

Randomisation was performed using odd and even numbers. Double blind randomisation was not possible because of the administration route of the interventions (IV vs sublingual)

Follow-up time: 3 weeks

Use of steroids was not reported

Power calculations were not reported</td>
<td>Hydralazine: 0/35

Nifedipine: 0/44

Birth weight (mean, SD)

Hydralazine: 2400 (800)

Nifedipine: 2500 (800)

Admission to neonatal unit

Hydralazine: 13/35

Nifedipine: 11/44

Women outcomes:

Eclampsia

Hydralazine: 0/ 35

Labetalol: 0/44

Mode of birth (C-section)

Hydralazine: 24/ 35

Labetalol: 22/44</td>
<td>Random sequence generation: high risk (randomisation was performed using alternate allocation)

Allocation concealment: unclear risk (not reported)

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

Blinding (performance bias and detection bias): high risk (not blinded)

Incomplete outcome data: high risk (drop-out rate in the hydralazyne group was >20%, reasons not reported; drop out difference between groups > 20%)

Selective reporting: unclear risk (study protocol does not appear to have been registered)

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

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>January 1992 to June 1994

Source of funding

NR</td><td>Exclusion criteria

NR</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Martins-Costa, S., Ramos, J. G., Barros, E., Bruno, R. M., Costa, C. A., Goldin, J. R., Randomized, controlled trial of hydralazine versus nifedipine in preeclamptic women with acute hypertension, Clinical and Experimental Hypertension - Part B Hypertension in Pregnancy, 11, 25-44, 1992

Ref Id

776320</td><td>Sample size

N=37 (N= 20 in the nifedipine group and n=17 in the hydralazine group)

Characteristics
<table><tr><th></th><th>Hydralazine (n =17)</th><th>Nifedipine (n =20)</th></tr><tr><td>Age, years (mean, SD)</td><td>23 (6)</td><td>15 (5)</td></tr><tr><td>No. of women with pre-eclampsia[a] n (%)</td><td>17 (100%)</td><td>20 (100%)</td></tr><tr><td>Proteinuria (g/24h) (mean, SD)</td><td>3.2 (4.3)</td><td>2.8 (5)</td></tr><tr><td>Ethnicity - white</td><td>12 (70.5%)</td><td>15 (75%)</td></tr><tr><td>Ethnicity - black</td><td>5 (29.5%)</td><td>5 (25%)</td></tr></table></td><td>Interventions

Hydralazine 5mg IV

Nifedipine 10 mg PO

Frequency NR</td><td>Details

Concurrent treatment: the hydralazine group received a placebo capsule PO and the nifedipine group received placebo IV. A total of 7 out of 17 cases in the hydralazine group and 6 out of 20 cases in the nifedipine group needed additional treatment (differences between these were not significant).

Neonatal steroids were
not mentioned in the study

Randomisation was performed by</td><td>Results

Neonatal outcomes

Stillbirth

Hydralazine: 0/17

Nifedipine: 2/20

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

Hydralazine: 0/17

Nifedipine: 1/20

Birth weight (g) (mean , SD)

Hydralazine: 2216 (609)

Nifedipine: 2404 (864)</td><td>Limitations

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

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

Allocation concealment: low risk

Blinding of participants and personnel: low risk

Blinding of outcome assessment: low risk

Incomplete outcome data: low risk (no drop-outs were reported)</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 the effect of hydralazine or nifedipine on lowering blood pressure in **acute pre-eclampsia** **Study dates** NR **Source of funding** NR	**No. of postnatal women included n (%)** 0 0 **Nulliparous** 17 (100%) 20 (100%) **Mean (SD) sBP at entry** 172 (14) 169 (13) **Mean (SD) dBP at entry** 118 (8) 119 (6) [a]Definition for pre-eclampsia: dBP ≥ 110 mmHg and significant proteinuria (at least 300 mg in 24 hour collection urine, or a minimum of 3 pluses as measured by Dipstick) **Inclusion criteria** dBP ≥ 110 mmHg, ≥ 28 gestational weeks; significant proteinuria (at least 300 mg in 24 hour collection urine, or a minimum of 3 pluses as measured by Dipstick); no use of antihypertensives prior to study entry; absence of other medical, surgical or obstetric problem; normotensive prior to their 20th gestational week **Exclusion criteria** NR		a nurse drawing an envelope from a jumble box. Clinicians and patients were blinded to treatment allocation Duration of follow up for outcome data: 2 hours Initial goal was to study 100 women, but due to time constraints, sample size was reduced to 37. No sample size calculations were mentioned in the study	**Gestational age at birth, mean weeks (SD)** Hydralazine: 36 (2) Nifedipine:36 (2) *Maternal outcomes* **Severe hypertension** Hydralazine: 0/17 Nifedipine: 0/20 **Placental abruption** Hydralazine group: 0/17 Nifedipine group:1/20 **Mode of birth (C-section)** Hydralazine group: 13/17 Nifedipine group:13/20	**Selective reporting:** unclear risk (study protocol does not appear to have been registered) **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>Owens, M. Y., Thigpen, B., Parrish, M. R., Keiser, S. D., Sawardecker, S., Wallace, K., Martin Jr, J. N., Management of preeclampsia when diagnosed between 34-37 weeks gestation: deliver now or deliberate until 37 weeks?, Journal of the Mississippi State Medical Association, 55, 208-211, 2014

Ref Id

776473

Country/ies where the study was carried out

US

Study type

March 2002 to June 2008

Aim of the study

To determine whether induction of labour as</td>
<td>N=169 (n= 75 in the induction of labour group and n=94 in the expectant management group)

Characteristics
<table>
<tr><th></th><th>Induction of labour (n =94)</th><th>Expectant management (n =75)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>23.1 (5.5)</td><td>24.3 (6.3)</td></tr>
<tr><td>No of women with mild pre-eclampsia without severe features (ACOG 2002 criteria)</td><td>94 (100%)</td><td>75 (100%)</td></tr>
<tr><td>Gestational age at treatment, weeks (mean, SD)</td><td>35.14 (0.99)</td><td>34.97 (0.98)</td></tr>
<tr><td>Ethnicity: white n (%)</td><td>21 (22%)</td><td>15 (20%)</td></tr>
<tr><td>Ethnicity: black n (%)</td><td>70 (75%)</td><td>54 (72%)</td></tr>
<tr><td>Ethnicity: Hispanic n (%)</td><td>1 (1%)</td><td>1 (1%)</td></tr>
</table>
</td>
<td>Induction of labour : women in this group were delivered via induction of labour or caesarean birth within 12 hours of randomisation

Expectant management: women in this group remained as inpatient of the hospital and received assessment of signs, symptoms and laboratory values (every 3 days) suggestive of disease progression. These women were carried to 37 weeks gestation unless there was spontaneous onset of labour or rupture of membranes, suspected placental abruption, development of severe features of pre-eclampsia (severe hypertension, low platelet count, impaired liver function, etc.) or fetal compromise.</td>
<td>Concurrent treatment: magnesium sulphate prophylaxis intrapartum and immediately postpartum.

Women were randomised using stratified and random permuted blocks of 2 in consecutively numbered opaque envelopes.

Follow-up time: 72 hours

No information was provided regarding power calculations or use of steroids.</td>
<td>Neonatal outcomes

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

Induction of labour : 19 /94

Expectant management:11 / 75

Birth weight

Induction of labour : 2941 (426.05)

Expectant management: 2766.3 (508.98)

Admission to neonatal unit

Induction of labour : 20 /94

Expectant management: 14 / 75

Women outcomes:

Severe hypertension

Induction of labour : 3 /94</td>
<td>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

Random sequence generation: low risk (random permuted blocks of 2)

Allocation concealment: low risk (opaque sealed envelopes)

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: unclear risk (drop out is not reported)

Selective reporting: unclear risk (protocol does not appear to have been registered)</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
compared to expectant results in improved outcomes in the management of women with mild pre-eclampsia without severe features **(non-acute)** **Study dates** March 2002 to June 2008 **Source of funding** The Division of Maternal-Fetal Medicine	<table><tr><td>**Native American n (%)**</td><td>2 (2%)</td><td>5 (7%)</td></tr><tr><td>**Nulliparous n (%)**</td><td>38 (40%)</td><td>24 (36%)</td></tr></table> **Inclusion criteria** Gestational age 34 to 36 weeks, with an estimated fetal weight > 2000 g, presence of mild pre-eclampsia without severe features (ACOG 2002 criteria) **Exclusion criteria** Maternal- fetal- pregnancy complications			Expectant management: 20/ 75 **Eclampsia** Induction of labour : 0 /94 Expectant management:1 / 75 **HELLP** Induction of labour : 0 /94 Expectant management: 1/ 75 **Mode of birth** (C-section) Induction of labour : 42 /94 Expectant management:28 / 75	**Other information**
Full citation Rezaei, Zahra, Sharbaf, Fatemeh Rahimi, Pourmojieb, Mino,	**Sample size** N = 50 (n=25 in the hydralazine group and n=25 in the nifedipine group) **Characteristics**	**Interventions** Hydralazine 5mg IV and repeated in doses of 10 mg , up to 5 injections in 10mg doses, up to a maximum of 5	**Details** Concurrent treatment: women were receiving prophylactic magnesium	**Results** **Minutes to achieve effective control of blood pressure (sBP/dBP 150/90-100) mean (SD)**	**Limitations** **Methodological limitations assessed using the Cochrane collaboration's tool**

<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>Youefzadeh-Fard, Yashar, Motevalian, Manijeh, Khazaeipour, Zahra, Esmaeili, Sara, Comparison of the efficacy of nifedipine and hydralazine in hypertensive crisis in pregnancy, Acta medica Iranica, 49, 701-6, 2011

Ref Id

804184

Country/ies where the study was carried out

Iran

Study type

RCT

Aim of the study

To determine the time needed to lower blood pressure in women with severe pre-eclampsia or</td>
<td>
<table>
<tr><th></th><th>Hydralazine (n = 25)</th><th>Nifedipine (n =25)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>29.6 (6)</td><td>29.4 (5.8)</td></tr>
<tr><td>Gestational age at treatment, weeks (mean, SD)</td><td>34.2 (3.3)</td><td>35.6 (2.5)</td></tr>
<tr><td>Gravidity mean (SD)</td><td>2.6 (1.6)</td><td>2.6 (2)</td></tr>
<tr><td>sBP at entry mean (SD)</td><td>169.2 (16.1)</td><td>166.8 (9.9)</td></tr>
<tr><td>dBP at entry mean (SD)</td><td>111.4 (6.2)</td><td>109.4 (5.3)</td></tr>
<tr><td>No. of women with pre-eclampsia[a]</td><td>NR</td><td>NR</td></tr>
<tr><td>No. of women with superimposed pre-eclampsia[b]</td><td>NR</td><td>NR</td></tr>
</table>
[a,b] definition for pre-eclampsia or superimposed pre-eclampsia was not reported

Inclusion criteria
</td>
<td>injections in intervals of 20 minutes

Nifedipine 10 mg capsules and repeated in doses of 20 mg with intervals of 20 minutes up to 5 doses, or when target BP was reached (150/90-100)</td>
<td>sulphate to avoid convulsion

Randomisation was performed using a random number table. Study was not blinded.

Duration of follow-up: 24 hours

To detect a 40% difference in the time interval required to achieve the therapeutic blood pressure, with α=0.05 and β=0.2, it was determined that 25 patients would be required in each group.</td>
<td>Hydralazine: 34.8 (18.8)

Nifedipine: 24 (10)</td>
<td>for assessing risk of bias

Random sequence generation: low risk (random number table was used)

Allocation concealment: unclear risk (no information was reported)

Blinding of participants and personnel: high risk (no blinding)

Blinding of outcome assessment: high risk (no blinding)

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

Incomplete outcome data: low risk (drop-outs were not reported)

Selective reporting: low risk (all expected outcomes appear to be reported)

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

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>superimposed pre-eclampsia

Study dates

NR

Source of funding

NR</td><td>Gestational age of at least 24 weeks, with a diagnosis of severe pre-eclampsia or superimposed pre-eclampsia

Exclusion criteria

Women with heart disease, renal impairment and cerebrovascular accident</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

Schoen, Corina N., Moreno, Sindy C., Saccone, Gabriele, Graham, Nora M., Hand, Lauren C., Maruotti, Giuseppe M., Martinelli, Pasquale, Berghella, Vincenzo, Roman, Amanda, Outpatient versus inpatient management for superimposed preeclampsia without severe features: a retrospective, multicenter study, The journal of maternal-fetal &</td><td>Sample size

N=365 (N=198 in the outpatient management group and n=167 in the inpatient management group)

Characteristics
<table><tr><td></td><td>Outpatient management (n =198)</td><td>Inpatient management (n =167)</td></tr><tr><td>Age, years (mean, SD)</td><td>28.4 (5.4)</td><td>32.4 (4.1)</td></tr><tr><td>Chronic hypertension and superimposed pre-eclampsia without severe features[a]</td><td>198 (100)</td><td>167 (100)</td></tr></table></td><td>Interventions

Outpatient management: 1 pw visit to clinician or high-risk nurse practitioner; 2 pw non-stress tests; once every 3 to 4 weeks, fetal growth ultrasound. Complete blood count and a comprehensive metabolic panel was done regularly (at the clinician´s discretion). All women had daily monitoring of blood pressure (home device).

Inpatient management: women were managed 2 to 3 times daily NST</td><td>Details

Consecutive treatment:
all women were prescribed methyldopa, labetalol or nifedipine to control BP. Rarely, amlodipine was used.

The decision to manage women as inpatient or outpatient was at the clinician´s discretion.

No details were reported regarding use of statins or power sample calculations.</td><td>Results

Neonatal outcomes

Stillbirth (include if reported as part of perinatal mortality)

Outpatient management: 2/198

Inpatient management: 2/167

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

Outpatient management: 35/198

Outpatient management: 49/167

Birth weight</td><td>Limitations

Limitations were assessed using the Newcastle- Ottawa scale for cohort studies

Selection

1) Representativeness of the exposed cohort: somewhat represented(*)

2) Selection of the non-exposed cohort: drawn from the same community as the exposed cohort (*)

3) Ascertainment of exposure: secure record (*)

Comparability</td></tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
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, 1-7, 2017 **Ref Id** 776641 **Country/ies where the study was carried out** Italy and US **Study type** Retrospective cohort study **Aim of the study** To assess whether women with superimposed pre-eclampsia without severe features can be	Gestational age at treatment, weeks (mean, SD) 33.9 (4.5) 34.9 (3.6) Singleton pregnancy n (%) 198 (100) 167 (100) Ethnicity: white 138 (69) 110 (65.9) Ethnicity: black 50 (25) 44 (26.3%) Ethnicity: other 10 (5) 15 (9) Parity (median, range) 2 (0-8) 2 (0-7) [a] ACOG criteria; chronic hypertension was defined as a history of hypertension prior to the pregnancy or a BP ≥ 140/90 prior to 20 weeks. Superimposed pre-eclampsia without severe features was defined as a sudden increase in blood pressure that was previously well controlled, or a need to increase antihypertensive medication; new onset proteinuria ≥ 300 mg per 24 h or > 0.3 protein/creatinine ratio (mg/dL),or a sudden increase in proteinuria in a women who had proteinuria before or early in pregnancy. **Inclusion criteria**			Outpatient management: 2764 (1021) Inpatient management: 2419 (837) **Gestational age at birth, mean weeks, SD** Outpatient management: 35.9 (3.1) Inpatient management: 35.1 (2.9) **Admission to neonatal unit** Outpatient management: 80/198 Inpatient management: 80/167 *Maternal outcomes:* **HELLP** Outpatient management: 0/198 Inpatient management: 0/167	1) Comparability of cohorts on the basis of the design or analysis controlled for confounders: study controls for other factors, namely age, BMI, smoking, ethnicity, gravidity, parity, prior pre-eclampsia, diabetes mellitus, prior medical condition, IUR (*) *Outcome* 1) Assessment of outcome: record linkage (*) 2) Was follow-up long enough for outcomes to occur? : not applicable (this is a retrospective cohort study) 3) Adequacy of follow-up of cohorts: complete follow-up , all subjects accounted for (*) Overall rating: good quality study **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
managed in an outpatient setting **Study dates** January 2008 to July 2015 **Source of funding** NR	Women with superimposed pre-eclampsia without severe features and with singleton pregnancies. **Exclusion criteria** Women with superimposed pre-eclampsia with a gestational age ≥37 weeks; women with superimposed pre-eclampsia with severe features.			**Placental abruption** Outpatient management: 10/198 Inpatient management: 8/167 **Mode of birth** (C-section) Outpatient management: 55/198 Inpatient management: 50/167	
Full citation Sibai,B.M., Barton,J.R., Akl,S., Sarinoglu,C., Mercer,B.M., A randomized prospective comparison of nifedipine and bed rest versus bed rest alone in the management	**Sample size** N= 200 (N=100 in the nifedipine group and n= 100 in the no intervention group) **Characteristics** **Nifedipine (n =100)** / **No intervention (n =100)** **Age, years (mean, SD)**: 20.5 (4.2) / 20.3 (4.2)	**Interventions** Nifedipine: 40 mg/day increased every 2 to 3 days as needed to a maximum of 120 mg/day to keep sBP/dBP below 140/90 mmHg (method of administration was not reported) No intervention: bed rest Stable women without proteinuria (protein < 300 mg in 24 hours) and with BP	**Details** Concurrent treatment: prenatal vitamins and iron supplements (dose was not reported) Randomisation was done with a computer-generated list of random numbers. Concealment was	**Results** *Neonatal outcomes* **Stillbirth (include if reported as part of perinatal mortality)** Nifedipine: 0/99 No intervention:0/101 **Neonatal death up to 7 days (include if reported**	**Limitations** **Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias** **Random sequence generation:** low risk (random allocation generation)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
of preeclampsia remote from term, American Journal of Obstetrics and Gynecology, 167, 879-884, 1992 **Ref Id** 194652 **Country/ies where the study was carried out** US **Study type** RCT **Aim of the study** To assess whether nifedipine as compared to no intervention improves maternal and neonatal outcomes in women with mild pre-eclampsia (non-acute management) **Study dates** NR	**No. with pre-eclampsia[a] n (%)** 100 (100%) 100 (100%) **HELLP[b] n (%)** 3 (3%) 5 (5%) **Number of women with proteinuria > 300 mg per 24 hours** 83(83%) 85(85%) **Gestational age at treatment, weeks (mean, SD)** 32.8 (2.8) 33.4 (2.7) **sBP at entry (mean, SD)** 143.8 (5.6) 143.5 (5.8) **dBP at entry (mean, SD)** 93.9 (4.1) 94.2 (4.4 **Inclusion criteria** Women with mild pre-eclampsia 26 to 36 weeks' gestational age; with persistent elevation of BP (sBP 140-160 mmHg and dBP 90-110 mmHg); proteinuria (>300 mg per 24 hours) and/or elevated uric acid levels (≥6 mg/dl) **Exclusion criteria**	persistently below 140/90 mmHg were managed on an ambulatory basis (N not reported). These women were hospitalised again in the event of disease progression.	done using sealed envelopes No steroids were given to women. Simple size calculations were NR Follow-up length was not reported	**as part of perinatal mortality)** Nifedipine: 0/99 No intervention:0/101 **Small-for-gestational-age (BW<10th centile)** Nifedipine: 15/99 No intervention:13/101 **Gestational age at birth, mean weeks (SD)** Nifedipine: 36.1 (2.8) No intervention:36.7 (2.5) **Preterm birth (<37 weeks)** Nifedipine: 12/99 No intervention:0/101 **Admission to neonatal unit** Nifedipine: 30/99 No intervention:21/101 *Women outcomes:* **HELLP** Nifedipine: 4/98 No intervention:2/99	**Allocation concealment:** low risk (sealed envelopes were used) **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 if drop-out (20% and difference between groups <20%) **Selective reporting:** unclear risk (protocol does not appear to have been registered) **Other information**

<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>Source of funding

NR</td>
<td>Women with co-occurring complications or with fetal compromise</td>
<td></td>
<td></td>
<td>Placental abruption

Nifedipine: 3/98

No intervention:2/99

Onset of labour (induction)

Nifedipine: 3/98

No intervention:2/99

Mode of birth (C-section)

Nifedipine: 42/98

No intervention:35/99</td>
<td></td>
</tr>
<tr>
<td>Full citation

Sibai, B. M., Gonzalez, A. R., Mabie, W. C., Moretti, M., A comparison of labetalol plus hospitalization versus hospitalization alone in the management of preeclampsia remote from term, Obstetrics and Gynecology,</td>
<td>Sample size

N=186 (n=92 randomised to labetalol and n=94 randomised to no intervention)

Characteristics

<table><tr><th></th><th>Labetalol (n =92)</th><th>No intervention (n =94)</th></tr><tr><td>Age, years (mean, SD)</td><td>NR</td><td>NR</td></tr></table></td>
<td>Interventions

Labetalol 300 mg/day increased every 2 to 3 days as needed, maximum 2400 mg/day (method of administration was not reported)

No intervention</td>
<td>Details

Randomisation was performed with a computer generated list of random numbers and treatment allocation was concealed using a sealed envelope.

No other medications were used except iron supplements and prenatal vitamins</td>
<td>Results

Neonatal outcomes

Stillbirth

Labetalol 0/94

No intervention 0/97

Neonatal death

Labetalol: 1/94

No intervention: 0/97

SGA

Labetalol: 18/94</td>
<td>Limitations

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

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

Allocation concealment: low risk (women were allocated with sealed envelopes)</td>
</tr>
</table>

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
70, 323-327, 1987 **Ref Id** 442107 **Country/ies where the study was carried out** US **Study type** RCT **Aim of the study** To assess the effectiveness of labetalol as compared to no intervention in pregnancy outcomes of women with pre-eclampsia **Study dates** Not reported **Source of funding** Not reported	<table><tr><td>No. with pre-eclampsia[a] n (%)</td><td>92 (100)</td><td>94 (100)</td></tr><tr><td>Gestational age at entry (mean weeks [SD])</td><td>32.4 (3)</td><td>32.6 (2.4)</td></tr></table> [a] *sBP 140 to 160 and dBP 90 to 110 with proteinuria (more than 300mg/24h) and elevated uric acid levels (≥6 mg/dl)* **Inclusion criteria** 25 to 35 week´s gestation; sBP between 140 and 160 mmHg and dBP between 90 and 110 mmHg with proteinuria (>300mg/ 24 hours) and elevated uric acid levels (>4.6 mg/dL). **Exclusion criteria** Women with co-occurring conditions		No details were provided regarding use of statins and power sample calculations	No intervention: 9/97 **Birth weight** Labetalol: 220.4 (756) No intervention: 258 (762) **Admission to neonatal unit** Labetalol: 38/94 No intervention: 40/97 **Women outcomes** **Mode of birth (C-section)** Labetalol 39/92 No intervention 34/94	**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 details above) **Incomplete outcome data:** low risk (no drop out was reported) **Selective reporting:** unclear risk (study protocol does not appear to have been registered) **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>Subhedar, Vaidehi, Inamdar, Saunitra, Hariharan, C., Subhedar, Siddharth, Comparison of efficacy of labetalol and methyldopa in patients with pregnancy-induced hypertension, 2, 27, 2013

Ref Id

826157

Country/ies where the study was carried out

India

Study type

RCT

Aim of the study

To assess the effectiveness of methyldopa as compared with labetalol in pregnancy outcomes of</td>
<td>N= 180 (n= 90 randomised to the labetalol group and n=90 randomised to the methyldopa group)

Characteristics
<table>
<tr><th>Nifedipine (n =30)</th><th>Methyldopa (n = 90)</th><th>Labetalol (n=90)</th></tr>
<tr><td>Age, years (mean, SD NR)</td><td>24.41</td><td>24.85</td></tr>
<tr><td>No. with pre-eclampsia[a] n</td><td>90 (100)</td><td>90 (100)</td></tr>
<tr><td>Primigravida</td><td>53 (58.89)</td><td>49 (54.44)</td></tr>
<tr><td>dBP at entry</td><td>109.86 mmHg</td><td>109.48 mmHg</td></tr>
</table>
a Chromic hypertension: BP≥ 140/90 mmHg on 2 separate occasion 6 hours apart, Proteinuria 1+ dipstick in two midstream urine samples collected 4 hours apart, and after 20 weeks of pregnancy till term

Inclusion criteria

BP ≥140/90 mmHg on 2 separate occasion 6 hours apart, Proteinuria 1+ dipstick in two midstream urine samples collected 4 hours apart, and after 20 weeks of pregnancy till term

Exclusion criteria

Multiple pregnancy, eclampsia, and women with preexisting or concurrent medical disorders like diabetes mellitus, cardiac diseases, renal disease,</td>
<td>Methyldopa 250 mg tid

Labetalol 100mg tid.

If there was no fall in BP even after 48 hrs of drug therapy, dose of the medication was doubled</td>
<td>No details regarding unse of concurrent medication, randomisation, power sample calculations ir use of statins were provided.</td>
<td>Women outcomes

MAP

Labetalol: 96.90 (2.70)

Methyldopa: 98.15 (3.44)

Onset of labour (induction)

Labetalol: 23/90

Methyldopa: 18/90</td>
<td>Methodological limitations assessed using the Cochrane collaboration's tool for assessing risk of bias

Random sequence generation: unclear risk (no method of randomisation was reported)

Allocation concealment: unclear risk (no method of randomisation was reported)

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 details above)

Incomplete outcome data: low risk (no drop out was reported)

Selective reporting: high risk</td>
</tr>
</table>

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>women with pre-eclampsia

Study dates

September 2010 to September 2012

Source of funding

No funding sources</td><td>thyrotoxicosis, hemophilia and chronic hypertension attributable to hypertension during their pregnancy</td><td></td><td></td><td></td><td>Other information</td></tr>
<tr><td>Full citation

Vermillion, S. T., Scardo, J. A., Newman, R. B., Chauhan, S. P., A randomized, double-blind trial of oral nifedipine and intravenous labetalol in hypertensive emergencies of pregnancy, American Journal of Obstetrics & Gynecology, 181, 858-61, 1999

Ref Id

392829</td><td>Sample size

N= 50 (n=25 in the nifedipine group and n=25 in the labetalol group)

Characteristics<table><tr><th></th><th>Nifedipine (n =25)</th><th>Labetalol (n =25)</th></tr><tr><td>Age, years (mean, SD)</td><td>27.2 (7.3)</td><td>27 (6.4)</td></tr><tr><td>No. with pre-eclampsia[a] n (%)</td><td>NR</td><td>NR</td></tr><tr><td>Chronic hypertension with superimposed pre-eclampsia[b]</td><td>NR</td><td>NR</td></tr></table></td><td>Interventions

Nifedipine po in combination with placebo IV (50g of isotonic sodium chloride solution)

Labetalol IV in combination with oral placebo (cornstarch powder)</td><td>Details

No concurrent treatments were reported

Randomisation was performed using a computer-generation log, which was only available to the study pharmacists. Patients and clinicians were blinded to the randomisation regimens.

Follow-up: 24 hours

To detect a 20% difference in the</td><td>Results

Minutes (mean, SD) to achieve effective control of blood pressure (blood pressure goal = <160 mmHg systolic and <100 mm Hg diastolic)

Nifedipine: 25 (13.6)

Labetalol: 43.6 (25.4)</td><td>Limitations

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

Random sequence generation: low risk (performed using a computer-generation log)

Allocation concealment: unclear (no concealment method was reported)

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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out US **Study type** RCT **Aim of the study** To assess the efficacy of nifedipine and labetalol in the acute management of hypertensive disorders of pregnancy - **acute treatment** **Study dates** NR **Source of funding** NR	**Gestational age at treatment, weeks (mean, SD)** 34.3 (5.1) 33.6 (6) **Ethnicity: black** 14 (56%) 17 (68%) **No. of postnatal women included n (%)** 10 (40%) 11 (44%) **sBP at entry mean (SD)** 178 (7.8) 177 (8.4) **dBP at entry mean (SD)** 109 (5.3) 109 (6.5) [a,b] pre-eclampsia and chronic hypertension with superimposed pre-eclampsia were defined according to the American College of Obstetricians and Gynaecologists criteria **Inclusion criteria** Women with hypertensive emergencies of pregnancy (defined as sBP ≥ 170 or dBP ≥ 105 mmHg) **Exclusion criteria** Presence of a atrial-ventricular heart block; moderate to severe asthma; pre-exposure to the study medications up to 24 hours		time interval required to achieve the therapeutic blood pressure goal, with $\propto = 0.05$ and $\beta = 0.1$, it was established that 25 women would need to be allocated to each treatment group.		**Blinding of outcome assessment:** low risk (double blind trial) **Blinding (performance bias and detection bias):** low risk (see above details) **Incomplete outcome data:** low risk (no drop-outs were reported) **Selective reporting:** unclear risk (protocol does not appear to have been registered) **Other information**

<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

Vigil-De, Gracia P, Reyes, Tejada O, Calle, Miñaca A, Tellez, G, Chon, Vy, Herrarte, E, Villar, A, Ludmir, J, Expectant management of severe preeclampsia remote from term: the MEXPRE Latin Study, a randomized, multicenter clinical trial, American Journal of Obstetrics and Gynecology, 209, 425.e1-8, 2013

Ref Id

776840

Country/ies where the study was carried out

Panama, Ecuador, Guatemala, Peru

Study type

RCT</td>
<td>Sample size

N= 264 (n= 133 in the prompt birth group and n= 131 in the expectant management group)

Characteristics
<table>
<tr><th></th><th>Induction of labour

(n =133)</th><th>Expectant management

(n =131)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>27.9 (6.6)</td><td>28.4 (6.7)</td></tr>
<tr><td>No. with severe pre-eclampsia[a] n (%)</td><td>107 (80.4%)</td><td>100 /76.3%)</td></tr>
<tr><td>Superimposed pre-eclampsia[b] n (%)</td><td>19 (14.2%)</td><td>19 (14.5%)</td></tr>
<tr><td>No. of women with severe gestational hypertension[c] n (%)</td><td>7 (5.4%)</td><td>12 (9.2%)</td></tr>
<tr><td>Mean (SD) urinary protein, 24 h</td><td>2.2 (2.8)</td><td>2.2 (2.4)</td></tr>
<tr><td>Multiple pregnancy n (%)</td><td>4 (3%)</td><td>7 (5.2%)</td></tr>
</table>
</td>
<td>Interventions

Induction of labour: women received glucocorticoid therapy followed by birth in 24 to 72 hours

Expectant management: women were treated expectantly and received glucocorticoid therapy followed by birth only for fetal or maternal indications or reaching 34 week gestation</td>
<td>Details

Concurrent treatment: bed rest to prevent and manage seizures and magnesium sulphate as a 4g IV loading dose followed by 1g IV per hour for 24 to 48 hours. In the prompt birth group, magnesium sulphate was continued until 24 hours after birth. Women with severe hypertension (≥160/110 mmHg) were administered bolus doses of hydralazine, labetalol or oral nifedipine along with 4 doses of 6 mg of dexamethasone intramuscularly or 2 doses of 12 mg of betamethasone intramuscularly given 24 hours apart. Some women with severe hypertension also received oral</td>
<td>Results

Induction of labour

Neonatal outcomes

Stillbirth (defined as death in utero and death from birth to 28 days after birth)

Induction of labour: 13/137

Expectant management:12/138

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

Induction of labour: 13/137

Expectant management:30/138

Birth weight mean (SD)

Induction of labour: 1543 (438)

Expectant management: 1659 (509)

Admission to neonatal unit

Induction of labour: 95/137</td>
<td>Limitations

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

Random sequence generation: unclear risk (method not reported)

Allocation concealment: unclear risk (not reported)

Blinding of participants and personnel: high risk (open trial)

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

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

Selective reporting: unclear risk (protocol does not appear to have been registered)

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

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To assess whether expectant management improves outcomes as compared to induction of labour in women with **severe pre-eclampsia**- acute management **Study dates** NR **Source of funding** Marjorie Milham Research Fund, Pennsylvania Hospital	<table><tr><td>**Ethnic origin: white (latin) n (%)**</td><td>133 (100%)</td><td>131 (100%)</td></tr><tr><td>**Nulliparous n (%)**</td><td>55 (41.3%)</td><td>53 (39.8%)</td></tr><tr><td>**sBP at entry mean (SD)**</td><td>161.6 (15.5)</td><td>161.3 (14.9)</td></tr><tr><td>**dBP at entrymean (SD)**</td><td>105.9 (9.9)</td><td>105.4 (8.6)</td></tr></table> [a] **severe pre-eclampsia:** elevated BP (at least 140/90 mmHg) with proteinuria (0.3 g or greater in a 24 h urine specimen) associated with one of the following symptoms: sBP ≥ 160 or sBP ≥110,proteinuria of at least 5g in a 2 hours urine specimen, headache, visual disturbances, epigastric pain, or tinnitus. [b] **Superimposed pre-eclampsia:** definition not provided [c] **Severe Gestational hypertension:** sBP/dBP ≥160/110 mmHg **Inclusion criteria** Gestational age between 28 and 33 weeks 'gestation with severe hypertensive disorders; women with singleton or twin pregnancy. **Exclusion criteria**		antihypertensive medication (α methyldopa, nifedipine or hydralazine). The administration of oral antihypertensive medication after the acute management of severe hypertension was at the discretion of the clinicians. Women were randomly allocated in a 1:1 ratio. The study was not blinded. Duration of follow up for outcome data and sample size calculations were not reported	Expectant management:102/138 *Women outcomes:* **Eclampsia (defined as generalised convulsions not caused by epilepsy or HELLP)** Induction of labour: 1/137 Expectant management:1/138 **HELLP (defined as platelet count ≤ 150000 aspartate aminotransferase ≥ 70 units/L, alanine aminotransferase ≥ 40 units/L)** Induction of labour: 21/137 Expectant management:18/138 **Placental abruption** Induction of labour: 2/133 Expectant management:10/131	This study should be stratified as was developed in low/middle income countries **Other information**

<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>Eclampsia, HELLP, pre-eclampsia with renal failure or pulmonary oedema, active vaginal bleeding, ruptured membranes, placenta previa, diabetes mellitus or gestational diabetes, pre-existing renal disease, or autoimmune disease.

Women with major fetal abnormalities, fetal growth restriction, deficiency of amniotic fluid, and reverse amniotic artery Doppler flow were also excluded.</td><td></td><td></td><td>Mode of birth (C-section)

Induction of labour: 118/133

Expectant management:124/131</td><td></td></tr>
<tr><td>Full citation

Vigil-De Gracia, P., Lasso, M., Ruiz, E., Vega-Malek, J. C., de Mena, F. T., Lopez, J. C., Severe hypertension in pregnancy: Hydralazine or labetalol. A randomized clinical trial, European Journal of Obstetrics Gynecology and Reproductive Biology, 128, 157-162, 2006

Ref Id

776841</td><td>Sample size

N= 200 (n= 100 in the hydralazine group and n= 100 in the labetalol group)

Characteristics
<table>
<tr><th></th><th>Hydralazine (n = 100)</th><th>Labetalol (n = 100)</th></tr>
<tr><td>Age, years (mean, SD)</td><td>29.9 (6.4)</td><td>29.3 (6.8)</td></tr>
<tr><td>No. with severe pre-eclampsia[a] n (%)</td><td>54 (54%)</td><td>57 (57%)</td></tr>
<tr><td>Severe pre-eclampsia with HELLP[b] n (%)</td><td>1 (1%)</td><td>1 (1%)</td></tr>
<tr><td>Superimposed pre-eclampsia[c]</td><td>15 (15%)</td><td>15 (15%)</td></tr>
</table></td><td>Interventions

Hydralazine 5mg IV every 20 minutes until dBP ≤ 110 mmHg or sBP ≤ 160 mmHg (up to 5 consecutive doses) Labetalol 20 mg IV every 20 minutes until dBP ≤ 110 mmHg or sBP ≤ 160 mmHg (up to 5 consecutive doses)</td><td>Details

Concurrent treatment: Four 6-mg doses of dexamethasone were given intramuscularly 12h apart for pregnancies between 24 and 34 weeks gestation. A plasma volume expansion was given to all women in the study at a rate of 75ml/h. In the presence of oliguria, 1 or 2 fluid boluses of 300-500 ml were administered.

Randomisation was performed with a computer-generated list by</td><td>Results

Neonatal outcomes

Neonatal death up to 7 days (include if reported as part of perinatal mortality) Hydralazine: 2/102 Labetalol: 2/103

Birth weight (mean, SD) Hydralazine: 2677 (770) Labetalol: 2646 (898)

Admission to neonatal unit Hydralazine: 32/102 Labetalol: 32/103

Women outcomes:

Maternal death Hydralazine: 0/100 Labetalol: 0/100

Severe hypertension (dBP/ sBP 160 or 110 mmHg) Hydralazine: 5/100 Labetalol: 5/100</td><td>Limitations

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

Random sequence generation: low risk (computer generated) Allocation concealment: low risk (sequentially numbered opaque envelopes)

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

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

Study details	Participants			Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Panama **Study type** RCT **Aim of the study** To assess the efficacy of hydralazine and labetalol for lowering blood pressure in pregnancy - acute management **Study dates** Recruitment was between 1 December 2003 to 17 November 2004 **Source of funding** NR	**Eclampsia[d] n (%)**	1 (1%)	2 (2%)		means of sequentially numbered, opaque, sealed enveloped. The study was not blind. Duration of follow up for outcome data was not reported. It was estimated that 186 women would need to enroll to detect an 80% reduction in maternal hypertension using labetalol. The authors allowed for a 10% of rate failure to meet the inclusion criteria.	**Eclampsia** Hydralazine: 0/100 Labetalol: 0/100 **HELLP** Hydralazine: 2/100 Labetalol: 2/100 **Placental abruption** Hydralazine: 2/100 Labetalol: 1/100 **Mode of birth (C-section)** Hydralazine: 51/100 Labetalol: 56/100	**Incomplete outcome data:** low risk (drop-out<20% and difference between groups <20%) **Selective reporting:** unclear risk (protocol does not appear to have been registered) **Other information**
	No. of women with chronic hypertension[e] n (%)	8 (8%)	8 (8%)				
	No. of women with gestational hypertension[f] n (%)	20 (20%)	17 (17%)				
	Urinary protein (24h)	1268 (2133)	1135 (1683)				
	Gestational age at treatment, weeks (mean, SD)	35.9 (3.5)	35.3 (4)				
	Multiple pregnancy n (%)	2 (2%)	4 (4%)				
	Parity mean (SD)	2.3 (1.7)	1.9 (1.3)				
	sBP ≥ 160 mmHg at entry	89	88				
	dBP ≥ 110 mmHg at entry	51	51				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	a severe pre-eclampsia: elevated BP (at least 140/90 mmHg) with proteinuria (a dipstick reading of 1+ or more) associated with one of the following symptoms: headache, visual disturbances, epigastric pain, oliguria, elevated transaminases, elevated creatinine level, hemolysis, low platelet count, intrauterine growth restriction, low amniotic fluid levels, and pulmonary edema **or** an elevated BP (≥160/110 mmHg)+ proteinuria in the absence of any of the above mentioned features. **b HELLP:** diagnosis of hypertensive disorder plus one of the following: LDH ≥ 600 U/l, total bilirubin ≥ 1.2 mg/dl, hemolysis (2 or more findings); characteristic peripheral blood smear; low hemoglobin count; AST ≥ 70 U/l; ALT ≥ 50; LDH ≥ 600 U/l ; low platelet count ≤ 150 000 platelets/ µl **c Superimposed pre-eclampsia:** (1) for women who had gestational hypertension and no proteinuria at < 20 weeks' gestation, superimposed PE was defined as sudden increase in BP (if hypertension had previously been controlled,), new-onset proteinuria (≥0.3 g of protein in a 24-h specimen); platelet count < 100,000 cells/mm3; along with one of the following symptoms: headache, loss of vision in part of the eye, or epigastric pain. (2) For those women with pre-gestational hypertension and proteinuria before 20 weeks' gestation, any of the following symptoms: sudden increase in proteinuria, blood pressure (if previously controlled), thrombocytopenia, increase in alanine aminotransferase; and/or the following symptoms: headache, loss of vision in part of the eye, or epigastric pain. **d Eclampsia:** presence of seizures in a person with hypertensive disoders of pregnancy that cannot be attributed to other causes				

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
	e Chronic hypertension: pre-gestational hypertension, persistent BP elevations of at least 140/90 mmHg before the 20th week of gestation **f Gestational hypertension:** BP elevation detected for the first time after mid-pregnancy without proteinuria **Inclusion criteria** ≥ 24 weeks gestation; sBP ≥ 160 mmHg and/ or dBP ≥ 110 mmHg; no concurrent antihypertensive treatment and no contraindications to hydralazine or labetalol **Exclusion criteria** NR				

Appendix E – Forest plots

(No forest plots were generated for comparisons 1-3, 7, 8 and 10 as no meta-analyses were performed)

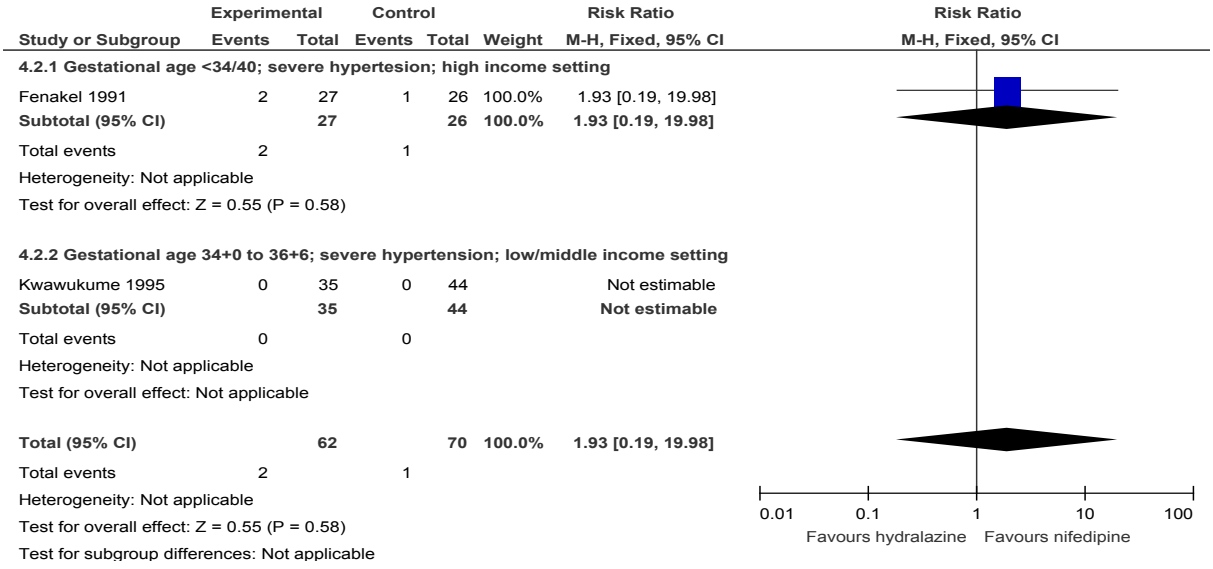
Comparison 4. Hydralazine versus nifedipine (acute management)

Outcomes for babies

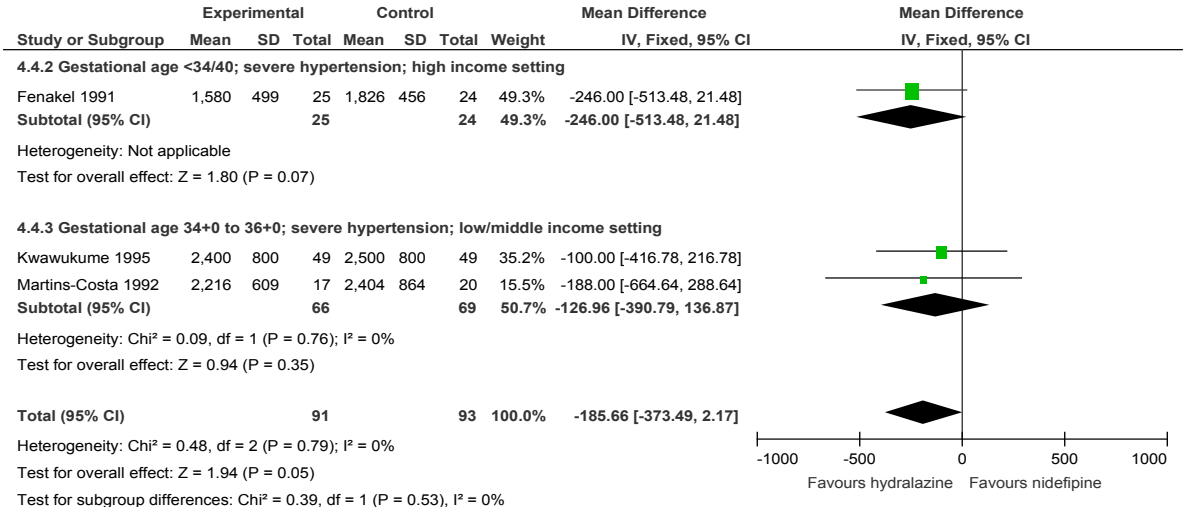
Critical outcomes

Neonatal death

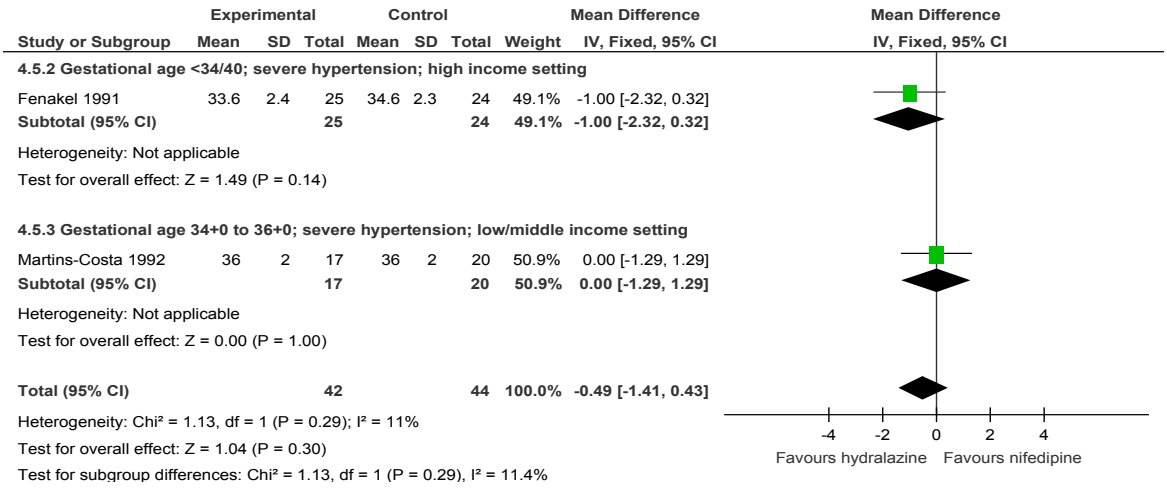
Figure 1: Comparison 4. Hydralazine versus nifedipine (acute management)



Birth weight



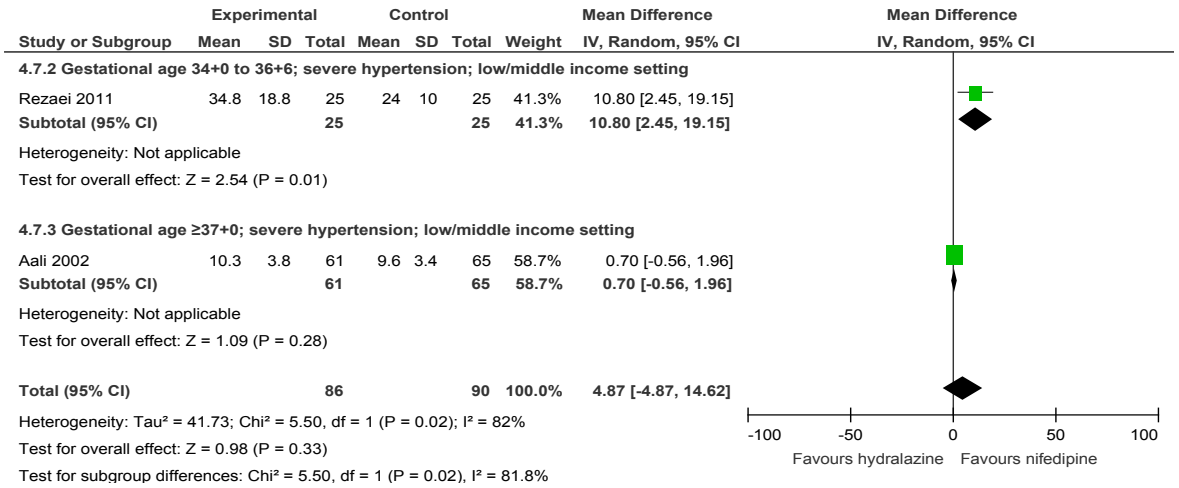
Gestational age at birth (weeks)



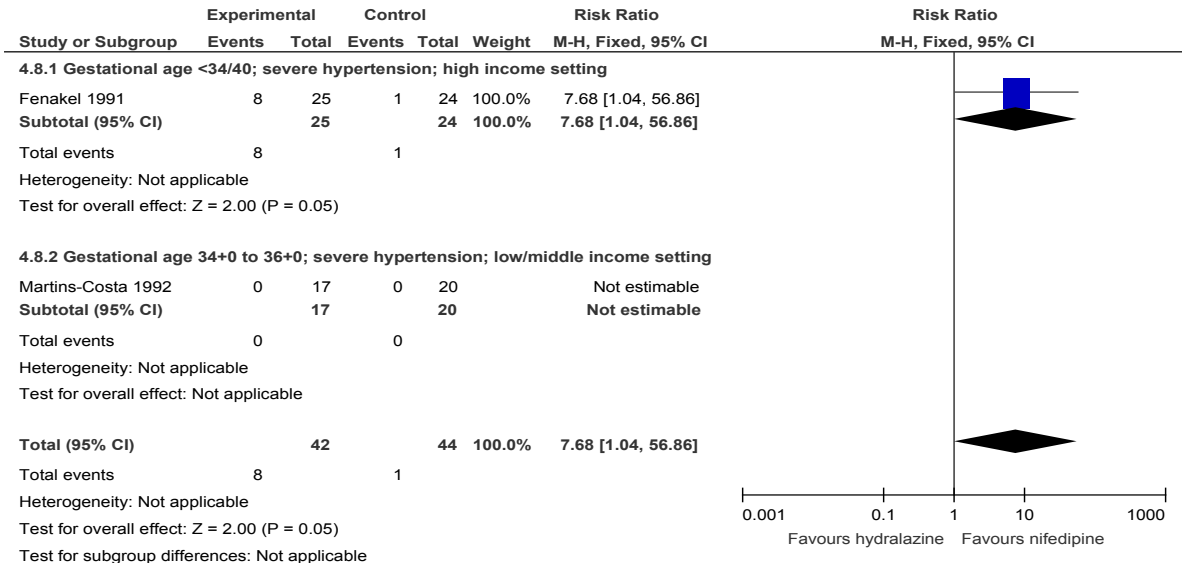
Outcomes for women

Critical outcomes

Minutes needed to achieve effective control of blood pressure

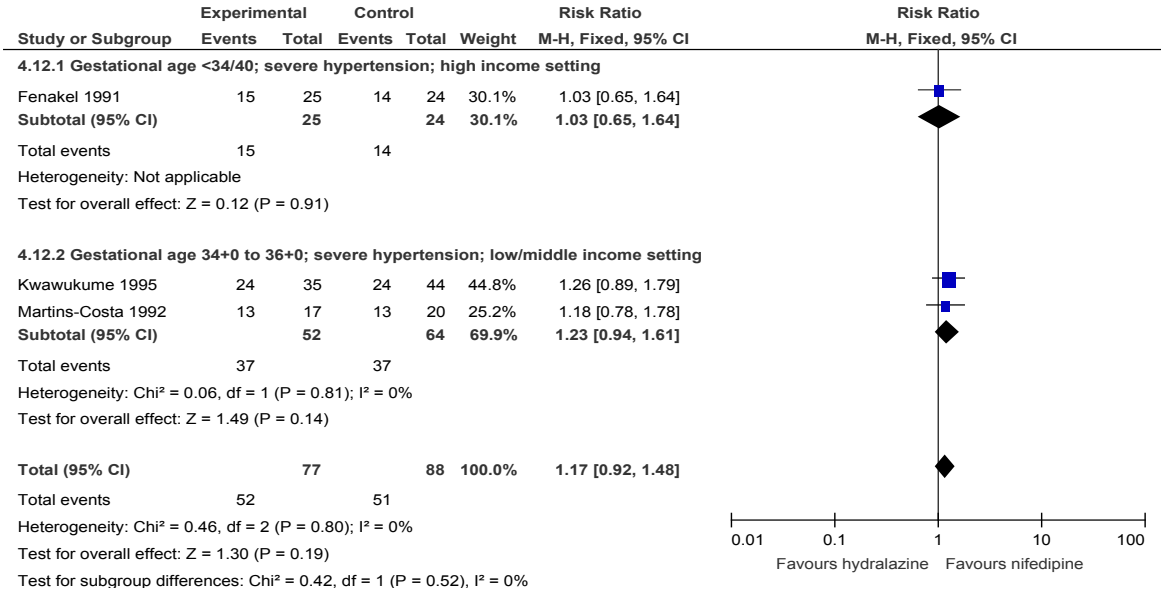


Severe hypertension



Important outcomes

Mode of birth



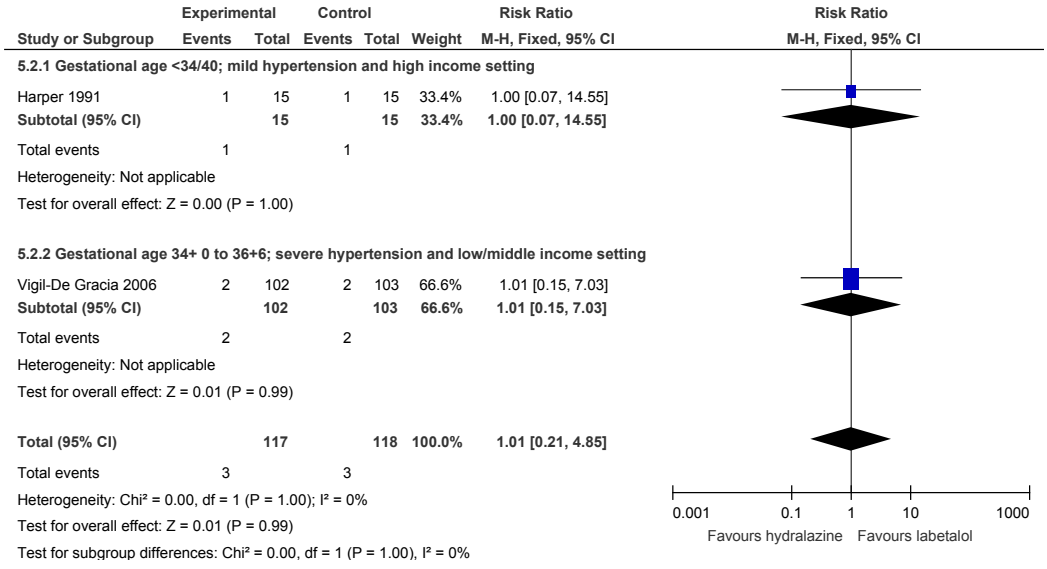
Comparison 5. Hydralazine versus labetalol (acute management)

Outcomes for babies

Critical outcomes

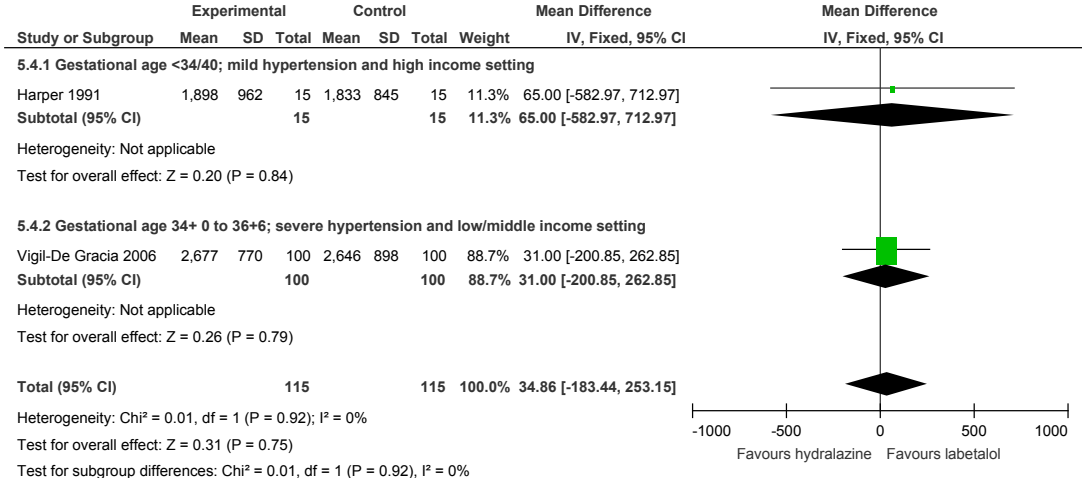
Neonatal death

Figure 2: Comparison 5. Hydralazine versus labetalol (acute management)



Important outcomes

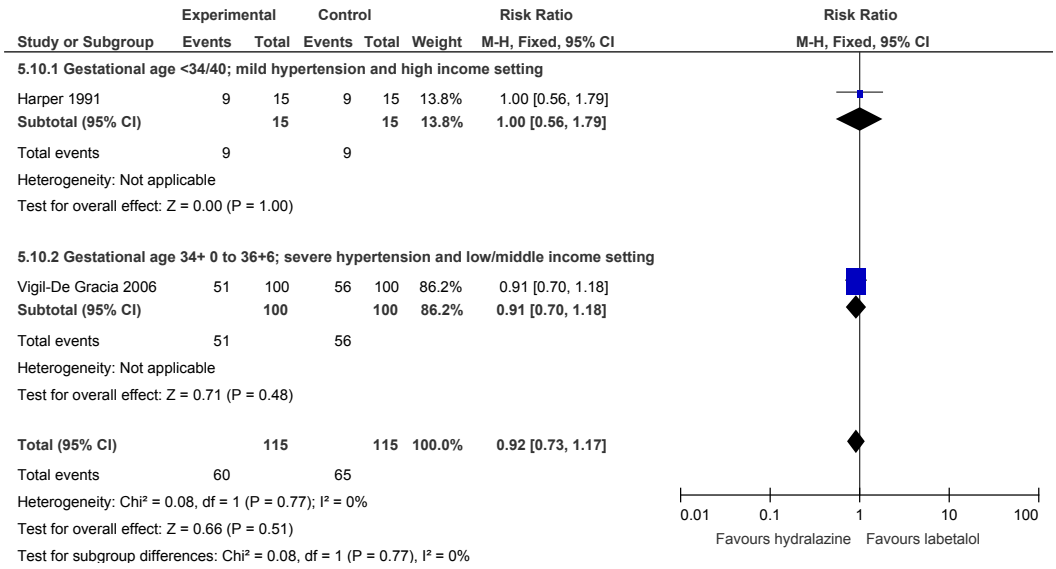
Birth weight



Outcomes for women

Important outcomes

Mode of birth (C-section)



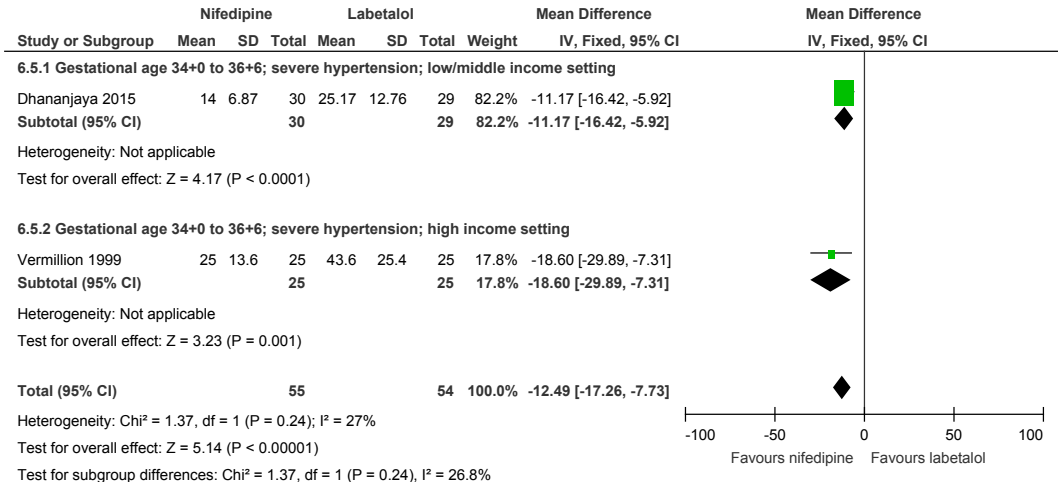
Comparison 6. Nifedipine versus labetalol

Outcomes for women

Critical outcomes

Minutes needed to effective control of blood pressure

Figure 3: Comparison 6. Nifedipine versus labetalol



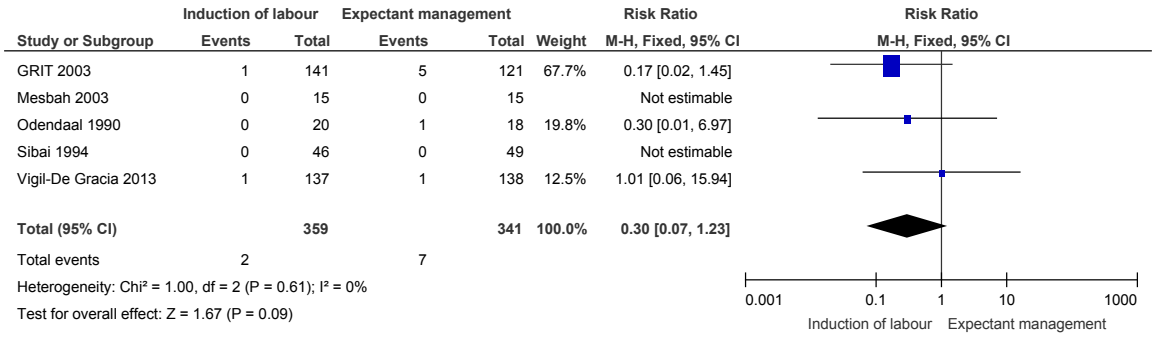
Comparison 9. Immediate birth versus expectant management

Outcomes for babies

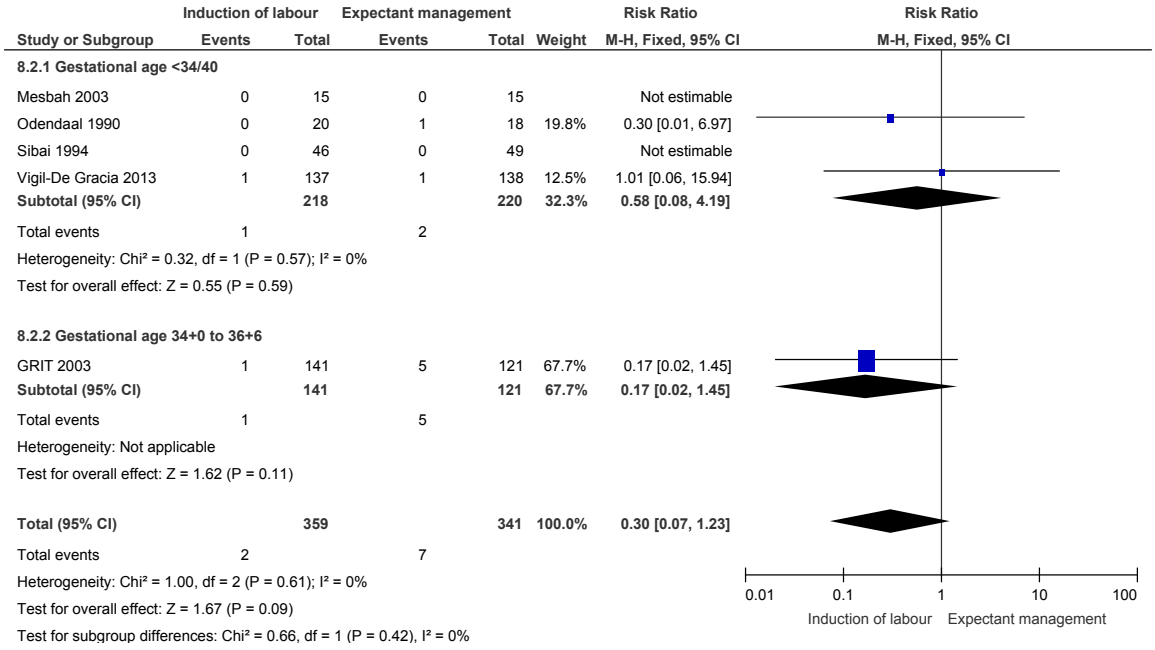
Critical outcomes

Stillbirth (overall estimate)

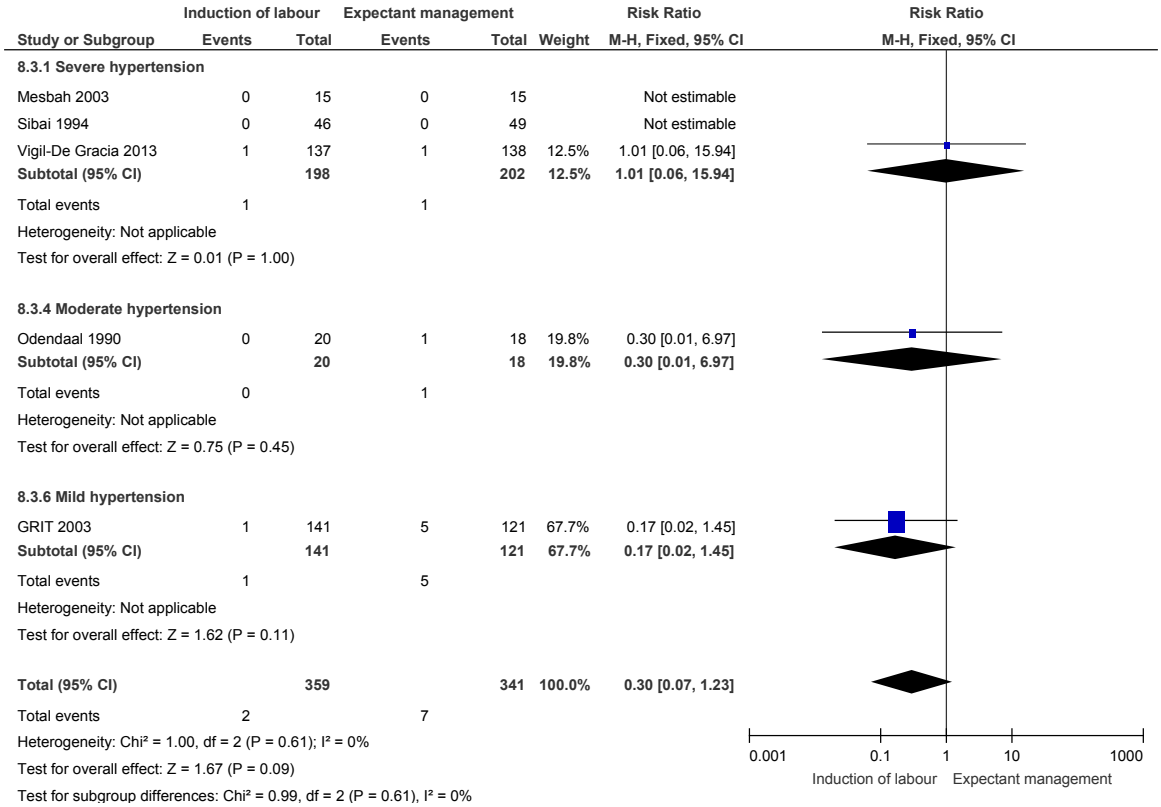
Figure 4: Comparison 9. Immediate birth versus expectant management



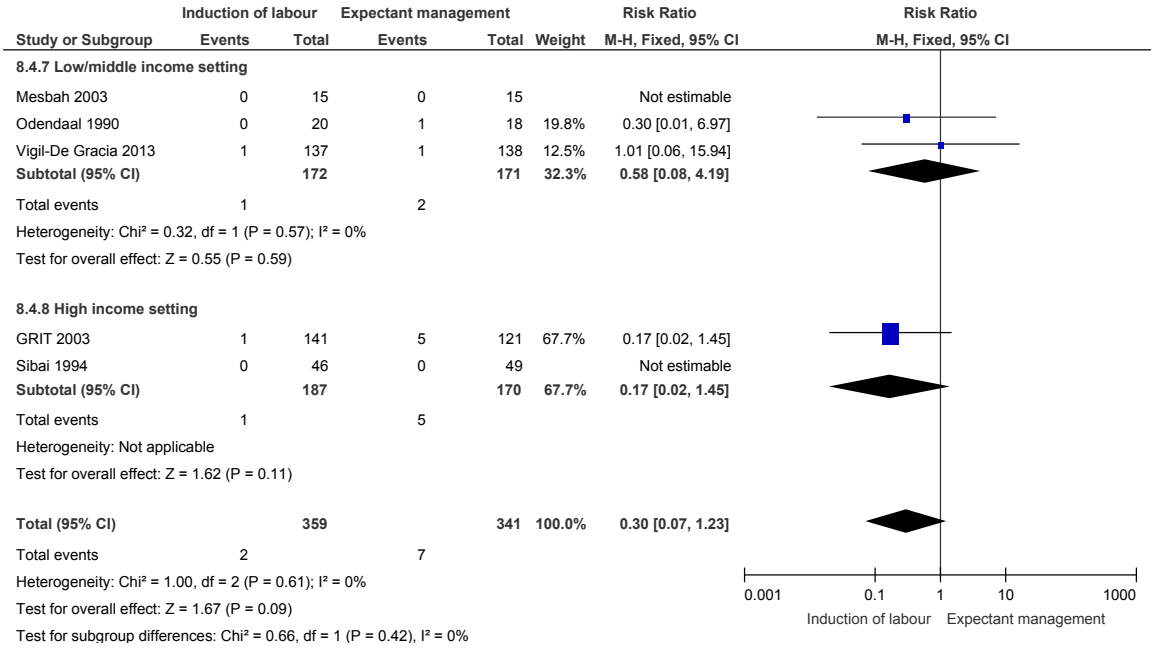
Stillbirth by gestational age



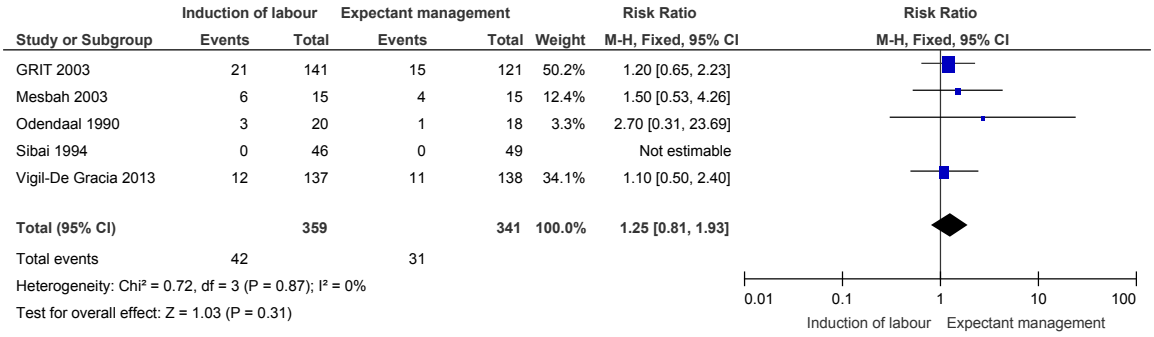
Stillbirth by severity of hypertension



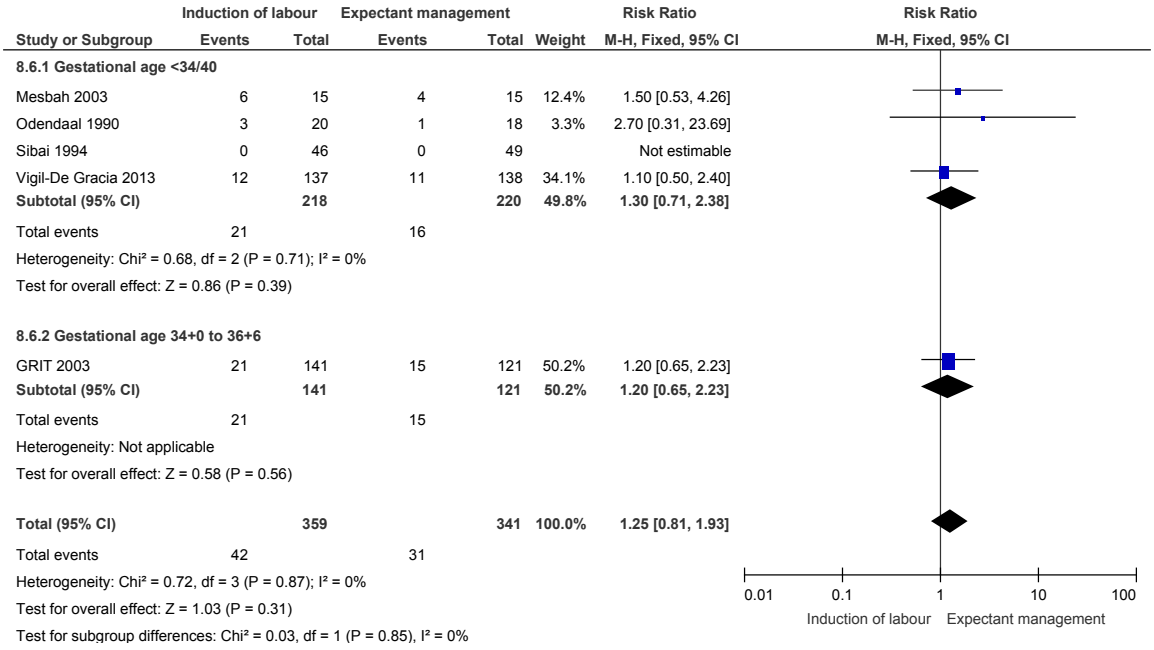
Stillbirth by income setting



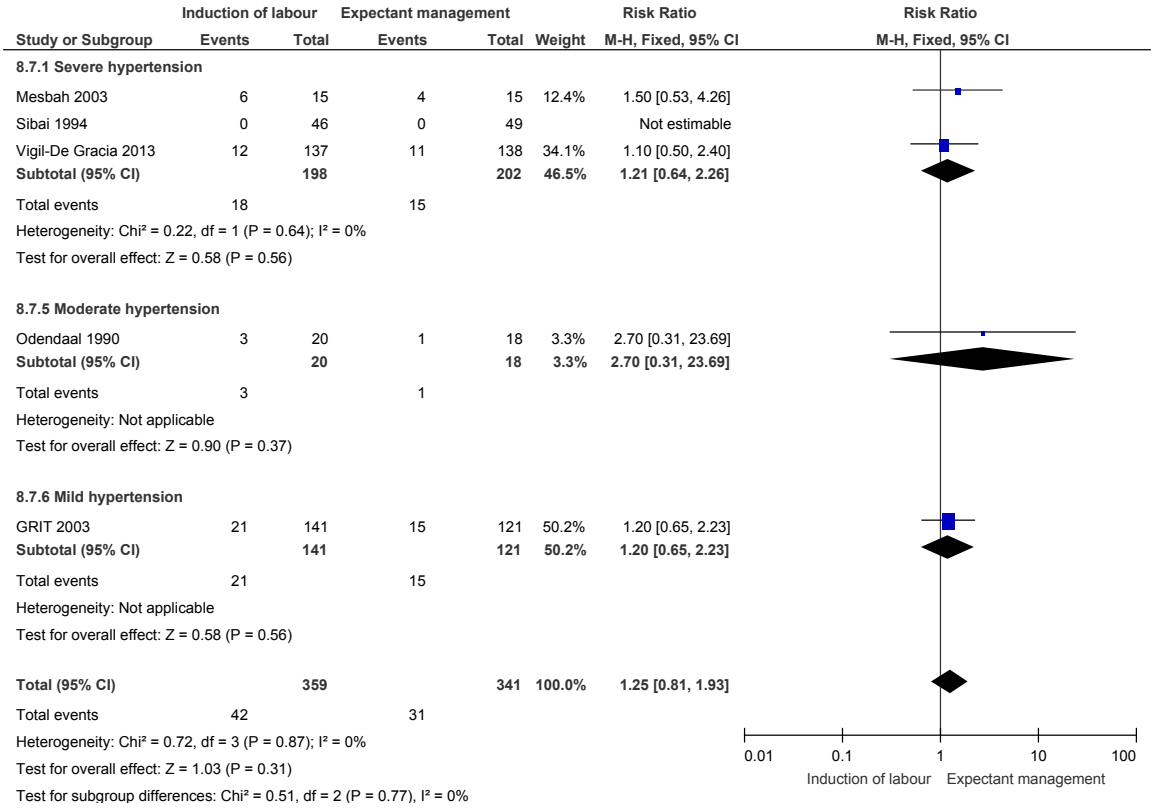
Neonatal death (overall estimate)



Neonatal death by gestational age

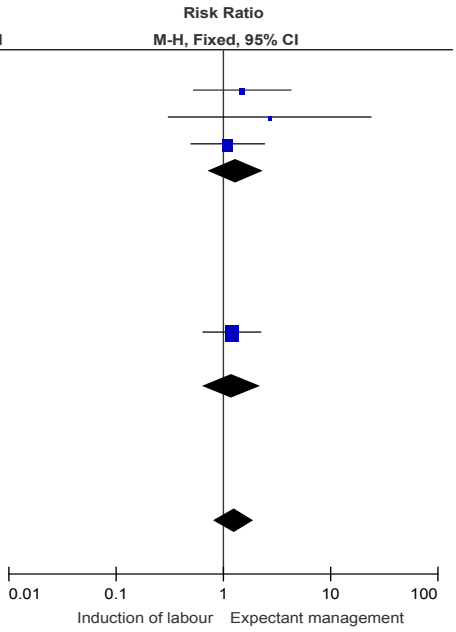


Neonatal death by severity of hypertension



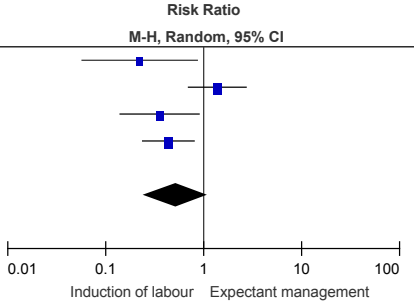
Neonatal death by income setting

Study or Subgroup	Induction of labour Events	Total	Expectant management Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.8.7 Low/middle income setting						
Mesbah 2003	6	15	4	15	12.4%	1.50 [0.53, 4.26]
Odendaal 1990	3	20	1	18	3.3%	2.70 [0.31, 23.69]
Vigil-De Gracia 2013	12	137	11	138	34.1%	1.10 [0.50, 2.40]
Subtotal (95% CI)		**172**		**171**	**49.8%**	**1.30 [0.71, 2.38]**
Total events	21		16			
Heterogeneity: Chi² = 0.68, df = 2 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.86 (P = 0.39)						
8.8.8 High income setting						
GRIT 2003	21	141	15	121	50.2%	1.20 [0.65, 2.23]
Sibai 1994	0	46	0	49		Not estimable
Subtotal (95% CI)		**187**		**170**	**50.2%**	**1.20 [0.65, 2.23]**
Total events	21		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Total (95% CI)		**359**		**341**	**100.0%**	**1.25 [0.81, 1.93]**
Total events	42		31			
Heterogeneity: Chi² = 0.72, df = 3 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.31)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%						

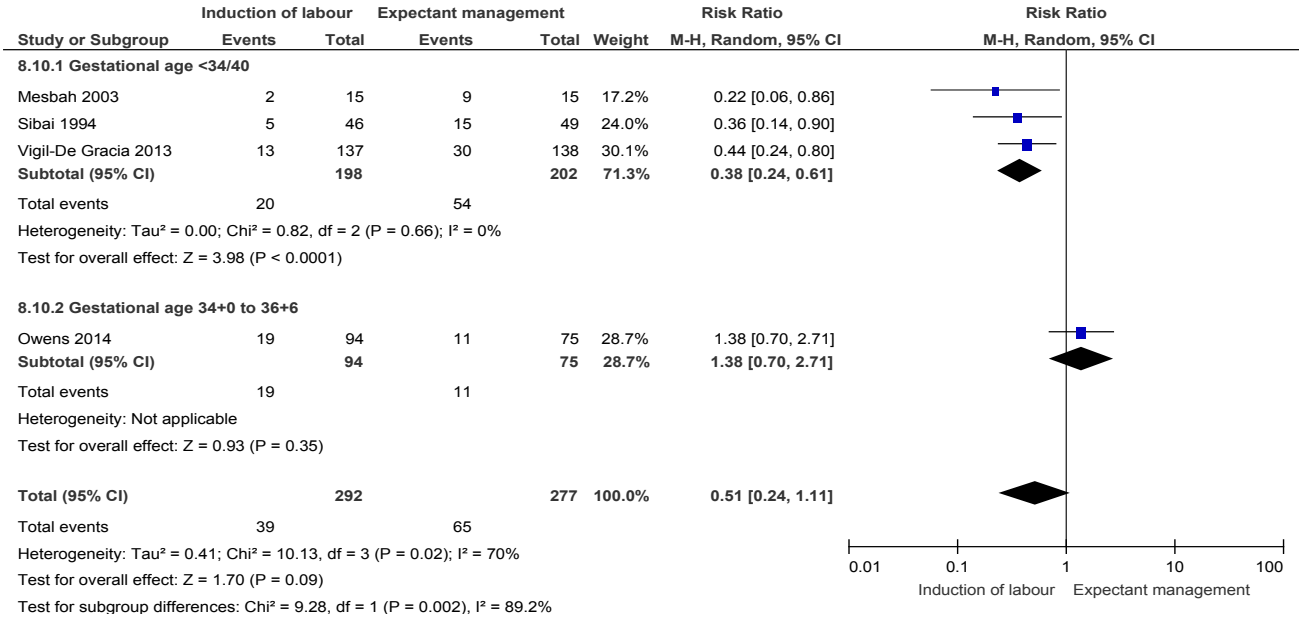


Small-for-gestational age (overall estimate)

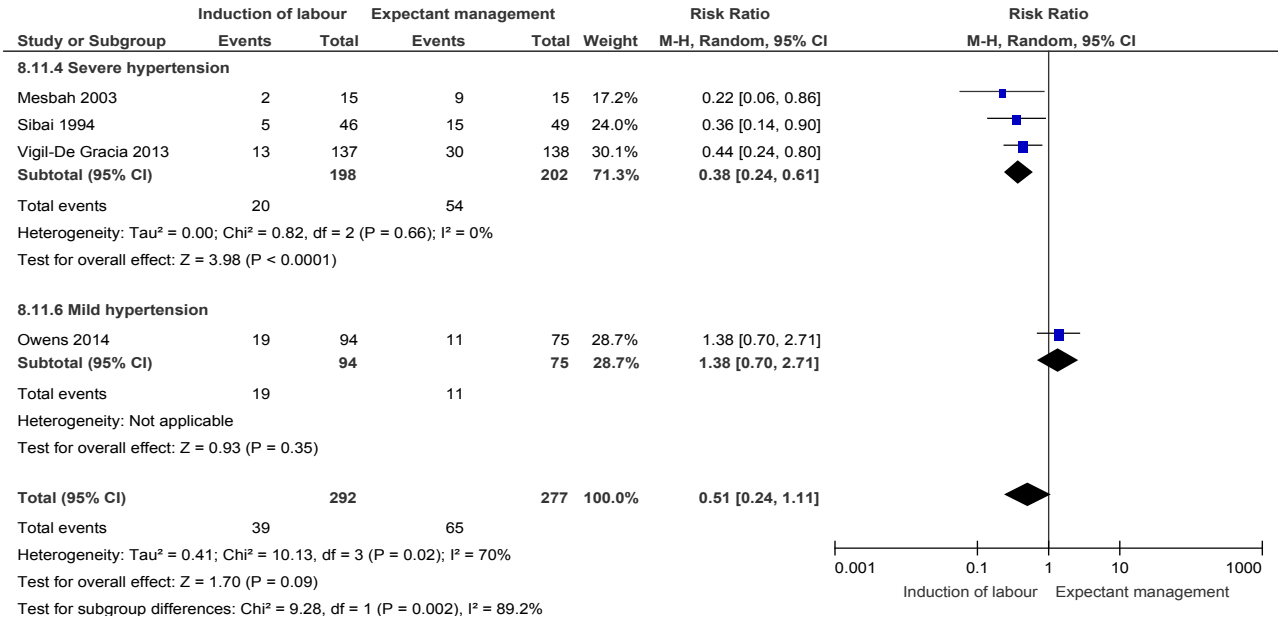
Study or Subgroup	Induction of labour Events	Total	Expectant management Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Mesbah 2003	2	15	9	15	17.2%	0.22 [0.06, 0.86]
Owens 2014	19	94	11	75	28.7%	1.38 [0.70, 2.71]
Sibai 1994	5	46	15	49	24.0%	0.36 [0.14, 0.90]
Vigil-De Gracia 2013	13	137	30	138	30.1%	0.44 [0.24, 0.80]
Total (95% CI)		**292**		**277**	**100.0%**	**0.51 [0.24, 1.11]**
Total events	39		65			
Heterogeneity: Tau² = 0.41; Chi² = 10.13, df = 3 (P = 0.02); I² = 70%						
Test for overall effect: Z = 1.70 (P = 0.09)						



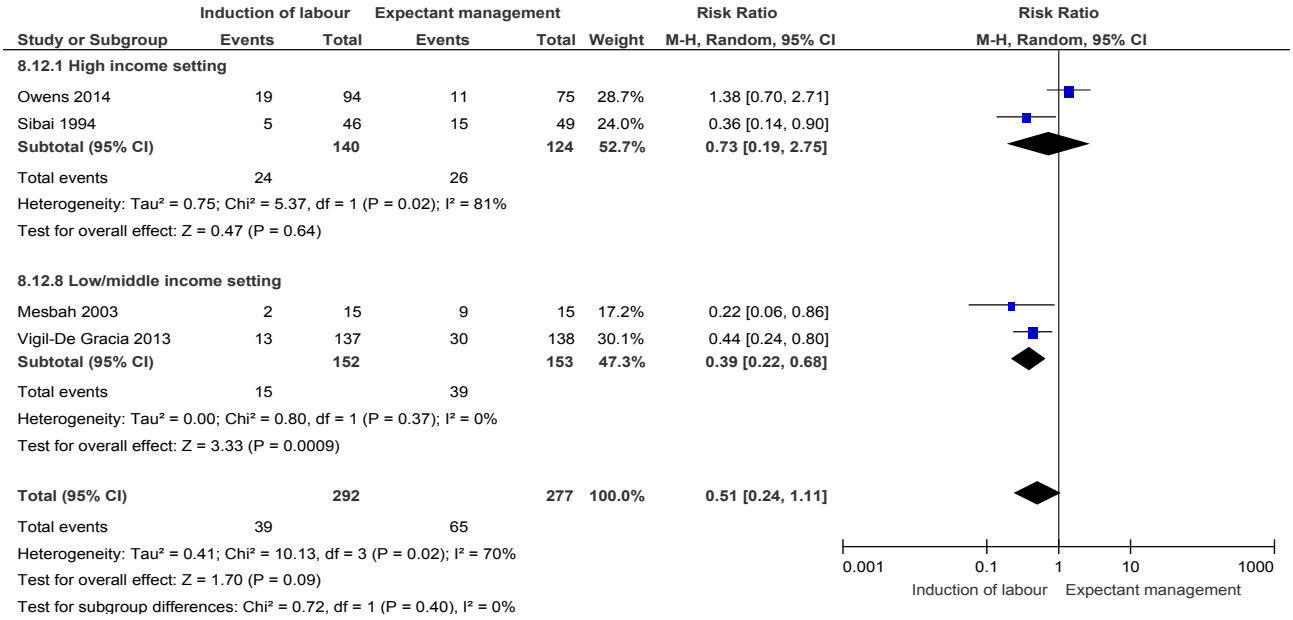
Small-for-gestational age by gestational age



Small-for-gestational age by severity of hypertension

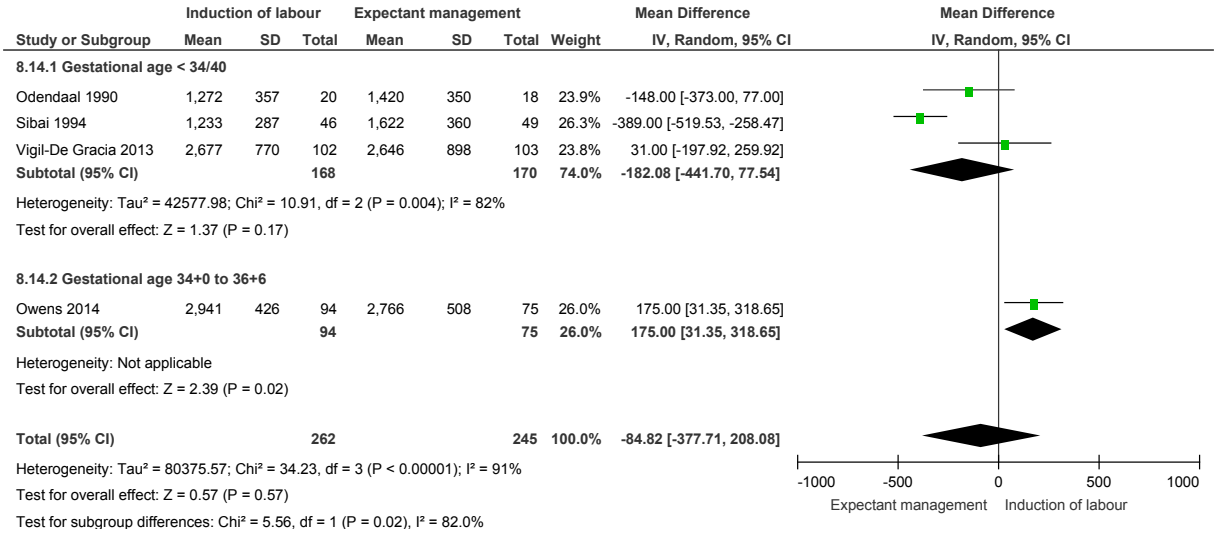


Small-for-gestational age by income setting

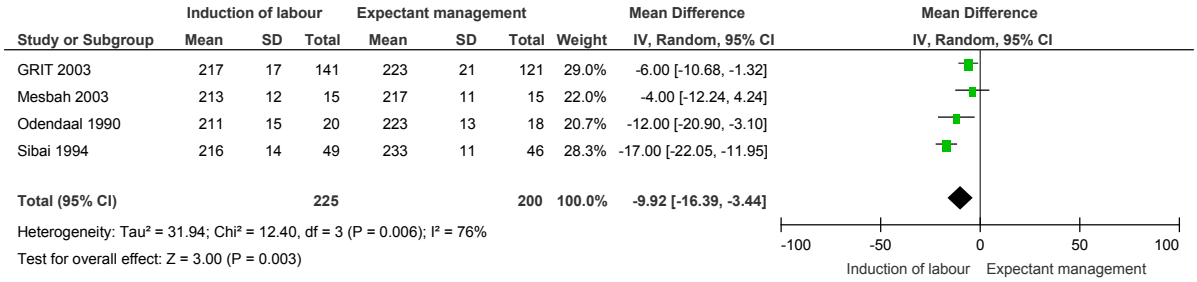


Important outcomes

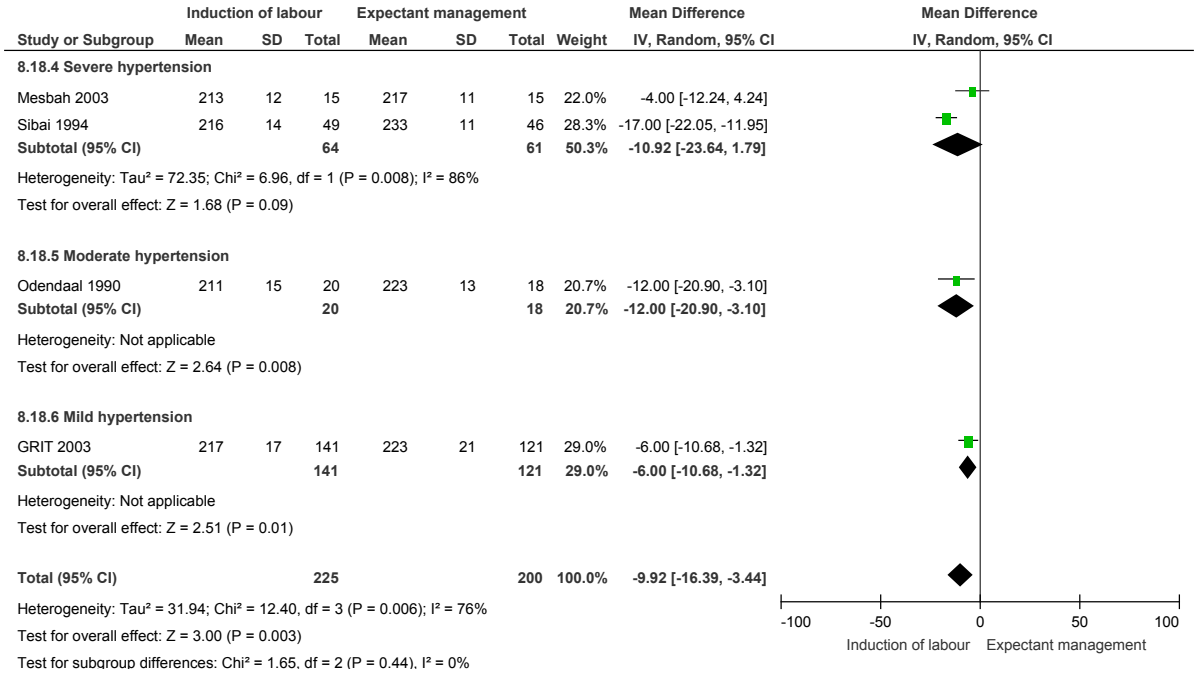
Birth weight by gestational age



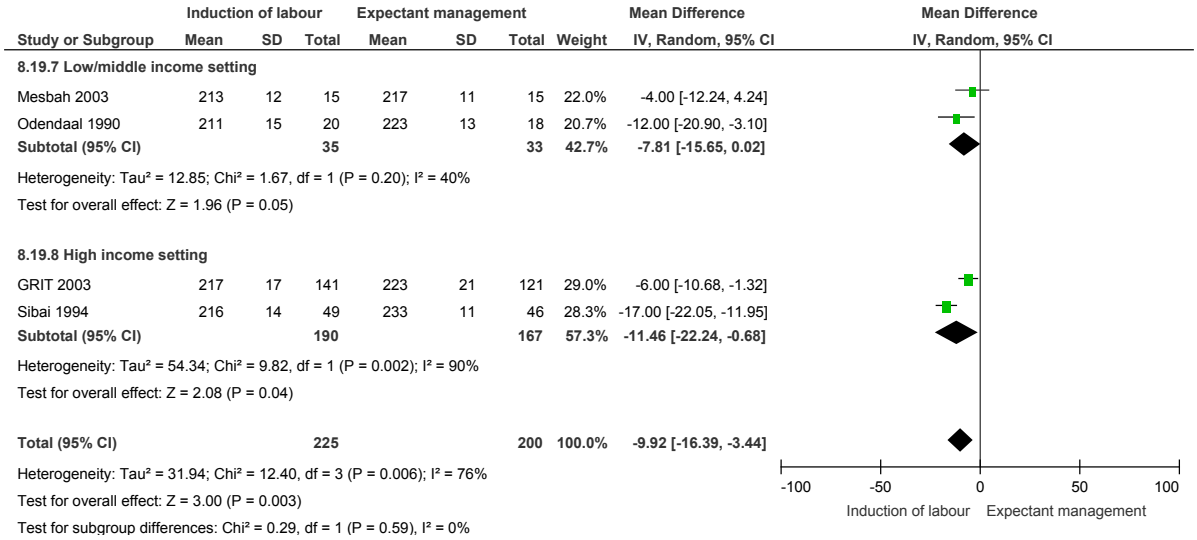
Gestational age at birth (overall estimate) (weeks)



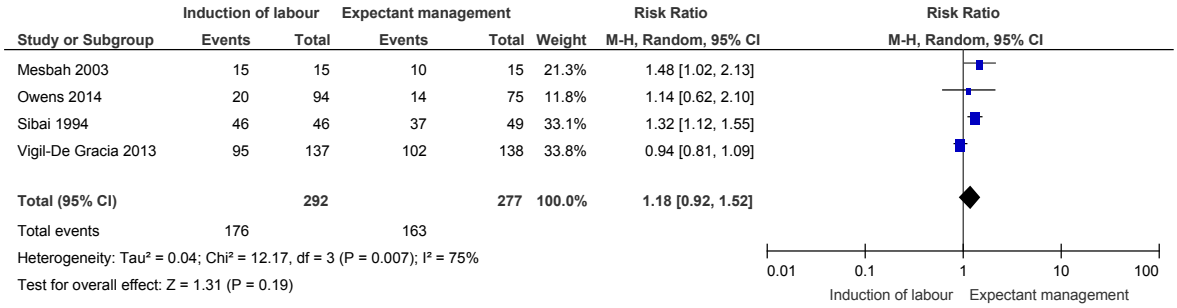
Gestational age at birth by severity of hypertension (weeks)



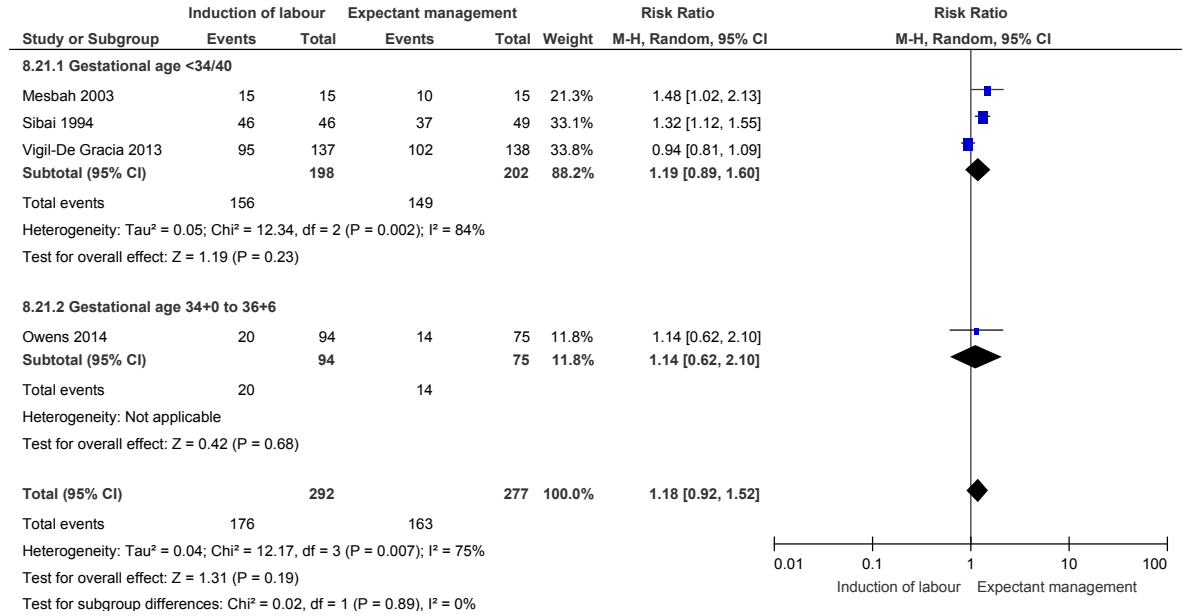
Gestational age at birth by income setting (weeks)



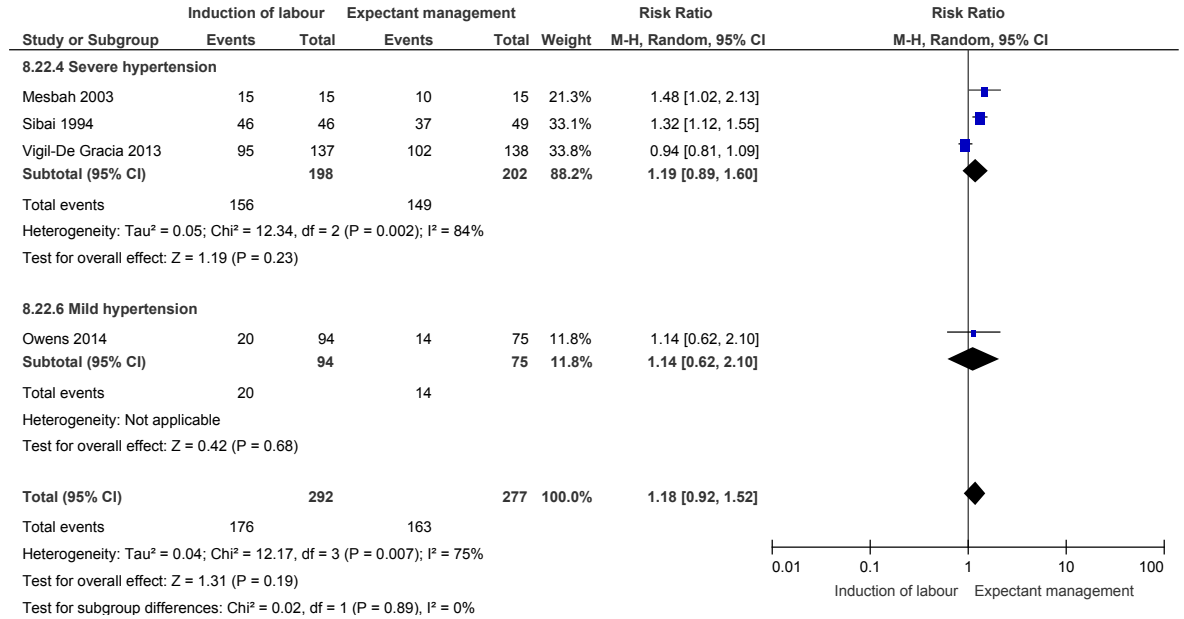
Admission to neonatal unit (overall estimate)



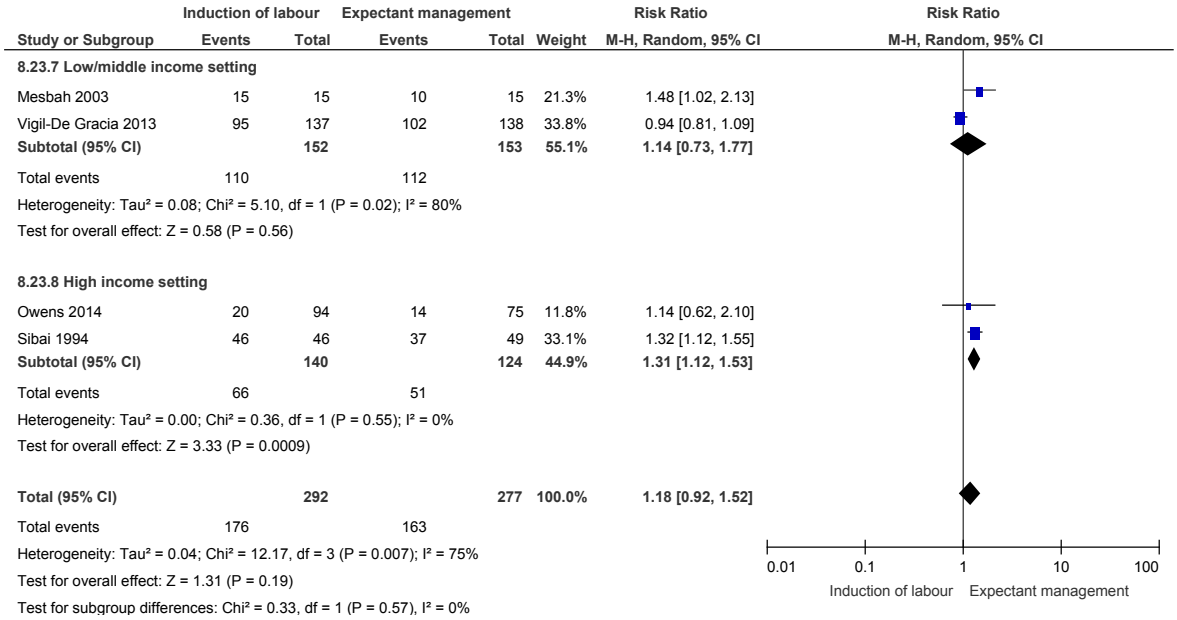
Admission to neonatal unit by gestational age



Admission to neonatal unit by severity of hypertension



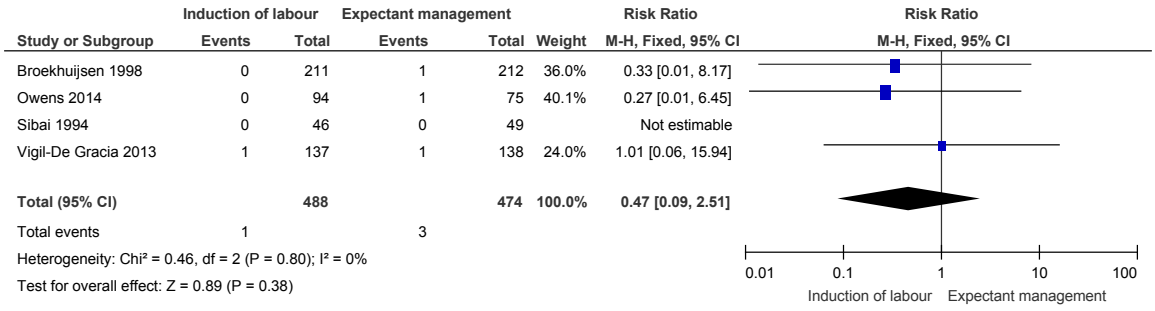
Admission to neonatal unit by income setting



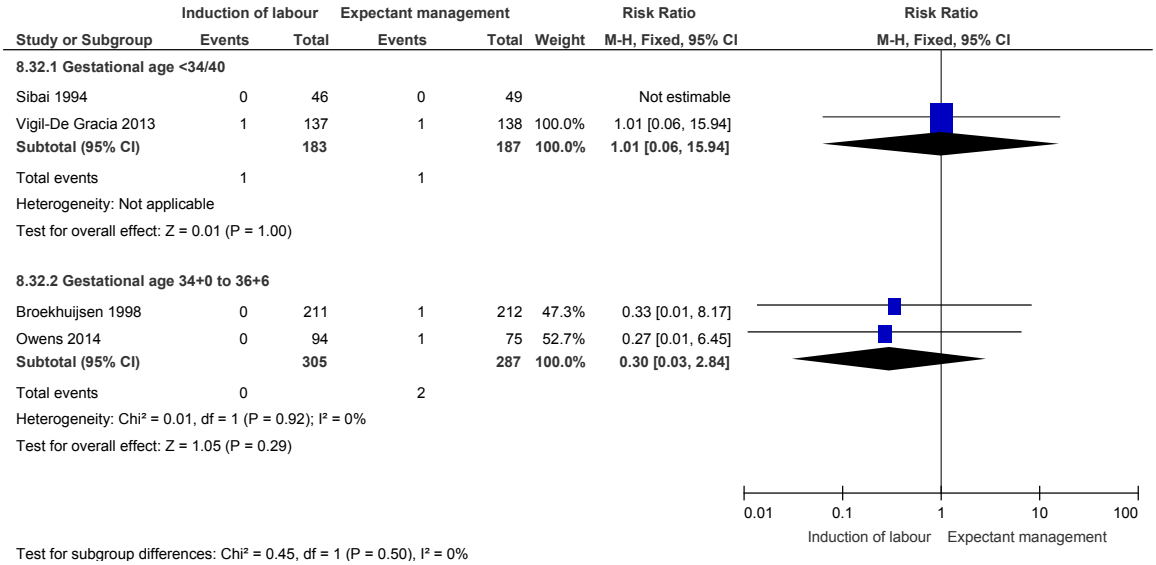
Outcomes for women

Important outcomes

Eclampsia (overall estimate)

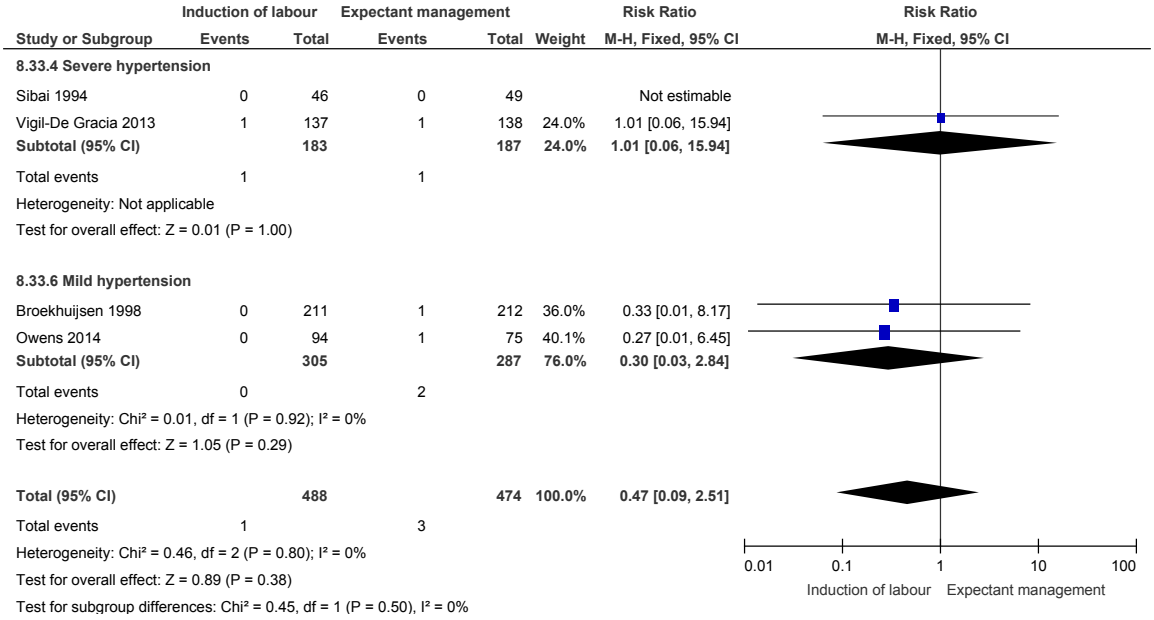


Eclampsia by gestational age



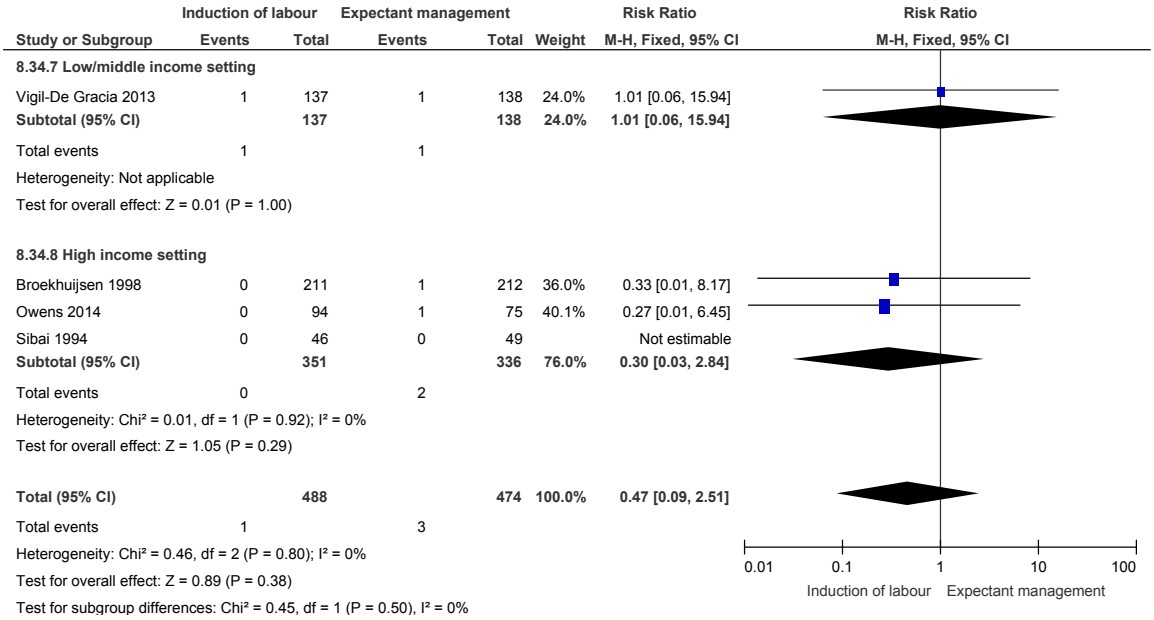
Test for subgroup differences: Chi² = 0.45, df = 1 (P = 0.50), I² = 0%

Eclampsia by severity of hypertension

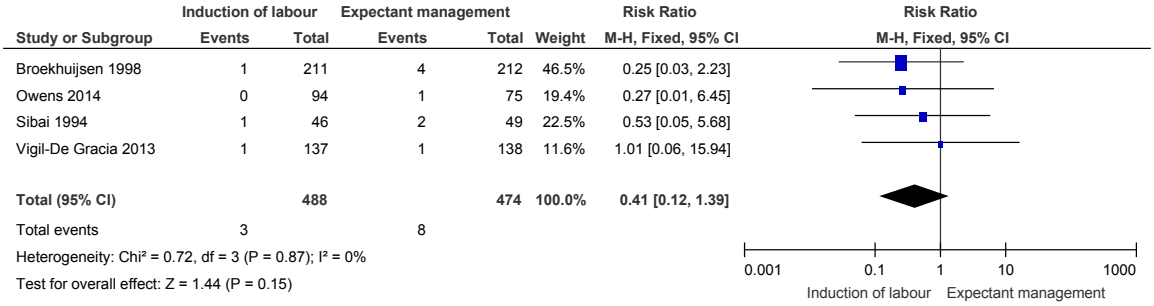


Test for subgroup differences: Chi² = 0.45, df = 1 (P = 0.50), I² = 0%

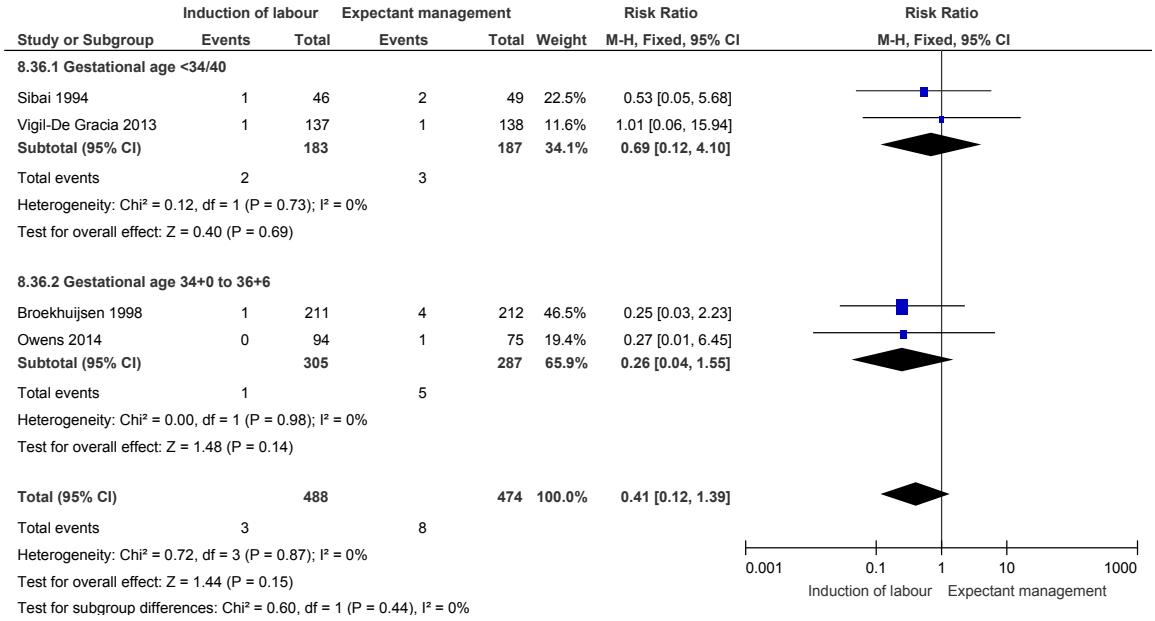
Eclampsia by income setting



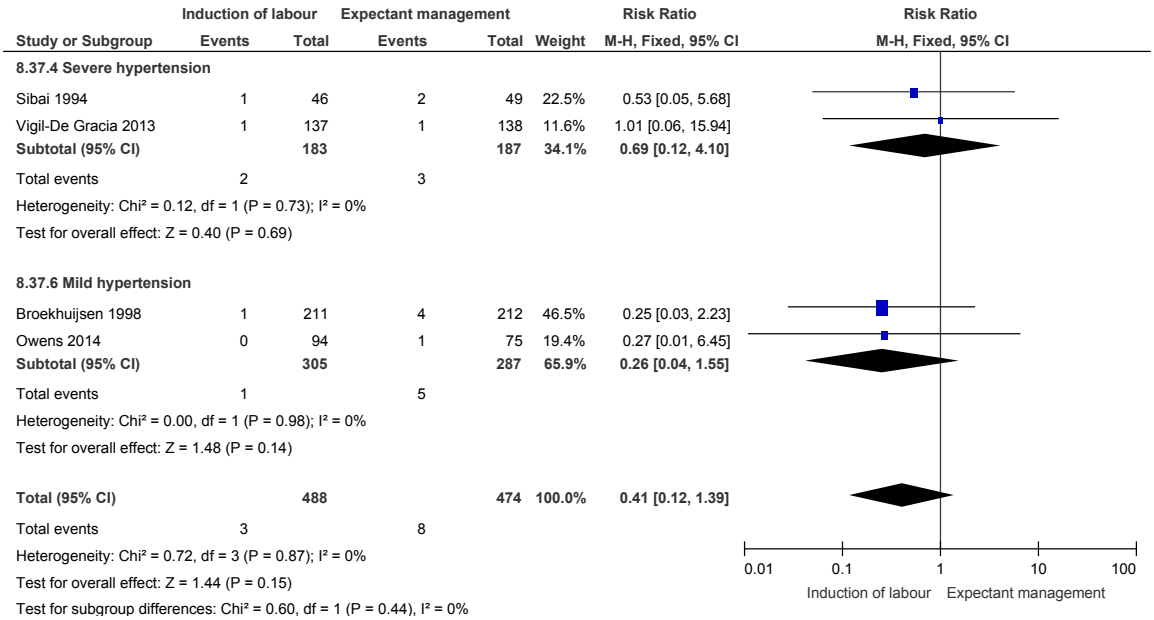
HELLP (overall estimate)



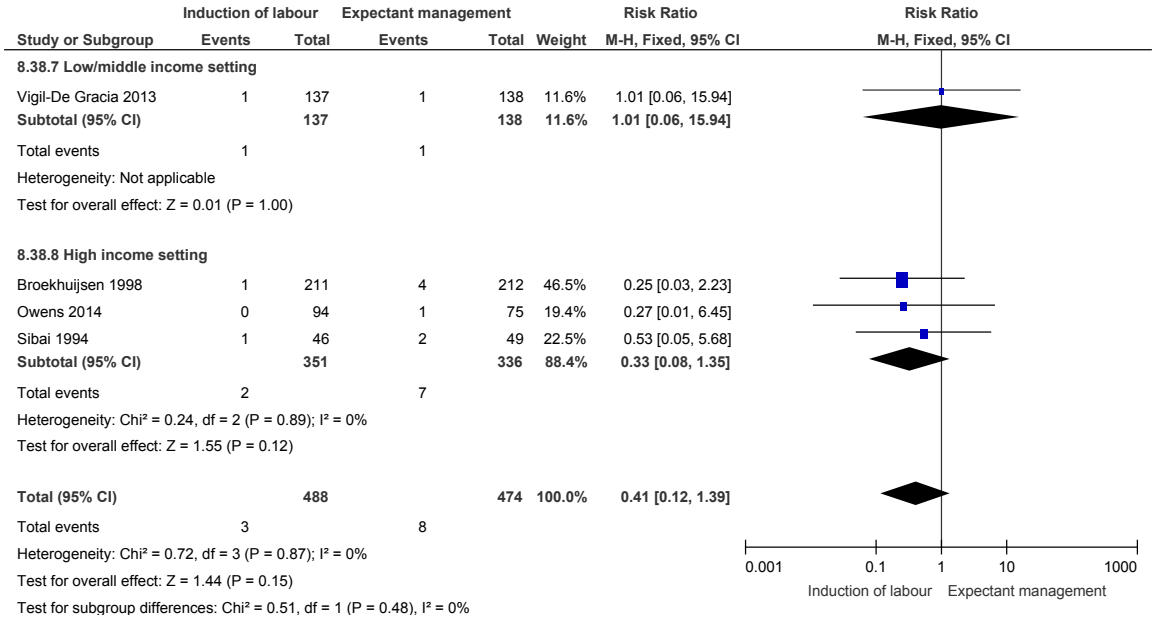
HELLP by gestational age



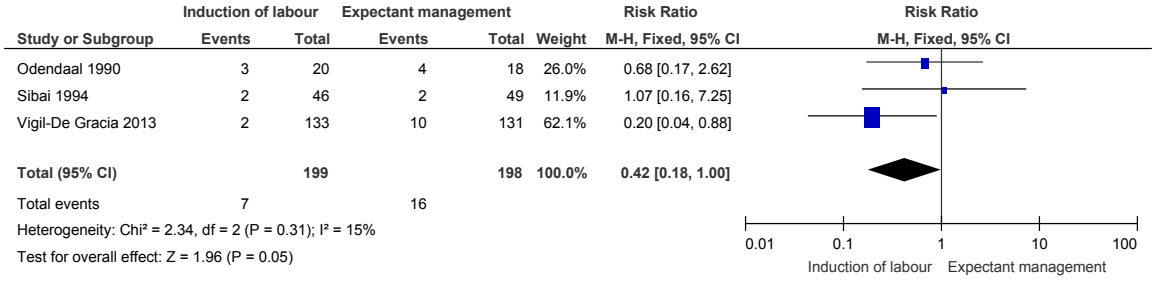
HELLP by severity of hypertension



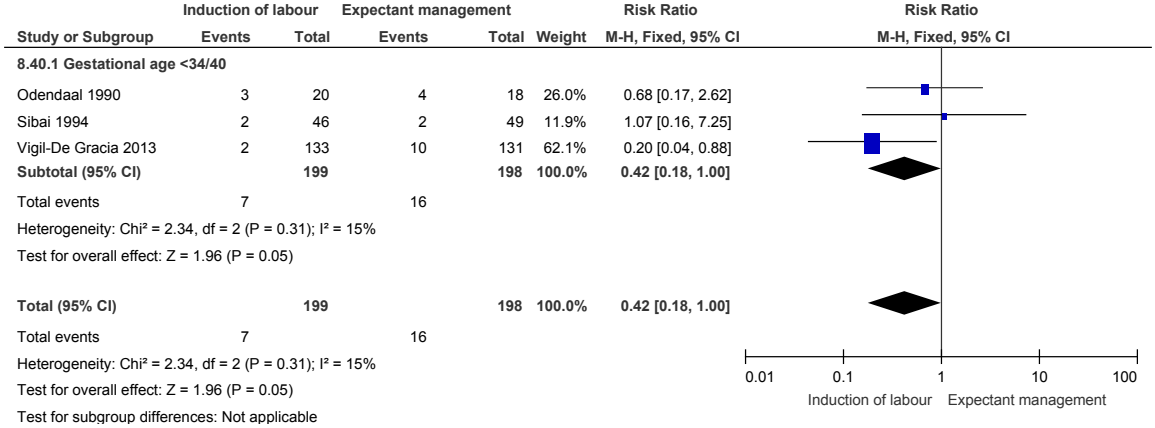
HELLP by income setting



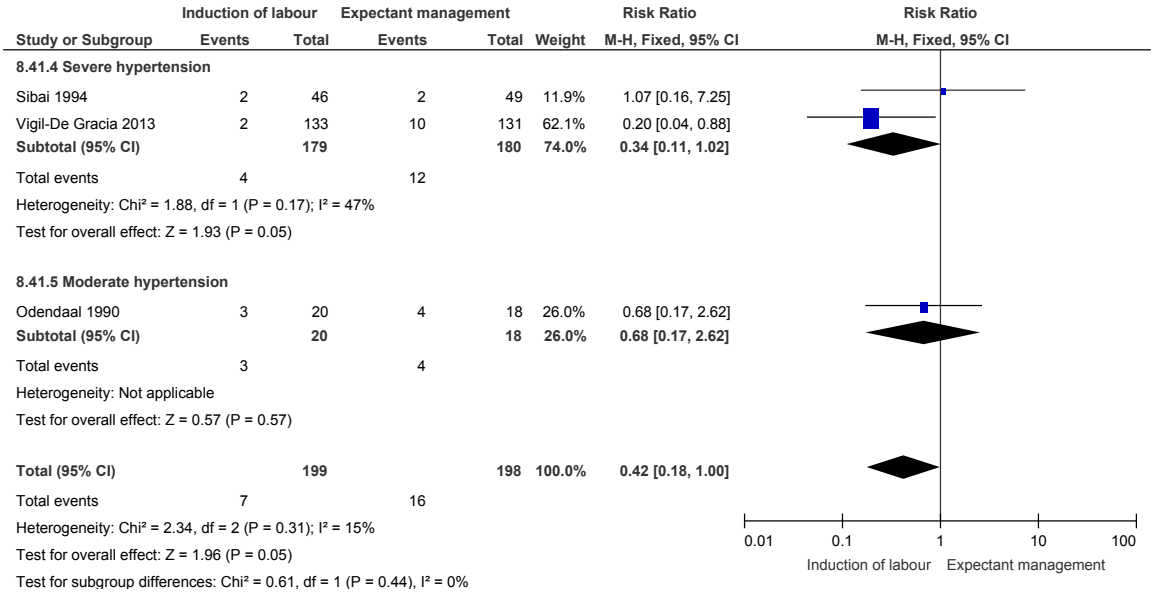
Placental abruption (overall estimate)



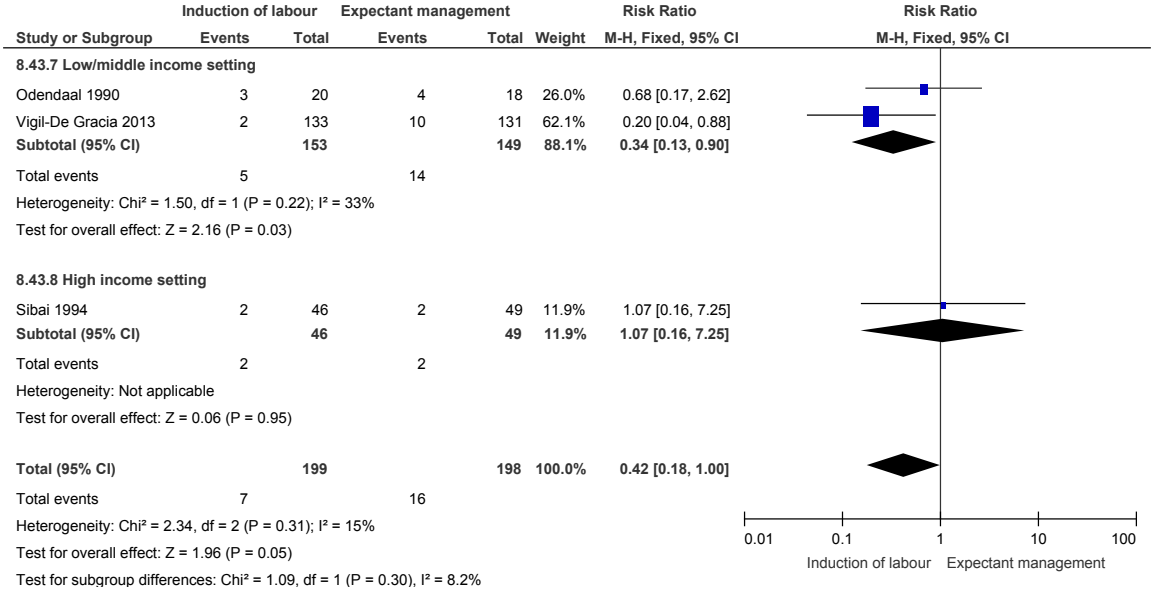
Placental abruption by gestational age



Placental abruption by severity of hypertension



Placental abruption by income setting

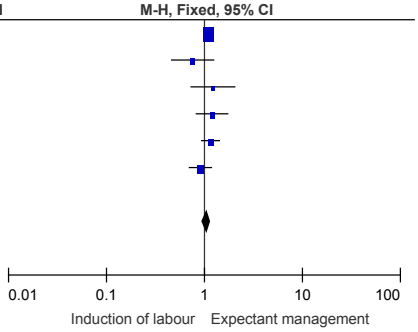


Mode of birth (overall estimate)

Study or Subgroup	Induction of labour Events	Total	Expectant management Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
GRIT 2003	137	141	107	121	41.9%	1.10 [1.02, 1.18]
Koopmans 2009	22	123	29	123	10.5%	0.76 [0.46, 1.24]
Mesbah 2003	11	15	9	15	3.3%	1.22 [0.73, 2.04]
Owens 2014	42	94	28	75	11.3%	1.20 [0.83, 1.73]
Sibai 1994	39	46	36	49	12.7%	1.15 [0.94, 1.42]
Vigil-De Gracia 2013	51	100	56	100	20.4%	0.91 [0.70, 1.18]
Total (95% CI)		**519**		**483**	**100.0%**	**1.05 [0.96, 1.15]**
Total events	302		265			

Heterogeneity: Chi² = 6.26, df = 5 (P = 0.28); I² = 20%

Test for overall effect: Z = 0.98 (P = 0.33)



Mode of birth by gestational age

Study or Subgroup	Induction of labour Events	Total	Expectant management Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.46.1 Gestational age <34/40						
Mesbah 2003	11	15	9	15	3.3%	1.22 [0.73, 2.04]
Sibai 1994	39	46	36	49	12.7%	1.15 [0.94, 1.42]
Vigil-De Gracia 2013	51	100	56	100	20.4%	0.91 [0.70, 1.18]
Subtotal (95% CI)		**161**		**164**	**36.3%**	**1.02 [0.87, 1.21]**
Total events	101		101			

Heterogeneity: Chi² = 2.51, df = 2 (P = 0.28); I² = 20%

Test for overall effect: Z = 0.28 (P = 0.78)

8.46.2 Gestational age 34+0 to 36+6						
GRIT 2003	137	141	107	121	41.9%	1.10 [1.02, 1.18]
Koopmans 2009	22	123	29	123	10.5%	0.76 [0.46, 1.24]
Owens 2014	42	94	28	75	11.3%	1.20 [0.83, 1.73]
Subtotal (95% CI)		**358**		**319**	**63.7%**	**1.06 [0.95, 1.18]**
Total events	201		164			

Heterogeneity: Chi² = 3.18, df = 2 (P = 0.20); I² = 37%

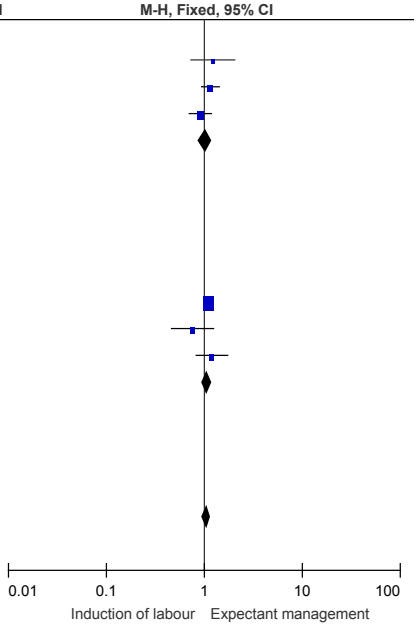
Test for overall effect: Z = 1.05 (P = 0.30)

Total (95% CI)		**519**		**483**	**100.0%**	**1.05 [0.96, 1.15]**
Total events	302		265			

Heterogeneity: Chi² = 6.26, df = 5 (P = 0.28); I² = 20%

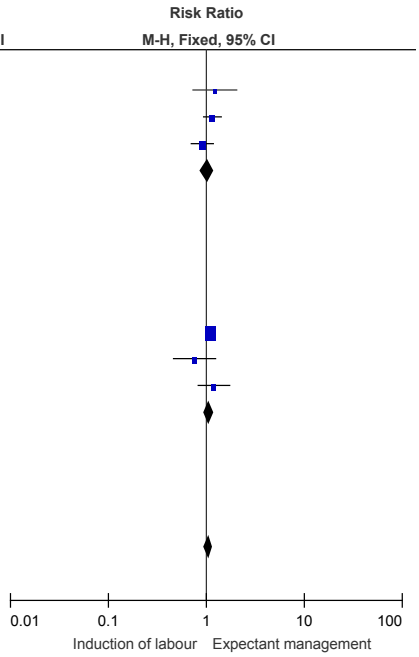
Test for overall effect: Z = 0.98 (P = 0.33)

Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%



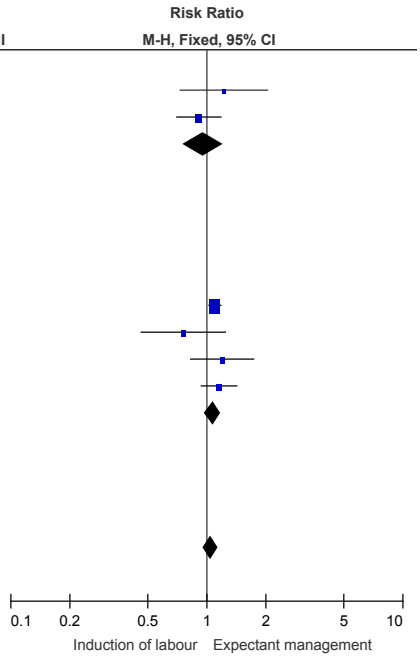
Mode of birth by severity of hypertension

Study or Subgroup	Induction of labour Events	Total	Expectant management Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.47.4 Severe hypertension						
Mesbah 2003	11	15	9	15	3.3%	1.22 [0.73, 2.04]
Sibai 1994	39	46	36	49	12.7%	1.15 [0.94, 1.42]
Vigil-De Gracia 2013	51	100	56	100	20.4%	0.91 [0.70, 1.18]
Subtotal (95% CI)		**161**		**164**	**36.3%**	**1.02 [0.87, 1.21]**
Total events	101		101			
Heterogeneity: Chi² = 2.51, df = 2 (P = 0.28); I² = 20%						
Test for overall effect: Z = 0.28 (P = 0.78)						
8.47.6 Mild hypertension						
GRIT 2003	137	141	107	121	41.9%	1.10 [1.02, 1.18]
Koopmans 2009	22	123	29	123	10.5%	0.76 [0.46, 1.24]
Owens 2014	42	94	28	75	11.3%	1.20 [0.83, 1.73]
Subtotal (95% CI)		**358**		**319**	**63.7%**	**1.06 [0.95, 1.18]**
Total events	201		164			
Heterogeneity: Chi² = 3.18, df = 2 (P = 0.20); I² = 37%						
Test for overall effect: Z = 1.05 (P = 0.30)						
Total (95% CI)		**519**		**483**	**100.0%**	**1.05 [0.96, 1.15]**
Total events	302		265			
Heterogeneity: Chi² = 6.26, df = 5 (P = 0.28); I² = 20%						
Test for overall effect: Z = 0.98 (P = 0.33)						
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%						



Mode of birth by income setting

Study or Subgroup	Induction of labour Events	Total	Expectant management Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.48.7 Low/middle income setting						
Mesbah 2003	11	15	9	15	3.3%	1.22 [0.73, 2.04]
Vigil-De Gracia 2013	51	100	56	100	20.4%	0.91 [0.70, 1.18]
Subtotal (95% CI)		**115**		**115**	**23.6%**	**0.95 [0.76, 1.20]**
Total events	62		65			
Heterogeneity: Chi² = 1.02, df = 1 (P = 0.31); I² = 2%						
Test for overall effect: Z = 0.40 (P = 0.69)						
8.48.8 High income setting						
GRIT 2003	137	141	107	121	41.9%	1.10 [1.02, 1.18]
Koopmans 2009	22	123	29	123	10.5%	0.76 [0.46, 1.24]
Owens 2014	42	94	28	75	11.3%	1.20 [0.83, 1.73]
Sibai 1994	39	46	36	49	12.7%	1.15 [0.94, 1.42]
Subtotal (95% CI)		**404**		**368**	**76.4%**	**1.08 [0.98, 1.19]**
Total events	240		200			
Heterogeneity: Chi² = 3.03, df = 3 (P = 0.39); I² = 1%						
Test for overall effect: Z = 1.47 (P = 0.14)						
Total (95% CI)		**519**		**483**	**100.0%**	**1.05 [0.96, 1.15]**
Total events	302		265			
Heterogeneity: Chi² = 6.26, df = 5 (P = 0.28); I² = 20%						
Test for overall effect: Z = 0.98 (P = 0.33)						
Test for subgroup differences: Chi² = 0.87, df = 1 (P = 0.35), I² = 0%						



Appendix F – GRADE tables

Table 5:Clinical evidence profile. Comparison 1: labetalol versus nicardipine (acute management)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Labetalol**	**Nicardipine**	**Relative (95% CI)**	**Absolute**		
Minutes needed to achieve effective control of blood pressure (follow-up mean 1 hour; Better indicated by lower values)												
1 (Elatrous 2002)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	30	30	-	MD 1.29 higher (1.31 lower to 3.89 higher)	LOW	CRITICAL

1 The quality of the evidence was downgraded by 1 level as this was a single blind trial with unclear risk of reporting bias
2 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (3.68 x +/-0.5=+/-1.84)

Table 6: Clinical evidence profile. Comparison 2: labetalol versus no intervention (non-acute management)

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**		
Stillbirth												
1 (Sibai 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/94 (0%)	0/97 (0%)	-	-	MODERATE	CRITICAL
Neonatal death up to 7 days												
1 (Sibai 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/94 (1.1%)	0/97 (0%)	RR 3.09 (0.13 to 75.03)[5]	-	VERY LOW	CRITICAL
SGA												
1 (Sibai 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	18/94 (19.1%)	9/97 (9.3%)	RR 2.06 (0.98 to 4.36)	98 more per 1000 (from 2	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		
										fewer to 312 more)		
Birth weight (grams, better indicated by higher values)												
1 (Sibai 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	94	97	-	MD 54 lower (269.29 lower to 161.29 higher)	MODERATE	IMPORTANT
Gestational age at birth (weeks, better indicated by higher values)												
1 (Sibai 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	92	94	-	MD 0.10 lower (0.96 lower to 0.76 higher)	MODERATE	IMPORTANT
Admission to neonatal unit												
1 (Sibai 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	38/94 (40.4%)	40/97 (41.2%)	RR 0.98 (0.70 to 1.38)	8 fewer per 1000 (from 124 fewer to 157 more)	VERY LOW	IMPORTANT
Severe hypertension												
1 (Sibai 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	5/92 (5.4%)	14/94 (14.9%)	RR 0.36 (0.14 to 0.97)	95 fewer per 1000 (from 4 fewer to 128 fewer)	LOW	CRITICAL
Placental abruption												
1 (Sibai 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/92 (2.2%)	0/94 (0%)	RR 5.11 (0.25 to 104.96)	-	VERY LOW	IMPORTANT
Mode of birth (C-section)												

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		
1 (Sibai 1987)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	39/92 (42.4%)	34/94 (36.2%)	RR 1.17 (0.82 to 1.68)	61 more per 1000 (from 65 fewer to 246 more)	LOW	IMPORTANT

1 The quality of the evidence was downgraded by 1 level as the study was not blinded and there was an unclear risk of reporting 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 (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 corresponding absolute risk was not calculated as no events were reported in the control arm

Table 7: Clinical evidence profile. Comparison 3: labetalol versus methyldopa (acute management)

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		
Blood pressure control: MAP (follow-up mean 7 days; Better indicated by lower values)												
1 (Subhedar 2016)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	90	90	-	MD 1.25 lower (2.15 to 0.35 lower)	VERY LOW	CRITICAL
Onset of labour (induction) (follow-up mean 7 days)												
1 (Subhedar 2016)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none	23/90 (25.6%)	18/90 (20%)	RR 1.28 (0.74 to 2.2)	56 more per 1000 (from 52 fewer to	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Labetalol	Methyldopa	Relative (95% CI)	Absolute	Quality	Importance
										240 more)		

1 The quality of the evidence was downgraded by 2 levels due to an unclear randomisation method, unclear allocation concealment, a high risk of selective reporting and no blinding
2 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (2.91 x +/- 0.5= +/- 1.45)
3 The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)

Table 8: Clinical evidence profile. Comparison 4: hydralazine versus nifedipine (acute management)

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydralazine	Nifedipine	Relative (95% CI)	Absolute	Quality	Importance
Stillbirth												
1 (Martins-Costa 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/17 (0%)	2/20 (10%)	RR 0.23 (0.1 to 4.55)	77 fewer per 1000 (from 90 fewer to 355 more)	VERY LOW	CRITICAL
Neonatal death up to 7 days (overall estimate) (follow-up mean 3.5 weeks)												
2 (Fenakel 1991, Kwawukume 1995)	randomised trials	very serious[3,4]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/62 (3.2%)	1/70 (1.4%)	RR 1.93 (0.19 to 19.98)	13 more per 1000 (from 12 fewer to 271 more)	VERY LOW	CRITICAL
Neonatal death up to 7 days - *Gestational age <34/40; severe hypertension; high income setting* (follow-up mean 4 weeks)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydralazine	Nifedipine	Relative (95% CI)	Absolute	Quality	Importance
1 (Fenakel 1991)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/27 (7.4%)	1/26 (3.8%)	RR 1.93 (0.19 to 19.98)	36 more per 1000 (from 31 fewer to 730 more)	VERY LOW	CRITICAL
Neonatal death up to 7 days - *Gestational age 34+0 to 36+6; severe hypertension; low/middle income setting* (follow-up mean 3 weeks)												
1 (Kwawukume 1995)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/35 (0%)	0/44 (0%)	-	-	LOW	CRITICAL
SGA												
1 (Martins-Costa 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	1/20 (5%)	RR 0.39 (0.02 to 8.97)	31 fewer per 1000 (from 49 fewer to 399 more)	MODERATE	CRITICAL
Birth weight (overall estimate) (follow-up mean 2.3 weeks; Better indicated by higher values)												
3 (Fenakel 1991, Kwawukume 1995, Martins-Costa 1992)	randomised trials	very serious[1,3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	91	93	-	MD 185.66 lower (373.49 lower to 2.17 higher)	LOW	IMPORTANT
Birth weight - *Gestational age <34/40; severe hypertension; high income setting* (follow-up mean 4 weeks; Better indicated by higher values)												
1 (Fenakel 1991)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	25	24	-	MD 246 lower (513.48 lower to 21.48 higher)	VERY LOW	IMPORTANT
Birth weight - *Gestational age 34+0 to 36+0; severe hypertension; low/middle income setting* (follow-up mean 1.55 weeks; Better indicated by higher values)												

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydralazine	Nifedipine	Relative (95% CI)	Absolute	Quality	Importance
2 (Kwawukume 1995, Martins-Costa 1992)	randomised trials	very serious[1,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	66	69	-	MD 126.96 lower (390.79 lower to 136.87 higher)	LOW	IMPORTANT
Gestational age at birth (overall estimate) (follow-up mean 2.05 weeks; weeks, better indicated by higher values)												
2 (Fenakel 1991, Martins-Costa 1992)	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[6]	none	42	44	-	MD 0.49 lower (1.41 lower to 0.43 higher)	VERY LOW	IMPORTANT
Gestational age at birth - *Gestational age <34/40; severe hypertension; high income setting* (follow-up mean 4 weeks; weeks, better indicated by higher values)												
1 (Fenakel 1991)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious imprecision[5]	none	25	24	-	MD 1 lower (2.32 lower to 0.32 higher)	VERY LOW	IMPORTANT
Gestational age at birth - *Gestational age 34+0 to 36+0; severe hypertension; low/middle income setting* (follow-up mean 2 hours; weeks, better indicated by higher values)												
1 (Martins-Costa 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[9]	none	17	20	-	MD 0 higher (1.29 lower to 1.29 higher)	LOW	IMPORTANT
Admission to neonatal unit (follow-up mean 3 weeks)												
1 (Kwawukume 1995)	randomised trials	very serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	13/35 (37.1%)	11/44 (25%)	RR 1.49 (0.76 to 2.9)	123 more per 1000 (from 60 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	Hydralazine	Nifedipine	Relative (95% CI)	Absolute		
										475 more)		
Blood pressure control: Minutes needed to achieve effective control of BP (overall estimate) (Better indicated by lower values)												
2 (Aali 2002, Rezaei 2011)	randomised trials	very serious[9,10]	very serious[12]	no serious indirectness	very serious[13]	none	86	90	-	MD 4.87 higher (4.87 lower to 14.62 higher)	VERY LOW	IMPORTANT
Blood pressure control: Minutes needed to achieve effective control of BP - *Gestational age 34+0 to 36+6; severe hypertension; low/middle income setting* (follow-up mean 24 hours; Better indicated by lower values)												
1 Rezaei 2011)	randomised trials	very serious[10]	no serious inconsistency	no serious indirectness	serious imprecision[16]	none	25	25	-	MD 10.8 higher (2.45 to 19.15 higher)	VERY LOW	IMPORTANT
Blood pressure control: Minutes needed to achieve effective control of BP - *Gestational age ≥37+0; severe hypertension; low/middle income setting* (Better indicated by lower values)												
1 (Aali 2002)	randomised trials	very serious[9]	no serious inconsistency	no serious indirectness	serious[14]	none	61	65	-	MD 0.7 higher (0.56 lower to 1.96 higher)	VERY LOW	IMPORTANT
Severe hypertension (overall estimate) (follow-up mean 2.05 weeks)												
2 (Fenakel 1991, Martins-Costa 1992)	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	serious[15]	none	8/42 (19%)	1/44 (2.3%)	RR 7.68 (1.04 to 56.86)	152 more per 1000 (from 1 more to	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydralazine	Nifedipine	Relative (95% CI)	Absolute		
										1000 more)		
Severe hypertension - *Gestational age <34/40; severe hypertension; high income setting* (follow-up mean 4 weeks)												
1 (Fenakel 1991)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[15]	none	8/25 (32%)	1/24 (4.2%)	RR 7.68 (1.04 to 56.86)	278 more per 1000 (from 2 more to 1000 more)	VERY LOW	IMPORTANT
Severe hypertension - *Gestational age 34+0 to 36+0; severe hypertension; low/middle income setting*												
1 (Martins-Costa 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/17 (0%)	0/20 (0%)	-	-	MODERATE	IMPORTANT
Eclampsia (overall estimate) (follow-up mean 2.05 weeks)												
2 (Fenakel 1991, Kwawukume 1995)	randomised trials	very serious[3,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/60 (0%)	0/68 (0%)	-	-	LOW	IMPORTANT
Placental abruption (follow-up mean 2 hours)												
1 (Martins-Costa 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/17 (0%)	1/20 (5%)	RR 0.39 (0.02 to 8.97)	31 fewer per 1000 (from 49 fewer to 399 more)	VERY LOW	IMPORTANT
Onset of labour (induction) (follow-up mean 4 weeks)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydralazine	Nifedipine	Relative (95% CI)	Absolute		
1 (Fenakel 1991)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[15]	none	21/25 (84%)	17/24 (70.8%)	RR 1.19 (0.87 to 1.61)	135 more per 1000 (from 92 fewer to 432 more)	VERY LOW	IMPORTANT
Mode of birth (C-section) (follow-up mean 2.3 weeks)												
3 (Fenakel 1991, Kwawukume 1995, Martins-Costa 1992)	randomised trials	very serious[1,3,4]	no serious inconsistency	no serious indirectness	very serious[15]	none	52/77 (67.5%)	51/88 (58%)	RR 1.17 (0.92 to 1.48)	99 more per 1000 (from 46 fewer to 278 more)	VERY LOW	IMPORTANT
Mode of birth (C-section) - *Gestational age <34/40; severe hypertension; high income setting* (follow-up mean 4 weeks)												
1 (Fenakel 1991)	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/25 (60%)	14/24 (58.3%)	RR 1.03 (0.65 to 1.64)	17 more per 1000 (from 204 fewer to 373 more)	VERY LOW	IMPORTANT
Mode of birth (C-section) - *Gestational age 34+0 to 36+0; severe hypertension; low/middle income setting* (follow-up mean 1.55 weeks)												
2 (Kwawukume 1995, Martins-Costa 1992)	randomised trials	very serious[1,4]	no serious inconsistency	no serious indirectness	serious[15]	none	37/52 (71.2%)	37/64 (57.8%)	RR 1.23 (0.94 to 1.61)	133 more per 1000 (from 35 fewer to 353 more)	VERY LOW	IMPORTANT

1 The quality of the evidence was downgraded by 1 level due to an unclear method of randomisation and unclear risk of reporting 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 2 levels due to an unclear risk of bias in the method of randomisation, unclear allocation concealment, unclear blinding of participants and personnel and unclear risk of reporting bias
4 The quality of the evidence was downgraded by 2 levels due to a high risk of bias in the randomisation method, unclear risk of allocation concealment, no blinding of participants and outcome assessors, a high risk of incomplete outcome data and unclear risk of reporting bias
5 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (456 x +/-0.5=+/-228)
6 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (2.15 x +/-0.5=1.07)
7 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (2.3 x +/- 0.5 = +/-1.15)
8 The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 MID thresholds (2 x +/- 0.5 = +/-1)
9 The quality of the evidence was downgraded by 2 levels due to an unclear risk of allocation concealment, no blinding, and an unclear risk of reporting bias
10 The quality of the evidence was downgraded by 2 levels due to an unclear risk of random sequence generation, single blind trial and an unclear risk of reporting bias
11 The quality of the evidence was downgraded by 1 level as the I^2 was greater than 75%
12 The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 MID thresholds (6.7 x +/-0.5= +/- 3.35)
13 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (10 x +/-0.5=+/-5)
14 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (3.4 x +/- 0.5= +/-1.7)
15 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (1.25)
16 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (10 x +/- 0.5 = +/- 0.5)

Table 9: Clinical evidence profile. Comparison 5: hydralazine versus labetalol (acute management)

Quality assessment							Number of patients		Effect			
Number of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Hydralazine**	**Labetalol**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Stillbirth (follow-up mean 2 hours)												
1 (Harper 1991)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/15 (6.7%)	0/15 (0%)	RR 3 (0.13 to 68.26)[6]	-	VERY LOW	CRITICAL
Neonatal death up to 7 days (overall estimate)												
2 (Harper 1991, Vigil-De Gracia 2006)	randomised trials	serious [1]	no serious inconsistency	serious[3]	very serious[2]	none	3/117 (2.6%)	3/118 (2.5%)	RR 1.01 (0.21 to 4.85)	0 more per 1000 (from 20 fewer to 98 more)	VERY LOW	CRITICAL
Neonatal death up to 7 days - *Gestational age <34/40; mild hypertension and high income setting* (follow-up mean 2 hours)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydralazine	Labetalol	Relative (95% CI)	Absolute		
1 (Harper 1991)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/15 (6.7%)	1/15 (6.7%)	RR 1 (0.07 to 14.55)	0 fewer per 1000 (from 62 fewer to 903 more)	VERY LOW	CRITICAL
Neonatal death up to 7 days - *Gestational age 34+ 0 to 36+6; severe hypertension and low/middle income setting*												
1 (Vigil-De Gracia 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	2/102 (2%)	2/103 (1.9%)	RR 1.01 (0.15 to 7.03)	0 more per 1000 (from 17 fewer to 117 more)	VERY LOW	CRITICAL
SGA												
1 (Harper 1991)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/15 (53.3%)	10/15 (66.7%)	RR 0.80 (0.44 to 1.45)	133 fewer per 1000 (from 373 fewer to 300 more)	VERY LOW	CRITICAL
Birth weight (overall estimate) (Better indicated by higher values)												
2 (Harper 1991, Vigil-De Gracia 2006)	randomised trials	serious [1]	no serious inconsistency	serious[3]	no serious imprecision	none	115	115	-	MD 34.86 higher (183.44 lower to 253.15 higher)	VERY LOW	IMPORTANT
Birth weight - *Gestational age <34/40; mild hypertension and high income setting* (follow-up mean 2 hours; Better indicated by higher values)												
1 (Harper 1991)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[5]	none	15	15	-	MD 65 higher	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydralazine	Labetalol	Relative (95% CI)	Absolute		
										(582.97 lower to 712.97 higher)		
Birth weight - *Gestational age 34+ 0 to 36+6; severe hypertension and low/middle income setting* (Better indicated by higher values)												
1 (Vigil-De Gracia 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	100	100	-	MD 31 higher (200.85 lower to 262.85 higher)	MODERATE	IMPORTANT
Admission to neonatal unit												
1 (Vigil-De Gracia 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	32/102 (31.4%)	32/103 (31.1%)	RR 1.01 (0.67 to 1.52)	3 more per 1000 (from 103 fewer to 162 more)	VERY LOW	IMPORTANT
Severe hypertension												
1 (Vigil-De Gracia 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	very serious[2]	none	5/100 (5%)	5/100 (5%)	RR 1 (0.3 to 3.35)	0 fewer per 1000 (from 35 fewer to 117 more)	VERY LOW	IMPORTANT
Eclampsia												
1 (Vigil-De Gracia 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	0/100 (0%)	0/100 (0%)	-	-	MODERATE	IMPORTANT
HELLP												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydralazine	Labetalol	Relative (95% CI)	Absolute		
1 (Vigil-De Gracia 2006)	randomised trials	no serious risk of bias	no serious inconsistency	very serious[3]	very serious[2]	none	2/100 (2%)	2/100 (2%)	RR 1.00 (0.14 to 6.96)	0 fewer per 1000 (from 17 fewer to 119 more)	VERY LOW	IMPORTANT
Placental abruption												
1 (Vigil-De Gracia 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	2/100 (2%)	1/100 (1%)	RR 2.00 (0.18 to 21.71)	10 more per 1000 (from 8 fewer to 207 more)	MODERATE	IMPORTANT
Mode of birth (C-section) (overall estimate)												
2 (Harper 1991, Vigil-De Gracia 2006)	randomised trials	serious [1]	no serious inconsistency	serious[3]	serious[6]	none	60/115 (52.2%)	65/115 (56.5%)	RR 0.92 (0.73 to 1.17)	45 fewer per 1000 (from 153 fewer to 96 more)	VERY LOW	IMPORTANT
Mode of birth (C-section) - *Gestational age <34/40; mild hypertension and high income setting*												
1 (Harper 1991)	randomised trials	serious [1]	no serious inconsistency	no serious indirectness	very serious[2]	none	9/15 (60%)	9/15 (60%)	RR 1.00 (0.56 to 1.79)	0 fewer per 1000 (from 264 fewer to 474 more)	VERY LOW	IMPORTANT
Mode of birth (C-section) - *Gestational age 34+ 0 to 36+6; severe hypertension and low/middle income setting*												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hydralazine	Labetalol	Relative (95% CI)	Absolute		
1 (Vigil-De Gracia 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	serious[6]	none	51/100 (51%)	56/100 (56%)	RR 0.91 (0.70 to 1.18)	50 fewer per 1000 (from 168 fewer to 101 more)	LOW	IMPORTANT
Maternal death												
1 (Vigil-De Gracia 2006)	randomised trials	no serious risk of bias	no serious inconsistency	serious[3]	no serious imprecision	none	0/100 (0%)	0/100 (0%)	-	-	MODERATE	IMPORTANT

1 The quality of the evidence was downgraded by 1 level due to an unclear risk of random sequence generation, unclear risk of blinding of participants, outcome assessors and personnel and an unclear risk of reporting 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 women with eclampsia, gestational hypertension and chronic hypertension accounted for approximately 30% of the participants included in the study
4 The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (845 x +/-0.5= +/-422.5)
5 The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (0.8)
6 The corresponding risk was not calculated as no events were reported in the control arm

Table 10: Clinical evidence profile. Comparison 6: nifedipine versus labetalol (acute management)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nidefipine	Labetalol	Relative (95% CI)	Absolute		
Neonatal mortality												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nidefipine	Labetalol	Relative (95% CI)	Absolute		
1 (Dhananjaya 2015)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	0/30 (0%)	1/29 (3.4%)	RR 0.32 (0.01 to 7.61)	23 fewer per 1000 (from 34 fewer to 228 more)	VERY LOW	CRITICAL
Birth weight (Better indicated by higher values)												
1 (Dhananjaya 2015)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[4]	none	30	29	-	MD 0.04 higher (0.26 lower to 0.34 higher)	VERY LOW	IMPORTANT
Gestational age at birth (weeks, better indicated by higher values)												
1 (Dhananjaya 2015)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious[5]	none	30	29	-	MD 0.68 higher (0.74 lower to 2.10 higher)	VERY LOW	IMPORTANT
Admission to neonatal unit												
1 (Dhananjaya 2015)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	10/30 (33.3%)	14/29 (48.3%)	RR 0.69 (0.37 to 1.30)	150 fewer per 1000 (from 304 fewer to 145 more)	VERY LOW	IMPORTANT
Minutes needed to achieve effective control of BP (Better indicated by lower values)												
2 (Dhananjaya 2015, Vermillion 1999)	randomised trials	very serious[1,6]	no serious inconsistency	serious[2,7]	serious imprecision[8]	none	55	54	-	MD 12.49 lower (17.26 to	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nidefipine	Labetalol	Relative (95% CI)	Absolute		
										7.73 lower)		
Minutes needed to achieve effective control of BP; *Gestational age 34+0 to 36+6; severe hypertension; low/middle income setting* (follow-up mean 24 hours; Better indicated by lower values)												
1 (Dhananjaya 2015)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	serious imprecision[10]	none	30	29	-	MD 18.60 lower (29.89 to 7.31 lower)	VERY LOW	CRITICAL
Minutes needed to achieve effective control of BP; *Gestational age 34+0 to 36+6; severe hypertension; high income setting* (follow-up mean 24 hours; Better indicated by lower values)												
1 (Vermillion 1999)	randomised trials	serious[6]	no serious inconsistency	serious[7]	serious imprecision[9]	none	25	25	-	MD 11.17 lower (16.42 to 5.92 lower)	VERY LOW	CRITICAL
HELLP												
1 (Dhananjaya 2015)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	1/30 (3.3%)	0/29 (0%)	RR 2.90 (0.12 to 68.50)[11]	-	VERY LOW	IMPORTANT
Eclampsia												
1 (Dhananjaya 2015)	randomised trials	very serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	3/30 (10%)	2/29 (6.9%)	RR 1.45 (0.26 to 8.06)	31 more per 1000 (from 51 fewer to 487 more)	VERY LOW	IMPORTANT

1 The quality of the evidence was downgraded by 2 levels due to an unclear risk bias in the of method of randomisation, allocation concealment, blinding of participants and personnel and an unclear risk of reporting bias
2 The quality of the evidence was downgraded by 1 level as >20% of the participants presented with GH, eclampsia, chronic hypertension or chronic hypertension with superimposed pre-eclampsia
[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 (0.66 x +/- 0.5=+/-0.33)
[5] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (3.27 x +/- 0.5= +/- 1.63)
[6] The quality of the evidence was downgraded by 1 level as there was an unclear risk of bias in allocation concealment and an unclear risk of reporting bias
[7] The quality of the evidence was downgraded by 1 level as >20% of the participants were postnatal
[8] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (19.08 x +/-0.5=+/-9.54)
[9] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (12.76 x +/-0.5= +/-6.38)
[10] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (25.4 x +/-0.5=+/-12.7)
[11] The corresponding absolute risk was not calculated as no events were reported in the control arm

Table 11: Clinical evidence profile. Comparison 7: nifedipine versus no intervention (non-acute management)

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nifedipine	No intervention	Relative (95% CI)	Absolute	Quality	Importance
Stillbirth												
1 (Sibai 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/99 (0%)	0/101 (0%)	-	-	MODERATE	CRITICAL
Neonatal death												
1 (Sibai 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/99 (0%)	0/101 (0%)	-	-	MODERATE	CRITICAL
SGA												
1 (Sibai 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	15/99 (15.2%)	13/101 (12.9%)	RR 1.18 (0.59 to 2.34)	23 more per 1000 (from 53 fewer to 172 more)	VERY LOW	CRITICAL
Gestational age at birth (weeks, better indicated by higher values)												
1 (Sibai 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	99	101	-	MD 0.60 lower (1.34 lower to 0.14 higher)	MODERATE	IMPORTANT

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nifedipine	No intervention	Relative (95% CI)	Absolute	Quality	Importance
Preterm birth (<37 weeks)												
1 (Sibai 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	12/99 (12.1%)	0/101 (0%)	RR 25.50 (1.53 to 424.92)	-	MODERATE	IMPORTANT
Admission to neonatal unit												
1 (Sibai 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious4	none	30/99 (30.3%)	21/101 (20.8%)	RR 1.46 (0.90 to 2.36)	96 more per 1000 (from 21 fewer to 283 more)	LOW	IMPORTANT
HELLP												
1 (Sibai 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/98 (4.1%)	2/99 (2%)	RR 2.02 (0.38 to 10.78)	21 more per 1000 (from 13 fewer to 198 more)	VERY LOW	IMPORTANT
Placental abruption												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nifedipine	No intervention	Relative (95% CI)	Absolute		
1 (Sibai 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/98 (3.1%)	2/99 (2%)	RR 1.52 (0.26 to 8.87)	11 more per 1000 (from 15 fewer to 159 more)	VERY LOW	IMPORTANT
Onset of labour (induction)												
1 (Sibai 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/98 (3.1%)	2/99 (2%)	RR 1.52 (0.26 to 8.87)	11 more per 1000 (from 15 fewer to 159 more)	VERY LOW	IMPORTANT
Mode of birth (C-section)												
1 (Sibai 1992)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	42/98 (42.9%)	35/99 (35.4%)	RR 1.21 (0.85 to 1.72)	74 more per 1000 (from 53 fewer to 255 more)	LOW	IMPORTANT

1 The quality of the evidence was downgraded by 1 level as the trial was not blinded

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 (1.25)

Table 12: Clinical evidence profile. Comparison 8: methyldopa versus no intervention (non-acute management)

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methyldopa	No intervention	Relative (95% CI)	Absolute		
Perinatal death												
1 (Elhassan 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	4/34 (11.8%)	6/36 (16.7%)	RR 0.71 (0.22 to 2.29)	48 fewer per 1000 (from 130 fewer to 215 more)	VERY LOW	CRITICAL
Control of blood pressure: sBP (Better indicated by lower values)												
1 (Elhassan 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[5]	none	34	36	-	MD 5.70 lower (9.03 to 2.37 lower)	VERY LOW	
Control of blood pressure: dBP (Better indicated by lower values)												
1 (Elhassan 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious imprecision[3]	none	34	36	-	MD 2.20 higher (0.32 lower to 4.72 higher)	VERY LOW	
Eclampsia												
1 (Elhassan 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	3/34 (8.8%)	10/36 (27.8%)	RR 0.32 (0.1 to 1.06)	189 fewer per 1000 (from 250 fewer to 17 more)	VERY LOW	
Mode of birth (C-section)												
1 (Elhassan 2002)	randomised trials	very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	14/34 (41.2%)	14/36 (38.9%)	RR 1.06 (0.6 to 1.88)	23 more per 1000 (from 156 fewer to	VERY LOW	

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Methyldopa	No intervention	Relative (95% CI)	Absolute	Quality	Importance
										342 more)		

1 The quality of the evidence was downgraded by 2 levels due to an unclear risk of bias in the random sequence generation, an unclear risk of allocation concealment, no blinding, an unclear risk of incomplete outcomes and an unclear risk of reporting 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 MID threshold (2.3 x +/-0.5=+/-1.15)
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 MID threshold (6.5 x +/- 0.5=+/-3.25)

Table 13: Clinical evidence profile. Comparison 9: immediate birth versus expectant management

Quality assessment							Number of patients		Effect			
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute	Quality	Importance
Stillbirth (overall estimate)												
5 (GRIT 2003, Mesbah 2003, Odendaal 1990, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[1,2,3,4,5]	no serious inconsistency	serious[6]	very serious[7]	none	2/359 (0.56%)	7/341 (2.1%)	RR 0.3 (0.07 to 1.23)	14 fewer per 1000 (from 19 fewer to 5 more)	VERY LOW	CRITICAL
Stillbirth by gestational age - Gestational age <34/40												
4 (Mesbah 2003, Odendaal	randomised trials	very serious[1,2,3,4,5]	no serious inconsistency	serious[6,8]	very serious[7]	none	1/218 (0.46%)	2/220 (2.1%)	RR 0.58 (0.08 to 4.19)	4 fewer per 1000 (from 8	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
1990, Sibai 1994, Vigil-De Gracia 2013)										fewer to 29 more)		
Stillbirth by gestational age - Gestational age 34+0 to 36+6												
1 (GRIT 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/141 (0.71%)	5/121 (4.1%)	RR 0.17 (0.02 to 1.45)	34 fewer per 1000 (from 40 fewer to 19 more)	VERY LOW	CRITICAL
Stillbirth by severity of hypertension - Severe hypertension												
3 (Mesbah 2003, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[2,4,5]	no serious inconsistency	serious[8]	very serious[7]	none	1/198 (0.51%)	1/202 (0.5%)	RR 1.01 (0.06 to 15.94)	0 more per 1000 (from 5 fewer to 74 more)	VERY LOW	CRITICAL
Stillbirth by severity of hypertension - Moderate hypertension												
1 (Odendaal 1990)	randomised trials	very serious[3]	no serious inconsistency	serious[6]	very serious[7]	none	0/20 (0%)	1/18 (5.6%)	RR 0.3 (0.01 to 6.97)	39 fewer per 1000 (from 55 fewer to 332 more)	VERY LOW	CRITICAL
Stillbirth by severity of hypertension - Mild hypertension												
1 (GRIT 2003)	randomised trials	serious[1]	no serious inconsistency	serious[6]	very serious[7]	none	1/141 (0.71%)	5/121 (4.1%)	RR 0.17 (0.02 to 1.45)	34 fewer per 1000 (from 40 fewer to 19 more)	VERY LOW	CRITICAL
Stillbirth by income setting - Low/middle income setting												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
3 (Mesbah 2003, Odendaal 1990, Vigil-De Gracia 2013)	randomised trials	very serious[2,3,5]	no serious inconsistency	serious[6,8]	very serious[7]	none	1/172 (0.58%)	2/171 (1.2%)	RR 0.58 (0.08 to 4.19)	5 fewer per 1000 (from 11 fewer to 37 more)	VERY LOW	CRITICAL
Stillbirth by income setting - High income setting												
2 (GRIT 2003, Sibai 1994)	randomised trials	serious[1,4]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/187 (0.53%)	5/170 (2.9%)	RR 0.17 (0.02 to 1.45)	24 fewer per 1000 (from 29 fewer to 13 more)	VERY LOW	CRITICAL
Neonatal death (overall estimate)												
5 (GRIT 2003, Mesbah 2003, Odendaal 1990, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[1,2,3,4,5]	no serious inconsistency	serious[6,8]	serious[10]	none	42/359 (11.7%)	31/341 (9.1%)	RR 1.25 (0.81 to 1.93)	23 more per 1000 (from 17 fewer to 85 more)	VERY LOW	CRITICAL
Neonatal death by gestational age - Gestational age <34/40												
4 (Mesbah 2003, Odendaal 1990, Sibai 1994, Vigil-De	randomised trials	very serious[2,3,4,5]	no serious inconsistency	serious[6,8]	very serious[7]	none	21/218 (9.6%)	16/220 (7.3%)	RR 1.3 (0.71 to 2.38)	22 more per 1000 (from 21 fewer to 100 more)	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
Gracia 2013)												
Neonatal death by gestational age - Gestational age 34+0 to 36+6												
1 (GRIT 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	21/141 (14.9%)	15/121 (12.4%)	RR 1.2 (0.65 to 2.23)	25 more per 1000 (from 43 fewer to 152 more)	VERY LOW	CRITICAL
Neonatal death by severity of hypertension - Severe hypertension												
3 (Mesbah 2003, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[2,4,5]	no serious inconsistency	serious[8]	very serious[7]	none	18/198 (9.1%)	15/202 (7.4%)	RR 1.21 (0.64 to 2.26)	16 more per 1000 (from 27 fewer to 94 more)	VERY LOW	CRITICAL
Neonatal death by severity of hypertension - Moderate hypertension												
1 (Odendaal 1990)	randomised trials	very serious[3]	no serious inconsistency	serious[6]	very serious[7]	none	3/20 (15%)	1/18 (5.6%)	RR 2.7 (0.31 to 23.69)	94 more per 1000 (from 38 fewer to 1000 more)	VERY LOW	CRITICAL
Neonatal death by severity of hypertension - Mild hypertension												
1 (GRIT 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	21/141 (14.9%)	15/121 (12.4%)	RR 1.2 (0.65 to 2.23)	25 more per 1000 (from 43 fewer to 152 more)	VERY LOW	CRITICAL
Neonatal death by income setting - Low/middle income setting												
3 (Mesbah 2003,	randomised trials	very serious[2,3,5]	no serious inconsistency	serious[6,8]	very serious[7]	none	21/172 (12.2%)	16/171 (9.4%)	RR 1.3 (0.71 to 2.38)	28 more per 1000 (from 27	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
Odendaal 1990, Vigil-De Gracia 2013)										fewer to 129 more)		
Neonatal death by income setting - High income setting												
2 (GRIT 2003, Sibai 1994)	randomised trials	very serious[1,3]	no serious inconsistency	no serious indirectness	very serious[7]	none	21/187 (11.2%)	15/170 (8.8%)	RR 1.2 (0.65 to 2.23)	18 more per 1000 (from 31 fewer to 109 more)	VERY LOW	CRITICAL
SGA (overall estimate)												
4 (Mesbah 2003, Owens 2014, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[2,4,5,11]	serious[12]	serious[8]	serious[9]	none	39/292 (13.4%)	65/277 (23.5%)	RR 0.51 (0.24 to 1.11)	115 fewer per 1000 (from 178 fewer to 26 more)	VERY LOW	CRITICAL
SGA by gestational age - Gestational age <34/40												
3 (Mesbah 2003, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[2,4,5]	no serious inconsistency	serious[8]	no serious imprecision	none	20/198 (10.1%)	54/202 (26.7%)	RR 0.38 (0.24 to 0.61)	166 fewer per 1000 (from 104 fewer to 203 fewer)	VERY LOW	CRITICAL
SGA by gestational age - Gestational age 34+0 to 36+6												
1 (Owens 2014)	randomised trials	very serious[11]	no serious inconsistency	no serious indirectness	very serious[7]	none	19/94 (20.2%)	11/75 (14.7%)	RR 1.38 (0.7 to 2.71)	56 more per 1000 (from 44	VERY LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
										fewer to 251 more)		
SGA by severity of hypertension - Severe hypertension												
3 (Mesbah 2003, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[2,4,5]	no serious inconsistency	serious[8]	no serious imprecision	none	20/198 (10.1%)	54/202 (26.7%)	RR 0.38 (0.24 to 0.61)	166 fewer per 1000 (from 104 fewer to 203 fewer)	VERY LOW	CRITICAL
SGA by severity of hypertension - Mild hypertension												
1 (Owens 2014)	randomised trials	very serious[11]	no serious inconsistency	no serious indirectness	very serious[7]	none	19/94 (20.2%)	11/75 (14.7%)	RR 1.38 (0.7 to 2.71)	56 more per 1000 (from 44 fewer to 251 more)	VERY LOW	CRITICAL
SGA by income setting - High income setting												
2 (Owens 2014, Sibai 1994)	randomised trials	very serious[4,11]	serious[12]	no serious indirectness	very serious[7]	none	24/140 (17.1%)	26/124 (21%)	RR 0.73 (0.19 to 2.75)	57 fewer per 1000 (from 170 fewer to 367 more)	VERY LOW	CRITICAL
SGA by income setting - Low/middle income setting												
2 (Mesbah 2003, Vigil-De Gracia 2013)	randomised trials	very serious[2,5]	no serious inconsistency	serious[8]	no serious imprecision	none	15/152 (9.9%)	39/153 (25.5%)	RR 0.39 (0.22 to 0.68)	155 fewer per 1000 (from 82 fewer to 199 fewer)	VERY LOW	CRITICAL
Birth weight by gestational age - Gestational age < 34/40 (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	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
3 (Odendaal 1990, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[3,4,5]	very serious[13]	serious[6,8]	serious[14]	none	168	170	-	MD 182.08 lower (441.7 lower to 77.54 higher)	VERY LOW	IMPORTANT
Birth weight by gestational age - Gestational age 34+0 to 36+6 (Better indicated by lower values)												
1 (Owens 2014)	randomised trials	very serious[14]	no serious inconsistency	no serious indirectness	serious[15]	none	94	75	-	MD 175 higher (31.35 to 318.65 higher)	VERY LOW	IMPORTANT
Gestational age at birth (overall estimate) (days, better indicated by lower values)												
4 (GRIT 2003, Mesbah 2003, Odendaal 1990, Sibai 1994)	randomised trials	very serious[1,2,3,4]	very serious[13]	serious[6]	serious[16]	none	225	200	-	MD 9.92 lower (16.39 to 3.44 lower)	VERY LOW	IMPORTANT
Gestational age by severity of hypertension - Severe hypertension (Better indicated by lower values)												
2 (Mesbah 2003, Sibai 1994)	randomised trials	serious[2,4]	very serious[13]	no serious indirectness	serious[17]	none	64	61	-	MD 10.92 lower (23.64 lower to 1.79 higher)	VERY LOW	IMPORTANT
Gestational age by severity of hypertension - Moderate hypertension (Better indicated by lower values)												
1 (Odendaal 1990)	randomised trials	very serious[3]	no serious inconsistency	serious[6]	serious[18]	none	20	18	-	MD 12 lower (20.9 to	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
										3.1 lower)		
Gestational age by severity of hypertension - Mild hypertension (Better indicated by lower values)												
1 (GRIT 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[19]	none	141	121	-	MD 6 lower (10.68 to 1.32 lower)	LOW	IMPORTANT
Gestational age at birth by income setting - High income setting (days, better indicated by lower values)												
2 (GRIT 2003, Sibai 1994)	randomised trials	serious[1,4]	very serious[13]	no serious indirectness	serious[20]	none	190	167	-	MD 11.46 lower (22.24 to 0.68 lower)	VERY LOW	IMPORTANT
Gestational age at birth by income setting - Low/middle income setting (days, better indicated by lower values)												
2 (Mesbah 2003, Odendaal 1990)	randomised trials	very serious[2,3]	no serious inconsistency	serious[6]	serious[21]	none	35	33	-	MD 7.81 lower (15.65 lower to 0.02 higher)	VERY LOW	IMPORTANT
Admission to neonatal unit (overall)												
4 (Mesbah 2003, Owens 2014, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[2,4,5,16]	very serious[13]	serious[8]	serious[10]	none	176/292 (60.3%)	163/277 (58.8%)	RR 1.18 (0.92 to 1.52)	106 more per 1000 (from 47 fewer to 306 more)	VERY LOW	IMPORTANT
Admission to neonatal unit by gestational age - Gestational age <34/40												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
3 (Mesbah 2003, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[2,4,5]	very serious[13]	serious[8]	serious[10]	none	156/198 (78.8%)	149/202 (73.8%)	RR 1.19 (0.89 to 1.6)	140 more per 1000 (from 81 fewer to 443 more)	VERY LOW	IMPORTANT
Admission to neonatal unit by gestational age - Gestational age 34+0 to 36+6												
1 (Owens 2014)	randomised trials	very serious[11]	no serious inconsistency	no serious indirectness	very serious[7]	none	20/94 (21.3%)	14/75 (18.7%)	RR 1.14 (0.62 to 2.1)	26 more per 1000 (from 71 fewer to 205 more)	VERY LOW	IMPORTANT
Admission to neonatal unit by severity of hypertension - Severe hypertension												
3 (Mesbah 2003, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[2,4,5]	very serious[13]	serious[8]	serious[10]	none	156/198 (78.8%)	149/202 (73.8%)	RR 1.19 (0.89 to 1.6)	140 more per 1000 (from 81 fewer to 443 more)	VERY LOW	IMPORTANT
Admission to neonatal unit by severity of hypertension - Mild hypertension												
1 (Owens 2014)	randomised trials	very serious[11]	no serious inconsistency	no serious indirectness	very serious[7]	none	20/94 (21.3%)	14/75 (18.7%)	RR 1.14 (0.62 to 2.1)	26 more per 1000 (from 71 fewer to 205 more)	VERY LOW	IMPORTANT
Admission to neonatal unit by income setting - High income setting												
2 (Owens 2014, Sibai 1994)	randomised trials	very serious[4,11]	no serious inconsistency	no serious indirectness	serious[10]	none	66/140 (47.1%)	51/124 (41.1%)	RR 1.31 (1.12 to 1.53)	127 more per 1000 (from 49 more to	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
										218 more)		
Admission to neonatal unit by income setting - Low/middle income setting												
2 (Mesbah 2003, Vigil-De Gracia 2013)	randomised trials	very serious[2,5]	very serious[13]	serious[8]	very serious[7]	none	110/152 (72.4%)	112/153 (73.2%)	RR 1.14 (0.73 to 1.77)	102 more per 1000 (from 198 fewer to 564 more)	VERY LOW	IMPORTANT
Cerebral palsy												
1 (GRIT 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	7/141 (5%)	1/121 (0.83%)	RR 6.01 (0.75 to 48.14)	41 more per 1000 (from 2 fewer to 390 more)	VERY LOW	IMPORTANT
Impaired vision												
1 (GRIT 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	5/141 (3.5%)	1/121 (0.83%)	RR 4.29 (0.51 to 36.22)	27 more per 1000 (from 4 fewer to 291 more)	VERY LOW	IMPORTANT
Moderate hearing impairment												
1 (GRIT 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/141 (1.4%)	5/121 (4.1%)	RR 0.34 (0.07 to 1.74)	27 fewer per 1000 (from 38 fewer to 31 more)	VERY LOW	IMPORTANT
Severe hypertension post-intervention (overall estimate; mild hypertension; gestational age 34+0 to 36+6; high income setting)												
1 (Owens 2014)	randomised trials	very serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/94 (3.2%)	20/75 (26.7%)	RR 0.12 (0.04 to 0.39)	235 fewer per 1000 (from 163	LOW	CRITICAL

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
										fewer to 256 fewer)		
Eclampsia (overall estimate)												
4 (Broekhuijsen 2015, Owens 2014, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[4,5,11,22]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/488 (0.2%)	3/474 (0.63%)	RR 0.47 (0.09 to 2.51)	3 fewer per 1000 (from 6 fewer to 10 more)	VERY LOW	IMPORTANT
Eclampsia by gestational age - Gestational age <34/40												
2 (Sibai 1994, Vigil de Gracia 2013)	randomised trials	very serious[4,5]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/183 (0.55%)	1/187 (0.53%)	RR 1.01 (0.06 to 15.94)	0 more per 1000 (from 5 fewer to 80 more)	VERY LOW	IMPORTANT
Eclampsia by gestational age - Gestational age 34+0 to 36+6												
2 (Broekhuijsen 2015, Owens 2014)	randomised trials	very serious[11,22]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/305 (0%)	2/287 (0.7%)	RR 0.3 (0.03 to 2.84)	5 fewer per 1000 (from 7 fewer to 13 more)	VERY LOW	IMPORTANT
Eclampsia by severity of hypertension - Severe hypertension												
2 (Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[4,5]	no serious inconsistency	serious[8]	very serious[7]	none	1/183 (0.55%)	1/187 (0.53%)	RR 1.01 (0.06 to 15.94)	0 more per 1000 (from 5 fewer to 80 more)	VERY LOW	IMPORTANT
Eclampsia by severity of hypertension - Mild hypertension												
2 (Broekhuijsen 2015,	randomised trials	very serious[11,22]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/305 (0%)	2/287 (0.7%)	RR 0.3 (0.03 to 2.84)	5 fewer per 1000 (from 7	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
Owens 2014)										fewer to 13 more)		
Eclampsia by income setting - High income setting												
3 (Broekhuijsen 2015, Owens 2014, Sibai 1994)	randomised trials	very serious[4,11,22]	no serious inconsistency	no serious indirectness	very serious[7]	none	0/351 (0%)	2/336 (0.6%)	RR 0.3 (0.03 to 2.84)	4 fewer per 1000 (from 6 fewer to 11 more)	VERY LOW	IMPORTANT
Eclampsia by income setting - Low/middle income setting												
1 (Vigil-De Gracia 2013)	randomised trials	very serious[5]	no serious inconsistency	serious[8]	very serious[7]	none	1/137 (0.73%)	1/138 (0.72%)	RR 1.01 (0.06 to 15.94)	0 more per 1000 (from 7 fewer to 108 more)	VERY LOW	IMPORTANT
HELLP (overall estimate)												
4 (Broekhuijsen 2015, Owens 2014, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[4,5,11,22]	no serious inconsistency	serious[8]	very serious[7]	none	3/488 (0.61%)	8/474 (1.7%)	RR 0.41 (0.12 to 1.39)	10 fewer per 1000 (from 15 fewer to 7 more)	VERY LOW	IMPORTANT
HELLP by gestational age - Gestational age <34/40												
2 (Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[4,5]	no serious inconsistency	serious[8]	very serious[7]	none	2/183 (1.1%)	3/187 (1.6%)	RR 0.69 (0.12 to 4.10)	5 fewer per 1000 (from 14 fewer to 50 more)	VERY LOW	IMPORTANT
HELLP by gestational age - Gestational age 34+0 to 36+6												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
2 (Broekhuijsen 2015, Owens 2014)	randomised trials	very serious[11,22]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/305 (0.33%)	5/287 (1.7%)	RR 0.26 (0.04 to 1.55)	13 fewer per 1000 (from 17 fewer to 10 more)	VERY LOW	IMPORTANT
HELLP by severity of hypertension - Severe hypertension												
2 (Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[4,5]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/183 (1.1%)	3/187 (1.6%)	RR 0.69 (0.12 to 4.1)	5 fewer per 1000 (from 14 fewer to 50 more)	VERY LOW	IMPORTANT
HELLP by severity of hypertension - Mild hypertension												
2 (Broekhuijsen 2015, Owens 2014)	randomised trials	very serious[11,22]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/305 (0.33%)	5/287 (1.7%)	RR 0.26 (0.04 to 1.55)	13 fewer per 1000 (from 17 fewer to 10 more)	VERY LOW	IMPORTANT
HELLP by income setting - High income setting												
3 (Broekhuijsen 2015, Owens 2014, Sibai 1994)	randomised trials	very serious[4,11,22]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/351 (0.57%)	7/336 (2.1%)	RR 0.33 (0.08 to 1.35)	14 fewer per 1000 (from 19 fewer to 7 more)	VERY LOW	IMPORTANT
HELLP by income setting - Low/middle income setting												
1 (Vigil-De Gracia 2013)	randomised trials	very serious[5]	no serious inconsistency	serious[8]	very serious[7]	none	1/137 (0.73%)	1/138 (0.72%)	RR 1.01 (0.06 to 15.94)	0 more per 1000 (from 7 fewer to 108 more)	VERY LOW	IMPORTANT
Placental abruption (overall estimate)												
3 (Odendaal 1990,	randomised trials	very serious[3,4,5]	no serious inconsistency	serious[6,8]	serious[9]	none	7/199 (3.5%)	16/198 (8.1%)	RR 0.42 (0.18 to 1.00)	47 fewer per 1000 (from 66	VERY LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
Sibai 1994, Vigil-De Gracia 2013)										fewer to 0 more)		
Placental abruption by gestational age - Gestational age <34/40												
3 (Odendaal 1990, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[3,4,5]	no serious inconsistency	serious[6,8]	serious[9]	none	7/199 (3.5%)	16/198 (8.1%)	RR 0.42 (0.18 to 1.00)	47 fewer per 1000 (from 66 fewer to 0 more)	VERY LOW	IMPORTANT
Placental abruption by severity of hypertension - Severe hypertension												
2 (Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[4,5]	no serious inconsistency	serious[8]	serious[9]	none	4/179 (2.2%)	12/180 (6.7%)	RR 0.34 (0.11 to 1.02)	44 fewer per 1000 (from 59 fewer to 1 more)	VERY LOW	IMPORTANT
Placental abruption by severity of hypertension - Moderate hypertension												
1 (Odendaal 1990)	randomised trials	very serious[3]	no serious inconsistency	serious[6]	very serious[7]	none	3/20 (15%)	4/18 (22.2%)	RR 0.68 (0.17 to 2.62)	71 fewer per 1000 (from 184 fewer to 360 more)	VERY LOW	IMPORTANT
Placental abruption by income setting - High income setting												
1 (Sibai 1994)	randomised trials	very serious[4,11,22]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/46 (4.3%)	2/49 (4.1%)	RR 1.07 (0.16 to 7.25)	3 more per 1000 (from 34 fewer to 255 more)	VERY LOW	IMPORTANT
Placental abruption by income setting - Low/middle income setting												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
2 (Odendaal 1990, Vigil-De Gracia 2013)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	serious[9]	none	5/153 (3.3%)	14/149 (9.4%)	RR 0.34 (0.13 to 0.90)	62 fewer per 1000 (from 9 fewer to 82 fewer)	VERY LOW	IMPORTANT
Mode of birth (c-section) (overall estimate)												
6 (GRIT 2003, Koopmans 2009, Mesbah 2003, Owens 2014, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[3,4,5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	302/519 (58.2%)	265/483 (54.9%)	RR 1.05 (0.96 to 1.15)	27 more per 1000 (from 22 fewer to 82 more)	LOW	IMPORTANT
Mode of birth (c-section) by gestational age - Gestational age <34/40												
3 (Mesbah 2003, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[2,4,5]	no serious inconsistency	serious[8]	no serious imprecision	none	101/161 (62.7%)	101/164 (61.6%)	RR 1.02 (0.87 to 1.21)	12 more per 1000 (from 80 fewer to 129 more)	VERY LOW	IMPORTANT
Mode of birth (c-section) by gestational age - Gestational age 34+0 to 36+6												
3 (GRIT 2003, Koopmans 2009, Owens 2014)	randomised trials	very serious[1,11,23]	no serious inconsistency	no serious indirectness	no serious imprecision	none	201/358 (56.1%)	164/319 (51.4%)	RR 1.06 (0.95 to 1.18)	31 more per 1000 (from 26 fewer to 93 more)	LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
Mode of birth (c-section) by severity of hypertension - Severe hypertension												
3 (Mesbah 2003, Sibai 1994, Vigil-De Gracia 2013)	randomised trials	very serious[2,4,5]	no serious inconsistency	serious[8]	no serious imprecision	none	101/161 (62.7%)	101/164 (61.6%)	RR 1.02 (0.87 to 1.21)	12 more per 1000 (from 80 fewer to 129 more)	VERY LOW	IMPORTANT
Mode of birth (c-section) by severity of hypertension - Mild hypertension												
3 (GRIT 2003, Koopmans 2009, Owens 2014)	randomised trials	very serious[1,11,23]	no serious inconsistency	no serious indirectness	no serious imprecision	none	201/358 (56.1%)	164/319 (51.4%)	RR 1.06 (0.95 to 1.18)	31 more per 1000 (from 26 fewer to 93 more)	LOW	IMPORTANT
Mode of birth (c-section) by income setting - High income setting												
4 (GRIT 2003, Koopmans 2009, Owens 2014, Sibai 1994)	randomised trials	very serious[1,4,11,23]	no serious inconsistency	no serious indirectness	no serious imprecision	none	240/404 (59.4%)	200/368 (54.3%)	RR 1.08 (0.98 to 1.19)	43 more per 1000 (from 11 fewer to 103 more)	LOW	IMPORTANT
Mode of birth (c-section) by income setting - Low/middle income setting												
2 (Mesbah 2003, Vigil de Gracia 2013)	randomised trials	very serious[2,5]	no serious inconsistency	serious[8]	serious[9]	none	62/115 (53.9%)	65/115 (56.5%)	RR 0.95 (0.76 to 1.20)	28 fewer per 1000 (from 136 fewer to 113 more)	VERY LOW	IMPORTANT
Maternal death (overall estimate)												

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate birth	Expectant management	Relative (95% CI)	Absolute		
1 (Vigil-De Gracia 2013)	randomised trials	very serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/100 (0%)	0/100 (0%)	not pooled	not pooled	LOW	IMPORTANT

[1] The quality of the evidence was downgraded by 1 level due to an unclear risk of incomplete data
[2] The quality of the evidence was downgraded by 1 level due to an unclear risk of bias due to blinding, a high risk of incomplete data and an unclear risk of reporting bias
[3] The quality of the evidence was downgraded by 2 levels due to an unclear risk of random sequence generation, allocation concealment, blinding, incomplete outcome data and an unclear risk of reporting bias
[4] The quality of the evidence was downgraded by 1 level due to an unclear risk of blinding and unclear risk of reporting bias
[5] The quality of the evidence was downgraded by 1 level due to an unclear risk of random sequence generation, allocation concealment, not blinded and unclear risk of reporting bias
[6] 5% of the included women did not present with pre-eclampsia
[7] The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)
[8] 7% of the included women did not present with pre-eclampsia
[9] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (0.8)
[10] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 default MID threshold (1.25)
[11] The quality of the evidence was downgraded by 1 level as there was an unclear risk of incomplete outcome data and the trial was not blinded
[12] The quality of the evidence was downgraded by 1 level as the I square ≥ 50% (but < 75%)
[13] The quality of the evidence was downgraded by 2 levels as the I square ≥ 75%
[14] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (350 x +/- 0.5 = +/-175)
[15] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (508.98 x +/- 0.5= +/- 254.49)
[16] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (24 x +/-0.5= +/- 12)
[17] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (11 x +/- 0.5= +/- 5.5)
[18] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (13 x +/- 0.5 = +/- 6.5)
[19] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (21 x +/- 0.5= +/- 10.5)
[20] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (16X +/5 0.5 = +/- 16)
[21] The quality of the evidence was downgraded by 1 level as the 95% CI crossed 1 MID threshold (12 x +/- 0.5 = +/- 6)
[22] The quality of the evidence was downgraded by 1 level as this was an open label trial and the outcome assessors were not blinded
[23] The quality of the evidence was downgraded by 1 level as there was an unclear risk of allocation concealment and the trial was not blinded

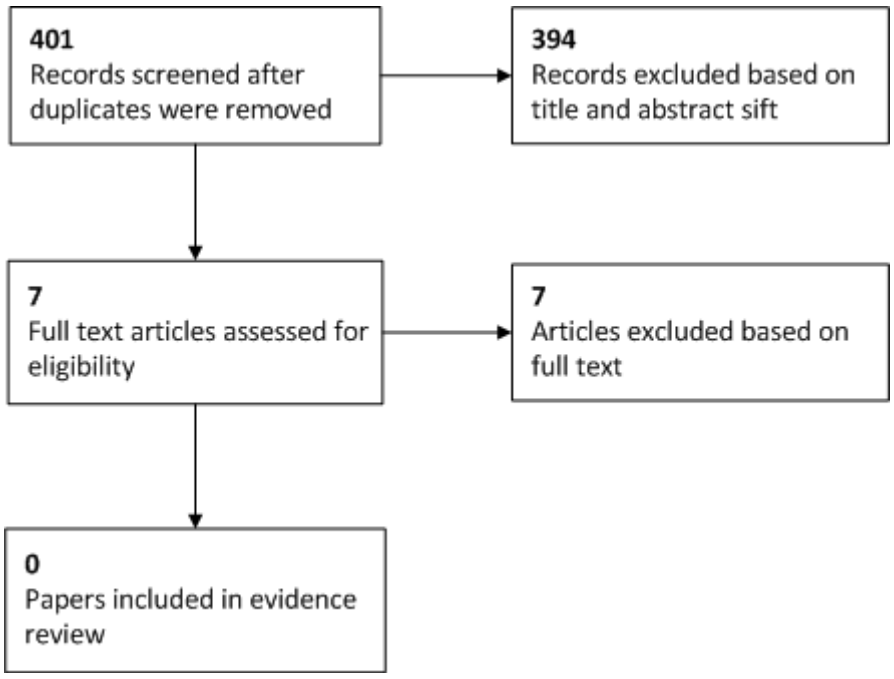
Table 14: Clinical evidence profile. Comparison 10: outpatient management versus inpatient management

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Outpatient management	Inpatient management	Relative (95% CI)	Absolute		
Stillbirth												
1 (Schoen 2017)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	2/198 (1%)	2/167 (1.2%)	RR 0.84 (0.12 to 5.92)	2 fewer per 1000 (from 11 fewer to 59 more)	VERY LOW	CRITICAL
SGA												
1 (Schoen 2017)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	5/198 (2.5%)	49/167 (29.3%)	RR 0.60 (0.41 to 0.88)	117 fewer per 1000 (from 35 fewer to 173 fewer)	VERY LOW	CRITICAL
Birth weight (Better indicated by higher values)												
1 (Schoen 2017)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	198	167	-	MD 345 higher (154.37 to 535.63 higher)	VERY LOW	IMPORTANT
Gestational age at birth (weeks, better indicated by higher values)												
1 (Schoen 2017)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	198	167	-	MD 0.80 higher (0.18 to 1.42 higher)	LOW	IMPORTANT
Admission to neonatal unit												
1 (Schoen 2017)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	80/198 (40.4%)	80/167 (47.9%)	RR 0.84 (0.67 to 1.06)	77 fewer per 1000 (from 158 fewer to 29 more)	VERY LOW	IMPORTANT
HELLP												
1 (Schoen 2017)	observational studies	no seriou	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/198 (0%)	0/167 (0%)	-	-	LOW	IMPORTANT

Quality assessment							Number of patients		Effect		Quality	Importance
Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Outpatient management	Inpatient management	Relative (95% CI)	Absolute		
		s risk of bias										
Placental abruption												
1 (Schoen 2017)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	10/198 (5.1%)	8/167 (4.8%)	RR 1.05 (0.43 to 2.61)	2 more per 1000 (from 27 fewer to 77 more)	VERY LOW	IMPORTANT
Mode of birth (C-section)												
1 (Schoen 2017)	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[1]	none	55/198 (27.8%)	50/167 (29.9%)	RR 0.93 (0.67 to 1.28)	21 fewer per 1000 (from 99 fewer to 84 more)	VERY LOW	IMPORTANT

1 The quality of the evidence was downgraded by 2 levels as the 95% CI crossed 2 default MID thresholds (0.8 and 1.25)
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 1 level as the 95% CI crossed 1 MID (837 x +/-0.5= +/- 418.5)

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 economic analysis was conducted for this review question.

Appendix K – Excluded studies

Clinical studies

Table 15: Clinical excluded studies with resons for exclusion

Study	Reason for Exclusion
Altman, D, Carroli, G, Duley, L, Farrell, B, Moodley, J, Neilson, J, Smith, D, Do women with pre-eclampsia, and their babies, benefit from magnesium sulphate? The Magpie Trial: a randomised placebo-controlled trial, Lancet (London, England), 359, 1877-1890, 2002	Magnesium study
Bain,E.S., Middleton,P.F., Crowther,C.A., Maternal adverse effects of different antenatal magnesium sulphate regimens for improving maternal and infant outcomes: A systematic review, BMC Pregnancy and Childbirth, 13 , 2013. Article Number, -, 2013	Systematic review about the management of gestational hypertension and preeclampsia. The relevant references for management of preeclampsia were included in this systematic review
Belfort, M. A., Saade, G. R., Yared, M., Grunewald, C., Herd, J. A., Varner, M. A., Nisell, H., Change in estimated cerebral perfusion pressure after treatment with nimodipine or magnesium sulfate in patients with preeclampsia, American Journal of Obstetrics and Gynecology, 181, 402-7, 1999	No relevant outcomes have been reported
Bond, Diana M., Gordon, Adrienne, Hyett, Jon, de Vries, Bradley, Carberry, Angela E., Morris, Jonathan, Planned early delivery versus expectant management of the term suspected compromised baby for improving outcomes, Cochrane Database of Systematic Reviews, 2015	Review protocol
Chappell,L.C., Enye,S., Seed,P., Briley,A.L., Poston,L., Shennan,A.H., Adverse perinatal outcomes and risk factors for preeclampsia in women with chronic hypertension: a prospective study, Hypertension, 51, 1002-1009, 2008	Not a randomised trial
Charoenvidhya, Dhirapatara, Manotaya, Saknan, Magnesium sulfate maintenance infusion in women with preeclampsia: a randomized comparison between 2 gram per hour and 1 gram per hour, Journal of the Medical Association of Thailand = Chotmaihet thangphaet, 96, 395-8, 2013	Study unavailable
Chissell, S., Botha, J. H., Moodley, J., McFadyen, L., Intravenous and intramuscular magnesium sulphate regimens in severe pre-eclampsia, South African medical journal = Suid-Afrikaanse tydskrif vir geneeskunde, 84, 607-10, 1994	No relevant outcomes were reported
Cluver, Catherine, Novikova, Natalia, Koopmans, Corine M., West, Helen M., Planned	This systematic review included a mix of participants with chronic hypertension and pre-

Study	Reason for Exclusion
early delivery versus expectant management for hypertensive disorders from 34 weeks gestation to term, The Cochrane database of systematic reviews, 1, CD009273, 2017	eclampsia. The relevant studies have been included in Q1 and Q4 respectively
Dasgupta, S, Ghosh, D, Seal, Sl, Kamilya, G, Karmakar, M, Saha, D, Randomized controlled study comparing effect of magnesium sulfate with placebo on fetal umbilical artery and middle cerebral artery blood flow in mild preeclampsia at ? 34 weeks gestational age, Journal of Obstetrics and Gynaecology Research, 38, 763-771, 2012	No relevant outcomes were reported
Duffy, J. M. N., Hirsch, M., Kawsar, A., Pealing, L., Showell, M., Williamson, P., Khan, K., Ziebland, S., McManus, R. J., Completeness of safety reporting in 79 randomised trials, 31 615 participants, evaluating therapeutic interventions for pre-eclampsia: A systematic review, BJOG: An International Journal of Obstetrics and Gynaecology, 124, 37, 2017	Abstract
Duley, L., Gulmezoglu, A. M., Henderson-Smart, D. J., Magnesium sulphate and other anticonvulsants for women with pre-eclampsia, Cochrane database of systematic reviews (Online), CD000025, 2003	This systematic review also included postnatal women and not all the comparisons included were relevant for the protocol of this systematic review (phenytoin, diazepam,nimodipine, etc)
Duvekot, J., Bax, C., Bloemenkamp, K., Dijk, P., Van Drongelen, J., Franssen, M., Franx, A., Ganzevoort, W., Oudijk, M., Porath, M., Van Der Post, J., Scheepers, H., Steegers, E., Van Wassenaer-Leemhuis, A., Van Der Wilk, E., Mol, B. W., Temporizing management versus termination of pregnancy in women with severe preeclampsia at 28-34 weeks (TOTEM-Trial), American Journal of Obstetrics and Gynecology, 212, S246, 2015	Abstract
Ernawati,, Gumilar, Erry, Kuntoro,, Soeroso, Joewono, Dekker, Gus, Expectant management of preterm preeclampsia in Indonesia and the role of steroids, 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, 29, 1736-40, 2016	Randomisation is to methylprednisolone versus placebo, i.e. steroids are the intervention assessed
Fogleman, Corey D., Magnesium sulfate and other anticonvulsants for women with preeclampsia, American family physician, 83, 1269-70, 2011	Summary of the Cochrane review developed by Duley et al
Gordon, R. M., Payne, B., Firoz, T., Magee, L., Sawchuck, D., Tu, D., Vidler, M., Von Dadelszen, P., Magnesium sulphate for prevention and treatment of eclampsia in low and middle income countries: Systematic review	Abstract

Study	Reason for Exclusion
of tested regimens, Pregnancy Hypertension, 2, 328, 2012	
Habli, M, Levine, Rj, Qian, C, Sibai, B, Neonatal outcomes in pregnancies with preeclampsia or gestational hypertension and in normotensive pregnancies that delivered at 35, 36, or 37 weeks of gestation, American Journal of Obstetrics and Gynecology, 197, 406.e1-7, 2007	The main aim of the trial was to prevent preeclampsia
Haddad, Bassam, Sibai, Baha M., Expectant management in pregnancies with severe pre-eclampsia, Seminars in Perinatology, 33, 143-51, 2009	Systematic review including randomised and non randomised studies. The relevant randomised studies have been included in this review
Hanff, Lidwien M., Vulto, Arnold G., Bartels, Pieter A., Roofthooft, Daniella W. E., Bijvank, Bas Nij, Steegers, Eric A. P., Visser, Willy, Intravenous use of the calcium-channel blocker nicardipine as second-line treatment in severe, early-onset pre-eclamptic patients, Journal of Hypertension, 23, 2319-26, 2005	Not a randomised trial
Hong, Yj, Lin, Cf, Chen, Jc, Pan, P, Wong, Kl, Wei, Tt, Nifedipine in preeclampsia for cesarean section, Ma zui xue za zhi / Anaesthesiologica Sinica, 31, 43-48, 1993	Study in Chinese
Ismail, A. A., Medhat, I., Tawfic, T. A., Kholeif, A., Evaluation of calcium-antagonist (Nifedipine) in the treatment of pre-eclampsia, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 40, 39-43, 1993	Only p-values were reported for the relevant outcome (blood pressure control)therefore, no abstractable data
Jamil, M., Basharat, A., Ayub, S., Comparison of effects of nifedipine versus hydralazine in patients with severe preeclampsia in a tertiary care hospital in Pakistan, International Journal of Gynecology and Obstetrics, 131, E245, 2015	Abstract
Kashanian, Maryam, Koohpayehzadeh, Jalil, Sheikhansari, Narges, Bararpour, Foroozan, Sahraian, Ghazal, Asadolla, Sara, A comparison between the two methods of magnesium sulfate administration for duration of 12 versus 24 h after delivery in patients with severe preeclampsia, 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, 29, 2282-7, 2016	Magnesium was administered after delivery
Khan, K. S., Joshi, R., Chien, P. F., A randomised controlled trial of intravenous magnesium sulphate versus placebo, British Journal of Obstetrics and Gynaecology, 105, 809-10, 1998	Letter for the author
Krishna,K., Krishna,L., Bhat,S., Shailaja,N., Kumari,B., A randomised controlled trial of oral	Abstract

Study	Reason for Exclusion
nifedipine and intravenous labetalol in pregnant women with severe pre eclampsia and eclampsia, BJOG: An International Journal of Obstetrics and Gynaecology, 120, 79-80, 2013	
Lai, T. C., Liao, C. Y., Maternal magnesium sulfate treatment and infant outcomes, Journal of Obstetrics and Gynaecology Research, 43, 56-57, 2017	Abstract
Mabie,W.C., Gonzalez,A.R., Sibai,B.M., Amon,E., A comparative trial of labetalol and hydralazine in the acute management of severe hypertension complicating pregnancy, Obstetrics and Gynecology, 70, 328-333, 1987	>60% of women were postnatal
Magee, L. A., Yong, P. J., Espinosa, V., Cote, A. M., Chen, I., von Dadelszen, P., Expectant management of severe preeclampsia remote from term: a structured systematic review, Hypertension in Pregnancy, 28, 312-47, 2009	This systematic review included observational and RCT studies. The relevant RCTs have already been included in this systematic review
Martin, J. N., Owens, M. Y., Thigpen, B., Parrish, M. R., Keiser, S. D., Wallace, K., Management of late preterm pregnancy complicated by mild preeclampsia: A prospective randomized trial, Pregnancy Hypertension, 2, 180, 2012	Abstract
McDonald, S., Dzaja, N., Lutsiv, O., Duley, L., Maternal and infant outcomes on magnesium sulphate for preeclampsia/eclampsia: A systematic review comparing outcomes within trials with outcomes outside of trials, Pregnancy Hypertension, 1, S29, 2010	Abstract
McDonald, Sarah D., Lutsiv, Olha, Dzaja, Nancy, Duley, Lelia, A systematic review of maternal and infant outcomes following magnesium sulfate for pre-eclampsia/eclampsia in real-world use, International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics, 118, 90-6, 2012	This systematic review included randomised and non-randomised studies. Those randomised were included in this systematic review
Montan, S., Anandakumar, C., Arulkumaran, S., Ingemarsson, I., Ratnam, S., Randomised controlled trial of methyldopa and isradipine in preeclampsia--effects on uteroplacental and fetal hemodynamics, Journal of Perinatal Medicine, 24, 177-84, 1996	Not relevant comparator (isradipine)
Mundle, S., Bracken, H., Faragher, B., Easterling, T., Haycox, A., Turner, M., Alfirevic, Z., Winikoff, B., Weeks, A., Induction of labour in pre-eclamptic women: A randomised trial comparing the foley balloon catheter with oral misoprostol, International Journal of Gynecology and Obstetrics, 131, E497, 2015	This trial assessed different methods to induce labour (i.e. foley balloon catherer versus oral misoprostol), which is not relevant for the protocol of this systematic review
Riaz,M., Porat,R., Brodsky,N.L., Hurt,H., The effects of maternal magnesium sulfate treatment	Not a randomised trial

Study	Reason for Exclusion
on newborns: a prospective controlled study, Journal of Perinatology, 18, 449-454, 1998	
Scardo, J. A., Vermillion, S. T., Newman, R. B., Chauhan, S. P., Hogg, B. B., A randomized, double-blind, hemodynamic evaluation of nifedipine and labetalol in preeclamptic hypertensive emergencies, American Journal of Obstetrics and Gynecology, 181, 862-6, 1999	Only p-values were reported for the relevant outcome (mean arterial blood pressure)therefore, no abstractable data
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	Trial of women with sustained severe hypertension, women did not present with pre-eclampsia
Turnbull, Da, Wilkinson, C, Gerard, K, Shanahan, M, Ryan, P, Griffith, Ec, Kruzins, G, Stamp, Ge, Clinical, psychosocial, and economic effects of antenatal day care for three medical complications of pregnancy: a randomised controlled trial of 395 women, Lancet (London, England), 363, 1104-1109, 2004	No relevant population (women with ruptured membrane or gestational hypertension)
Von Dadelszen, P., Magee, L. A., Antihypertensive medications in management of gestational hypertension-preeclampsia, Clinical Obstetrics and Gynecology, 48, 441-459, 2005	Literature review about the management of gestational hypertension and preeclampsia. The relevant references for management of preeclampsia were included in this systematic review
Voto LS, Quiroga CA, Lapidus AM, Catuzzi P, Imaz FU, Margulies M. Effectiveness of antihypertensive drugs in the treatment of hypertension in pregnancy. Clinical and Experimental Hypertension. Part B: Hypertension in Pregnancy. 1990 Jan 1;9(3):339-48.	Unavailable
Voto, L. S., Treatment and prevention of preeclampsia with low molecular weight heparin, statins, placental growth factor, antithrombin III for the prevention of preeclampsia and fetal death, Journal of Perinatal Medicine, 43, 2015	Abstract
Walss, Rodríguez Rj, Villarreal, Ordaz F, Management of severe pre-eclampsia in the puerperium. Comparative study of sublingual nifedipine and hydralazine, Ginecologia y Obstetricia de Mexico, 59, 207-210, 1991	Article in Spanish
Yefet, E., Kuzmin, O., Schwartz, N., Basson, F., Nachum, Z., Labor induction versus expectant management in pregnancies with elevated HCG or AFP in the second trimester triple test, American Journal of Obstetrics and Gynecology, 216, S394-S395, 2017	Participants had higher risk screening tests only, but no other antenatal complications (no pre-eclampsia)
Zarean, Elaheh, Tarjan, Amal, Effect of Magnesium Supplement on Pregnancy Outcomes: A Randomized Control Trial, Advanced biomedical research, 6, 109, 2017	No relevant interventions, preeclampsia was an outcome of pregnancy

Economic studies

Table 16: Economic excluded studies with reasons for exclusion

Study	Reason for exclusion
Blackwell SC, Tomlinson MW, Berman S, Redman ME, Hassan SS, Berry SM, Hallak M, Sorokin Y, Cotton DB. The use of magnesium sulfate to prevent seizures in the pre-eclamptic gravida: A cost-effectiveness analysis. Prenatal and Neonatal Medicine 6(5):pp. 310-317. 2001	Not cost-utility analysis. Costs reflect US setting and are therefore of limited relevance to UK setting.
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 pre-eclampsia.
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	Available as abstract only
Simon, J, Gray, A, Duley, L. Cost-effectiveness of prophylactic magnesium sulphate for 9996 women with pre-eclampsia from 33 countries: economic evaluation of the Magpie Trial. BJOG, 113: 144-151. 2006	Not cost-utility analysis. Costs are grouped together for several country and so are of limited applicability to UK specifically.
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	Less applicable to UK context than de novo evaluation conducted for the previous iteration of this guidance.
Zakiyah N, Postma MJ, Baker PN, van Asselt AD. Pre-eclampsia Diagnosis and Treatment Options: A Review of Published Economic Assessments. PharmacoEconomics, 33(10), 1069-82. 2015	Review of existing economic evidence
Zakiyah N, Van Asselt AD, Baker PN, Postma MJ. Economic assessment of preeclampsia: Screening, diagnosis, treatment options, and long term outcomes-A systematic review. Value in Health 17 (7) A506-A507 2014	Review of existing economic evidence

Appendix L – Research recommendations

In which women with pre-eclampsia is inpatient management associated with better outcomes for mothers and babies?

Why this is important?

There is currently high unwanted variance between (and within) maternity units in the proportion of women with pre-eclampsia who are admitted for inpatient management after diagnosis and no evidence to guide appropriate place of care. There was good evidence that the fullPIERS and PREP-S models are useful tools to identify women at higher and lower risk of adverse outcomes due to pre-eclampsia. The committee agreed that a risk of 30% or more would be an indication for admission into hospital for surveillance and appropriate intervention. However, the committee also agreed that the models should not be used in isolation. Admission to hospital for monitoring may be recommended for women with pre-eclampsia for other reasons, such as severe hypertension or other severe features of pre-eclampsia, even if their risk does not reach the 30% threshold.

The tools predict adverse outcomes in women, but are not designed to predict outcomes for babies. We do not know which decision-making tool is superior nor the implications on the benefits, acceptability and risks of adopting a fullPIERS or PREP-S risk threshold of 30% to determine the need for inpatient management. Inpatient monitoring is necessary and appropriate for some pregnant hypertensive women but has resource and family implications, and further research would help inform discussions and planning for families and health professionals.

Table 17: Research recommendation rationale

Research question	In which women with pre-eclampsia is inpatient management associated with better outcomes for mothers and babies?'
Importance to 'patients' or the population	Better understanding of the risks and benefits for a women with pre-eclampsia and her baby of inpatient compared with outpatient management would facilitate appropriate stratification of care pathways and improve outcomes.
Relevance to NICE guidance	Current draft NICE guidance (2019) states 'For women with pre-eclampsia, use either the fullPIERS or PREP-S validated risk prediction models to guide decisions about place of care and the need for in utero transfer. When choosing which model to use, take into account the fact that fullPIERS is intended for use at all gestational ages, but PREP-S is intended for use up to 34 weeks of pregnancy and be aware that the fullPIERS and PREP-S models do not predict outcomes for babies. The current recommendations include: Offer admission to hospital for surveillance and any interventions needed if there are concerns for the wellbeing of the woman or baby. For example: • fullPIERS or PREP-S risk of 30% or more • sustained systolic blood pressure of 160 mmHg or higher • any maternal biochemical or haematological investigations that cause concern, for example new and persistent rise in creatinine (90 µmol/L or more, 1 mg/dL), alanine transaminase (over 70 IU/L, or twice upper limit of normal range), or new and persistent fall in platelet count (under 150,000 cells/µL)

Research question	In which women with pre-eclampsia is inpatient management associated with better outcomes for mothers and babies?'
	• any clinical signs that cause concern (for example, signs of impending eclampsia, pulmonary oedema or other sign of severe pre-eclampsia) • suspected fetal compromise However, it is not currently known whether using these criteria to determine place of care improves outcomes for women and their babies
Relevance to the NHS	High: the decision to admit or not admit a woman with pre-eclampsia has an impact on the use of NHS resources
National priorities	High
Current evidence base	Eight publications providing external validation of 4 prediction models (fullPIERS, miniPIERS, PREP-L and PREP-S) are currently available: (Agrawal 2014, Akkermans 2014, Almeida 2017, Payne 2014, Payne 2015, Thangaratinam 2017, Ukah 2017, and Ukah 2018). In the context of this review, prediction models assessed the individualised risk of developing adverse maternal or fetal outcomes by combining prognostic factors of an individual. Prognostic test accuracy studies Six publications have been assessed by NICE (Chan 2005, Laskin 2011, Livingston 2014, Thangaratinam 2011, Ukah 2017, Waugh 2017). These studies aimed to assess the performance of different tests to predict adverse maternal and fetal outcomes Current evidence is moderate to high using GRADE criteria.
Equality	All women with pre-eclampsia should receive equal treatment, regardless of where they live.

Table 18: Research recommendation modified PICO table

Criterion	Explanation
Population	Pregnant women with pre-eclampsia
Prognostic or risk factor	Pre-eclampsia with place of care varying
Outcome	• **Maternal adverse outcomes, for example** ○ Severe pre-eclampsia ○ Eclampsia ○ Maternal mortality ○ Maternal morbidity ○ Placental abruption ○ Need for delivery (any delivery/delivery for pre-eclampsia) • **Perinatal adverse outcomes** ○ Preterm delivery (<34 weeks) ○ Perinatal mortality (stillbirths and death during first 7 days of life) ○ Stillbirth ○ Neonatal death (during first 28 days of life) ○ Serious neonatal morbidity • **Patient acceptability** • **Health economic analysis of cost-effectiveness** • **Timing** ○ Up to 48 hours

Criterion	Explanation
	○ Up to 7 days ○ Over 7 days
Study design	The study design should be detailed and justified by the applicants. It is likely that a head to head trial of inpatient versus outpatient management will not be acceptable or feasible and therefore other cohort study designs should be explored.
Timeframe	Minimum duration of follow-up: To primary discharge of woman and baby.