Table 4: Clinical evidence tables

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

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

Ref Id

787414

Country/ies where the study was carried out

Brazil</td>
<td>Sample size

Total population:

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

Women with chronic hypertension:

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

Characteristics

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

n = 498</td><td>Placebo

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

Aspirin group: 60mg aspirin to be taken daily

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

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

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

The study was analysed on an intention to treat basis.

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

Pre-eclampsia in women with chronic hypertension†

Aspirin group: 23/231

Placebo group: 16/224

Preterm delivery < 37 weeks in women with chronic hypertension‡

Aspirin group: 56/231

Placebo group: 70/225

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

Aspirin group: 26/233

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

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

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

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

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

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

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

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

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

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

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

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

Ref Id

659083

Country/ies where the study was carried out

UK

Study type

RCT

Aim of the study

To assess the effectiveness of atenolol in women with chronic hypertension

Study dates

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

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

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

Inclusion criteria</td>
<td>Interventions

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

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

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

Follow-up length: 20 weeks

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

Neonatal outcomes

Stillbirth

Atenolol:1/ 15

Placebo: 0/14

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

Atenolol:10/15

Placebo:0/14

Birth weight

Atenolol:2620 g (SDs not reported)

Placebo:3530 g (SDs not reported)

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

Gestational age at delivery

Atenolol: 39.5 (no SD was reported)

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

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

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

Allocation concealment: unclear risk (not reported)

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

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

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

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

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

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

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

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

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

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>outcomes of expectant management of stable mild to moderate chronic hypertension as compared with planned delivery, International Journal of Gynecology and Obstetrics, 127, 15-20, 2014

Ref Id

337201

Country/ies where the study was carried out

Egypt and Saudi Arabia

Study type

RCT

Aim of the study

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

Birth weight

Induction of labour: 2800 (600)

Expectant management: 3200 (600)

Gestational age at delivery

Induction of labour: 35.7 (1.2)

Expectant management:38.1 (2.7)

Preterm birth (weeks were not reported)

Induction of labour: 10/38

Expectant management:12/38

Admission to neonatal unit

Induction of labour: 12/38

Expectant management:3/38

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

Allocation concealment: unclear risk (not reported)

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

Blinding of outcome assessment: unclear risk (not reported)

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

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

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

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

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

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td>pressure [BP ≥ 160/110] not responding to anti-hypertensive medications, or prepartum fetal asphyxia).</td><td></td><td></td><td></td></tr>
<tr><td>Full citation

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

Ref Id

776154</td><td>Sample size

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

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

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

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

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

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

Follow-up: 10 weeks (approximately)

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

Neonatal outcomes

Birth weight (<2500)

Exercise: 9/56

No intervention: 11/53

Birth weight (2500-3999)

Exercise: 41/56

No intervention: 35/53

Birth weight (≥4000)

Exercise: 5/56

No intervention: 11/53

Admission to neonatal unit

Exercise: 12/56

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ref Id

776372

Country/ies where the study was carried out

UK

Study type

RCT

Aim of the study

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

Study dates</td>
<td>Sample size

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

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

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

Labetalol: 100 mg/4 times per day

Methyldopa: 250 mg 4 times per day

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

Follow-up time: 5 weeks

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

Neonatal outcomes:

Stillbirth

Labetalol: 0/38

Methyldopa: 0/34

Neonatal death up to 7 days

Labetalol: 2/38

Methyldopa: 0/34

Small-for-gestational-age

Labetalol: 13/38

Methyldopa: 15/34

Birth weight

Labetalol: 2356 (724)

Methyldopa: 2349 (863)

Gestational age at delivery

Labetalol: 36.2 (2.3)

Methyldopa: 36.1 (3.2)

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

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

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

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

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

Blinding of outcome assessment: unclear risk (not reported)

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

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

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

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

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

Ref Id

788545</td>
<td>Total population:

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

Women with chronic hypertension or nephropathy:

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

Characteristics

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

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

Analysis was conducted on an intention to treat basis.

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

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

Aspirin group: 25/134

Control group: 22/98

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

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

Allocation concealment: unclear risk (not reported)

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

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

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

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

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

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Vanegas, O., Persico, N., Nicolaides, K. H., Aspirin for Evidence-Based Preeclampsia Prevention trial: effect of aspirin in prevention of preterm preeclampsia in subgroups of women according to their characteristics and medical and obstetrical history, American Journal of Obstetrics and Gynecology, 217, 585, 2017

Ref Id

788591

Country/ies where the study was carried out

Multicentre

Study type

Multicentre RCT

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

n = 798</th><th>Placebo

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

Analyses were performed on an intention to treat basis.

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

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

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

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

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

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

Other information

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

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

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>continued until April 2016.

Source of funding

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

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

Ref Id

776552

Country/ies where the study was carried out

UK</td><td>Sample size

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

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

Methyldopa: dose and route of administration was not reported

No intervention</td><td>Details

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

Follow-up: not reported

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

Neonatal outcomes

Stillbirth

Methyldopa: 1/98

No intervention:9/92

Birth weight (kgs)

Methyldopa: 3.13 (0.50)

No intervention:3.09 (0.60)

Gestational age at delivery

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

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

Random sequence generation: unclear risk (not reported)

Allocation concealment: unclear risk (not reported)

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

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

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td>companies (Merck, Sharp, Dohme Ltd.)</td></tr>
<tr><td>Full citation

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

Ref Id

659222

Country/ies where the study was carried out

US

Study type

RCT</td><td>Sample size

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

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

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

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

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

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

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

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

Neonatal outcomes

Perinatal deaths

No intervention:1/90

Methyldopa: 1/88

Labetalol: 1/86

Small-for-gestational-age

No intervention:8/90

Methyldopa: 6/88

Labetalol: 7/86

Preterm birth (<37 weeks)

No intervention:9/90

Methyldopa: 11/88

Labetalol: 10/86

Maternal outcomes:

Superimposed pre-eclampsia

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

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

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

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

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

Blinding of outcome assessment: unclear risk (not reported)

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

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

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

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

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

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr><td>of Sydney, Australia).</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Full citation

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

Ref Id

78531

Country/ies where the study was carried out

Finland</td><td>Sample size

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

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

n = 103</th><th>Placebo

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

Aspirin group: 50mg aspirin to be taken daily

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

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

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

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

Aspirin group: 9/97

Control group: 11/100

Exacerbation of hypertension

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

Aspirin group: 21/97

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

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

Random sequence generation: unclear risk (insufficient details provided)

Allocation concealment: unclear risk (no details reported)

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

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

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

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

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

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

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

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

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

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

<table>
<tr><th>Study details</th><th>Participants</th><th>Interventions</th><th>Methods</th><th>Outcomes and Results</th><th>Comments</th></tr>
<tr>
<td>Journal of Gynaecology & Obstetrics, 25, 35-40, 1987

Ref Id

392871

Country/ies where the study was carried out

US

Study type

RCT

Aim of the study

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

Study dates

Not reported

Source of funding

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

Inclusion criteria

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

Exclusion criteria

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

Gestational age at delivery

Methyldopa: 273 (2.93)

Placebo: 263 (3.48)

Maternal outcomes:

Superimposed pre-eclampsia

Methyldopa: 5/13

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

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

Blinding of outcome assessment: low risk (double blind)

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

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

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

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